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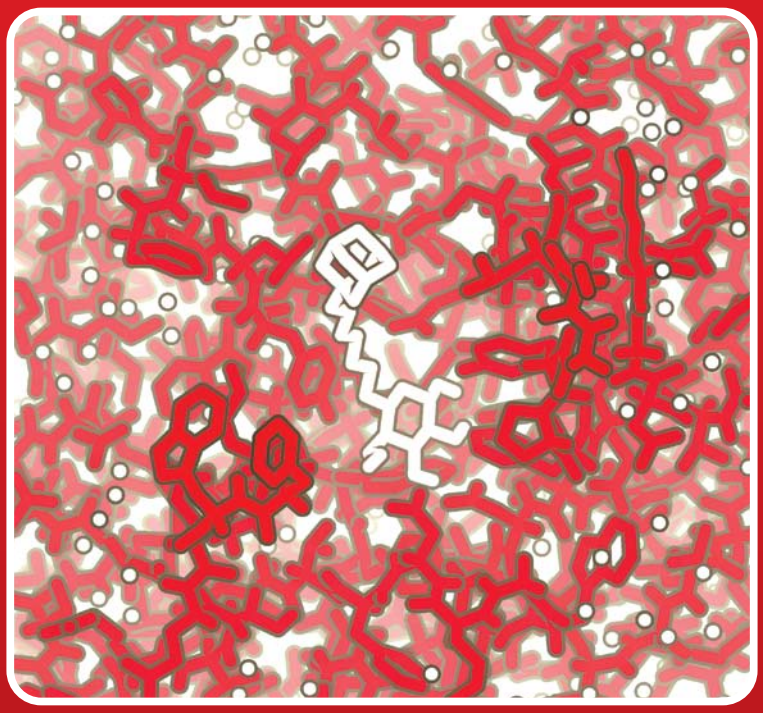

Tom Wennekes

LIPOPHILIC IMINOSUGARS

Synthesis and Evaluation as Inhibitors of Glucosylceramide Metabolism

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The cover and back depict a model of the enzyme glucocerebrosidase with the lipophilic iminosugar N-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin bound in its active site. Adapted from the X-ray crystal structure of active site bound N-nonyl-1-deoxynojirimycin (PDB code: 2v3e) reported by Futerman and co-workers.

'Buy the ticket, take the ride'

Hunter S. Thompson

Table of Contents

List of Abbreviations

4-MU	4-methylumbelliferyl/ 7-hydroxy-4-methylcoumarin
Ac	acetyl
Ada	adamantane
All	allyl
AMP	5-(adamantan-1-yl-methoxy)-pentyl
AMP-DNM	*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin
APT	attached proton test
aq	aqueous
Ar	aromatic
ATP	adenosine triphosphate
AUC	area under curve
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
C1P	ceramide-1-phosphate
calcd	calculated
CAN	ceric ammonium nitrate
cat	catalytic
CBE	conduritol-B-epoxide
Cer	ceramide
CerS	dihydroceramide synthase
CERT	ceramide transport protein
CFTR	cystic fibrosis transmembrane conductance regulator
cGMP	current good manufacturing practices
CMP	cytidine monophosphate
CMT	chaperone mediated therapy
CoA	coenzyme A
COSY	correlation spectroscopy
C_q	quaternary carbon atom
CSA	camphersulfonic acid
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
dd	doublet of doublet
ddd	double doublet of doublet
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopopyl azodicarboxylate
DiPEA	*N*,*N*-diisopropyl-*N*-ethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMDP	2,5,-dihydroxymethyl-3,4-dihydroxy-pyrrolidine
DMF	*N*,*N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPPA	diphenylphosphoryl azide
DRMD	detergent resistant microdomain
DSC	differential scanning calorimetry
dt	double triplet
DTTA	di-*p*-toluoyl-L-tartaric acid
e.g.	*exempli gratia* (for example)
eq	(molar) equivalents
ER	endoplasmic reticulum
ERAD	ER-associated degradation pathway
ERT	enzyme replacement therapy
ESI	electron spray ionization
Et	ethyl
et al.	*et alii* (and others)
EtOAc	ethylacetate
Fmoc	9H-fluoren-9-ylmethoxycarbonyl
Fuc	fucose
g	gram(s)
Gal	galactose
GalNAc	*N*-acetylgalactoseamine
GBA1	glucocerebrosidase
GBA2	β-glucosidase 2
GBA3	cytosolic β-glucosidase
GC	gas chromatography
GCS	glucosylceramide synthase
GDP	guanosine diphosphate
Glc	glucose
GlcA	glucuronic acid
GlcNAc	*N*-acetylglucoseamine
GLTP	glycolipid transfer protein
Glu	glutamic acid
GLUT-4	glucose transporter 4
GPI	glycosyl phosphatidylinositol
GSL	glycosphingolipid
GSLs	glycosphingolipids
h	hour(s)
HbA1c	hemoglobin-A1c

HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HOMA	homeostatic model assessment
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	Hertz
IC_{50}	inhibitor concentration resulting in 50% inhibition of enzyme activity
iNKT	invariant natural killer T cells
IR	infrared
IR	insulin receptor
IRS-1	insulin receptor substrate
J	coupling constant
kDa	kilo Dalton
L	liter(s)
LCMS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
LPH	lactase-phlorizin hydrolase
LPP	lipid phosphate phosphatase
m	*meta*
M	molar(s)
m	multiplet
m/z	mass over charge ratio
Man	mannose
MCR	multicomponent reaction
Me	methyl
MeOH	methanol
mg	milligram(s)
MHz	mega Hertz
min	minute(s)
mL	milliliter(s)
mmol	millimol(s)
MRT	mean retention time
MS	mass spectrometry
Ms	methanesulfonyl (mesyl)
MSA	methansulfonic acid
MTBE	methyl *tert*-butyl ether
NADPH	nicotinamide adenine dinucleotide phosphate
NaH	sodium hydride
NAP	2-naphthylmethyl
NBD	4-nitrobenzo-2-oxa-1,3-diazole
Neu5Ac	*N*-acetylneuraminic acid
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
o	*ortho*
OGT	oral glucose tolerance
p	*para*
Pd/C	palladium on activated charcoal
PDMP	D-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol
PE	petroleum ether
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	part per million
q	quartet
ref	reference
R_F	retardation factor
RNA	ribonucleic acid
rt	room temperature
s	singlet
S1P	sphingosine-1-phosphate
Sap	saposin
SAR	structure–activity relationship
sat	saturated
SAWU-3CR	Staudinger/aza-Wittig/Ugi three-component reaction
SL	sphingolipid
SM	sphingomyelin
SPC	sphingosylphosphorylcholine
Sph	sphingosine
SRT	substrate reduction therapy
t	tertiary
t	triplet
$t_{½}$	half life
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethyl-1-piperdinyloxy (free radical)
Tf	trifluoromethanesulfonyl (triflate)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TLR2	Toll-like recepeptor 2
tMB	1,1,3,3-tetramethylbutyl
TNF-α	tumor necrosis factor -α
t_R	retention time
Tr	triphenylmethylene (trityl)
Ts	*para*-toluenesulfonyl (tosyl)
UDP	uridine diphosphate
Xyl	xylose
Z	benzyloxycarbonyl

1 General Introduction and Outline

Glycosphingolipids, Carbohydrate-processing Enzymes and Iminosugar Inhibitors

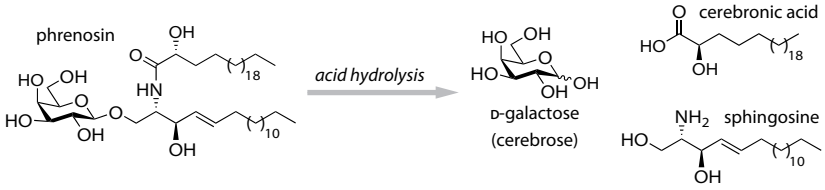
General Introduction

The study described in this thesis was conducted with the aim of developing lipophilic iminosugars as selective inhibitors for three enzymes involved in glucosylceramide metabolism. Glucosylceramide, a β-glycoside of the lipid ceramide and the carbohydrate D-glucose, is a key member of a class of biomolecules called the glycosphingolipids (GSLs). One enzyme, glucosylceramide synthase (GCS), is responsible for its synthesis and the two other enzymes, glucocerebrosidase (GBA1) and β-glucosidase 2 (GBA2), catalyze its degradation. Being able to influence glucosylceramide biosynthesis and degradation would greatly facilitate the study of GSL functioning in (patho)physiological processes. This chapter aims to provide background information and some history on the various subjects that were involved in this study. The chapter will start out with a brief overview of the discovery of GSLs and the evolving view of the biological role of GSLs and carbohydrate containing biomolecules in general during the last century. Next, the topology and dynamics of mammalian GSL biosynthesis and degradation will be described with special attention for the involved carbohydrate-processing enzymes. Following this, the known functions of GSLs in health and diseases will be discussed together with the therapeutic opportunities for inhibitors of glucosylceramide metabolism. The chapter ends with an introduction on iminosugars and a concise overview of the presently known small-molecule inhibitors of the three targeted enzymes.

1.1 About Thudichum's Discovery of (Glyco)sphingolipids and Glycobiology.

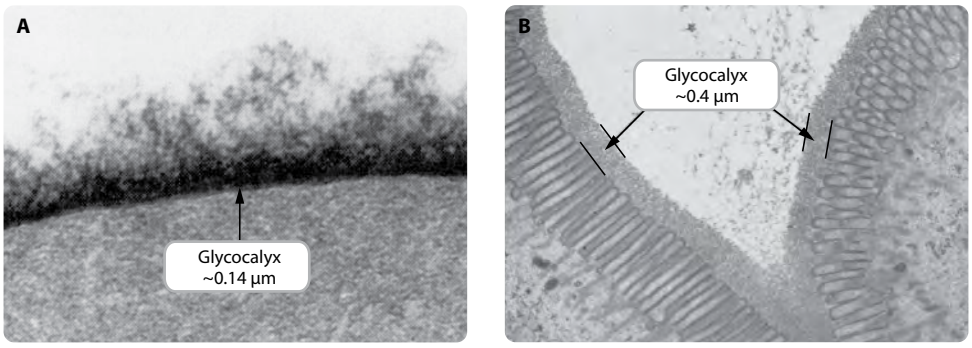
Johan L.W. Thudichum was born in 1829 and after attending the Medical School in Giessen – being taught among others by Justus von Liebig – he embarked on a prosperous scientific career. After having been active on subjects ranging from urology to vinology he embarked at the end of the 1870s on a study of the chemical composition of the brain. During these investigations he isolated several compounds from ethanolic brain extracts that he named cerebrosides. One of these, phrenosin, he subjected to acid hydrolysis and this produced three distinct components after fractional crystallization (Scheme 1). One he identified as a fatty acid and another proved to be an isomer of D-glucose that he coined cerebrose, now known as D-galactose. The third component with an 'alkaloidal nature' however presented 'many enigmas' to Thudichum and therefore he named it sphingosine, after the myth of the Sphinx's riddle.[1,2]

Scheme 1. Compounds isolated by Thudichum after the acid hydrolysis of phrenosin.



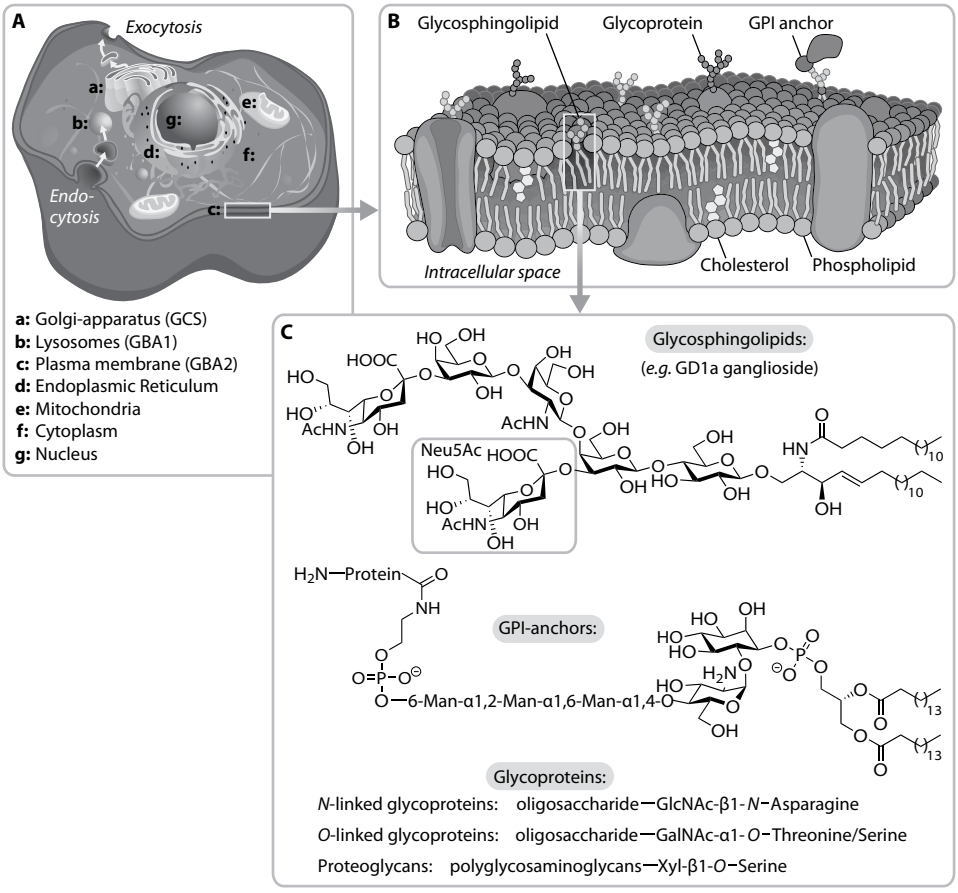
Thudichum's discovery did not receive due recognition during his lifetime (1829–1901), because up to about 1910 the authorities in this field fiercely defended the hypothesis that brain matter consisted of one giant molecule, the protagon, from which all simpler compounds were derived as breakdown products.[1] However, by the 1930s, Thudichum was fully vindicated and in 1947, Herbert E. Carter eventually published the molecular structure for sphingosine and proposed the term sphingolipids (SLs) for its derivatives.[3] Nowadays it is known that galactosylsphingolipids, like phrenosin, are among the most prevalent sphingolipids found in the brain, functioning as critical components in the myelin isolation of the axons of neuronal cells.

Figure 1. The glycocalyx covering an erythrocyte (**A**)[4] and the microvilli of intestinal absorptive cells (**B**).[6]



By the 1960s, numerous more complexly glycosylated sphingolipid derivatives had been discovered. In many of those the sialic acid, 5-*N*-acetylated neuraminic acid (Neu5Ac; Figure 2C), proved to cap the oligosaccharide.[4,5] These glycosphingolipids are generally named gangliosides. During this time, electron microscopy imaging of tissues and cells that were stained for carbohydrates also showed that most mammalian cells are covered with a dense and complex layer of carbohydrates, called the glycocalyx (Figure 1).[4,6]

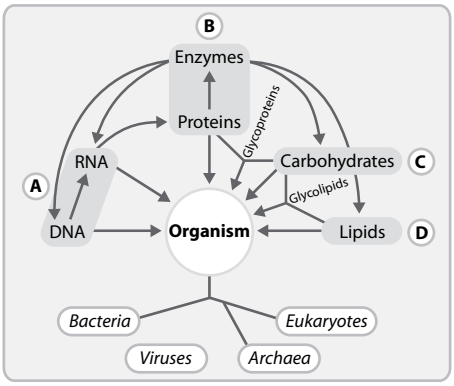
Figure 2 A: Cross-section of eukaryotic cell; **B**: Plasma membrane section; **C**: Structure of glycoconjugates.



The glycocalyx covers most mammalian cells and consists of a wide variety of oligosaccharides that are anchored to the plasma membrane as glycoconjugates with either a plasma membrane associated protein or lipid (Figure 2B). There are two types of lipid glycoconjugates. The first, GSLs, are anchored in the membrane via their ceramide lipid part. Ceramide consists of sphingosine that is *N*-acylated with a fatty acid. The *N*-acyl tail in ceramide is variable, but in mammalian glycoconjugates the most encountered is the *N*-palmitoylated (C_{16}) ceramide (Figure 2C). The glycosyl phosphatidylinositol (GPI) anchors are the second type of glycolipid.[7] These complex constructs consist of a

phosphatidylinisitol membrane anchor to which a (glycosylated) protein is attached via a tetrasaccharide linker. After biosynthesis, the lipid anchor of the GPIs is often remodeled and in yeast the diacylglycerol part is exchanged for a ceramide. Most oligosaccharides that are linked to a membrane protein do so via either the amino acid side chain amide of asparagins (*N*-linked glycoproteins) or the hydroxyl of serines or threonines (*O*-linked glycoproteins).[8] Until the 1980s it was mainly thought that the primary location of oligosaccharides was extracellular, on the cell surface or its intracellular topological equivalent, the endoplasmic reticulum (ER) and the Golgi apparatus. Also, besides their already known importance as a metabolic source of energy via glycolysis they were mainly thought to perform a structural role in cell biology and physiology. However, research by Hart and others during the eighties proved that proteins in the cytoplasm and nucleus of eukaryotic cells are also extensively glycosylated. Especially, cytosolic and nuclear serine and threonine residues are dynamically modified with an *O*-linked *N*-acetylglucosamine that seems to occur as abundant and often at the same sites as serine/threonine phosphorylation.[9,10]

Figure 3. Overview of interactions between the four molecular building blocks of life **A**: Nucleic acids, **B**: Proteins, **C**: Carbohydrates and **D**: Lipids.[14]



It is now known that the types and amounts of oligosaccharides linked to lipids and proteins on the outside and inside of the cell vary continuously depending on cell types and (patho)physiological conditions. Carbohydrates and their glycoconjugates play essential roles in cell to cell interaction and communication processes, regulation of protein activity and embryonal development amongst others. For instance, glycosphingolipids (GSLs) and glycoproteins on the surface of erythrocytes are at the root of the A/B/O blood antigen system. Dynamic glycosylation and deglycosylation of unfolded proteins secreted into the ER after translation regulates correct protein folding and quality control of protein synthesis. The research into these and other biological functions of carbohydrates and their conjugates, called glycobiology,[11-13] is expanding the understanding of how organisms function and the vital role of carbohydrates herein (Figure 3).[8,14]

1.2 Mammalian (Glyco)sphingolipid Metabolism.

Most of the enzyme catalyzed pathways of SL and GSL metabolism that take place in the ER, Golgi apparatus and lysosomes have been identified. Due to the lipophilic nature of the substrates in this metabolism most of the enzymes involved are integral membrane bound proteins. The following sections will describe SL and GSL metabolism from start to finish with an overview presented in Figure 7 on page 24.

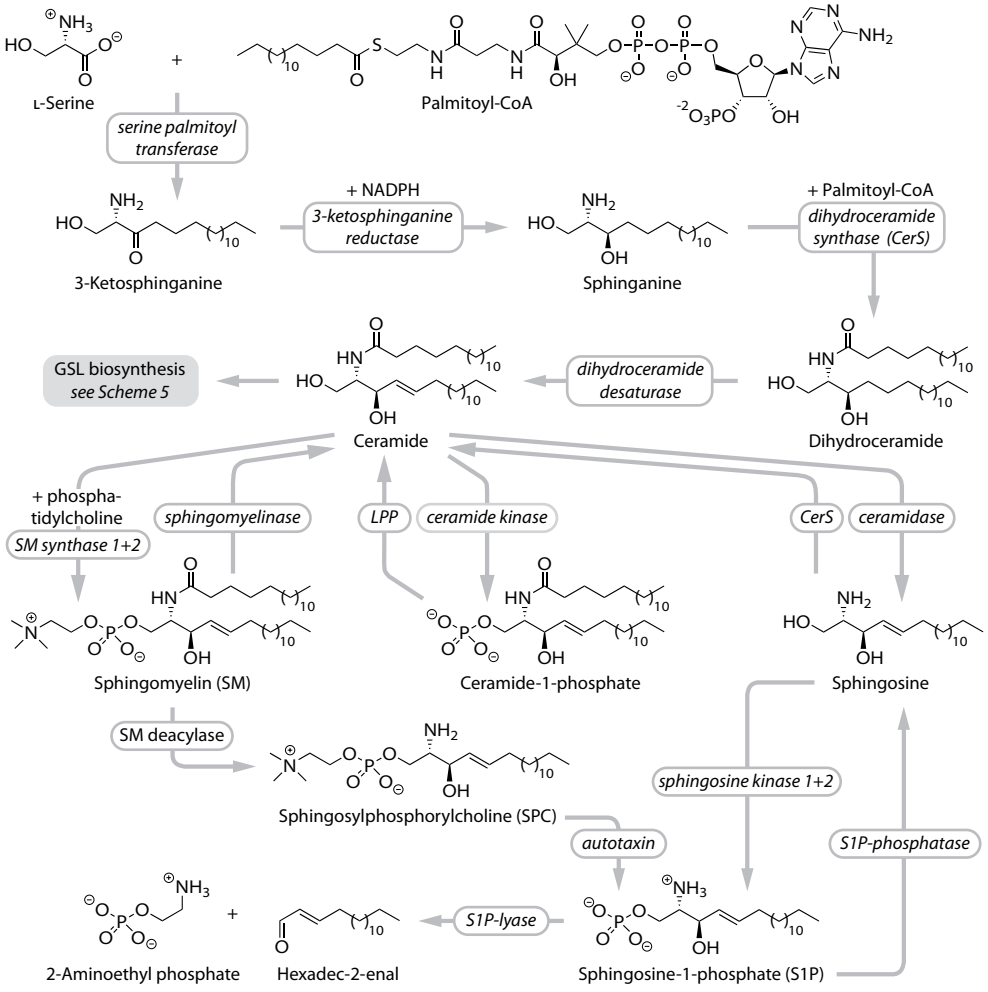
1.2.1 Sphingolipid Metabolism.[15-19] The *de novo* biosynthesis of SLs starts in the cytosolic leaflet of the ER membranes. Here ceramide is synthesized by a sequence of four enzyme catalyzed reactions from L-serine and two molecules of coenzyme A (CoA) activated fatty acid (see Scheme 2 on the next page). Palmitoyl-CoA is almost always used in the synthesis of 3-ketosphinganine. However, varying CoA-activated esters are used in the *N*-acylation of sphinganine. Depending on the tissue and function of SLs and GSLs, the length and saturation of the *N*-acyl tail of ceramide is highly variable in SLs and GSLs. Throughout this thesis however only the more common type of ceramide is depicted, which is made using two molecules of CoA-activated palmitic acid.

Next, the formed ceramide in the ER is a key precursor in the synthesis of five other sphingolipids and two distinct classes of GSLs. First, ceramide is transported by the recently discovered transport protein, CERT, to the cytosolic membrane of the *trans*-Golgi apparatus.[20,21] Here it randomly flip-flops and equilibrates between the cytosolic and luminal side of the *trans*-Golgi membrane. On the luminal inside sphingomyelin synthase 1 converts ceramide into sphingomyelin (SM) by transfer of a phosphorylcholine headgroup from phospholipids. The positively charged SM can no longer flip-flop unassisted. A second enzyme, SM2, is located at the plasma membrane and converts ceramide into sphingomyelin at this location. A neutral and acidic form of the enzyme sphingomyelinase is able to regenerate ceramide from SM. This enzyme is located predominantly in the lysosomes and at the plasma membrane, but is also excreted extracellularly. Alternatively, ceramide can also be phosphorylated by ceramide kinase (CERK). The kinase is transported from the cytosol to the plasma membrane upon specific signals. Its product, ceramide-1-phosphate, can be hydrolyzed back to ceramide by lipid phosphate phosphatase (LPP).[22] Acid, alkaline and neutral ceramidases, located respectively in the lysosome, plasma membrane and Golgi/ER, are capable of deacylating ceramide to generate pools of sphingosine at specific cellular locations. This sphingosine can be phosphorylated to sphingosine-1-phosphate (S1P) by sphingosine kinase 1 that operates at the plasma membrane and can also be excreted extracellularly. A second sphingosine kinase 2 is located at the ER near the nucleus.[23] S1P levels can be downregulated in turn by S1P-phosphatase. Finally, there is the SL, sphingosylphosphorylcholine (SPC), of which the presence in mammalian cells and plasma has been known for a long time.[24,25] Only recently however has research started to tentatively reveal aspects of its metabolism and biological functions. The extracellularly excreted enzyme, SM deacylase, hydrolyzes the acyl tail from SM to generate SPC. A

dedicated catabolic enzyme for SPC has not been found yet. The plasma circulating enzyme autotaxin however, whose primary function is the formation of lysophosphatidic acid, is capable of converting SPC into S1P.

The cellular orchestration of these complex interconversions between SLs is called the sphingomyelin cycle and is a testament to the role of these SLs in extra- and intracellular signaling pathways. The only currently known exit pathway from this interconnected SL metabolism is degradation of S1P by S1P-lyase in the ER.

Scheme 2. Overview of the biosynthesis and catabolism of mammalian sphingolipids.



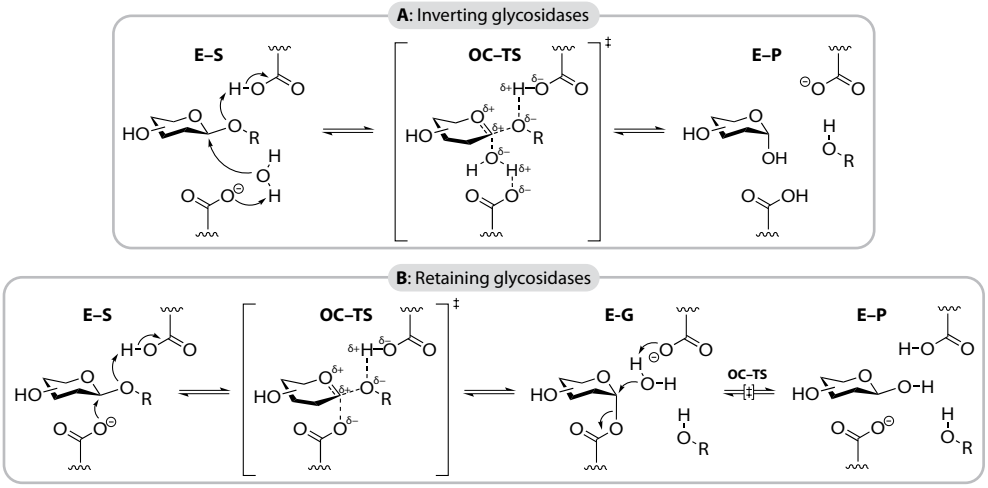
1.2.2 Glycosyltransferase and Glycosidase Mode of Action. Before discussing the biosynthesis and catabolism of GSLs this section will first describe how the two classes of carbohydrate-processing enzymes that regulate these processes work. Glycosyltransferases and glycosidases respectively catalyze the formation and hydrolysis of glycosidic bonds.

The regulation of their expression and activity is responsible for the enormous complexity of carbohydrate structures found in nature. Each of the two classes can be subdivided into families based on similarities in their amino acid sequence. Currently, 113 families of glycosidases and 91 families of glycosyltransferases are known.[26]

The glycosidases[27-29] are the most thoroughly studied of the two. The research until today has shown that there is much diversity in the 3D structure and folding among glycosidases as opposed to a highly conserved active site architecture. The active site of the various glycosidase families functions via one of two fundamental mechanisms that differ in the stereochemical outcome of the reaction and result in either inversion or retention at the anomeric center. The two enzymes, GBA1 and GBA2, responsible for degradation of glucosylceramide are both examples of glycosidases. GBA1 is known to operate as a retaining glycosidase for GBA2 it is not known yet.

Inverting glycosidases operate via a single-displacement mechanism in which water attacks the anomeric center and displaces the aglycone. This reaction is assisted in the enzyme's active site by two carboxylic acid residues from either aspartic or glutamic acid side chains. These side chains are separated by approximately 10 Å that allows simultaneous entry of both the substrate and water in the active site. One of the carboxylic acids acts as a general base for the attacking water molecule and the other as a general acid that protonates the glycosidic bond (Scheme 3A). Displacement of the aglycone by water produces the hemi acetal product via an oxo-carbenium-ion-like transition state (OC-TS).

Scheme 3. General mechanism for inverting (**A**) and retaining (**B**) glycosidases (a β-glycoside is shown here).



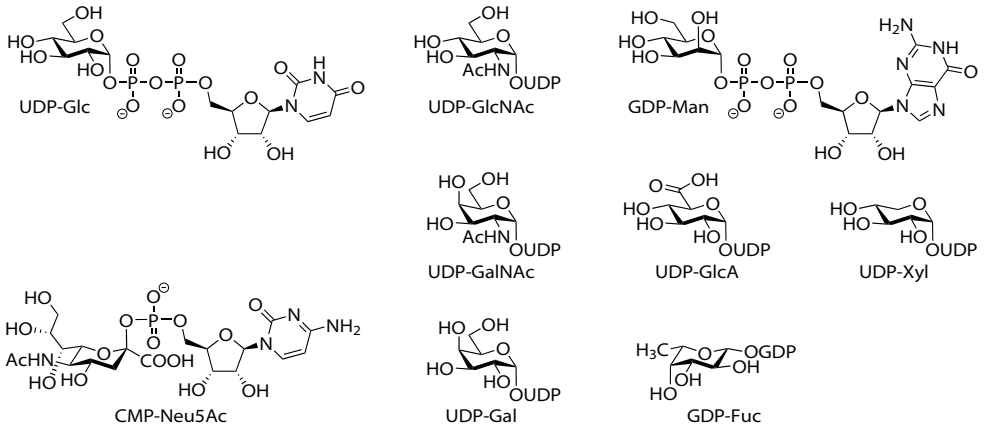
E–S: Enzyme–substrate complex; **OC–TS**: Oxocarbenium-ion-like transition state; **E–G**: Covalent enzyme–glycoside intermediate; **E–P**: Enzyme–product complex; R = substrate aglycon.

In 1953, Koshland proposed that retaining glycosidases operate via a double displacement mechanism that involves a covalent enzyme-glycosyl intermediate. However, Philips

proposed a stabilized oxo-carbenium-ion as intermediate. In 2001, Withers and co-workers were able to confirm the Koshland model by isolation and characterization of the covalent intermediate for the retaining glycosidase, hen egg-white lysozyme.[30] Extensive studies confirmed that this mechanism is used by almost all retaining glycosidases and that it is catalyzed by two carboxylic acid residues that are approximately 5 Å apart. The first step, much the same as in the inverting glycosidases, involves the protonation of the leaving group oxygen by one of the carboxylic acid residues. However, the narrower active site does not accommodate water at this stage and instead the closely positioned second carboxylate residue attacks at the anomeric center to produce a covalent enzyme-glycosyl intermediate. The aglycon diffuses out of the active site and in a second step a water molecule attacks the anomeric center of the intermediate under base catalysis of the remaining carboxylate to achieve hydrolysis (Scheme 3B).

Glycosyltransferases[31] use activated donor carbohydrates that contain a (substituted) phosphate as leaving group. Mammalian glycosyltransferases almost exclusively catalyze glycosidic bond formation using one of nine activated carbohydrate donors that contain an anomeric nucleoside (di)phosphate (Figure 4). Nucleotide carbohydrate-dependent glycosyltransferases are referred to as Leloir enzymes.

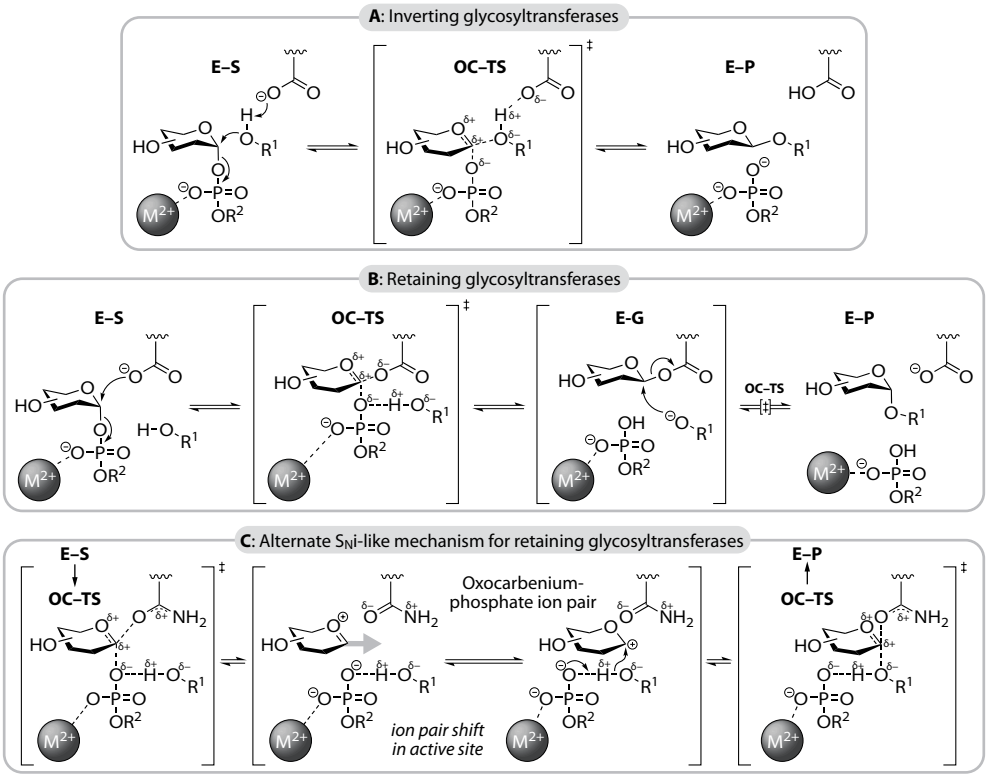
Figure 4. The nine nucleotide-carbohydrate donors used by mammalian glycosyltransferases.



Structural and mechanistic investigations of transferases have lagged behind those of glycosidases. However, the available X-ray crystal structures and amino acid sequences have already indicated that contrary to glycosidases only two common structural folds exist among transferases. The GT-A and GT-B fold differ in the topology of the so-called Rossmann fold, which is a common fold in proteins that bind nucleotide containing ligands. Just as for glycosidases, two mechanistic classes can be defined that are differentiated by the stereochemical outcome of either inversion or retention at the anomeric center of the reaction product. This mechanistic subdivision is unrelated to the presence of a GT-A or GT-B fold. Departure of the nucleotide-phosphate leaving group in GT-A fold transferases is typically facilitated by a divalent metal cation that

is coordinated in the active site by an aspartic-X-aspartic (DXD) motif. GT-B fold transferases use appropriately placed positively charged amino acid residues in the active site instead of a metal cation.

Scheme 4. General mechanism for inverting (**A**) and retaining (**B**) glycosyltransferases and an alternate S_Ni mechanism (**C**) for retaining transferases (an α-glycoside donor and GT-A transferase are shown here).



E–S: Enzyme–substrate complex; **OC–TS**: Oxocarbenium-ion-like transition state; **E–G**: Covalent enzyme–glycoside intermediate; **E–P**: Enzyme–product complex; M^{2+}: divalent magnesium or manganese cation. R^1 = acceptor hydroxyl; R^2 = donor nucleoside/nucleoside monophosphate.

The mechanism of inverting transferases involves a direct displacement S_N2-like mechanism and seems conserved among most GT-A/B transferases of this type (Scheme 4A).[31] The enzyme, GCS, responsible for glucosylceramide biosynthesis is an inverting glycosyltransferase. The mechanism of retaining transferases remains less clear. A double displacement mechanism, similar to inverting glycosidases has long been thought to occur, but trapping of the covalent enzyme-glycosyl intermediate that is required for proof of this mechanism has so far eluded researchers (Scheme 4B). There also seems to be a lack of conserved architecture in the active site where the nucleophilic amino acid side chain should be positioned. In the case of the LgtC retaining transferase from the *Neisseria meningitidis* bacteria the primary amide from glutamine was located at this position but its mutation to an alanine did not abolish all transferase activity.[32]

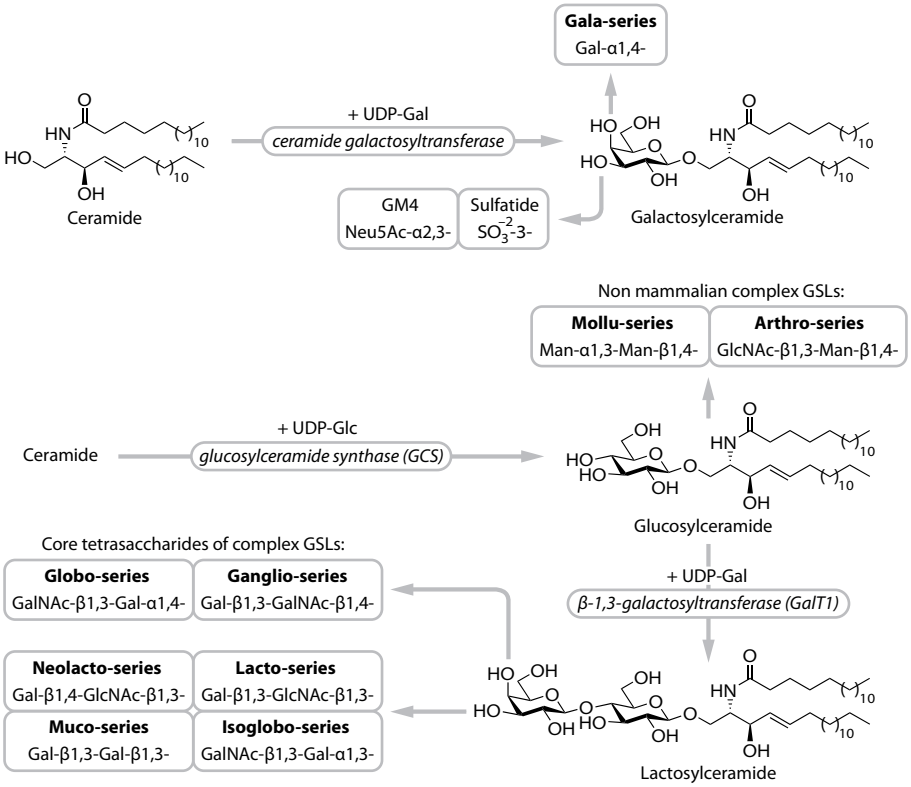
An alternate S_Ni-like (S_N1 internal return variation) mechanism for retaining transferases is gaining support among researchers and involves a discrete short-lived ion pair intermediate (Scheme 4C).[31] In this mechanism the nucleotide-diphosphate leaving group acts as a base for the acceptor and coordinates with it. The positively charged oxo-carbenium ion forms a discrete ion pair with the negatively charged phosphate-acceptor complex on the same face as where the phosphate is disconnected. A shift of this ion pair in the active site then allows attack of the acceptor from the same direction as the leaving group – resulting in retention. Due to the variation in the active site architecture of retaining glycosyltransferases it is likely that both of the discussed mechanisms (B and C) and hybrids of them occur depending on the transferase.

1.2.3 Mammalian Glycosphingolipid Biosynthesis. Besides the previously discussed SLs, ceramide is transformed into two distinct monosaccharide-containing GSLs. After its synthesis on the cytosolic side of the ER membrane, ceramide equilibrates to the luminal side via random flip-flopping. A recent study showed that when ceramide was inserted into the external leaflet of a phosphatidylcholine unilamellar vesicle it equilibrated to the inner leaflet with a half-time ($t_{½}$) below 1 min at 37 °C.[33]

Once ceramide arrives at the luminal side of the ER it is transformed into galactosylceramide by ceramide galactosyltransferase (CGalT).[34,35] This GSL is further diversified into the Gala-series of GSLs via either sulfation or glycosylation with Neu5Ac at its 3-*O*-position or further extension to oligosaccharides at its 4-*O*-position via a second α-linked D-galactose (Scheme 5).[17] ER localized ceramide is transported via vesicular transport to the cytosolic side of the *cis*-Golgi apparatus membrane. Here the membrane bound glycosyltransferase, glucosylceramide synthase (GCS), catalyzes the glycosylation of the primary hydroxyl in ceramide using UDP-glucose as donor glycoside. Interestingly, a recent study indicated that a region of the ER that is closely associated with mitochondria also shows an enzymatic activity capable of generating glucosylceramide.[36]

As mentioned, glucosylceramide synthase is an inverting transferase (Family 21; GT-A fold).[26] Its cDNA sequence was reported by Ichikawa in 1996 and encodes for a 45 kDa protein.[37] It possesses an *N*-terminal hydrophobic transmembrane stretch that anchors the enzyme to the cytosolic face of the Golgi membrane together with a hydrophobic loop near the *C*-terminal region.[38,223] A study by Pagano and co-workers has shown that GCS forms hetero dimers or oligomers with an unidentified 15 kDa protein.[39] Via site-directed mutagenesis and sequence comparisons with other transferases they also identified several active site amino acid residues and an amino acid near the *N*-terminus (His-193) that was important for substrate binding and inhibition of GCS by the inhibitor, PDMP (**7**; Figure 9 page 28).[40] GCS also possesses a DXD metal coordinating motif, but it appears to not require a divalent metal for catalysis.[41]

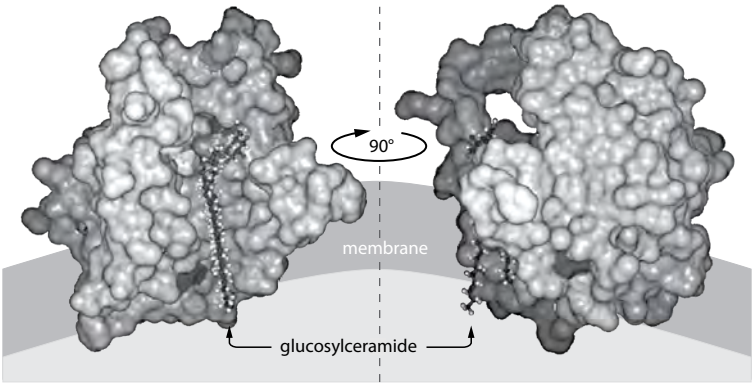
Scheme 5. Overview of the biosynthesis of (mammalian) glycosphingolipids.



Due to its tight membrane association no X-ray crystal structure of GCS has been determined yet. Based on the available data, Butters and co-workers did develop a computational model of GCS that is depicted in Figure 5 on the next page and shows a partly membrane immersed ceramide binding groove.[42] The product of GCS action, glucosylceramide, occupies a key position in the biosynthesis of GSLs because besides the Gala-series all more complex GSLs are derived from it. The fact that both GCS and glucosylceramide face the cytosolic side of the cellular membranes are distinguishing features in GSL biosynthesis: further synthesis of complex GSLs takes place exclusively on the inside (lumen) of the Golgi apparatus. Thus, glucosylceramide needs to traverse the Golgi lipid bilayer.

When glucosylceramide is introduced to the outer leaflet of a model membrane it only slowly flip-flops across unassisted ($t_{½}$ = 5 h at 20 °C). However, in the Golgi-apparatus membrane glucosylceramide undergoes rapid transbilayer movement ($t_{½}$ = 3 min at 20 °C). Studies indicate that an ATP-independent Golgi-localized 'flippase' protein is responsible that however has not been identified yet.[43] Other research has shown that the ATP-dependant P-glycoprotein multidrug transporter located throughout the cell is capable of acting as a rapid flippase for fluorescently labeled (NBD) glucosylceramide, galactosylceramide and sphingomyelin, but not lactosylceramide.[44]

Figure 5. Two views of a computational model of GCS with glucosylceramide bound in cleft.[42]



It has been determined that the majority of complex GSLs are synthesized at the *trans*-Golgi as opposed to glucosylceramide at the *cis*-Golgi.[45] It had been assumed that glucosylceramide was transported to the *trans*-Golgi by vesicular flow. However, De Matteis and co-workers recently reported that the protein FAPP2 is responsible and essential for this relocation.[46] Van Meer and co-workers reported that FAPP2 also transports glucosylceramide to the ER and that the closely related GLTP transport protein is capable of transporting it to the cell surface.[47]

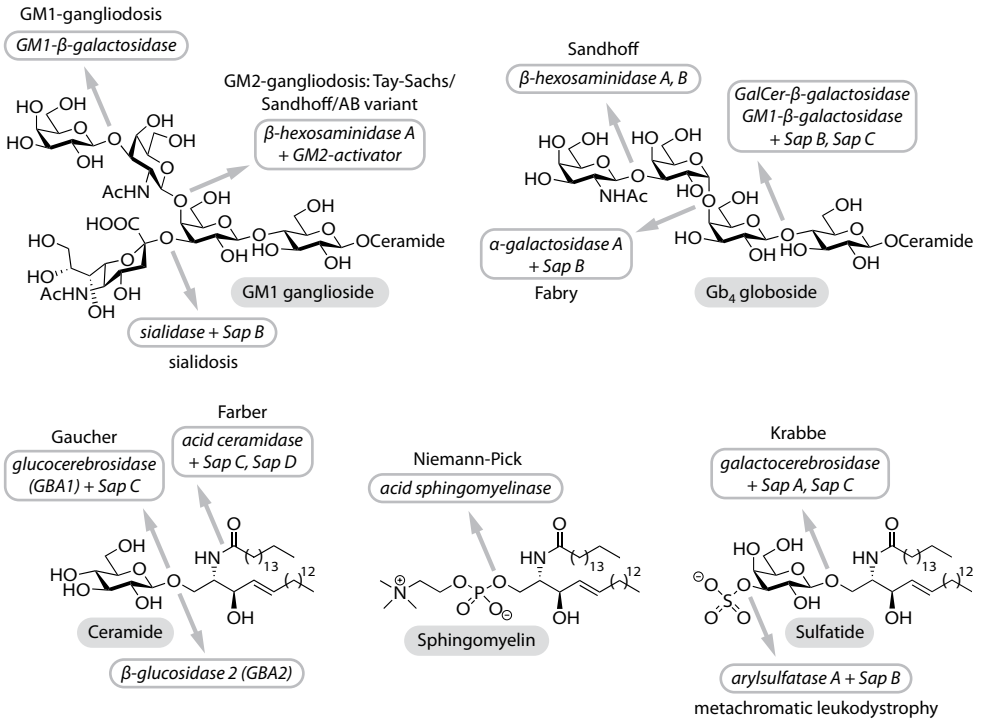
Having arrived at the *trans*-Golgi and flipped to the inside, the biosynthesis of GSLs continues with the synthesis of lactosylceramide by GalT1 (Scheme 5). Lactosylceramide is sequentially extended at either the 3-*O*-positon or the 4-*O*-position in a stepwise fashion by a panel of specialized transferases. This eventually results in the six distinct GSL-series that together form the cellular pallet of hundreds of unique GSLs in mammals – the core tetrasaccharides of these are depicted in Scheme 5.[48,49] Most of these GSLs consist of alternating and branched combinations of α- or β-linked glucose, galactose, *N*-acetylglucosamine and *N*-galactosamine. At their non-reducing end numerous of these complex GSLs are terminated with either L-fucose or acidic Neu5Ac. Two other non-mammalian series of complex GSLs also exist and originate from a β1,4-linked mannopyranoside to glucosylceramide. Complex GSLs in the Mollu-series[50] have been isolated from freshwater bivalves (*e.g.* molluscs) and GSLs from the Arthro-series[51] from several species of arthropods (*e.g. Drosophila* flies).

After their biosynthesis GSLs are transported to the cell surface by exocytosis where they perform their functions, which are described in sections 1.3.1 to 1.3.11. The maintenance and change of GSL patterns on the cell surface requires a delicate balance between GSL biosynthesis and their degradation (catabolism).

1.2.4 Mammalian (Glyco)sphingolipid Catabolism. The catabolism of GSLs starts by endocytosis of GSL containing regions of the plasma membrane. GSL containing regions of the membrane associate with the membrane protein caveolin-1.[52] Grouping of this

protein induces a flask-like invagination of the plasma membrane – called a caveolae – that is taken up by the cell and enters endocytotic vesicular flow.[53] The endosomes can be transported to the Golgi for alteration of their SL and GSL content or to the lysosomes. The GSL containing domains are thought to form smaller vesicles inside the endosomes (Figure 7). These so-called multi-vesicular bodies are targeted to the lysosome for degradation. After merger with a lysosome the catabolism of GSLs starts.[54]

Scheme 6. Overview of mammalian (glyco)sphingolipid catabolism. Responsible enzyme/glycosidase and activator protein are indicated at glycosidic linkage. The catabolism associated hereditary diseases are indicated above/below and discussed in section 1.3.3.

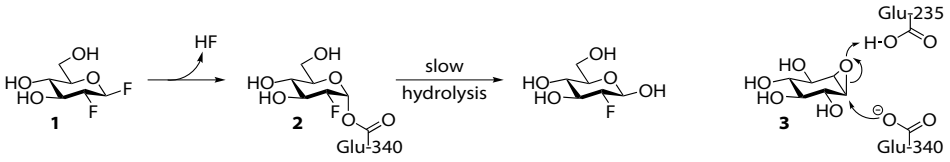


Catabolism takes place at the membrane surface of internal lysosomal membrane vesicles (Figure 7). The perimeter membrane of the lysosome is protected from degradation by a glycocalix composed of lysosome resistant glycoproteins.[54] Carbohydrate residues from the non-reducing end of the GSL oligosaccharides are sequentially cleaved off one carbohydrate residue at a time by the action of exo-glycosidases (Scheme 6). Contrary to the biosynthetic enzymes all catabolic glycosidases are non-membrane bound and dissolved in the lysosome. However, their GSL substrates are embedded in intralysosomal membranes. Therefore GSLs with less than four carbohydrate residues require the presence of specific (glyco)sphingolipid activator proteins (Sap) that assist the glycosidases in interacting with their target substrate. Five such proteins are currently known, saposin-A, -B, -C, -D and the GM2-activator protein. It is telling of their role in

catabolism that for *in vitro* assays of these glycosidases their action can be replaced by detergents. Scheme 6 provides an overview of the glycosidases and activator proteins associated with GSL degradation.[17,54]

The penultimate step in GSL catabolism is the hydrolysis of the β-glycosidic bond in glucosylceramide by glucocerebrosidase (GBA1) to yield D-glucose and ceramide. The retaining glycosidase GBA1 (family 30) is a ~65 kDa protein in its glycosylated form and the activator protein saposin C is essential for its *in vivo* functioning.[54] In 1994, Withers and co-workers identified the active site catalytic nucleophile as the side chain carboxylate of glutamic acid-340.[55] This was ascertained by feeding the enzyme mechanism-based inhibitor **1** that reacts with this nucleophile to provide a stable covalent enzyme-'substrate' intermediate (**2**) that could be analyzed by mass spectrometry (Scheme 7). Inhibitor **1** achieves this via the electron negative fluorine atom on the 2-position that drastically slows down the second hydrolysis step by increasing the required activation energy to the oxocarbenium-ion-like transition state. This also holds for the first step, but here the reactive anomeric fluoride leaving group compensates for this. In 2003, Futerman and co-workers published the first X-ray crystal structure of GBA1.[56] Later a crystal structure of GBA1 was reported with the irreversible covalent inhibitor, conduritol-B-epoxide (**3**; CBE), bound to Glu-340 (Scheme 7). This study also confirmed Glu-235 as the acid/base catalyst of GBA1.[57]

Scheme 7. Overview of the action of mechanism based glycosidase inhibitors **1** and CBE (**3**).



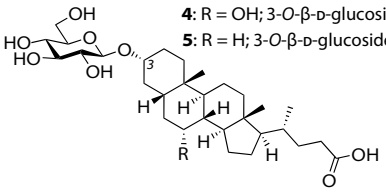
Interestingly, Futerman and co-workers also performed a structural comparison of GBA1 with closely related glycosidases and found a close correspondence with a bacterial xylanase.[58] Although mammals also produce D-xylose containing oligosaccharides (proteoglycans), a mammalian xylanase has so far not been found yet. With β-xylanase activity having been detected in rat lysosomes[59] and GBA1 being able to hydrolyze artificial β-xylosides,[60] GBA1 might represent a candidate for this missing xylanase.

Recently, Saenger, Maier and co-workers published the X-ray crystal structure of the GBA1 activator, saposin C.[61] This study and another report[62] propose that saposin C assists by a dual action. First, Sap C associates with the glucosylceramide carrying intralysosomal vesicles. When two Sap C bound vesicles encounter each other the two Sap C proteins dimerize via domain swapping that in turn induces the two vesicles to fuse together (clip-on model).[61] Additionally, in areas of these vesicles where Sap C proteins bind and congregate they decreases membrane thickness and cause perturbed membrane edges that facilitates interaction of GBA1 with glucosylceramide.[62] Sap C has also been shown to directly bind to GBA1 and thereby increase its enzymatic activity.[224]

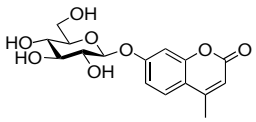
Besides glucosylceramide based GSLs, the Gala-series GSLs are also degraded in the lysosome (Scheme 6). All these GSLs eventually yield a pool of monosaccharides and ceramide. Deacylation of ceramide to a fatty acid and sphingosine by acid ceramidase represents the final catabolic step of GSLs in the lysosome. Sphingosine, the fatty acids and the monosaccharides are all recycled by the cell.

Contrary to all other GSLs, glucosylceramide is also catabolized via a second non-lysosomal pathway. Aerts and co-workers reported this hydrolytic activity in 1993.[63] Recently, the activity was identified as β-glucosidase 2 (GBA2).[60,64] GBA2 was previously already known for its capacity to hydrolyze bile acid glucosides (*e.g.* **4** and **5**; Figure 6) and extensively investigated to this end by Matern and co-workers.[65-67] GBA2 is a 105 kDa protein with a transmembrane region and has not been assigned yet to a specific family of glycosidases. Contrary to GBA1, it is not sensitive to inhibition by CBE (**3**).[60] The enzyme has a neutral pH optimum opposed to the acidic optimum of GBA1. *N*- and *C*-terminal fusion proteins of GBA2 with green fluorescent protein show the highest fluorescence near the plasma membrane.[60] Addition of the fluorescent substrate, 4-methylumbelliferyl-β-D-glucoside (**6**; Figure 6), to the medium of cell cultures that express GBA2 shows almost instantaneous GBA2 activity that indicates it might be anchored to the outer plasma membrane.[60] GBA2 was also found to be enriched in the apical membrane of epithelial cells.[68] Additionally, experiments with fluorescently labeled glucosylceramide showed that the ceramide generated by GBA2 action was rapidly converted to sphingomyelin.[60] This might be explained if GBA2 is co-localized with the enzyme SMS2 on the outer plasma membrane. The function of GBA2 is currently not known. However, inhibition of GBA2 activity in certain strains of mice is associated with impaired spermatogenesis, a result that is confirmed in studies with a GBA2 knock out mouse model.[64,69,70]

Figure 6. Structure of 4-methylumbelliferyl-β-D-glucoside (**6**) and two bile acid glucosides (**4** and **5**).



4: R = OH; 3-*O*-β-D-glucoside of chenodeoxycholic acid
5: R = H; 3-*O*-β-D-glucoside of lithocholic acid



4-MU-β-D-glucoside (**6**)

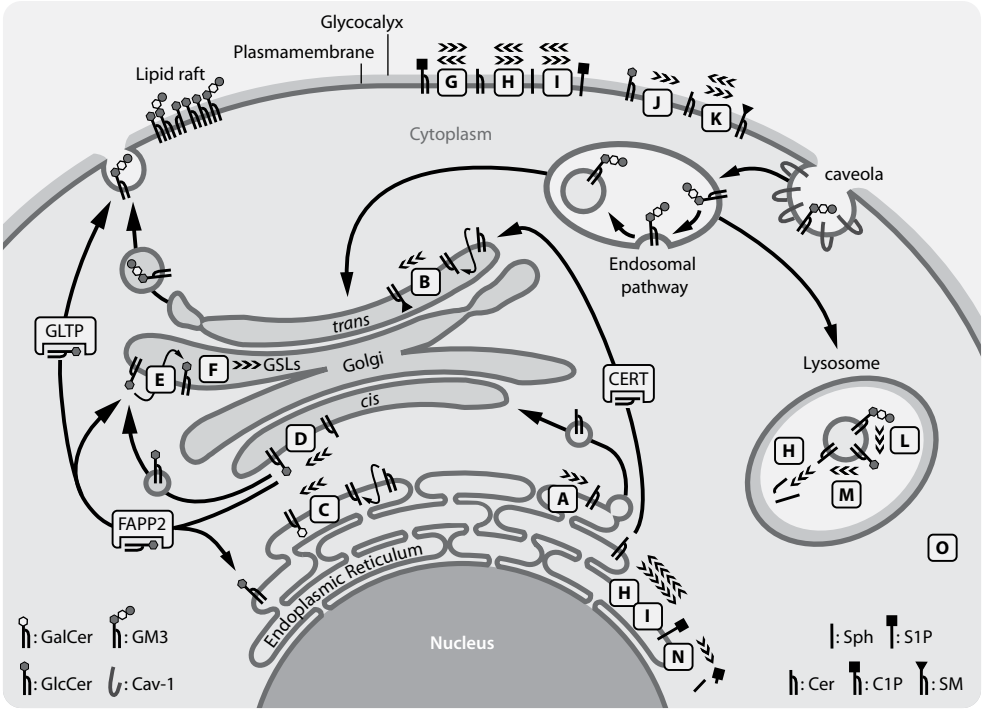
Two other distinct glycosidases have also been implicated in glucosylceramide catabolism, but their activity has not been fully substantiated yet**.** Two publications have reported that the β-glucosidase, LPH, is capable of hydrolyzing glucosylceramide. LPH is a ~300 kDa retaining glycosidase (family 1) that is sensitive to CBE (**3**). The enzyme is membrane bound at the outer plasma membrane and is exclusively expressed in the microvilli of intestinal epithelial cells. LPH is also able to hydrolyze galactosylceramide, lactosylceramide and glucosyl- and galactosylsphingosine, but not GM1 ganglioside (structure in Scheme 6).[71,72] LPH might therefore play a role in the intestinal digestion of food derived GSLs. Humans on an typical Western diet ingest roughly 300 mg of (glyco)

sphingolipids per day, mainly by consumption of egg, dairy and meat products.[73]

The β-glucosidase, GBA3, is a cytosolic retaining glycosidase (family 1) with a broad substrate specificity that includes artificial hydrophobic β-glucosides and β-galactosides. Recently determined X-ray structures of GBA3 revealed its two catalytic residues (nucleophile: Glu-371; acid/base: Glu 165). The ~60 kDa protein is CBE (**3**) insensitive and expressed in the cytosol and operates optimally at a neutral pH. Its reported ability to degrade glucosylceramide is still topic of debate.[74,75]

The facts contained in the previous sections about (glyco)sphingolipid biosynthesis and catabolism, with emphasis on the cellular topology and dynamics, are summarized in Figure 7. Most of the enzymes involved in (glyco)sphingolipd metabolism have been elucidated. The next challenge lies in understanding the complex dynamics and topology of this metabolism, which plays a crucial part in the functions of SLs and GSLs in both health and disease.[18]

Figure 7. Cellular topology and dynamics of mammalian SL/GSL biosynthesis and catabolism.



A: *De novo* synthesis of ceramide; **B**: Synthesis of sphingomylin (SM) by SMS1; **C**: Synthesis of GalCer by CGalT; **D**: Synthesis of GlcCer by GCS **E**: GlcCer flippase; **F**: Synthesis of lactosylceramide and complex GSLs (*e.g.* GM3); **G**: Synthesis of ceramide-1-phosphate (C1P) by CERK and hydrolysis by LPP; **H**: Deacylation of ceramide to sphingosine (Sph) by ceramidase; **I**: Synthesis of sphingosine-1-phosphate (S1P) by sphingosine kinase 1 and hydrolysis by S1P-phosphatase; **J**: Hydrolysis of GlcCer by GBA2 (by LPH in intestines?); **K**: Synthesis of SM by SMS2 and hydrolysis by sphingomyelinase; **L**: Stepwise hydrolysis of complex GSLs; **M**: Hydrolysis of GlcCer by GBA1; **N**: Degradation of S1P by S1P-lyase; **O**: GlcCer hydrolysis by GBA3 (?); Cav-1: Caveolin-1 (GSL endocytosis).

1.3 Functions of (Glyco)sphingolipids in Health and Disease.

GSLs and SLs were initially thought to be merely structural membrane components. However, the large heterogeneity in SL and GSL structures due to variation in the sphingosine base, *N*-acylation and glycosylation pattern suggests a high degree of functional complexity. Research over the past decades has proven that (glyco) sphingolipids are involved in many (patho)physiological process. As in many other areas of biology much has been learned about SLs and GSLs from the study of diseases where their metabolism and functioning has gone awry. The following sections describe some of the biological functions that are attributed to SLs and GSLs in health and disease with a focus on GSLs. For several of the GSL associated diseases, inhibitors of glucosylceramide metabolism are being used or investigated for therapeutic applications and these will also be summarized.

1.3.1 Sphingolipids and Cellular Signaling. The SLs have been implicated in numerous intra- and extracellular signaling processes. Sphingomyelin is the most common SL and comprises as much as 30% of the total membrane lipids in certain tissues.[76] In the plasma membrane, sphingomyelin predominantly associates with cholesterol and GSLs to form microdomains. Besides this role in membrane structure, sphingomyelin mainly seems to serve as a reservoir and precursor for the site specific generation of other bioactive SLs. This role as a precursor is facilitated by the fact that it can be synthesized at two different locations in the cell and converted to ceramide by the neutral, alkaline and acid sphingomyelinases distributed throughout the cell. As shown in Scheme 2, ceramide can be converted to ceramide-1-phophate and via sphingosine to sphingosine-1-phosphate. After exposure to heat shock, oxidative stress and other damaging conditions, cells produce elevated levels of ceramide among other responses. These elevated ceramide levels have been implicated as second messengers in signal transduction pathways that lead to cell death (apoptosis).[18] Less is known about the function of ceramide-1-phosphate, but it is implicated in inflammatory signaling pathways and as a promoter of cell survival.[22,77] Sphingosine is thought to serve as an intracellular regulator for the activity of several kinases. Sphingosine-1-phosphate is an extracellular ligand for several G-protein coupled receptors and is involved in many signaling pathways involving cell migration, cell growth and vascular maturation (angiogenesis). In general, sphingosine-1-phosphate has an opposite effect to ceramide in that it promotes cell growth and survival.[22,77] Finally, the less well studied sphingosylphosphorylcholine has been shown to stimulate cell division and has also been implicated in pro-inflammatory signaling pathways.[24,25] It appears that a delicate balance between the various levels of these bioactive SLs and where in the cell they are generated is essential for maintaining health.

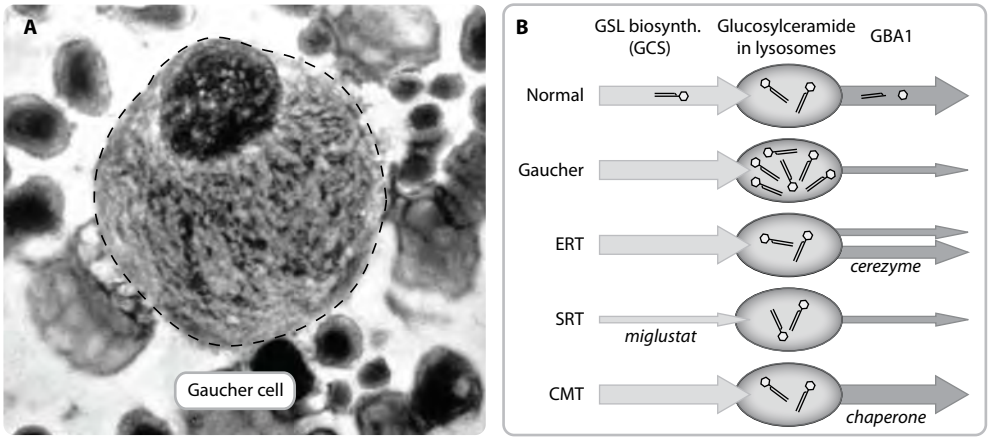
1.3.2 Glycosphingolipids and Lipid Rafts. The functions of GSLs on the cell surface can be roughly divided into two basic functions: involvement in cell adhesion/recognition processes by interactions with GSLs and lectins on other cells, and in modulation of

signal transduction by influencing receptor proteins on the cell surface. During the late eighties it was discovered that GSLs and SLs don't always distribute homogeneously in the outer plasma membrane. Instead they often form defined microdomains, also called lipid rafts, together with cholesterol.[78-81] Many proteins have been found to be associated with these microdomains including most GPI anchored proteins, flotillins, caveolins, certain G proteins coupled receptors, the epidermal growth factor receptor and the insulin receptor. The microdomains exist in a gel-like liquid ordered phase (l_o) that have a lower diffusion rate then the surrounding liquid disordered (l_d) phospholipid-rich plasma membrane. Initially, these lipid rafts were isolated by extraction of membranes at 4 °C in the presence of specific detergents and were therefore called detergent resistant microdomains (DRMDs). The existence of lipid rafts was questioned for a long time with the valid question being wether the composition and dynamics of detergent extracted membranes at 4 °C resembled their composition at 37 °C in live cells. However, since then evidence in favor of lipid rafts has increased and they have also been visualized in living cells by other less intrusive techniques like Förster/fluorescence resonance energy transfer (FRET) and single molecule fluoresence. With their existence confirmed the following current definition of lipid rafts illustrates the future challenges in their further characterization: membrane rafts are small (10–200 nm), heterogeneous, highly dynamic, sterol- and sphingolipid-enriched domains that compartmentalize cellular processes. Although most current research on rafts focuses on the outside of the cell, their original proposed role was in intracellular sorting. Using BODIPY labeled GSLs, Pagano and co-workers have shown that lipid rafts also occur intracellularly and that GSLs in these lipid rafts play an important role in caveolae mediated endocytosis and endosomal sorting of many cellular proteins.[82,83]

1.3.3 Lysosomal Sphingolipidoses. The importance of SLs and GSLs in mammalian physiology is underlined by the fact that virtually no hereditary diseases exist that impair their biosynthesis. Systemic deletion of the GCS gene in a mouse model resulted in lethality during the early stages of embryogenesis.[84] On the contrary, a hereditary disease exists for almost every catabolic step in SL and GSL degradation (see Scheme 6 on page 21). Collectively known as the sphingolipidoses, they are each caused by mutations in genes that encode the lysosomal SL or GSL catabolic enzymes.[17,54] The mutation causes lowered lysosomal levels of the enzyme or impairment of its catalytic activity, thus leading to deficient degradation and accumulation of the enzyme's substrate in the lysosomes. The most prevalent among the sphingolipidoses is Gaucher disease with an incidence of about 1:50000 among the general population.[85-88] Gaucher disease is an autosomal recessive disorder caused by mutations in the GBA1 gene. Impaired degradation of glucosylceramide occurs in all cells of the body, but pathologic accumulation in the lysosomes mainly occurs in the macrophages. These cells have a heightened influx of GSLs due to their phagocytosis of senescent blood cells and other necrotic cells in the body. The severe storage of glucosylceramide in the macrophages results in an increase

in size (~20 » ~100 μM) and a transformation into so-called Gaucher cells that cause the observed pathology (Figure 8A).

Figure 8 A: Transformed macrophage; **B**: Schematic overview of Gaucher disease and its potential therapies.



The clinical symptoms were first described by Philippe Gaucher in 1882 and currently over 200 distinct mutations in the GBA1 gene are known to cause Gaucher disease. The symptoms observed in patients with these mutations vary from mild to severe and correlate closely with residual lysosomal GBA1 activity. Mutations that cause complete GBA1 deficiency result in skin permeability issues and result in lethality either prenatally or shortly after birth.[88] Gaucher disease symptoms are categorized into three different phenotypes (type I, II and III). Type I Gaucher disease is the most common and its symptoms among others can involve enlargement of liver and spleen, weakened bones and anaemia. The more severe types II and III also involve neurological symptoms. Type II is the most severe form and symptoms set in shortly after birth and lead to death within the first year of life. Type III manifests itself during later childhood and shows a slower progression of neurological complications. Scheme 6 provides an overview of the other sphingolipidoses for which the details are not discussed here but are extensively reviewed in literature.[17,54] Contrary to Gaucher disease, in some of these sphingolidoses it is a deficiency in the activator protein that causes lysosomal accumulation. In Krabbe and Fabry disease an *N*-deacylated metabolite of the primary storage material is responsible for many of the clinical symptoms – globotriaosylsphingosine[89] in Fabry disease and psychosine[54] in Krabbe disease.

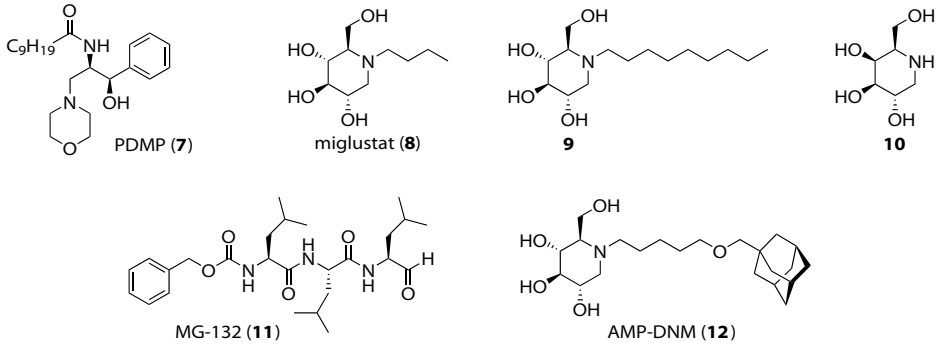
1.3.4 Therapeutic Strategies for Gaucher Disease. Many of the sphingolipidoses remain untreatable, but especially for type I Gaucher disease several therapies are available and also under development. The theoretical basis for all these therapeutic approaches is the 'threshold theory' which states that the rate of substrate influx into the lysosomes and the degradation capacity determine the onset and severity of the disease (Figure 8B). In

a cellular model the overt onset of glucocylceramide storage in macrophages was shown to occur only when overall GBA1 activity in the lysosomes drops below ~15% of normal activity.[90] Therefore even minor improvements of lysosomal GBA1 activity can result in major improvements for patients.

The first therapy to be developed for Gaucher disease was enzyme replacement therapy (ERT). In the 1970 and 80s, Brady and co-workers developed the intravenous administration of GBA1 that was purified from human placenta tissue to Gaucher patients.[91,92] A proportion of this functional GBA1 enzyme ends up in the lysosomes of Gaucher cells and thereby temporarily increases the degradation capacity (Figure 8B). During the 1990s, the placenta derived enzyme was replaced by a recombinant GBA1 derivative.[93] At present about 5000 type I Gaucher patients receive ERT with this form of GBA1, called cerezyme. Drawbacks of this therapy are its intravenous delivery, its high costs and the impossibility to treat Gaucher patients with neurological symptoms due to the inability of cerezyme to pass the blood-brain barrier.

Already in 1980, Radin and Vunnam proposed the concept that downregulation of glucosylceramide influx into the lysosomes by inhibiting GCS with inhibitor PDMP (**7**) could alleviate the symptoms of Gaucher disease (Figure 8B).[94] In 1994, Platt and co-workers reported the inhibition of GCS by the *N*-butylated 1-deoxynojirimycin derivative **8** and the use of this effect to lower glucosylceramide accumulation in an *in vitro* model of Gaucher disease.[95] The concept and results with **8** were further developed into what is now called substrate reduction therapy (SRT). After clinical trials in Gaucher patients, **8** (now called miglustat or zavesca) was approved as an orphan drug in SRT for Gaucher disease in 2002. The drug is administered orally to type I Gaucher patients for whom ERT is unsuitable. Close to a hundred patients are presently receiving SRT with **8**.[96-98]

Figure 9. Structures of compounds mentioned in sections 1.3.4 to 1.3.11.

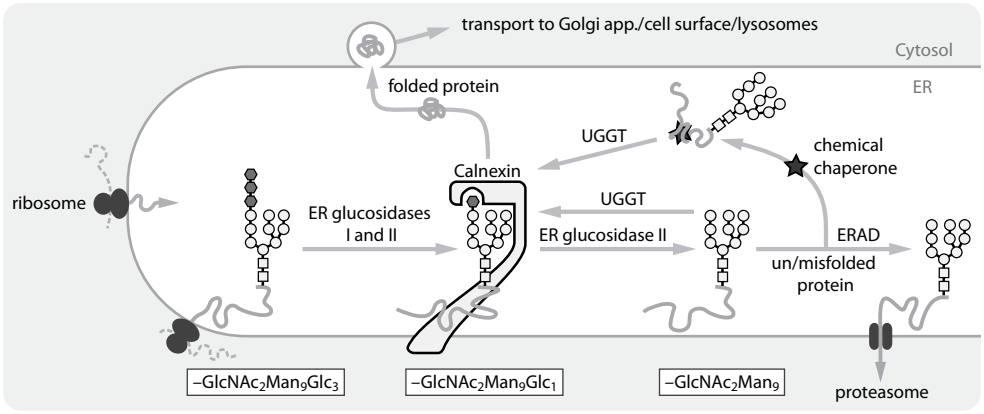


The clinical studies with miglustat and longer *N*-alkyl chain derivatives have shown that they are metabolically stable and excreted mostly via the kidney (plasma $t_{½}$ = 6.3 h). Oral administration of **8** (100 mg, 0.46 mmol), three times a day, results in a steady-state plasma concentration of 5 μM after ~5 weeks that is sufficient to partially inhibit GSL

biosynthesis.[97] The entry of these iminosugars into the cell (within 1 minute) appears to occur via passive diffusion or endocytosis and membrane flip-flopping. A longer *N*-alkyl chain (like in **9**) results in more protein and membrane binding and this phenomenon might be one of the reasons for their higher inhibition potency for GCS when compared to **8**.[99] Experiments with radiolabeled iminosugar derivatives showed that the compounds were able to pass the blood-brain barrier.[100] This represents a major advantage over ERT, because it enables the potential treatment of Gaucher disease with a neurological symptoms – currently 30 type III patients receive SRT with **8**. The radiolabel study also revealed that longer *N*-alkyl chain iminosugars displayed a slower penetration into the body from the intestine, but eventually did reach higher overall levels. The effect of lowering GSL levels with **8** is reversible and the levels show full recovery within 24 h after removal of **8**. The toxicity of **8** is low and the cellular LD_{50} lies in the high mM-range.[98] The side effects of **8** at therapeutic concentrations are predominantly caused due to inhibition of other carbohydrate-processing enzymes. The major side-effects associated with SRT for Gaucher disease are related to the ability of **8** to inhibit glycosidases in the intestinal microvilli that results in diarrhea, flatulence and abdominal bloating. Miglustat is also able to inhibit ER glucosidases I and II that play a major role in the quality control of protein synthesis and folding. However, this requires concentrations of **8** in 10000-fold excess compared to the required dose for inhibition of GCS. It is the quality control of protein synthesis and folding in the ER where a potential third therapeutic opportunity for treating Gaucher disease and related sphingolipidoses exists.

After transcription of the GBA1 gene in the nucleus the generated messenger RNA is translated by ribosomes that are bound to the cytosolic membrane of the ER. The synthesized protein is secreted into the luminal compartments of the ER. Here the largely unfolded protein is decorated with a distinct *N*-linked oligosaccharide (*N*-$GlcNAc_2Man_9Glc_3$) after which it enters the folding/quality control machinery. The protein folds into its active conformation in which it is assisted and monitored by various chaperone proteins (see Figure 10 on the next page). Many of the Gaucher associated mutations of the GBA1 gene result in improper or retarded folding in the ER. Consequently, many GBA1 proteins never reach the lysosome and are instead rejected, secreted into the cytosol, and degraded by the proteasome. The third therapy that is currently in development for Gaucher disease is called chaperone mediated therapy (CMT).[85,101,102] It is based on the concept that an active-site directed inhibitor of an enzyme (a pharmacological chaperone) can already bind an enzyme during the folding process in the ER and thereby stabilize the proper protein conformation. This stabilization of the critical region of the enzyme during folding might result in a larger percentage of properly folded enzymes that reaches the lysosome (Figure 8B).

Figure 10. Overview of ER protein folding + quality control and the putative action of a chaperone in CMT.



Description: During protein folding, ER glucosidases I and II remove two of the three glucose residues after which the chaperones calnexin (membrane bound) or calreticulin (solubilized) recognize the trimmed oligosaccharide and assist the protein in folding. If ER glucosidase II cleaves the final glucose residue and if the protein is properly folded it is transported via vesicle flow for further processing in the Golgi (glycosylation). However, if after ER glucosidase II action it is not yet properly folded, UDP-glucose glycoprotein:glucosyltransferase (UGGT) recognizes the protein and probes its folding. The protein is now either reglucosylated by UGGT and reassisted in folding by calnexin/calreticulin or rejected and entered into the ER-associated degradation pathway (ERAD).

Application of this concept was first reported in 1999 by Fan and co-workers for the deficient α-galactosidase in the sphingolipidose, Fabry disease.[103] They observed that the iminosugar inhibitor, galactostatin (**10**; Figure 9) enhanced enzyme activity in cells of Fabry patients, when administrated at concentrations lower than those required for inhibition of the enzyme. Since this first report, the CMT concept has also been demonstrated to work for several common mutated forms of GBA1 in Gaucher disease – albeit in cellular assays. Many reports have since appeared that evaluate a multitude of different inhibitors, mainly iminosugar-based, for application in CMT for Gaucher disease (see Figures 19–22 on pages 45 to 47 for an overview of their structures with references). Most reports describe the incubation for 4–5 days of the inhibitor together with cells that express a specific Gaucher disease associated deficient GBA1 after which the artificial 4MU-glucoside substrate (**6**) is added and GBA1 activity is determined. The activity measurement is repeated in the presence of CBE (**3**) to correct for the activity of GBA2. Several studies have also shown with fluorescent markers of both GBA1 and the lysosome that increased amounts of GBA1 indeed reach the lysosome after treatment. However, it has yet to be shown that actual glucosylceramide degradation increases in the lysosomes of intact treated cells. A recent report showed that a combination of the iminosugar chaperone **9** with the proteasome inhibitor MG-132 (**11**) results in a synergistic effect and greater improvements of GBA1 activity in the lysosome.[104] However, because **9** also inhibits GCS, GBA2 and ER glucosidases I and II; and MG-132 also has secondary activities it is far from clear what actions of these compounds actually lead to the observed improvement in GBA1 activity.

1.3.5 Glycosphingolipids and the Brain. Starting with Tudichum's work, the importance of GSLs in brain tissue was noticed early on in GSL research. Although still not understood, especially Neu5Ac-terminal acidic gangliosides seem to play an important role in neurochemistry. They are found in high concentrations in brain tissue and can constitute up to 25% of the outer membrane lipid content. During embryogenesis and the post-natal period a small subset of acidic gangliosides are highly expressed in the developing brain. In the adult brain the levels of gangliosides are much lower but many more types of gangliosides are expressed.[18] Several knock out mouse models of the glycosyltransferases in GSL biosynthesis have shed some light on their functioning in the brain. Selective deletion of GCS in neural cells prevented the formation of the brain gangliosides and resulted in the birth of animals with severe neural defects that died within 3 weeks.[105] Knock out models of several transferases involved in the biosynthesis of more complex gangliosides have also been developed. These models indicate that a certain degree of functional redundancy exists among the brain gangliosides, because the mutant animals show only minor defects and other gangliosides seem to substitute for the functions of the missing ones.[18,106] Brain gangliosides have also been implicated in several neurological diseases. Parkinson like symptoms are one of the hallmarks of more severe forms of Gaucher disease.[107] Thus decreased functioning of GBA1 may predispose people for Parkinson disease. GSLs also seem to play a contradictory role in Alzheimer's disease. Activity of GCS was found to be lowered in brains affected with Alzheimer.[108] This caused an increase in ceramide and a decrease in levels of complex GSLs that in turn caused abnormal functioning of neural cells. Abnormal functioning could be prevented by infusions with ganglioside GM1. Contrary to this, GM1 enriched lipid rafts have also been shown to play a critical role in the pathology of Alzheimer disease by promoting the formation of amyloid deposits or plaques by aggregation of amyloid β-protein.[109]

1.3.6 Glycosphingolipids and the Skin. GSLs and SLs play vital roles in normal skin functioning. Ceramides and keratins are the essential components of the epidermal stratum corneum that makes the skin of all land dwelling animals impermeable to water and thereby prevents lethal dehydration.[110] The ceramides occupy the extracellular spaces of the stratum corneum and are characterized by *N*-acylation of the sphingosine backbone with long ω-hydroxy fatty acid chains (C_{30}–C_{36}).[17] The ceramides are thought to be excreted into the extracellular space by exocytosis of glucosylceramide and sphingomyelin intermediates. Skin cells simultaneously excrete vesicles that contain GBA1, Sap C and sphingomyelinase that hydrolyze these intermediates to generate skin ceramides at the required location. Indeed glucosylceramide constitutes ~4% of the total epidermal lipid mass. A knock out mouse model with a keratinocyte specific GCS deficiency recently proved the vital role of glucosylceramide as a intermediate in maintaining skin barrier functioning.[111] The mutant animals displayed a grossly abnormal stratum corneum and died of dehydration within 5 days after birth. Inhibition of GBA1 activity by topical exposure of skin to CBE (**3**) also caused impaired skin functioning.[110] Correspondingly,

skin abnormalities are also observed in patients with severe forms of Gaucher disease. Many skin diseases such as psoriasis also show abnormal SL and GSL metabolism.

Recently it was shown that one of the causes of the severe skin disorder, *Harlequin ichthyosis*, was a mutation that results in a deficient ABCA12 lipid transporter. This deficiency results in impaired extracellular delivery of glucosylceramide. The pathology could be remedied in a cellular model by corrective ABCA12 gene transfer.[112]

In patients with atopic dermatitis the enzyme SM deacylase was found over expressed together with 300% higher levels of sphingosylphosphorylcholine (SPC).[113] Extracellularly excreted SM deacylase in the epidermis was also found to be capable of deacylating glucosylceramide to glucosylsphingosine.[114] The increased activity of this enzyme has been proposed to contribute to dermatitis pathology by preventing sufficient generation of ceramides in the stratum corneum.

1.3.7 (Glyco)sphingolipids and Cystic Fibrosis. Cystic fibrosis is an autosomal recessive hereditary disorder caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) – a member of the family of ABC transporter proteins. The mutations cause lowered expression and activity of CFTR that affects the exocrine organs (*e.g.* lungs, intestines and pancreas). One of the clinical symptoms that play a major role in the morbidity of cystic fibrosis is a gradual destruction of lung tissue through chronic and recurrent bacterial infections by *Pseudomonas aeruginosa*. Recent research has revealed that a delicate balance of SLs and GSLs is required for normal CFTR functioning and that a SL imbalance is involved in respiratory system pathology of cystic fybrosis.

One facet of the respiratory system pathology is excessive angiogenesis in the infected lung tissue. This process is promoted by binding of sphingosine-1-phosphate to extracellular receptors. In healthy individuals, CFTR is involved in the active uptake of extracellular sphingosine-1-phosphate, which decreases the availability of this SL for promoting angiogenesis during inflammation.[115] Pier and co-workers have shown that CFTR localizes to GM1 ganglioside-containing lipid rafts upon contact of lung epithelial cells with *P. aeruginosa*.[116] They also proved that direct binding of *P. aeruginosa* to CFTR in lipid rafts is essential for recruitment of the major vault protein to rafts, internalization of the bacteria and proper host resistance to further infection.[117]

Ceramide also plays a vital role in both the normal and aberrant immune response against *P. aeruginosa* infection of lung tissue. First, ceramide that is produced from sphingomyelin via sphingomyelinase at the basolateral membrane of airway epithelial cells inhibits anion transport by CFTR at the apical membrane and thereby augments cystic fibrosis pathogenesis.[118] Gulbins and co-workers have shown that *P. aeruginosa* infection also activates acid sphingomyelinase that locally releases ceramide into lipid rafts.[119] These ceramide enriched lipid rafts reorganize into larger and more stable rafts that are required for internalization and clearance of *P. aeruginosa* infection.

Cystic fibrosis patients show an age-dependant accumulation of ceramide in the epithelial lung tissue. CFTR dysfunction impairs cellular influx of Cl^- counter anions for H^+ acidification of specific cellular compartments. This phenomenon induces a lysosomal increase in pH (4.5 » 5.9) that decreases the activity of acid ceramidase by > 90% and even reverses its activity to generate ceramide. On the other hand the activity of acid sphingomyelinase is only inhibited by 35%. This metabolic imbalance causes an increase in ceramide. The excessive ceramide levels cause cell death by apoptosis that in turn causes a hypersensitivity to *P. aeruginosa* infection creating a vicious cycle of tissue infection and destruction.[120]

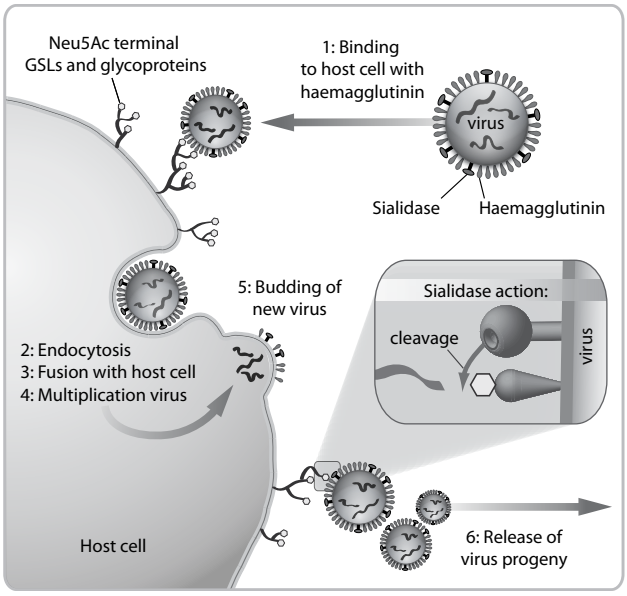
The most common CFTR mutation (F508del) that causes cystic fibrosis results in improper folding of most CFTR in the ER and degradation by the proteasome via ERAD. Becq and co-workers have reported that treatment with miglustat (**8**) is able induce a 12% increase in properly folded CFTR, which resulted in improved ion transport in cystic fibrosis epithelial cells.[121,122] They reasoned that the ability of **8** as an α-glucosidase inhibitor decreases F508del-CFTR degradation via ERAD during folding and *N*-glycan trimming in the ER. A recent patent by Aerts and Boot however demonstrates that treatment of F508del-epithelial cells with AMP-DNM (**12**), at concentrations that do not cause inhibition of α-glucosidase, also markedly improves the activity of ion transport by F508del-CFTR. In their experiment **12** inhibits GBA2 that shares the same cellular localization as CFTR.[68] The proposed mechanism of action is that inhibition of GBA2 lowers the level of ceramide in the microenvironment of F508del-CFTR and thereby improves its functioning.

1.3.8 Glycosphingolipids and Pathogens. GSLs are found at increased concentrations on the outer membranes of apical cells (*e.g.* cells that line the inside of stomach, intestines, respiratory track). Most types of these apical cells represent the initial barrier of the body with the external world and are therefore also the first to make contact with potential pathogens. Correspondingly, many pathogens have evolved mechanisms for exploiting these GSLs for infecting and invading their host. Especially, GSL-rich lipid rafts with terminal Neu5Ac carbohydrates are often hijacked by viruses, bacteria and protozoans for their propagation. The HIV-1, Ebola and Marburg viruses all use lipid rafts in binding to, entry in and budding from host cells.[123]

One of the most well studied examples is that of the influenza virus family that has only three different surface proteins of which the two most abundant are specifically aimed against the human host's terminal Neu5Ac GSLs and glycoproteins. The protein, called haemagglutinin, is a specific lectin for Neu5Ac and enables the virus to bind to the host cell after which it is endocytosed and multiplies itself (see Figure 11). The role of the second viral protein, a sialidase called neuraminidase, is to process progeny virus particles when they bud from the host cell, by hydrolyzing Neu5Ac from both the host cell and budding virus particle to achieve release from the host cell and prevent self-agglutination

of viruses. A major factor determining why humans are not yet readily infected by the H5N1 'bird-flu' is because it currently preferentially recognizes the terminal α2-3 linked Neu5Ac in bird respiratory tracks, where humans predominantly possess terminal α2-6 linked Neu5Ac in their respiratory tracks.[124]

Figure 11. Infuenza virus lifecycle and sialidase/haemagglutinin action.



1-Deoxynojirimycin based iminosugar derivatives such as miglustat (**8**; Figure 9) have been successfully applied to suppress the propagation of various viruses in cellular models.[125,126] Many viruses express glycoproteins on their surface and glucosidase inhibitors can disrupt proper processing of viral *N*-glycoproteins in the host ER by inhibiting trimming by ER glucosidase I+II and therefore calnexin/calreticulin binding. However, so far this has not resulted in a viable antiviral due to the excessive concentrations of inhibitor needed to achieve relevant levels in the ER when orally administered to patients.

An example of a bacterial pathogen that abuses host GSLs is *Helicobacter pylori*. It causes gastric ulcers and infects the gastric lining by lectin binding to the several host GSL among which the sialyl dimeric Lewis-X antigen (Neolacto series with one terminal Neu5Ac and two terminal L-fucose residues).[127] Depletion of surface GSLs by inhibition of GCS with miglustat (**8**) or PDMP (**7**) has been shown to successfully impair adherence of several bacteria species to host cells.[128,129] Another example is *Vibrio cholerae*. It expresses a sialidase that removes terminal Neu5Ac from complex GSLs (*e.g.* ganglioside GD1a) on the apical surface of the host's intestinal epithelial cells. This action exposes apical GM1 gangliosides to which the cholera toxin can bind that after internalization causes diarrhea.[130,131] As seen in the case of chronic respiratory track infection by *P. aeruginosa*

in cystic fibrosis, SLs and GSLs can also play an essential role in staging a proper immune response to infection by a pathogen.

1.3.9 (Glyco)sphingolipids in Immunology and Inflammation. A GSL derived from marine sponges and not found in humans, α-galactosylceramide, is a ligand for a specific subset of immune T cells, invariant natural killer T (iNKT) cells. Upon recognition of α-galactosylceramide, which is presented by CD1d molecules on antigen presenting cells, the iNKT cells rapidly secrete cytokines (IL-4 and interferon-γ) and downregulate cell surface T cell receptors. This results in the activation of various cells of the innate and adaptive immune system.[132,133]

One of the clinical symptoms in the sphingolipidosis, Sandhoff disease, is a reduced amount of iNKT cells. The deficient enzymes in Sandhoff disease are β-hexosaminidases A and B. Several studies have proposed that the inavailability of a specific degradation product of these enzymes, isoglobotrihexosylceramide (iGb3; Gal-α1,3-lactosylceramide), almost not formed in Sandhoff disease patients, is responsible for this effect. They have labeled iGb3 as the endogenous CD1d lipid ligand by which newly generated iNKI cells are positively selected in the thymus for proper functioning.[134] This GSL has also been implicated in the activation of NKT cells. Dendritic cells, activated by lipopolysaccharide from *Salmonella typhimurium*, were found to activate NKT cells by presentation of iGb3 to them.[135] These results were contradicted by two recent studies that showed the absence of iGb3 in the thymus of humans and that knock out mice for iGb3 biosynthesis possess a normal immune response.[136,137] However, observations that intacellular CD1d antigen loading occurs in low pH endosomal/lysosomal compartments and is dependant on the presence of saposin activator proteins does suggest that another GSL may still be the ligand. This is further substantiated by a report that GCS deficient cells either by gene knock out or PDMP (**7**) inhibition are unable to activate iNKT cells.[138]

A recent study found that the presence of GSLs from the acidic ganglioside series in lipid rafts increases the cell surface expression of Toll-like recepeptor 2 (TLR2) in brain microglia cells. These GSLs also enhanced the interaction of TLR2 with its intracellular adaptor protein Myd88 that leads to an inflammatory condition in the brain.[139]

Treatment of a chemically induced inflammatory condition of the bowels in a mouse model with the GCS inhibitor **12** showed a considerable reduction in the inflammatory condition. This indicates that GSL biosynthesis is involved in the inflammatory cascade of inflammatory bowel diseases.[140]

1.3.10 Glycosphingolipids and Cancer. Most tumor cells exhibit altered GSL patterns on their surface, abnormal SL signaling and increased GSL biosynthesis that together play a major role in tumor growth, angiogenesis and metastasis.[141,142] The human sialidase, Neu3, is found in caveolae containing lipid rafts in the plasma membrane and cleaves

terminal Neu5Ac residues from GSLs. It is overexpressed in many types of cancer and plays an important role in their malignant character.[143] Tumor cells also actively shed specific gangliosides from the cell surface in order to cloak themselves from the body's immune system.[144]

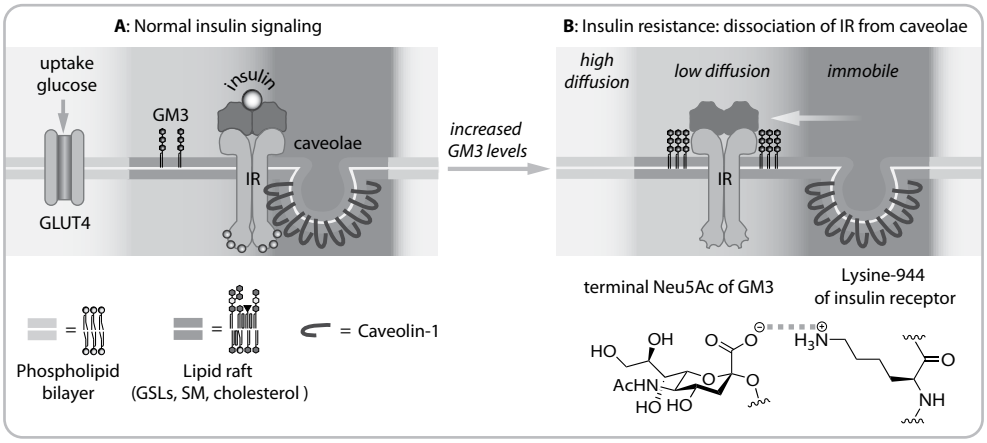
The effect of many chemotherapy agents and radiotherapies for treating cancers relies on their ability to increase levels of ceramide in tumor cells in order to activate ceramide-mediated apoptosis. Many tumors have increased expression levels and activity of GCS. This is thought in part to function as a detoxification method for the increased ceramide levels by conversion to glucosylceramide. Drug resistant cancer cell lines show up to threefold higher levels of glucosylceramide. Many tumors also achieve drug resistance by actively pumping out the drugs via the family of ABC transporter proteins. Overexpression of the most common of these efflux pumps, P-glycoprotein, coincides with abnormally high GCS activity in multidrug-resistant breast cancer, leukemia, melanoma and colon cancer. P-glycoprotein is a 170 kDa plasma membrane anchored protein that is situated in GSL containing lipid rafts. With expenditure of ATP it is capable of transporting a wide range of non-charged amphiphilic molecules – glucosylceramide among others – from the cytosol to the outer plasma membrane. Overexpression of the P-glycoprotein efflux pump is actually one of the most consistant hallmarks of drug resistance of many pathogens; antimalaria resistance of *Plasmodium falciparum*, chemotherapy resistance by the protozoan *Leishmania* and resistance to macrolide antibiotics by *S. pneumoniae*.[145,146]

Research has shown that inhibition of GCS by treatment of tumor cells with *N*-alkylated iminosugars (**8** and its derivatives) reduces tumor growth.[147,148] GCS inhibition with PDMP (**7**) and GCS silencing by iRNA's has been reported to reverse P-glycoprotein induced drug resistance in tumor cells.[149] However, other recent reports have also claimed there is no connection between GCS activity and drug resistance of cancers.[150]

1.3.11 (Glyco)sphingolipids and the Insulin Receptor. The insulin receptor is localized on the cell surface in GSL-containing lipid rafts that also house the membrane protein caveolin-1. This membrane protein creates stabile flask-like invaginations in the lipid raft called caveolae. The insulin receptor has a binding domain for caveolin-1 and their co-localization appears to be crucial for proper functioning of the insulin receptor (Figure 12A).[151] Many studies have also pointed to the role of SLs and GSLs in the pathology of insulin resistance in obesity linked type 2 diabetes.[152-154] Ceramide, sphingosine and sphingosine-1-phosphate are elevated in type 2 diabetes patients and obese insulin resistant mouse models. Ceramide has been demonstrated to inhibit insulin-stimulated glucose uptake by GLUT4 translocation and glycogen synthesis. The inhibitory effect of ceramide originates from its ability to block phosphorylation of Akt and protein kinase B in the downstream insulin signaling cascade.

The levels of GSLs such as glucosylceramide and ganglioside GM3 are also increased in a state of insulin resistance. Inokuchi and co-workers recently reported that the insulin receptor is also capable of binding GM3 in microdomains via interaction of the amine residue of lysine-944 with the acidic Neu5Ac of GM3 (Figure 12B). The study showed that the mobility of the insulin receptor is increased in GM3-enriched microdomains via this interaction that eventually causes insulin resistance by complete dissociation of the receptor from the caveolae.[151] Recent research also demonstrated that Gaucher disease, in which patients also have elevated GM3 levels, is associated with insulin resistance.[155] Several studies have shown that down regulation of GSL levels by inhibition of GCS by AMP-DNM (**12**)[156] or PDMP (**7**)[157] improves sensitivity of the insulin receptor in several type 2 diabetes animal models. Inhibition of GCS by **12** does not to influence the expression levels of components in the insulin signaling pathway, which is in line with its GSL level lowering mode of action.[158]

Figure 12. Lipid raft environment of the insulin receptor (IR) in normal conditions (**A**) and insulin resistance (**B**).



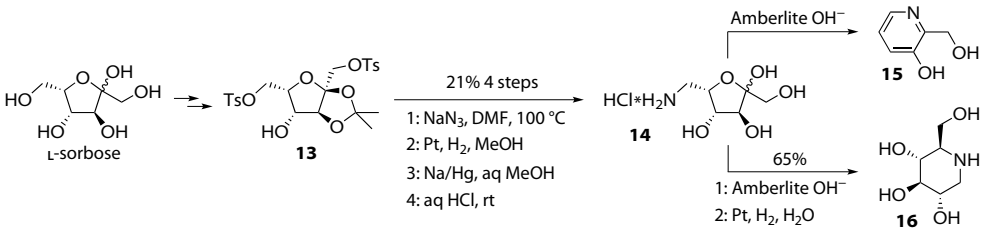
1.4 From Iminosugars to Inhibitors of Glucosylceramide Metabolism.

As can be judged from the previous sections, GSLs are involved in many biological processes both in health and disease of which most are still not fully understood. Small molecule inhibitors of the enzymes involved in the metabolism of glucosylceramide, GCS, GBA1 and GBA2, have been used as a handle to change the cellular levels of GSLs, for therapeutic purposes such as in SRT and CMT or to probe GSL functioning. Most of these inhibitors are based on the naturally occurring class of alkaloids called iminosugars. Iminosugars are carbohydrate derivatives in which the endocylic oxygen is replaced by a nitrogen atom. Contrary to many other naturally occurring compounds, iminosugars were first designed and synthesized in an organic chemistry laboratory before their isolation from a natural source.

1.4.1 The Discovery of Iminosugars. Ever since the ground breaking work on the chemistry and structure of carbohydrates by Emile Fisher during the 1880s and 90s,[159] organic chemists have used carbohydrates as starting materials in the synthesis of other either natural or non-natural derivatives. During the 1960 several groups investigated replacing the oxygen atom in carbohydrates with another heteroatom. The group of Paulsen chose the nitrogen atom and in 1966 they reported the conversion of known L-sorbose derivative (**13**) into a 6-amino-6-deoxy-L-sorbose derivative, which formed a furanose as its hydrochloric acid salt (**14**) and eliminated three water molecules to give a pyridine derivative (**15**) in neutral or alkaline solution (Scheme 8). However, when the free base of the amine was immediately hydrogenated it produced a 1-deoxy glucose analog with a ring nitrogen (**16**) accompanied by a minor amount of the equivalent C-5/L-idose epimer.[160,161]

Besides the quest to synthesize iminosugars, no real applications existed at the time for these compounds. In 1968, Inouye and co-workers characterized and synthesized an unstable antibiotic, nojirimycin (**17**), isolated from strains of *Streptomyces* (structure in Scheme 9).[162] When hydrogenated, **17** transformed into its stable 1-deoxynojirmycin analog which corresponded exactly to the glucose derivative (**16**) synthesized by Paulsen. In 1976, **16** was isolated from the mulberry tree and certain species of bacteria. Further research proved that **16** was a potent inhibitor of glycosidases and a whole field of research into the natural occurrence, synthetic preparation and inhibitory properties of **16** and its derivatives, nowadays called iminosugars, was initiated.[163,164]

Scheme 8. Synthesis of 1-deoxynojirimycin (**16**) as reported by Paulsen and co-workers.

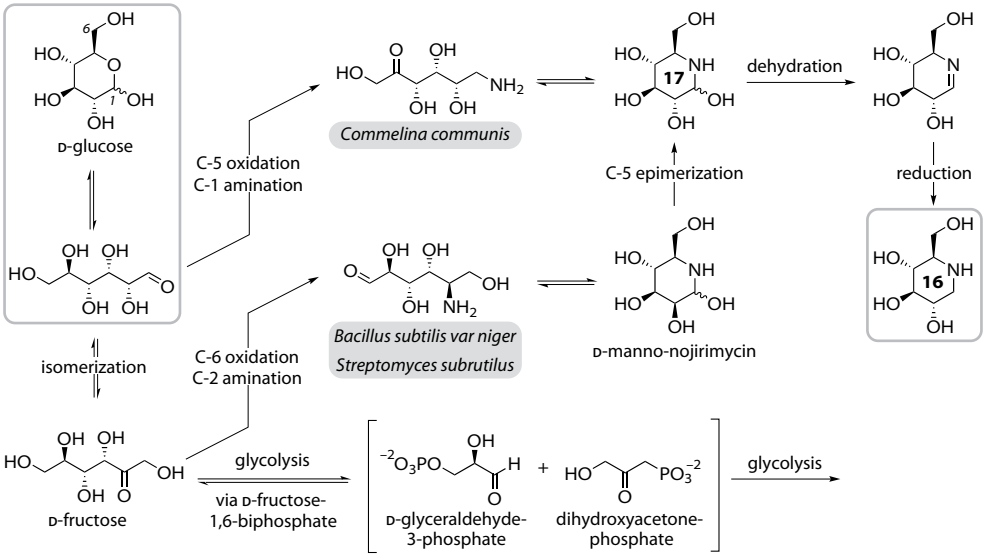


1.4.2 Biosynthesis of 1-Deoxynojirimycin. Compared to the large number of synthetic routes developed for the archetypical iminosugar **16**, for a relatively long time little was known about how **16** was synthesized in nature. Hardick and co-workers[165,166] researched its biosynthesis in two species of bacteria and Shibano and co-workers[167] in the plant *Commelina communis*. These studies proved that **16** is made from D-glucose in both the two species of bacteria and the plant. However, its biosynthesis from D-glucose follows two distinct paths. Both studies elucidated the biosynthesis of **16** through ^{13}C-1 labeled D-glucose feeding experiments and ^{13}C-NMR analysis of metabolites.

Hardick and co-workers showed that in both bacteria species D-glucose is first converted to D-fructose – via an enzyme catalyzed Lobry de Bruyn-Alberda van Ekenstein

isomerization (Scheme 9). Next, the amination and epimerization of C-2 and oxidation of C-6 in an undetermined order results in an intermediate that cyclizes to D-manno-nojirimycin. This intermediate is epimerized at C-2 to **17** and subsequently dehydrated at C-1 and reduced to provide **16**. Besides the expected ^{13}C labeling at C-6 of **16** they also found minor labeling at C-1. This result combined with the incorporation of ^{13}C at C-1 and C-6 in **16** after ^{13}C-1-D-glyceraldehyde feeding experiments proved that before entering the biosynthesis of **16**, D-fructose is also in equilibrium with the first steps of glycolysis.

Scheme 9. Proposed biosynthetic routes for **16** in a plant and two species of bacteria.



Shibano and co-workers found that in *Commelina communis* the C-1 position of **16** possessed the majority of the label. This indicated that here a more direct route of amination at C-1 and oxidation of C-5 was followed to produce **16**. Also here the label was divided over the C-1 and C-6 position that indicated prior equilibration of D-glucose to D-fructose and glycolysis (Scheme 9)

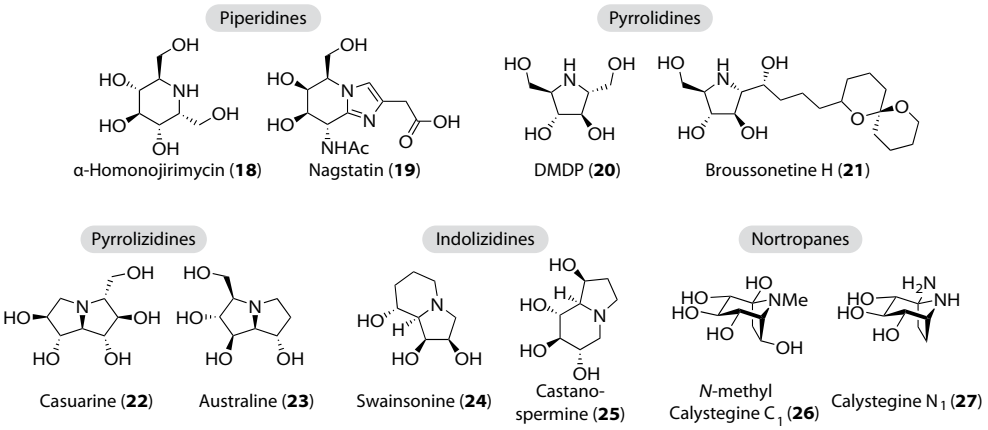
Besides **16**, countless other iminosugars have been isolated from natural sources such as plants, bacteria and fungi – as described in various comprehensive reviews[168,169] and books.[163,164] All these iminosugars are categorized in five classes based on their structure (Figure 13 on the next page). 1-Deoxynojirimycin (**16**) and nojirimycin (**17**) belong to the class called the piperidines. The most recent class discovered is that of the nortropanes during the 1990s. The calystegines from this class are even found at low concentrations in many common foods such as egg-plant, potatoes, tomatoes and chilli peppers.

One unifying property among these structurally diverse classes of iminosugars is their ability to inhibit glycosidases[168] and to a lesser extent glycosyltransferases.[170] Their structural diversity also results in a large degree of selectivity among iminosugars in the

inhibition of specific glycosidases and transferases. The known inhibitory activities of many natural and synthetic iminosugars as well as their therapeutic applications have been listed in two books on iminosugars.[163,164]

Promoted by therapeutic applications for this ability to inhibit carbohydrate-processing enzymes and difficulties in isolating large amounts from natural sources, much research since the 1970s has also focused on developing methodology for iminosugar synthesis.[163,164,171,172] During the late 1980s and early 90s, research into the application of iminosugars as antivirals led to the discovery of *N*-alkylated 1-deoxynojirimycins as potent ER glucosidase I and II inhibitors. One of these was miglustat (**8**) that in 1994 was also found to be an inhibitor of GCS. This discovery initiated the development of iminosugars as inhibitors of glucosylceramide metabolism. The next three sections will provide an overview of the different inhibitors of GCS, GBA1 and GBA2 that have so far been discovered – with a focus on iminosugar based inhibitors. Two reviews by Delgado and co-workers provide an overview of inhibitors of SL metabolic enzymes and also of GCS/GBA1.[173,174]

Figure 13. The five iminosugar classes with two examples of naturally occurring members.



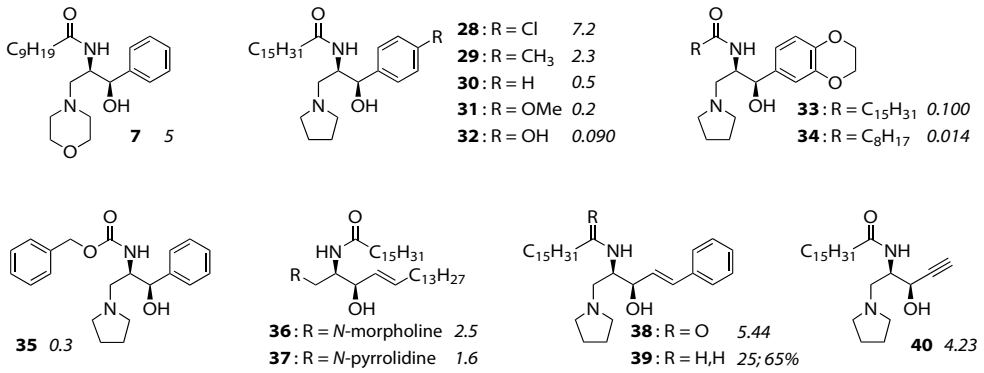
1.4.3 Inhibitors of Glucosylceramide Synthase. GCS is quite unique among glycosyl transferases in that an extended and structurally diverse range of potent inhibitors exist for it. In 1980 Vunnam and Radin reported the synthesis and activity of PDMP (**7**), the first example of a GCS inhibitor. It was part of a series of ceramide analogues in which the unsaturated alkyl chain of the sphingosine backbone was replaced by a phenyl group and the primary hydroxyl by several heterocycles (Figure 14).[94] Only analogues with D-*threo* stereochemistry – the opposite of ceramide – proved to inhibit GCS and kinetic analysis showed **7** to be uncompetitive for UDP-glucose and a mixed competitive inhibitor for ceramide.[175] Switching the heterocycle to a pyrrolidine (**30**) resulted in a tenfold increase in potency.[176] Subsequent investigation of *para*-substitions on the phenyl ring of **30** revealed a relationship between the IC_{50}, the hydrophilicity and the electron donating

capacity of the *para*-position (**28**–**32**; Figure 14).[177] An ethylenedioxy modification of the phenyl ring (**33**)[177] in combination with a shorter acyl C_9 chain has resulted in the most potent PDMP derivative (**34**) and GCS inhibitor to date.[178] Two other studies have shown that the acyl chain can be replaced by a benzyloxy carbonyl (**35**)[179] but not with an alkyl chain (**38** *vs.* **39**).[180] Derivatives **36** and **37** that more closely mimic ceramide also inhibited GCS comparably to PDMP.[181] Finally, van Calenbergh and co-workers recently reported that replacing the sphingosine mimicking aryl moiety of PDMP with a terminal alkyne (**40**) also results in a potent inhibitor of GCS.[180]

Evaluation of the selectivity of a structural homologue of **33** with an IC_{50} of 24 nM for GCS revealed that it did not inhibit the enzymes GBA1, GBA2, ER α-glucosidases I+II, debranching enzyme, sucrase and maltase.[182] Another study showed that **33** does not inhibit GCS in lower animals, plants, fungi or bacteria, but only inhibits human GCS.[183]

In general, the D-*threo* PDMP structure has proven a flexible and productive core for the design of GCS inhibitors. During the development of PDMP and its derivatives it was discovered that many of these compounds also inhibit the lysosomal phospholipase A2 that is capable of acylating ceramide to 1-*O*-acylceramide. Its inhibition results in increased cellular ceramide levels, which can lead to secondary effects of these inhibitors.[184]

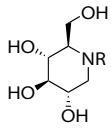
Figure 14. Overview of PDMP-based GCS inhibitors (in italic: IC_{50} values in μM or % inhibition at μM).



In 1994, Platt and co-workers reported that **8** (miglustat)[95] is able to inhibit GCS, which has since been used to develop substrate reduction therapy for Gaucher disease, as described in section 1.3.4. Due to this applications much attention has focused on the structure–activity relationship (SAR) of *N*-alkylated iminosugars.[42,185] These studies have shown that *N*-propyl (**44**) represents the minimum length for inhibition of GCS and that lengthening the *N*-alkyl chain further improves inhibition of GCS up to *N*-decyl alkylation (**47**; see Table 1 on the next page).[42] Linear aliphatic *N*-alkylation does not appear to be crucial as the IC_{50} of *N*-benzyl **58** is comparable to **8** (Figure 15).[185] Also *N*-5-(adamantan-1yl-methoxy)-pentyl (AMP) derivative **12**, published by Aerts *et al.* in 1998, proved a very potent inhibitor of GCS.[186] Lengthening the *N*-alkyl chain also increases

the cytotoxicity of these compounds (Table 1).[42] The exact nature of this toxicity is not fully understood but might be caused by membrane solubilisation due to their behavior as detergent amphiphiles. Van den Broek *et al.* have shown that introduction of an ether function into the *N*-alkyl chain decreases cytotoxicity (**47** compared to **51** in Table 1).[187]

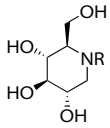
Table 1. IC_{50} in μM or % inhibition at μM and cytotoxicity for *N*-alkylated 1-deoxynojirimycins.

	Compound	GCS *in vitro*	Cell proliferation CC_{50}	ER α-glucosidase I *in vitro*	GBA1 *in vitro*
	**16**: R = H	2 mM (0%)[a]	> 5 mM[a]	1.44[a]	240[e]
	42: R = Me	200 (31%)[b]	-	-	150[e]
	43: R = Et	200 (52%)[b]	-	-	-
	44: R = Propyl	200 (69%)[b]	-	-	700[e]
	8: R = Butyl	34.4[c]	> 10 mM[a]	0.57[a]	270[e]
	45: R = Hexyl	23.8[c]	> 1 mM[c]	-	13[e]
	46: R = Octyl	16.6[c]	984.1[c]	-	0.82[e]
	9: R = Nonyl	7.4[c]	118.9[c]	0.29[a]	0.66[e]
	47: R = Decyl	3.1[c]	95.5[c]	0.48[d]	-
	48: R = Dodecyl	5.2[c]	39.7[c]	-	0.05[f]
	49: R = Hexadecyl	3.4[c]	25.1[c]	-	-
	50: R = Octadecyl	4.0[c]	36.6[c]	-	-
	51: R = 7-oxadecyl	3.2[a]	> 5 mM[a]	0.29[a]	-
	52: R = 7,10,13-trioxa-tetradecyl	200 (93%)[d]	-	-	-

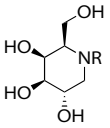
a[188]; b[189]; c[42]; d[185]; e[190]; f[191]

Miglustat (**8**) was first reported in 1988 by Fleet *et al.* as part of a panel of inhibitors of HIV virus replication.[192] Inhibition of ER α-glucosidase I and II causes this effect and in an attempt to dissociate this activity from GCS inhibition Platt and co-workers investigated modification of the iminosugar part of **8**. This study proved that *N*-butylated 2-acetamido-, D-*manno*- and L-*fuco*-1-deoxynojirimycin no longer inhibit GCS. However, D-*galacto* derivatives (**53** and **54**) do inhibit GCS and no longer inhibit ER glucosidase I or GBA1 (Figure 15).[189] Recently reported results have shown that L-*ido* derivatives (**55** and **56**[193]) and L-*altro* **57** also still inhibit GCS.[98,193]

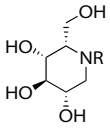
Figure 15. Overview of piperidine based GCS inhibitors (in italic: IC_{50} values in μM or % inhibition at μM).



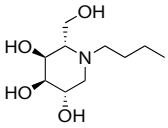
8 : R = Butyl *34.4*
9 : R = Nonyl *7.4*
12 : R = AMP *0.2*



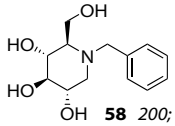
53 : R = Butyl *40*
54 : R = Nonyl *10.6*



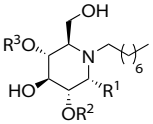
55 : R = Butyl *27*
56 : R = Pentyl *4.0*



57 *70*



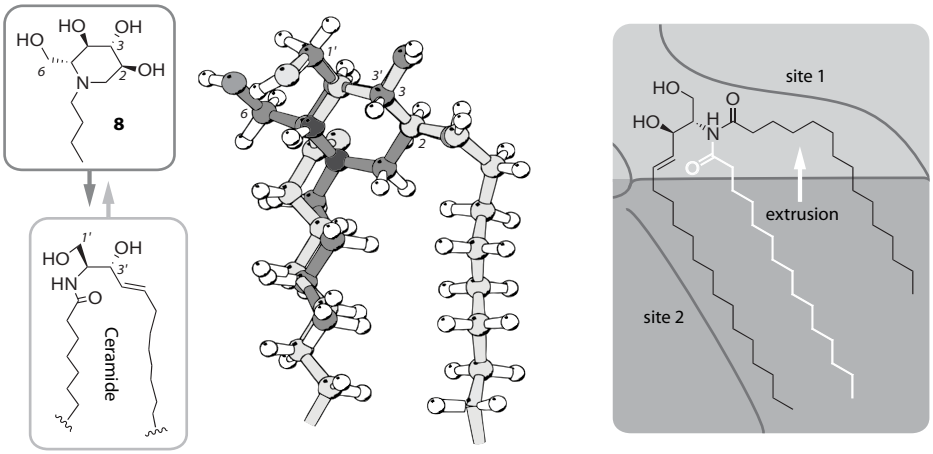
58 *200; 73%*



59 : R^1 = Octyl; R^2 = R^3 = H *174*
60 : R^1 = H; R^2 = Octyl, R^3 = H *164*
61 : R^1 = R^2 = H, R^3 = Octyl *134*
62 : R^1 = H; R^2 = R^3 = Octyl *1 mM; 26%*

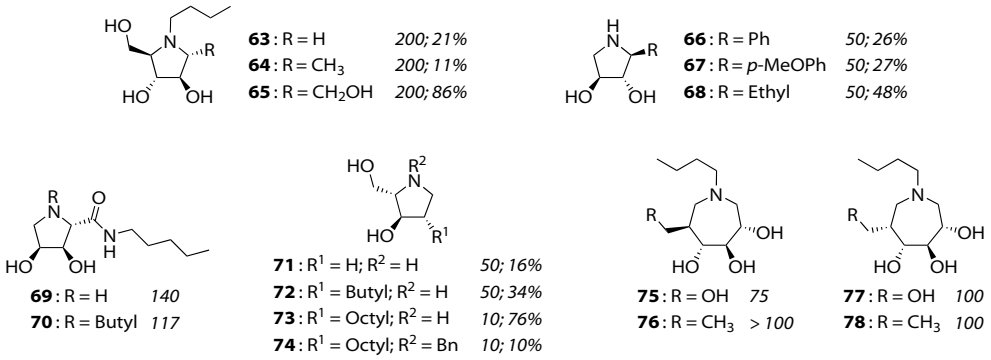
Due to the lack of a crystal structure for GCS it is not known how 1-deoxynojirimycin derived inhibitors bind its active site and what SAR governs this. A study by Butters and co-workers of the kinetics of GCS inhibition by **8** showed that it was non-competitive for UDP-glucose and competitive for ceramide.[185] On the other hand compound **9** proved non-competitive for both substrates.[42] These results combined with the close structural similarities of **8** and ceramide has led Butters to tentatively designate **8** as a ceramide mimic (Figure 16). A proposed model explains the difference between the binding kinetics of **8** and **9** by the presence of two hydrophobic sites for binding of ceramide in a predicted computational model of GCS. In this model a membrane embedded ceramide is required to be partially extracted for proper positioning of its primary hydroxyl in the active site. The sphingosine backbone binds with transmembrane site 2 and the acyl tail is partly extruded from the membrane to bind site 1. In this model the less lipophilic **8** is predicted to bind site 1 and the lipophilic **9** at site 2.[42] This model indicates that the attachment of a second lipophilic moiety at the 2-*O*-position hydroxyl of **8** or **9** could result in a better mimic of ceramide. However, a recent study by Compain, Martin and co-workers that reported the synthesis and evaluation of di- or trialkylated derivatives **59**–**62** showed this did not result in more potent GCS inhibitors (Figure 15).[194] Research described in Chapter 5 of this thesis corroborates this finding.

Figure 16. Model of miglustat (**8**) as a ceramide mimic as proposed by Butters and co-workers.[42,185]



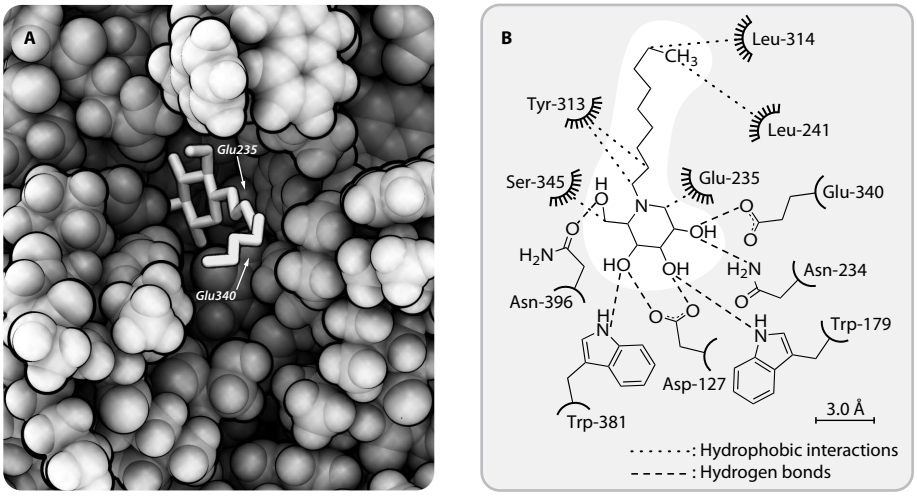
Several pyrrolidine iminosugars have also proven to be inhibitors of GCS. In 2000, Butters and co-workers revealed that DMDP derivative **65** was an inhibitor comparable in activity to **5** (Figure 17 on the next page).[185] Two studies by Davis and co-workers have also identified several pyrrolidine inhibitors (**66**–**70**).[195,196] Génisson *et al.* have developed pyrrolidines that mimic the sphingosine backbone (**71**-**74**) among which **73** proved to be a potent GCS inhibitor.[197] Finally, Blériot and co-workers recently reported moderately active azepane based inhibitors of GCS (**75**-**78**).[198]

Figure 17. Pyrrolidine and azepane based GCS inhibitors (in italic: IC_{50} values in μM or % inhibition at μM).



1.4.4 Inhibitors of Glucocerebrosidase. As mentioned in the previous section, miglustat (**8**) also inhibits GBA1 and increasing the length and hydrophobicity of the *N*-alkyl chain, similar as for GCS, also improves GBA1 inhibition (Table 1, **8**, **9** and **12** in Figure 19). Attachment of amantadine – itself an anti-influenza drug – to the *N*-alkyl tail via an amide linkage to produce AMP-DNM derivative **79** does not decrease GBA1 inhibition.[199] Inhibitor **79** has shown potential as a pharmacological chaperone of Gaucher disease associated GBA1.[199,200]

Figure 18. X-ray crystal structure of **9** in active site of GBA1 (**A**). Coordination of **9** by active site residues (**B**).[201]

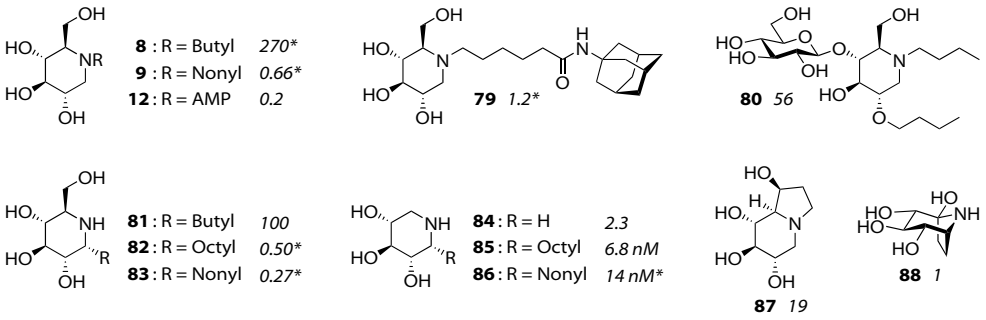


In 2007 Futerman, Sussman and co-workers published two crystal structure of GBA1 with **8** and **9** bound in its active site. Binding of **8** and **9** was very similar with the nonyl moiety of **9** making additional hydrophobic interactions with leucine residues near the entry to the active site (Figure 18). Remarkably, the nitrogen atom of both inhibitors did not coordinate with the two catalytic glutamic acid residues (Glu-340/235) or any

other active site residue.[201] These observations indicate that 1-deoxynojirimycin-based inhibitors of GBA1 appear to act as fortuitous binders of the active site. Extensive studies of the binding kinetics of numerous iminosugar-type inhibitors and their target glycosidases has shown that in general 1-deoxynojirimycin-based inhibitors are not true transition state analogs. To achieve true transition state mimicry for glycosidases and the associated increases in binding affinity requires sp^2 hybridization at the pseudo anomeric centre of the iminosugar (*e.g.* Nagstatin **19**[202] in Figure 13).[203]

With the ceramide mimicking model of **8** as a basis (Figure 16 left), Compain, Martin and co-workers reported the β-4-*O*-glucosylation of two *N*-alkylated 1-deoxynojirimycins. According to the model glycosylation at this position should result in mimics of glucosylceramide. Glycosylation of miglustat (**8**) resulted in loss of GBA1 inhibition. However, a 2-*O*, *N*-dibutylated-1-deoxynojirmycin – itself not a GBA1 inhibitor – did display inhibition of GBA1 upon β-4-*O*-glucosylation (**80**).[204]

Figure 19. Overview of structures and IC_{50} values in μM (italic) for GBA1 inhibitors.



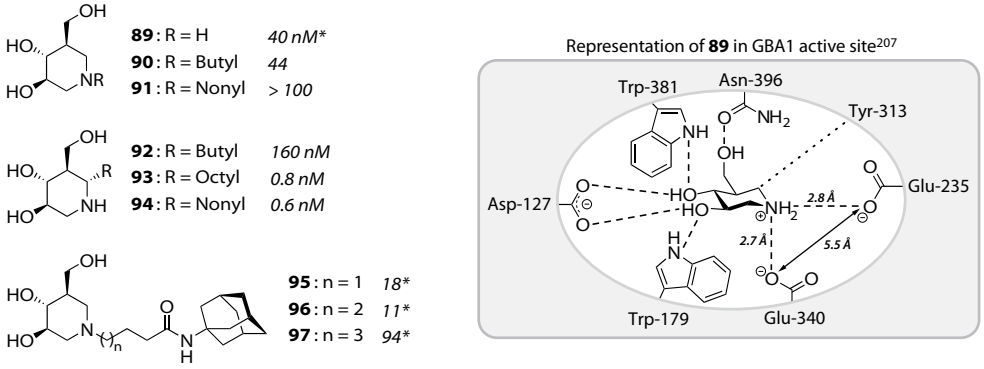
*: **8**[205]; **9**[104,206]; **79**[200,207]; **82**+**83**[190], **86**[208] show *in vivo* pharmacological chaperone activity for mutated GBA1.

Two other studies by the same group showed that D-*gluco*- (**81**–**83**)[190] and D-*xylo*-α-aza-*C*-glycosides (**84**–**86**)[208] are very potent GBA1 inhibitors (Figure 19). Evaluation of a series of naturally occurring iminosugars by Fan and co-workers identified castanospermine (**87**) and several calystegines (**88**: calystegine B2) as inhibitors of GBA1.[191] Isofagomine (**89**; see Figure 20 on the next page) proved to be the most potent GBA1 inhibitor in this screening (IC_{50} 40 nM) and was subsequently evaluated as a chemical chaperone in cells of Gaucher, Fabry and G_{M1}-gangliosidosis patients with promising results.

Petsko and co-workers reported the crystal structure of GBA1 with **89** in its active site in 2007 (Figure 20 right).[207] The secondary hydroxyls of **89** are coordinated by the same residues as reported for **8** and **9**, but it differs in that its nitrogen is coordinated by the two catalytic residues. Fan and co-workers have shown that a great difference in potency for GBA1 inhibition is observed between *N*-alkylation (**90** and **91**) of **89** or a alkyl tail on the C-6 position (**92**–**94**).[209] From this last series, isofagomine derivative **94** with an IC_{50} of 0.6 nM represents the most potent GBA1 inhibitor reported to date. Kelly and co-

workers have since shown that *N*-alkylation with an alkyl spaced amantadine-amide also provides GBA1 inhibitors (**95**–**97**) that are efficient pharmacological chaperones for two common mutated forms (N370S and G202R) of GBA1 in Gaucher disease.[210]

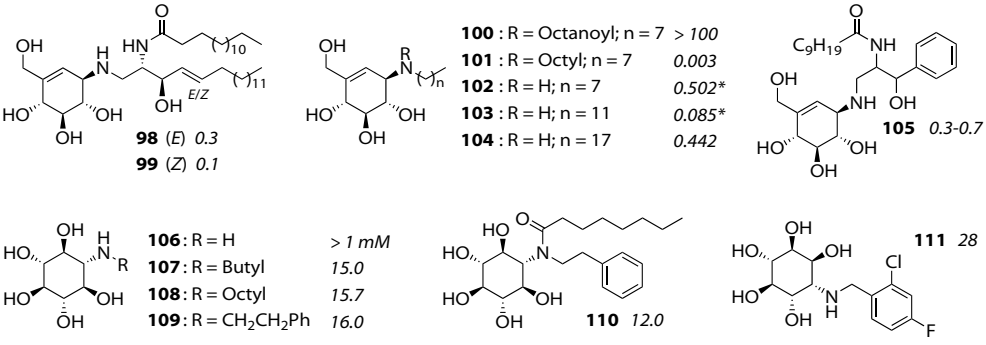
Figure 20. Overview of structures and IC_{50} values in μM (italic) for isofagomine-based GBA1 inhibitors.



*: Active as pharmacological chaperone for mutated GBA1 during *in vivo* evaluation.[191,210-212]

Besides the piperidine-based iminosugars, lipophilic aminocyclitols constitute a second important class of GBA1 inhibitors. In 1995, Ogawa and co-workers reported the *N*-alkylation of a naturally occurring aminocyclitol, β-valienamine, with either an *E* or *Z* ceramide moiety. This resulted in **98** and **99** that represented the first known selective inhibitors of GBA1 (Figure 21).[213] Replacing the complex ceramide moiety by one[214] or two[215] aliphatic alkyl chains also produced potent inhibitors (**100**–**104**) that were shown not to inhibit GCS. Derivatives of β-valienamine (**105**) inspired by PDMP also produced inhibitors of GBA1 regardless of the stereochemistry of the PDMP part. Using α-valienamine or a saturated β-valienamine analogue, β-validamine, in this design resulted in significantly decreased GBA1 inhibition.[216]

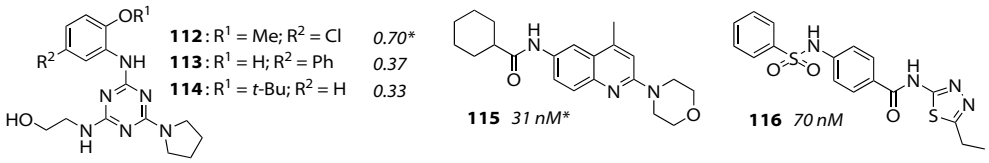
Figure 21. Overview of structures and IC_{50} values in μM (italic) for aminocyclitol-based GBA1 inhibitors.



*: Active as pharmacological chaperone for mutated GBA1 during *in vivo* evaluation.[217,218]

Delgado and co-workers have reported *N*-alkylated aminocyclitols **107**–**109** as GBA1 inhibitors (Figure 21). These were obtained by regio- and stereocontrolled opening of conduritol-B-epoxide (**3**). Aminocylitol **110** was the most potent GBA1 inhibitor and remarkably does not contain a basic amine function that is usually required for inhibition of GBA1.[219] These compounds were also evaluated as GCS inhibitors, but proved inactive. In a second combinatorial chemistry study by Delgado and co-workers, substitution of the nitrogen atom in two amincylitols cores was investigated that resulted in GBA1 inhibitors similar in structure and activity to **107**–**109**, as well as a new class of inhibitors, namely, **111**.[220]

Figure 22. Overview of structures and IC_{50} values in μM (italic) for aromatic-based GBA1 inhibitors.

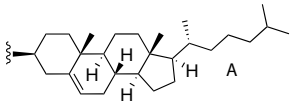


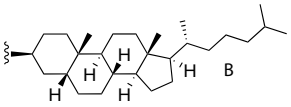
*: Active as pharmacological chaperone for mutated GBA1 during *in vivo* evaluation.[221]

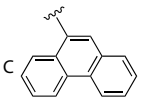
Finally, Sidransky and co-workers recently identified three novel classes of aromatic, achiral GBA1 inhibitors (**112**, **115** and **116**; Figure 22) by high throughput screening of a library of 59815 compounds.[221] Compound **112** proved the most promising for use as a GBA1 chemical chaperone and was further developed. Modifications at the pyrrolidine nitrogen and primary hydroxyl of **112** did not improve its potency, but several modifications of the phenyl ring did (**113** and **114**).[222]

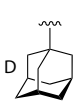
1.4.5 Inhibitors of β-Glucosidase 2. Before its identification as GBA2, Aerts and co-workers published a series of 1-deoxynojirimycin derivatives in 1999 that were evaluated in an enzyme assay for inhibition of the unidentified non-lysosomal glucosylceramidase activity (GBA2), GBA1 and GCS. As previously seen for GCS and GBA1 inhibition, longer *N*-alkyl chains here also resulted in more potent inhibitors of GBA2 (**8**, **44**, **117** and **118** in Table 2).[186] Several derivatives were also equipped with various C_5-spaced hydrophobic moieties and evaluated in an enzyme assay (see Table 2 on the next page). Hydrophobic moieties attached to the ring nitrogen via an amide linkage provided inactive to weak inhibitors of GBA2, GBA1 and GCS (**119**–**123**). However, potent inhibitors of GBA2 and also GBA1 and GCS were obtained when a hydrophobic 5-cholesteroloxy-pentyl (**124**) or 5-(adamantane-1yl-methoxy)-pentyl (**12**) moiety was attached to the ring nitrogen. Especially compound **12** with an IC_{50} of 1 nM proved a very potent inhibitor of GBA2.

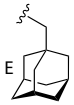
Table 2. Apparent *in vitro* IC_{50} values in μM for 1-deoxynojirimcyin derivatives.[186]

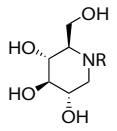
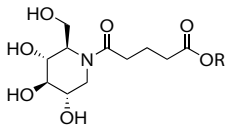
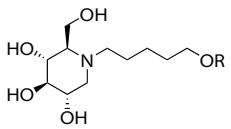










Compound		GCS	GBA1	GBA2	Lysosomal α-glucosidase
	**44**: R = Propyl	> 100[a]	332	0.120	9.2
	8: R = Butyl	50	400	0.230	0.1
	117: R = Pentyl	40[a]	8.5	0.038	3.7
	118: R = Heptyl	30[a]	13.5	0.028	1.3
	**119**: R = A	> 100[a]	NI	NI	NI
	120: R = B	> 100[a]	NI	NI	NI
	121: R = C	> 100[a]	0.44	39	NI
	122: R = D	> 100[a]	4.1	306	NI
	123: R = E	> 100[a]	3.2	461	NI
	**124**: R = A	7[a]	0.77	0.097	7.2
	12: R = E	0.2	0.2	0.001	0.4

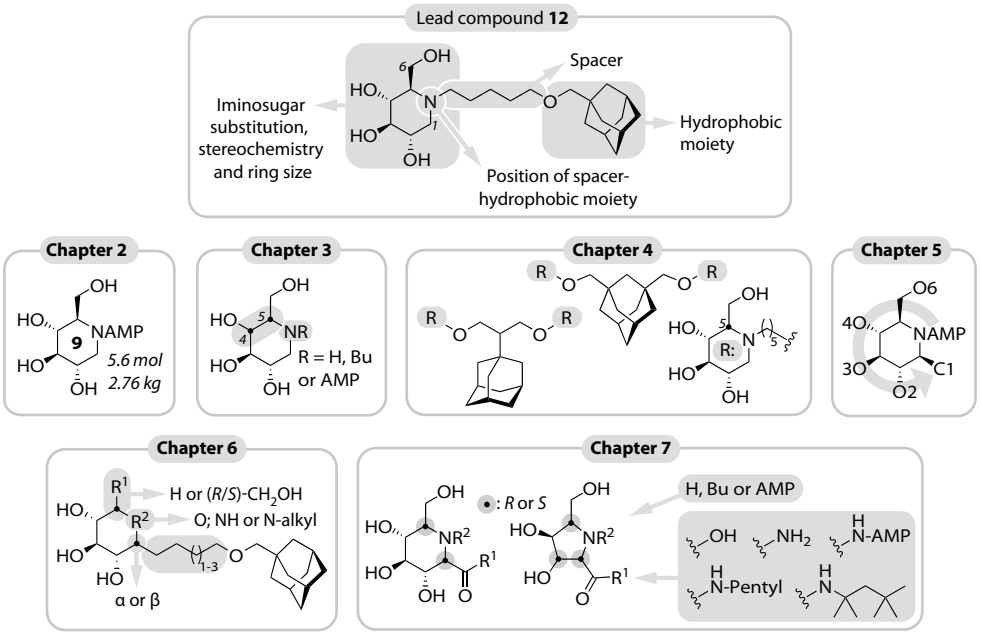
[a]unpublished data from Aerts *et al.;* NI = no inhibition at 100 μM .

Outline of Thesis

The library of lipophilic iminosugars published by Aerts and co-workers in 1999 initiated the research described in this thesis. Its most potent member, **12**, was a submicromolar inhibitor of GCS, GBA1 and GBA2. As can be judged from the inhibitory potencies as described in sections 1.4.3 to 1.4.5 many of the iminosugars, including **12**, currently in use or in development as therapeutics are not selective for their target enzyme. Being able to influence glucosylceramide biosynthesis and degradation in more selective fashion would facilitate the study of GSL functioning in (patho)physiological processes. More selective inhibitors would also help to elucidate their mode of action as therapeutics. Consequently, in the here presented study lipophilic iminosugar **12** was chosen as a lead compound in achieving this goal to develop selective inhibitors for GCS, GBA1 and GBA2.

Modifications of the structure of **12** can be achieved as follows (Figure 23): 1) variation of the length and nature of the spacer; 2) altering the hydrophobic adamantan-1-yl-methoxy group; 3) modification of the stereochemistry, substitution patterns and ring size of the iminosugar moiety and 4) alteration of the attachment site of the adamantan-1-yl-methoxy-spacer moiety on the iminosugar core.

Figure 23. Overview of potential modification sites in lead compound **12** and the chapters in this thesis.



For the study of the effects of inhibitor **12** in various biological applications a large supply of it was needed. Consequently, **Chapter 2** describes the development and implementation of a large scale synthetic route for **12** (Figure 23). The research described in **Chapter 3** investigates the mode of action by which **12** improves glycemic control in models of type 2 diabetes by varying the C-4/C-5 stereochemistry and *N*-alkylation of the iminosugar moiety. Dimeric iminosugar derivatives of **12** are develop and evaluated as potential bivalent inhibitors in **Chapter 4**. In **Chapter 5**, the synthesis and biological evaluation of derivatives of **12** is described in which AMP-moiety is moved to alternate positions on the 1-deoxynojirmycin ring. **Chapter 6** deals with the synthesis and evaluation of a small library of α/β-aza-*C*-glycoside derivatives based on **12**. **Chapter 7** presents the preparation of four diverse libraries of pyrrolidine and piperidine iminosugars in a combinatorial fashion via the tandem Staudinger/aza-Wittig/Ugi three-component reaction and their biological evaluation. **Chapter 8** provides a short summary of the research described in chapters 2 to 7 as well as an overview of results from work that is currently in progress for this study and some prospects for new research avenues.

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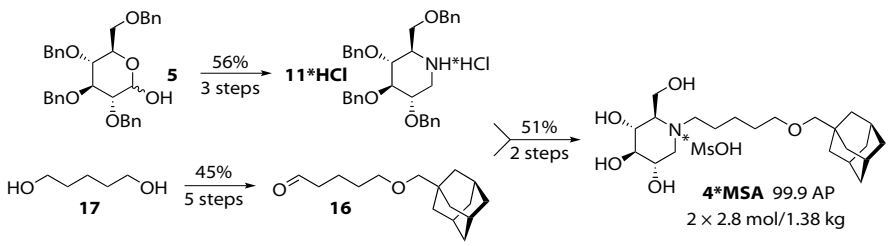
2 The Lead Lipophilic Iminosugar

Development and Optimization of its Large-scale Synthesis

Abstract

The lipophilic iminosugar **4** is the lead compound in the study of inhibitors of glucosylceramide metabolism and their potential applications. This chapter describes the development process of a synthetic route for the large-scale preparation of **4** from its initial version in an academic research laboratory at milligram-scale to the final optimized route at kilogram-scale. The definitive route starts with the separate synthesis of the building blocks **11** and **16** from commercially available **5** and **17**. Reductive amination of the two building blocks and subsequent hydrogenolysis of the penultimate gave **4**. Crystallization of **4** as its methanesulfonic acid salt produced multi-kilogram amounts of **4*MSA** in high purity (99.9%) under cGMP control.



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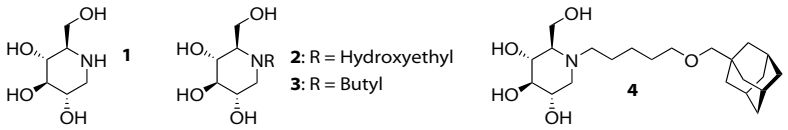
Introduction

Ever since the discovery of iminosugars during the sixties and the unearthing of their ability to inhibit glycosidases in the seventies, they have been subject of extensive studies in both organic chemistry and biochemistry.[1,2] Iminosugars (also known as azasugars) are polyhydroxylated alkaloids that can be regarded as monosaccharide analogues with nitrogen replacing the ring oxygen. From this extensive family of compounds, the best known member is 1-deoxynojirimycin (**1**) – a D-glucose configured iminosugar analogue (Figure 1). The first reports of its chemical synthesis were by Paulsen and co-workers in 1966, from 2,3-*O*-isopropylidene-α-L-sorbofuranose, and by Inouye in 1968, from 1,2-*O*-isopropylidene-α-D-glucofuranose (Figure 2).[3-5] In 1976 **1** was also discovered to occur in nature, when it was isolated from the leaves of mulberry trees[6] and certain species of bacteria.[7]

Figure 1. Structures of 1-deoxynojirimycin (**1**), Miglitol (**2**), Miglustat (**3**) and lead compound **4**.

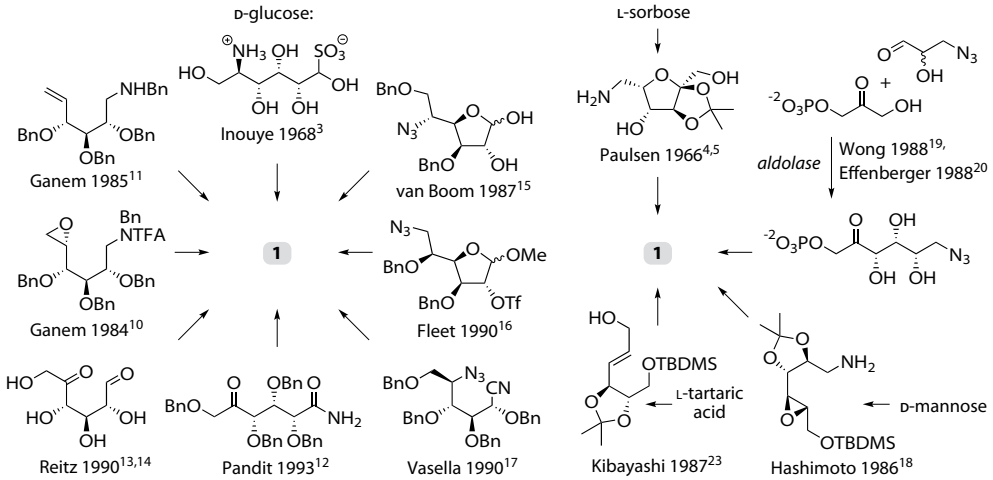


Since then numerous processes for the preparation of **1** have been reported.[8,9] Perhaps not surprisingly, most of these methods use D-glucose as a chiral starting material with an intramolecular cyclization as one of the last steps (Figure 2). Many methods first introduce a nitrogen containing function at C-1 and then create an electrophilic C-5 position for cyclization (L-*ido*-C-5/C-6 epoxide opening by Ganem[10]; aminomercuration of a C-5/C-6 alkene by Ganem[11]; reduction of a cyclic *N*-acyliminium ion from a C-5 keto-amide by Pandit[12]). Alternatively, Baxter and Reitz showed that C-1 nitrogen introduction and cyclization on C-5 can also be achieved in one step by double reductive amination of a hexosulose.[13,14] Alternatively, the nitrogen function can be introduced on C-5 (van Boom[15]) or C-6 (Fleet[16]). Vasella has synthesized **1** by a cycloaddition reaction of a D-glucose derived azido-nitrile.[17] D-Mannose has also been used as a starting material by Hasimoto.[18] Wong and Effenberger developed a chemoenzymatic syntheses for a C-5-keto-azide intermediate that could be cyclized to **1** under reductive conditions.[19-22] Finally, several syntheses starting from non-carbohydrate precursors have been reported, such as from L-tartaric acid by Kibayashi.[23] Many more syntheses of **1** have been published during recent years, but in most cases these are based on the above mentioned syntheses.

Further research into the biological activity of 1-deoxynojirimycin derivatives has already spawned two registered drugs. Miglitol (**2**)[24] is an oral drug for the treatment of type 2 diabetes and Miglustat (**3**)[25,26] is an oral drug for the treatment of Gaucher disease. In the latter case drug action takes place by inhibition of the enzyme glucosylceramide synthase (GCS). GCS is responsible for the biosynthesis of glucosylceramide, which is a member of the glycosphingolipid family and the crucial metabolic precursor in

the biosynthesis of almost all complex glycosphingolipids. Glycosphingolipids are components of the outer plasma membrane and as such are involved in many (patho) physiological processes.[27-30] Catabolism of glucosylceramide is effected by the glycosidase, glucocerebrosidase (GBA1). A second glycosidase – with unknown function – that is capable of cleaving the glycosidic bond of glucosylceramide has recently been identified independently by Aerts and Yildiz as β-glucosidase 2 (GBA2).[31,32]

Figure 2. Overview of synthetic strategies and intermediates in the synthesis of 1-deoxynojirimycin (**1**).



In the study of glucosylceramide metabolism and its inhibitors that is the subject of this thesis, the lipophilic iminosugar **4** was chosen as a lead compound for development of analogues and biological evaluation. Compound **4** inhibits all three enzymes involved in glucosylceramide metabolism and is a hundredfold more potent than Miglustat (**3**) in inhibiting GCS.[33] Besides a potential application of **4** in the treatment of Gaucher disease and related sphingolipidoses,[25,34] the role of glycosphingolipids in many other (patho)physiological processes points towards a wider range of applications. Recently, it became apparent that inhibition of GCS through oral dosage of compound **4** to *ob/ob* mice, which is a type 2 diabetes model, downregulates glycosphingolipid biosynthesis and restores insulin receptor sensitivity (see Chapter 3 for more details).[33] It has also been reported that administration of **4** to mice with chemically induced ulcerative colitis (inflammatory bowel disease) resulted in beneficial anti-inflammatory responses.[35] The crucial role of GCS at the root of glycosphingolipid biosynthesis and its role in these pathological processes makes it an interesting drug target and thereby GCS inhibitor **4** a promising therapeutic lead.

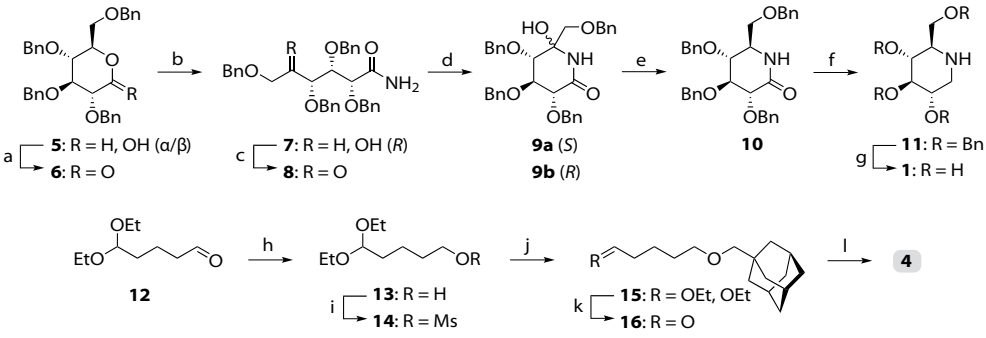
For potential clinical development of compound **4** access to a large supply was needed. Consequently, a study was started to develop an efficient chemical synthesis of **4**, suitable for preparation of kilogram amounts in a miniplant. This chapter describes the development and optimization of the synthetic route for compound **4** from its initial

synthesis in an academic research laboratory to the successfully implemented final synthetic route in a cGMP miniplant.

Results and Discussion

The first synthesis of compound **4** was reported by Pandit and Aerts in 1998, where it was part of a library of lipophilic iminosugars generated to produce a specific inhibitor for GBA2.[36,37] The strategy for its synthesis then was to first prepare two building blocks, 1-deoxynojirimycin (**1**) and 5-(adamantan-1-yl-methoxy)-pentanal (**16**) and condense these via a reductive amination to provide **4**. In this synthesis, **1** was derived from commercially available 2,3,4,5-tetra-*O*-benzyl-D-glucopyranose (**5**) by transformation of its lactone **6** to lactam intermediate **10**, which could be further reduced and deprotected to provide **1** in 29% yield over seven steps (Scheme 1).[12,36-38] Aldehyde **16** was obtained from commercially available glutaric dialdehyde[39] in five steps and 2% overall yield. Finally, reductive amination of **1** and **16** provided 60 mg of **4** in 50% yield. Although this route successfully produced **4**, it was unsuitable for larger scale synthesis of **4**. The main objections to this route were the low overall yield in the synthesis of **4** and the need for several column chromatography purifications. The larger quantities (~100 g) of **4** that were needed at that time for initial investigations into its biological applications,[31,33,35,40] required a search for alternate procedures for the production of **4**.

Scheme 1. First reported synthesis of lead compound **4**.

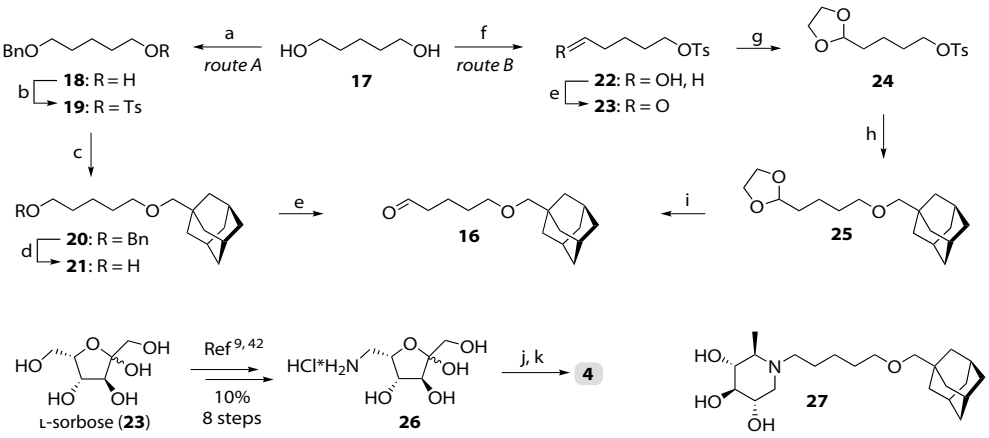


Reagents and conditions: [**a**] DMSO, Ac_2O, 12h, used crude. [**b**] NH_3 in MeOH, 1.5h, 86% 2 steps. [**c**] DMSO, Ac_2O, 12h, used crude. [**d**] NH_3 in MeOH, 1.5h, **9a**:**9b**; 1.8:1 92% 2 steps. [**e**] $NaBH_3CN$, $HCOOH/CH_3CN$, reflux, 2h, 79%. [**f**] $LiAlH_4$, THF, 70 °C, 3h, 63%. [**g**] $Pd(OH)_2/C$, 5 bar H_2, MeOH/EtOH, HCl, 48h, 74%. [**h**] $NaBH_4$, EtOH, 3h, 41%. [**i**] MsCl, Et_3N, DCM, 1h, used crude. [**j**] i: adamantanemethanol, NaH, DMF, 1h; ii: addition **14**, 70 °C, 4h, 34%. [**k**] 5% aq HCl, acetone, 1h, quantitative.

Development of an alternative route for **4** commenced with changing the starting material for the preparation of **16** to 1,5-pentanediol (**17**) and evaluation of two new synthetic routes for **16**. The first route (*A*; Scheme 2) started with the successive monobenzylation (**18**) and tosylation of **17**. Substitution of the tosylate (**19**) with adamantanemethanol proved more productive than that of mesylate **14** and provided **20** in 92% yield.

Hydrogenolysis of the benzyl ether and Swern oxidation of the resulting alcohol (**21**) provided **16** in 70% yield over 5 steps. The second route (*B*; Scheme 2) started according to a literature procedure[41] with successive monotosylation (**22**), Swern oxidation and protection of the resulting aldehyde (**23**) as the 1,3-dioxolane acetal to produce **24** in 61% yield over the three steps. Substitution of the tosylate (**24**) with adamantanemethanol yielded **25** in 71% yield after purification by distillation. Subsequent acidic hydrolysis of the acetal in **25** provided building block **16** in a yield of 43% over five steps. Despite the lower overall yield, route *B* was chosen for large scale process development, because crude **16** – contrary to **16** from route *A* – did not require column purification after the final step and was obtained more reproducible at a larger scale.

Scheme 2. First optimizations of synthesis 1-deoxynojirmycin (**1**), aldehyde **16** and lead compound **4**.



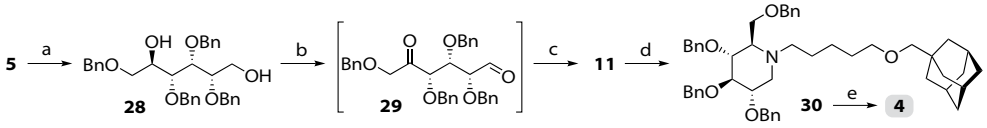
Reagents and conditions: [**a**] NaH (0.25 eq), BnBr (0.25 eq), THF, 80 °C, 20h, 94%. [**b**] TsCl, Et_3N, DMAP (cat), DCM, 0 °C » rt, 20h, 92%. [**c**] i: adamantanemethanol, NaH, DMF, 90 min; ii: 1 eq of **19**, 75 °C, 1h, 92%. [**d**] Pd/C, 5 bar H_2, EtOH, 20h, 97%. [**e**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: addition **21** or **22**, 1.5h; iii: Et_3N, –75 °C » rt, 2h, **16**: 92%; **23**: 91%. [**f**] TsCl, DMAP, Et_3N, DCM, 16h, 70%. [**g**] Ethylene glycol, *p*-TsOH, benzene, reflux, 95%. [**h**] 1: adamantanemethanol, NaH, DMF, 1h; 2: addition **21**, 70 °C, 4h, 71%. [**i**] 6M aq HCl, acetone, 74 °C, 15 min, quantitative. [**j**] PtO_2, 5 bar H_2, 16h, 70%. [**k**] **1*HCl**, **16**, Pd/C, 5 bar H_2, NaOAc, AcOH, EtOH, 65%.

Initially, for larger scale synthesis of the second building block (**1**) a route reported by Behlings and co-workers[42] and also found in patent literature[43] was selected. The route uses L-sorbose (**23**) as an economic starting material and is claimed to be suitable for kg-scale preparation of **1**. However, during process development this route proved low yielding at a large scale and several column purifications were unavoidable. Over eight steps this route yielded 10% of labile penultimate **26** (Scheme 2).[44] The final cyclization into **1** by reductive amination was carried out on 20 g batches of **26** via a platinum-catalyzed hydrogenolysis at 5 bar to produce the HCl salt of **1** in an average yield of 70%. The next stage was the optimization of the reductive amination between building blocks **1** and **16**. Initially, the best reproducible conditions were the use of sodium triacetoxyborohydride and sodium acetate in ethanol that provided **4** on a 1 g scale in an

unimproved yield of 50%. Alternatively, it was found that Pd/C catalyzed hydrogenolysis at 5 bar of **1** and **16** was more efficient and produced 17 g of **4** in a reproducible yield of ~65%. However, column purification of **4** proved necessary to remove an unexpected side product – 6-deoxy derivative **27** (its inhibitory profile is provided in Chapter 8). This side product originated from 1,6-dideoxynojirimcyin that was formed during the platinum-catalyzed hydrogenolysis of **26**. Overall, this route produced 64 g of **4** in 5% yield over ten steps.

The route for building block **16** was now set for translation to kg-scale synthesis (*B*; Scheme 2). On the other hand, the route explored for the second building block, 1-deoxynojirimycin (**1**) was unsuitable for this next stage, mainly because of the low overall yield and the requirement for column chromatography purification of several intermediates and lead compound **4**. In search of a shorter and more efficient route for the large scale synthesis of **1**, a procedure reported by Lopes *et al.* that transforms **5** into **1** in four steps was evaluated.[45] The key reaction in this synthesis is the cyclization of hexosulose **29** via a double reductive amination with ammonium formate to produce **11** (Scheme 3).

Scheme 3. Further optimization of synthesis lead compound **4**.



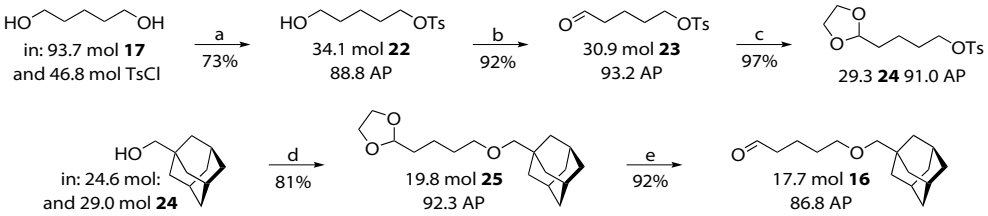
Reagents and conditions: [**a**] $LiAlH_4$, THF, 20h, used crude. [**b**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: addition **28**, 1.5h; iii: Et_3N, –75 °C » rt, 2h, **29** used crude. [**c**] $NaBH_3CN$, excess $HCOONH_4$, 3Å mol. sieves, MeOH, 0 °C to rt, 20h, 65% 3 steps. [**d**] 1.1 eq of **16**, Pd/C, 5 bar H_2, AcOH, EtOH, 20h, **30** used crude. [**e**] Pd/C, 1 bar H_2, HCl, EtOH, 20h, 89% 2 steps.

However, upon application of the original protocol, which uses a Pfitzner-Moffat oxidation and a double reductive amination at room temperature to produce **11**, irreproducible and low yields were obtained. After varying several parameters in the original protocol it was found that the procedure could be optimized by using a Swern oxidation to give **29** and most importantly to execute the double reductive amination of **29** at 0 °C in the presence of a larger excess of ammonium salt. First, **5** was reduced to glucitol **28** with $LiAlH_4$ in THF (Scheme 3). Crude **28** was subjected to a Swern oxidation, which after completion was concentrated under reduced pressure with moderate heating to minimize degradation of the unstable hexosulose intermediate (**29**). The reductive amination was carried out on crude **29** with an excess of ammonium formate in methanol at 0 °C under the agency of $NaBH_3CN$ and in the presence of 3Å molecular sieves. These conditions could reproducibly generate multi-gram amounts of **11** in yields of 60–65% over the three steps. The next reaction would be deprotection of **11** to **1**, but because of the persistent moderate yields obtained in the previous large scale reactions of **1** with aldehyde **16**, it was first investigated whether the reductive amination of **11** with **16** could improve

upon this. When **11** and **16** were exposed to Pd/C catalyzed hydrogenolysis at 5 bar in an ethanol/acetic acid mixture the sole product was **30**. After filtration and concentration, a second hydrogenolysis of crude **30**, now in the presence of hydrochloric acid, produced 2.8 g of target compound **4** in 89% over the two steps.

With this tandem reductive amination/deprotection method and the optimized synthesis of building blocks **11** and **16** in hand, the stage was set for translating the improved synthesis of **4** to a kg-scale miniplant process. Process development of the route for building block **16** focused on optimizing the purity of all intermediates and **16** itself without using column purification. This was quite a challenge as all intermediates are oily liquids and only **25** is stable enough for distillation. Suitable in-process control by HPLC (up to **24**) and GC (**25** and **16**) was developed, which enabled the reactions to be monitored and controlled in an efficient way to ensure complete conversions and effective work-up procedures. The synthesis of **16** started with monotosylation of **17** (Scheme 4). The formation of ditosylate could be minimized to <5% by using 0.5 equivalents of tosylchloride to produce **22**.

Scheme 4. cGMP miniplant synthesis of **4** with GC/HPLC purities of intermediates and **4** in area percent (AP).



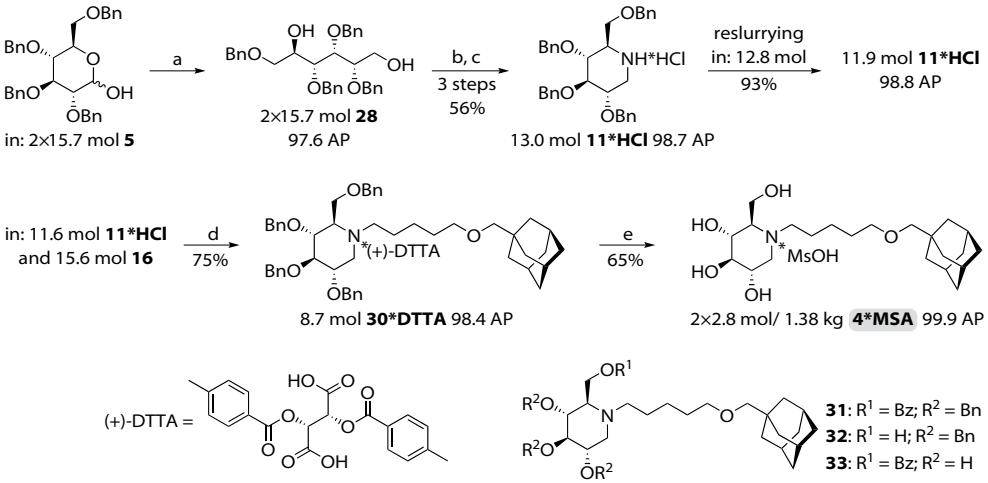
Reagents and conditions: [**a**] in: 93.7 mol **17**, 46.8 mol TsCl (0.5 eq), DMAP, Et_3N, DCM, 20h; Extractive purification. [**b**] in: 33.8 mol **22**, NaOCl, cat. TEMPO, cat. KBr, DCM, 3h; Extractive purification. [**c**] in: 30.4 mol **23**, ethyleneglycol, *p*-TsOH, MTBE, reflux, 3h; Extractive purification. [**d**] i: 24.6 mol adamantanemethanol (0.85 eq), NaH, DMF, 40 °C, 1.5h; ii: Addition 29.0 mol **24**, 40 °C, 3h; Extractive purification and short path distillation. [**e**] in: 19.3 mol **25**; 6M aq HCl, acetone, 40 °C, 1h; Extractive purification.

Swern oxidation of **22** was replaced by a TEMPO/bleach oxidation in order to prevent formation of dimethylsulfide and the difficult handling of all reaction phases thereof. Protection of aldehyde **23** resulted in the 1,3-dioxolane acetal **24** in 96 % yield. Instead of benzene, MTBE was used as reaction solvent because the lower reflux temperature prevented the onset of decomposition of both the starting material (**23**) and product (**24**). As fractional distillation is not feasible on kg-scale, 0.85 equivalent of adamantanemethanol was used in the S_N2 substitution of **24** to minimize the amount of unreacted adamantanemethanol. Remaining traces of adamantanemethanol could be removed with an extractive purification in which a **25** containing heptane phase was washed repeatedly with a methanol/water mixture. Finally, short path distillation provided **25** as a colorless oil in 92% yield related to adamantanemethanol or 68% related to **24**. During process development for the acidic hydrolysis of **25** it was observed that an equilibrium is reached at 8% remaining starting material and that prolonged reaction

times only lead to degradation of product **16**. A solution for this problem was found in performing the reaction two consecutive times with extractive workup in between. This diminished the remaining starting material to < 2% and yielded 5.1 kg of crude **16** in 45% yield over the five steps. The obtained purity of **16** allowed implementing the crude product in the subsequent reductive amination of **16** with **11**.

Process development of the route for the second building block **11** concentrated on adapting the challenging tandem oxidation/double reductive amination sequence to the miniplant and finding a suitable purification procedure for **11**. When the scale of this two-step sequence was increased the Swern reaction mixture took an increasing amount of time to concentrate. This extended exposure to heat resulted in marked degradation of intermediate **29** and as a result significantly lower yields of **11** (~20%). Omitting the concentration step and adding the crude Swern reaction mixture remedied this problem and test reactions now provided **11** in ~70% yield over the three steps.

Scheme 5. cGMP miniplant synthesis of **4** with GC/HPLC purities of intermediates and **4** in area percent (AP).



Reagents and conditions: [**a**] in: 2×15.7 mol **5**, $NaBH_4$, DCM/MeOH, 40 °C, 6h; Extractive purification. [**b**] i: $COCl_2$, DMSO, DCM, –75 °C, 0.5h; ii: Addition 23.0 mol **28**, –75 °C, 2h; iii: Addition Et_3N, –75 °C, 4h, No intermediate purification. [**c**] i: NH_4Ac, $NaCNBH_3$, Na_2SO_4, MeOH, 0 °C; ii: Addition neat Swern reaction mixture (**29**); iii: –5 °C » ambient, 16h; Precipitation as HCl salt. [**d**] i: in: 11.6 mol **11**; generation free base of **11**; ii: Addition 15.6 mol **16**; iii: 10 wt% Pd/C, atm H_2, AcOH/ EtOH (1/21, v/v), 20h; Crystallization as (+)-DTTA salt. [**e**] i: in: 2×4.3 mol **30**; generation freebase **30**; ii: aq NaOH saponification of **31** to **32**; iii: NaOH quench with HCl; iv: 10 wt% Pd/C, atm H_2, HCl/ EtOH, 20h; v: Precipitation as MsOH salt.

In the final production run two 8.5 kg batches of **5** were reduced quantitatively with $NaBH_4$ in refluxing DCM/methanol (Scheme 5). After extractive workup, a 12.5 kg portion of crude **28** was oxidized to hexosulose **29** and the reaction mixture resulting from the Swern oxidation was kept below –60°C and directly transferred (telescoped) to a 0 °C suspension of $NaBH_3CN$, NH_4OAc and Na_2SO_4 in methanol. Lab development had shown that the order of addition, the ammonium source, the temperature and the

methanol dilution (> 0.1M) are critical for this process. Molecular sieves could be replaced by Na_2SO_4 and instead of 20 eq. NH_4HCO_2 10 eq. NH_4OAc were used. The resulting reaction mixture, containing **11**, is contaminated with dimethylsulfide, which has to be completely removed to prevent poisoning of the palladium catalyst used in the final two steps. Treatment of crude **11** with an aq solution of sodium hypochlorite during workup accomplished this. During process development it was observed that **11** is an oil upon isolation, which in purified form only slowly solidifies over time. In order to facilitate purification and isolation, the hydrochloric acid salt of **11** was generated that could be precipitated from acetone at 0 °C and isolated via centrifugation to provide **11*HCl** as an off-white solid in 56% yield over the three reactions. Minor coloured impurities were removed by means of an additional reslurrying step in acetone that produced **11*HCl** with 93% recovery.

The synthesis of **30** was accomplished in the miniplant via the earlier described selective Pd/C catalyzed hydrogenation of the intermediate imine of **11** and **16** in the presence of acetic acid (Scheme 4). Aldehyde **16** was now applied in a larger excess (1.5 eq.) to ensure complete consumption of **11**. Excess **16** and its reduced form (**21**) were removed afterwards by formation of the HCl salt of **30** in methanol/water and washing repeatedly with heptane. As a minor side reaction partial de-benzylation was detected (ca. 10%), but this did not effect further processing to **4**. Penultimate **30** was chosen to be the cGMP starting material and was therefore required to be of defined composition and high in purity, but **30*HCl** is a difficult to handle non-crystalline hygroscopic solid Precipitation of **30** as the (+)-di-*p*-toluoyl-L-tartaric acid ((+)DTTA) salt provided 10.0 kg **30*(+)DTTA** as a stable crystalline solid (98.4 area% by HPLC incl. the de-benzylated side products).

The miniplant procedure for debenzylation of the penultimate **30*(+)DTTA** was identical to the earlier described catalytic hydrogenation in the presence of hydrochloric acid. However, HPLC analysis of a small test-batch of **4** indicated the presence of previously undetected 6-*O*-benzoylated **33** as a minor side product (~1%). Byproduct **33** probably originated from oxidation of the 6-*O*-benzyl ether in a minor amount of **11** during workup of the double reductive amination reaction mixture with sodium hypochlorite. The presence of side product **33** in end product **4** could be prevented by prior saponification of the benzoyl ester before starting the deprotection procedure during miniplant production. The free base of **30** was generated in MTBE, after which the solvent was exchanged from MTBE to ethanol and 6M sodium hydroxide was added. When HPLC analysis indicated complete saponification of **31** to **32**, the reaction mixture was acidified with hydrochloric acid and subjected to Pd/C hydrogenolysis at atmospheric hydrogen pressure. After removal of the catalyst by filtration, residual Pd was reduced to a level of < 20 ppm by a treatment with Ecosorb C-941. Inorganic salts were removed from the reaction mixture by treating crude **4*HCl** with ammonia in methanol and subsequently exchanging the solvent for dichloromethane from which all inorganic salts precipitated and in which **4** remained dissolved.

Previous biological studies were performed with **4*HCl** but it was evident that an alternative for this highly hygroscopic and non crystalline HCl salt had to be found. Free amine **4** also showed the same hygroscopic property and also proved to be unstable after prolonged storage at room temperature. A salt screening showed that the sulfonic acid salts of methansulfonic acid (MSA), ethanesulfonic acid and *p*-toluenesulfonic acid all provided stable, crystalline and non-hygroscopic salts. A brief toxicological study showed identical results for the **4*MSA** salt when compared to the previously evaluated **4*HCl** salt. Deprotection of two separate batches of **30*(+)DTTA** and crystallization of **4** with methanosulfonic acid in isopropanol provided two 1.38 kg batches of **4*MSA** in 65 % yield with a purity of 99.9 area% as judged by HPLC.

Conclusion

This chapter describes the development and implementation of a synthetic route for the reproducible preparation in a cGMP miniplant of kilogram amounts of GCS inhibitor **4*MSA** in high purity and with defined composition. This large scale synthetic preparation of **4** complements the large-scale chemoenzymatic synthesis of the related Miglustat (**3**) reported in 2002 by Landis and co-workers.[46] In this method − based on the work of Kinast and Schedel[47] − the key step is a regioselective oxidation of the C-5 hydroxyl function in *N*-butylglucamine by *Gluconobacter oxydans*.

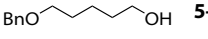
Experimental section

For research laboratory preparations: solvents and reagents were obtained commercially and used as received unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere. Residual water was removed from starting compounds by repeated coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. Reaction grade dimethylsulfoxide and methanol were stored on 3Å molecular sieves. Other reaction grade solvents were stored on 4Å molecular sieves. THF was distilled prior to use from $LiAlH_4$. Ethanol was purged of acetaldehyde contamination by distillation from zinc/KOH. DCM was distilled prior to use from P_2O_5. R_F values were determined from TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by spraying with a solution of $(NH_4)_6Mo_7O_{24}\times 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times 2H_2O$ (10 g/L) in 10% sulfuric acid or a solution of phosphomolybdic acid hydrate (7.5 wt% in ethanol) followed by charring at ~150 °C. Visualization of all deprotected iminosugar compounds during TLC analysis was accomplished by exposure to iodine vapour. Column chromatography was performed on silica gel (40–63 µm).

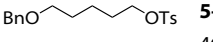
For cGMP glass plant preparations: all solvents and reagents were obtained commercially and used as received unless stated otherwise. Adamantanemethanol was obtained from Inter-Chemical Ltd. (Shenzhen, China) and 2,3,4,6-tetra-*O*-benzyl-D-glucose from Farmak (Olomouc, Czech Republic). Reactions were executed at ambient temperatures and under inert atmosphere unless stated otherwise. Reaction progress was monitored by HPLC and GC analysis. *HPLC in-process control*: Column: Waters Atlantis C_{18}; D: 4.6 mm × L: 150 mm; d_P: 3 µm; Eluent A: H_2O:MeOH = 80:20 + 0,05% TFA; Eluent B: MeOH:CH_3CN = 20:80 + 0.05%TFA; *Method A*: Gradient (t in min; A/B (v/v); flow in mL/ min): 0; 100/0; 0.8 » 1; 100/0;0.8 » 16; 17/83; 0.8 » 17; 100/0; 0.8. Injection volume: 10 µL; Temperature: 25 °C; Detection: λ = 225 nm; Runtime: 22 min; *Method B*: Gradient (t in min; A/B (v/v); flow in mL/ min): 0; 100/0; 0.80 » 1; 100/0; 0.80 » 16; 0/100; 0.80 » 18; 0/100; 0.80 » 19; 100/0; 0.80. Injection volume:

10 µL; Temperature: 25 °C; Detection: λ = 215 nm; Runtime: 24 min. *GC in-process control*: Column: HP1; L: 25 m × D: 320 µm, d_f: 1.05 µm; Flow: 2 mL/min; Oven temperature: 150 °C; 15 °C/min » 300 °C; 300 °C for 5 min; Split: 50; Injection / Detection temperature: 250 °C / 280 °C; Split/Flow: 100; Injection volume: 2 µL; Detection: FID; Runtime: 16 min. DSC measurements were conducted on a Mettler Toledo DSC822e (temperature program 50 °C to 300 °C at 10 °C/min). HPLC and GC in-process control chromatograms and DSC curves for miniplant preparations can be found in reference [44].

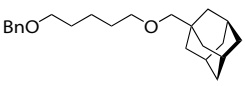
The ^{1}H- and ^{13}C-NMR, ^{1}H–^{1}H COSY and ^{1}H–^{13}C HSQC experiments were recorded on a 200/50 MHz, 300/75 MHz, 400/100 MHz, 500/125 MHz or 600/150 MHz spectrometer. Chemical shifts are given in ppm (δ) relative to the signal of the internal standard tetramethylsilane for $CDCl_3$ or the deuterated solvent signal for CD_3OD and *d6*-DMSO. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. High resolution mass spectra were recorded by direct injection (2 µL of a 2 µM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150–2000) and dioctylpthalate (m/z = 391.28428) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Optical rotations were measured on an automatic Propol polarimeter (Sodium D-line, λ = 589 nm). ATR-IR spectra were recorded on a Shimadzu FTIR-8300 fitted with a single bounce Durasample IR diamond crystal ATR-element and are reported in cm^{-1}.



5-Benzyloxypentan-1-ol (18). Sodium hydride (60% in mineral oil, 1.75 g, 43.7 mmol) was added in portions to a dry and cooled (0 °C) solution of 1,5-pentanediol (**17**, 18.25 g, 175 mmol) in THF (350 mL). The mixture was stirred for 10 min at rt and a sticky solid was formed. NaH (12.0 g, 43.8 mmol) was added in portions. Benzyl bromide (4.2 mL, 35 mmol) was added dropwise over a 2 min period and the resulting reaction mixture was refluxed at 80 °C for 20 h. The reaction mixture was cooled to rt and quenched by addition of little water. The mixture was poured into sat aq NaCl (400 mL) and extracted with Et_2O (2×300 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 50% EtOAc in PE) to provide **18** (6.36 g, 32.8 mmol) in 94% yield as a colorless oil. R_F = 0.60 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 6H, H_{Ar} Bn, 2×H_{Ar} Ts), 4.49 (s, 2H, CH_2 Bn), 3.63 (t, *J* = 6.0, 2H, CH_2-1 pentyl), 3.47 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 1.70 – 1.61 (m, 2H, CH_2 pentyl), 1.62 – 1.53 (m, 2H, CH_2 pentyl), 1.47 – 1.37 (m, 2H, CH_2 pentyl). MS (ESI): *m/z* 195.2 $[M+H]^+$.

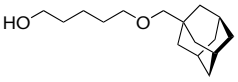


5-Benzyloxy-1-toluene-4′-sulfonyl-pentan (19). *Para*-toluenesulfonic chloride (8.86 g, 46.5 mmol) was added to a dry and cooled (0 °C) solution of **18** (6.02 g, 31.0 mmol), Et_3N (6.45 mL, 46.5 mmol) and DMAP (189 mg, 1.6 mmol) in DCM (93 mL). The reaction mixture was stirred for 20 h, warming to rt. The mixture was washed successively with 1M aq HCl (100 mL), sat aq $NaHCO_3$ (100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 25% EtOAc in PE) to furnish **19** (9.98 g, 28.6 mmol) in 92% yield as a colorless oil. R_F = 0.70 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3, 2H, 2×H_{Ar} Ts), 7.36 – 7.23 (m, 6H, H_{Ar} Bn, 2×H_{Ar} Ts), 4.46 (s, 2H, CH_2 Bn), 4.01 (t, *J* = 6.5, 2H, CH_2-1 pentyl), 3.41 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 2.42 (s, 3H, CH_3 Ts), 1.70 – 1.60 (m, 2H, CH_2 pentyl), 1.60 – 1.50 (m, 2H, CH_2 pentyl), 1.44 – 1.35 (m, 2H, CH_2 pentyl). MS (ESI): *m/z* 349.3 $[M+H]^+$.

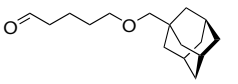


5-(Adamantan-1-yl-methoxy)-1-benzyloxy-pentane (20). A dry solution of adamantanemethanol (5.13 g, 30.9 mmol) in DMF (80 mL) was charged with NaH (1.895 g, 60% wt in mineral oil, 47.40 mmol) and subsequently stirred for 90 min. Next, a dry solution of **19** (9.77 g, 28.1 mmol) in DMF (5 mL) was added to the reaction and the mixture was

heated to 75 °C for 1 h, after which TLC analysis indicated complete consumption of **19** and the reaction mixture was allowed to cool to rt. The reaction was quenched (water, 5 mL) and concentrated. The residue was divided between Et_2O/sat aq $NaHCO_3$ (300 mL; 1/1) and extracted with Et_2O (3×150 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the resulting residue was purified by silica gel column chromatography (0% » 10% EtOAc in PE) to furnish **20** (8.82 g, 25.8 mmol) in 92% yield as a colorless oil. R_F = 0.81 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.32 (m, 4H, 4×H_{Ar} Bn), 7.26 (m, 1H, H_{Ar} Bn), 4.49 (s, 2H, CH_2 Bn), 3.47 (t, *J* = 5.8 Hz, 2H, CH_2-1), 3.37 (t, *J* = 6.6 Hz, 2H, CH_2-5), 2.94 (s, 2H, OCH_2-Ada), 1.95 (br s, 3H, 3×CH Ada), 1.72 – 1.62 (m, 8H, 3×CH_2 Ada, CH_2-2/4), 1.60-1.55 (m, 2H, CH_2-2/4), 1.52 (br d, *J* = 2.4 Hz, 6H, 3×CH_2 Ada), 1.43 (m, 2H, CH_2-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.6 (C_q Bn), 128.1 (2×CH_{Ar} Bn), 127.3 (2×CH_{Ar} Bn), 127.2 (CH_{Ar} Bn), 81.7 (OCH_2-Ada), 71.3 (CH_2-5), 70.2 (CH_2-1), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 29.5, 29.3 (CH_2-2, CH_2-4), 28.2 (3×CH Ada), 22.7 (CH_2-3). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1450, 1358, 1103, 1026, 910, 733, 694. MS (ESI): *m/z* 343.2 $[M+H]^+$.



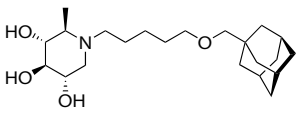
5-(Adamantan-1-yl-methoxy)-1-pentanol (21). Argon was passed through a solution of product **20** (8.82 g, 25.8 mmol) in EtOH (125 mL) for 30 min, after which a catalytic amount of Pd/C (300 mg, 10 wt % on act. carbon) was added. The reaction was shaken in a Parr-apparatus for 20 h under 5 bar of hydrogen pressure. Pd/C was removed by filtration over a glass microfiber filter and the filtrate was concentrated. The residue was purified by silica gel column chromatography (10% » 25% EtOAc in PE) to give **21** (6.24 g, 24.9 mmol) as a colorless oil in 97% yield. R_F = 0.31 (1:3; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.65 (t, *J* = 5.8 Hz, 2H, CH_2-1), 3.39 (t, *J* = 6.6 Hz, 2H, CH_2-5), 2.96 (s, 2H, OCH_2-Ada), 1.95 (br s, 3H, 3×CH Ada), 1.70-1.41 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 81.8 (OCH_2-Ada), 71.4 (CH_2-5), 62.3 (CH_2-1), 39.5 (3×CH_2 Ada), 37.0 (3×CH_2 Ada), 33.9 (C_q Ada), 32.2, 29.1 (CH_2-2, CH_2-4), 28.0 (3×CH Ada), 22.2 (CH_2-3). IR ν_{max}(thin film)/ cm^{-1}: 3333, 2901, 2847, 1728, 1450, 1366, 1258, 1103, 903, 733, 694. MS (ESI): *m/z* 253.2 $[M+H]^+$.



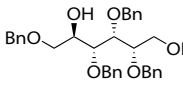
5-(Adamantan-1-yl-methoxy)-1-pentanal (16). A solution of oxalylchloride (789 µL, 9.0 mmol) in DCM (25 mL) was cooled to –78 °C. After dropwise addition of a solution of DMSO (1.28 mL, 18.0 mmol) in DCM (8.2 mL), the reaction mixture was stirred for 30 min while being kept below –70 °C. A dry solution of **21** (2.07 g, 8.2 mmol) in DCM (8.2 mL) was added dropwise to the reaction mixture at –78 °C. After stirring the reaction mixture for 2 h, while being kept below –65 °C, Et_3N (5.7 mL, 41 mmol) was added dropwise. The reaction mixture was allowed to warm to rt over 2 h. The reaction mixture was successively washed with 0.5M aq citric acid (2×30 mL) and water (2×30 mL). The organic phase was dried (Na_2SO_4), concentrated and the resulting residue was purified by flash silica gel column chromatography (5% » 15% EtOAc in PE) to give product **16** (8.82 g, 25.8 mmol) in 92% yield as a pale yellow oil.

Miniplant preparation procedure: At 30 °C and under rapid stirring 6M aq HCl (113.6 L) was added to a solution of **25** (5.68 kg, 19.29 mol) in acetone (56.9 L). The turbid reaction mixture was heated to 40 °C and stirred for 30 minutes. Stirring was stopped and the organic layer was analyzed with GC. After stirring for an additional 30 minutes at 40 °C, the reaction mixture was quenched by transfer to a 0 °C mixture of 3M aq NaOH (227.2 L) and MTBE (113.6 L) with the temperature being kept below 25 °C (additional 3M NaOH was added if pH was not >7). The layers were separated and the aq layer was extracted with MTBE (56.8 L). The combined organic layers were isolated, washed with water (56.8 L) and concentrated at 40 °C to a volume of ~5 L. The light yellow residue was dissolved in acetone (56.8 L) and under rapid stirring 6M aq HCl (56.8 L) was added with the temperature being kept below 40 °C. The reaction mixture was stirred for 1 hour to 40 °C with midway analysis by GC. The reaction mixture was quenched by rapid transfer to a 0 °C mixture of 3M aq NaOH (113.6 L) and MTBE (56.8 L)

with the temperature being kept below 25 °C (additional 3M NaOH was added if pH was not >7). The layers were separated and the aq layer was extracted with MTBE (28.4 L). The combined organic layers were successively washed with water (28.4 L) and saturated aq NaCl (28.4 L). The organic layer was isolated, concentrated at 40 °C (**16** slowly decomposes when heated above 40 °C for prolonged time) and degassed at 30 °C under full vacuum for 2 hours to afford **16** (5.10 kg, ~17.7 mol, 86.8 % area by GC) as a light yellow oil in ~92% yield, which still contained residual MTBE and was stable when stored under inert atmosphere, at -20 °C in the dark. GC in-process control: Method: see general methods; Sample preparation: 1 mL reaction mixture is extracted with 2 mL aq 3M NaOH and 1.5 mL MTBE. From the organic layer 1 mL is isolated as GC sample; t_R: **16** = 8.4 min; **25** = 10.2 min. R_F = 0.70 (1:3; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.78 (s, 1H, C(O)H-1), 3.39 (t, *J* = 5.9 Hz, 2H, CH_2-5), 2.95 (s, 2H, OCH_2-Ada), 2.47 (dt, *J* = 1.4 Hz, *J* = 7.3 Hz, 2H, CH_2-2), 1.95 (br s, 3H, 3×CH Ada), 1.76 – 1.52 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.4 (C(O)H-1), 81.8 (OCH_2-Ada), 70.8 (CH_2-5), 43.5 (CH_2-2), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 28.8 (CH_2-4), 28.1 (3×CH Ada), 18.8 (CH_2-3). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 2716, 1728, 1450, 1404, 1358, 1258, 1227, 1157, 1103, 1057, 1011, 941, 887, 810, 656. MS (ESI): *m/z* 251.3 $[M+H]^+$.



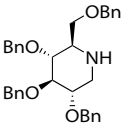
***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1,6-dideoxynojirimycin (27).** R_F = 0.44 (1:3; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$/ MeOD, 1/ 1) δ 3.69 – 3.62 (m, 1H, H-2), 3.38 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.25 (dd, *J* = 8.8, 1H, H-3), 3.19 – 3.11 (m, 2H, H-1a, H-4), 2.95 (s, 2H, OCH_2-Ada), 2.94 – 2.84 (m, 1H, C*H*H-1 pentyl), 2.80 – 2.67 (m, 1H, CH*H*-1 pentyl), 2.55 – 2.47 (m, 1H, H-5), 2.44 (dd, *J* = 11.2, 1H, H-1b), 1.93 (s, 3H, 3×CH Ada), 1.75 – 1.54 (m, 10H, 3×CH_2 Ada, CH_2-2, CH_2-4 pentyl), 1.52 (d, *J* = 2.2, 6H, 3×CH_2 Ada), 1.42 – 1.33 (m, 2H, CH_2-3 pentyl), 1.30 (d, *J* = 6.2, 3H, CH_3-6). ^{13}C NMR (100 MHz, $CDCl_3$/ MeOD, 1/ 1) δ 81.5 (OCH_2-Ada), 77.5, 73.8, 67.9 (C-2, C-3, C-4), 70.8 (CH_2-5 pentyl), 60.3 (C-5), 54.8 (C-1), 52.3 (CH_2-1 pentyl), 39.2 (CH_2 Ada), 36.7 (CH_2 Ada), 33.5 (C_q Ada), 28.7 (CH_2 pentyl), 27.8 (CH Ada), 23.4 (CH_2 pentyl), 22.7 (CH_2 pentyl), 13.7 (CH_3-6). HRMS: found 382.2961 $[M+H]^+$, calculated for $[C_{22}H_{39}NO_4+H]^+$ 381.2957.



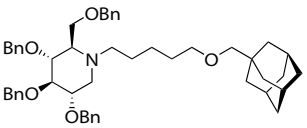
2,3,4,6-Tetra-*O*-benzyl-D-glucitol (28). $LiAlH_4$ (9.8 g, 259 mmol) was added in portions to a cooled (0 °C) and dry solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**5**, 40.0 g, 74 mmol) in THF (370 mL). The reaction mixture was stirred for 20 h, allowing it to warm to rt. The excess $LiAlH_4$ was quenched successively with EtOAc (50 mL, 1 h of stirring) and water at 0 °C. The mixture was diluted with EtOAc (400 mL) and washed with sat aq NH_4Cl (2×500 mL) and sat aq NaCl (250 mL). The organic phase was dried ($MgSO_4$) and concentrated to yield **28**, which was used crude in the next reaction. A small sample was purified by silica gel column chromatography (20% » 50% EtOAc in PE) for characterization purposes to provide **28** as a colorless oil.

Miniplant preparation procedure: A solution of **5** (8.50 kg, 15.72 mol) in DCM (42.5 L + 1.7 L for rinsing) was added to a suspension of $NaBH_4$ (1.61 kg, 42.45 mol) in DCM (11.1 L). The resulting suspension was vigorously stirred and heated to reflux (36–40 °C), during which methanol (11.1 L) was carefully added over a 6 hour period. Following the addition of methanol, the reaction mixture was heated for an additional hour, after which it was cooled to 20 °C and remaining hydrogen gas was evacuated with a nitrogen flow. The reaction mixture was quenched by careful addition of 2M aq H_3PO_4 (21.3 L) under vigorous stirring over a 2 hour period, cooling the reaction mixture to keep the temperature below 30 °C. After addition, the mixture was vigorously stirred for 30 minutes, whilst evacuating remaining hydrogen gas with a nitrogen flow. After the two-phasic mixture had settled for 1 hour, the organic phase was isolated and the turbid aq phase was back-extracted once with DCM (11.1 L). The combined organic layers were washed with water (2×11.1 L), concentrated and degassed at 30 °C under full vacuum for 2 hours to produce **28** (8.58 kg, 15.72 mol, 98.6% area by HPLC) as a colorless oil in quantitative yield.

HPLC in-process control: Method B; Sample preparation: 200 µL reaction mixture is added to a freshly prepared solution of 0.1 mL 2M aq H_2SO_4 in 15 mL CH_3CN and filled to 25 mL with methanol; t_R: **28** = 17.1 min; **5** = 18.1 min. R_F = 0.45 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 – 7.08 (m, 20H, H_{Ar} Bn), 4.70 (d, *J* = 11.3 Hz, 1H, C*H*H Bn), 4.64 (d, *J* = 11.3 Hz, 1H, CH*H* Bn), 4.63 (d, *J* = 11.7 Hz, 1H, CH Bn), 4.61 – 4.56 (m, 2H, 2×CH Bn), 4.53 (d, *J* = 11.4 Hz, 1H, CH Bn), 4.52 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.47 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.03 (m, 1H, H-5), 3.89 (dd, *J* = 3.6 Hz, *J* = 6.3 Hz, 1H, H-3), 3.80 – 3.75 (m, 2H, H-2, H-4), 3.71 (dd, $J_{H1a\text{-}H2}$ = 4.3 Hz, $J_{H1a\text{-}H1b}$ = 11.9 Hz, 1H, H-1a), 3.65 – 3.59 (m, 2H, CH_2-6), 3.55 (dd, $J_{H1b\text{-}H2}$ = 4.7 Hz, $J_{H1b\text{-}H1a}$ = 11.9 Hz, 1H, H-1b), 3.04 (br s, 1H, OH), 2.35 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 137.8, 137.8 (4×C_q Bn), 128.25, 128.23, 127.9, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 79.4 (C-2), 78.9 (C-3), 77.3 (C-4), 74.4, 73.3, 73.1, 72.9 (4×CH_2 Bn), 71.0 (C-6), 70.6 (C-5), 61.6 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3420, 3030, 2866, 1497, 1454, 1398, 1358, 1308, 1209, 1065, 1026, 910, 851, 820, 731, 694, 631. $[\alpha]^{20}_D$: +8.9° (c = 3.94, $CHCl_3$). MS (ESI): *m/z* 543.2 $[M+H]^+$; 565.1 $[M+Na]^+$.

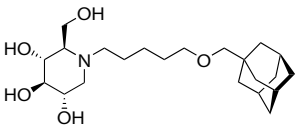


2,3,4,6-Tetra-*O*-benzyl-1-deoxynojirimycin (11). A solution of oxalylchloride (14.0 mL, 162.3 mmol) in DCM (296 mL) was cooled to –78 °C. After dropwise addition of a solution of DMSO (23.2 mL, 325.6 mmol) in DCM (99 mL) over 10 min, the reaction mixture was stirred for 40 min while being kept below –70 °C. Next, a dry solution of crude **28** (~74 mmol) in DCM (99 mL) was added dropwise to the reaction mixture over a 15 min period, while keeping the reaction mixture below –70 °C. After stirring the reaction mixture for 2 h below –65 °C, Et_3N (100 mL, 740 mmol) was added dropwise over a 10 min period, while keeping the reaction mixture below –65 °C. After addition, the reaction mixture was allowed to warm to –5 °C over 1 h (R_F hexosulose = 0.7 (1:1; EtOAc:PE). The reaction mixture was concentrated at a moderate temperature (~30 °C) with simultaneous coevaporation of dichloroethane (3×). The residue was dissolved in MeOH (1400 mL) and ammonium formate (80 g, 1258 mmol) was added. The mixture was cooled to 0 °C and stirred until all ammonium formate had dissolved. Activated 3Å molecular sieves (150 g) were added and reaction mixture was stirred for 10 min, after which sodium cyanoborohydride (18.6 g, 296 mmol) was added. The reaction mixture was kept at 0 °C for 1 h after which the cooling source was removed and the reaction was stirred for an additional 20 h. After removal of the molecular sieves over a glass microfibre filter, the filtrate was concentrated, dissolved in EtOAc (500 mL) and washed successively with sat aq $NaHCO_3$ (400 mL) and sat aq NaCl (300 mL). The combined aq phases were back-extracted with EtOAc (250 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (20% » 75% EtOAc in PE) to provide **11** (25.2 g, 48.1 mmol) in 65% yield over three steps as a light yellow crystalline solid. R_F = 0.25 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.14 (m, 20H, H_{Ar} Bn), 4.97 (d, *J* = 12.9 Hz, 1H, CH Bn), 4.87 – 4.82 (m, 2H, 2×CH Bn), 4.68 (d, *J* = 11.7 Hz, 1H, C*H*H Bn), 4.64 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.48 (d, *J* = 11.0 Hz, 1H, CH Bn), 4.45 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.40 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 3.65 (dd, $J_{H6a\text{-}H5}$ = 2.6 Hz, $J_{H6a\text{-}H6b}$ = 9.0 Hz, 1H, H-6a), 3.57 – 3.45 (m, 3H, H-2, H-3, H-6b), 3.34 (dd, *J* = 8.8 Hz, 1H, H-4), 3.22 (dd, $J_{H1a\text{-}H2}$ = 4.9 Hz, $J_{H1a\text{-}H1b}$ = 12.2 Hz, 1H, H-1a), 2.71 (ddd, $J_{H5\text{-}H6a}$ = 2.6 Hz, *J* = 5.9 Hz, *J* = 9.8 Hz, 1H, H-5), 2.48 (dd, $J_{H1b\text{-}H2}$ = 10.3 Hz, $J_{H1b\text{-}H1a}$ = 12.2 Hz, 1H, H-1b), 1.89 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 138.4, 138.3, 137.8 (4×C_q Bn), 128.24, 128.21, 127.84, 127.78, 127.70, 127.6, 127.5, 127.4 (CH_{Ar} Bn), 87.2 (C-3), 80.5 (C-2), 80.0 (C-4), 75.5, 75.0, 73.2, 72.6 (4×CH_2 Bn), 70.1 (C-6), 59.6 (C-5), 48.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3030, 2843, 1497, 1358, 1310, 1209, 1092, 1061, 1028, 945, 908, 866, 733, 694. Melting point range: 44.5–46.8 °C. $[\alpha]^{20}_D$: +27.7° (c = 3.16, $CHCl_3$). MS (ESI): *m/z* 524.5 $[M+H]^+$.

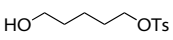


2,3,4,6-Tetra-*O*-benzyl-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (30). Argon was passed through a solution of compound **11** (4.19 g, 8.0 mmol) and **16** (3.00 g, 12.0 mmol) in EtOH/AcOH (50 mL; 10/1) for 15 min, after which a catalytic amount of Pd/C (419 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 30 min and the reaction was

stirred for 40 h under atmospheric hydrogen pressure, or until TLC analysis indicated complete consumption of **11**. Pd/C was removed by filtration over a glass microfiber filter, followed by thorough rinsing with EtOH. The filtrate was concentrated and coevaporated with toluene. The crude concentrated reaction mixture was used in the next step. A small sample was purified by silica gel column chromatography (0% » 10% Et_2O in toluene + 1% Et_3N) for characterization purposes to afford product **30** as a colorless oil. R_F = 0.52 (1:4; Et_2O:toluene + 1% Et_3N). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34 – 7.12 (m, 20H, H_{Ar} Bn), 4.95 (d, *J* = 11.1 Hz, 1H, C*H*H Bn), 4.87 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.81 (d, *J* = 11.1 Hz, 1H, CH*H* Bn), 4.68 (d, *J* = 11.6 Hz, 1H, C*H*H Bn), 4.65 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.48 (d, *J* = 10.9 Hz, 1H, CH*H* Bn), 4.46 (d, *J* = 12.2 Hz, 1H, C*H*H Bn), 4.41 (d, *J* = 12.2 Hz, 1H, CH*H* Bn), 3.67 – 3.64 (m, 2H, H-2, H-6a), 3.60 (dd, *J* = 9.0 Hz, 1H, H-4), 3.54 (d, $J_{H6b-H6a}$ = 10.2 Hz, 1H, H-6b), 3.45 (dd, *J* = 9.0 Hz, 1H, H-3), 3.34 (t, *J* = 6.5 Hz, 2H, OCH_2-5′pentyl), 3.09 (dd, J_{H1a-H2} = 4.8 Hz, $J_{H1a-H1b}$ = 10.8 Hz, 1H, H-1a), 2.95 (s, 2H, OCH_2-Ada), 2.68 (m, 1H, NC*H*H-1′ pentyl), 2.58 (m, 1H, NCH*H*-1′ pentyl), 2.31 (d, *J* = 9.0 Hz, 1H, H-5), 2.23 (dd, $J_{H1b-H1a}$ = 10.8 Hz, 1H, H-1b), 1.96 (br s, 3H, 3×CH Ada), 1.72-1.64 (m, 6H, 3×CH_2 Ada), 1.54 (br d, *J* = 2.4 Hz, 6H, 3×CH_2 Ada), 1.51 (m, 2H, CH_2-4′ pentyl), 1.44 (m, 1H, C*H*H-2′ pentyl), 1.36 (m, 1H, CH*H*-2′ pentyl), 1.22 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.0, 138.5, 137.7 (4×C_q Bn), 128.8, 128.4, 128.3, 128.27, 128.26, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{Ar} Bn), 87.3 (C-3), 81.9 (OCH_2-Ada), 78.53, 78.51 (C-2, C-4), 75.3, 75.1, 73.4, 72.7 (4×CH_2 Bn), 71.4 (OCH_2-5′ pentyl), 65.1 (C-6), 63.6 (C-5), 54.4 (C-1), 52.3 (NCH_2-1′pentyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.1 (C_q Ada), 29.4 (CH_2-4′pentyl), 28.3 (3×CH Ada), 24.1 (CH_2-3′pentyl), 23.3 (CH_2-2′pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 2799, 2183, 1497, 1454, 1367, 1315, 1258, 1207, 1173, 1155, 1092, 1070, 1028, 989, 910, 814, 731, 694, 648. $[\alpha]^{20}_D$: –3.3° (c = 0.86, $CHCl_3$). MS (ESI): *m/z* 758.0 $[M+H]^+$; 780.4 $[M+Na]^+$.

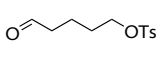


***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (4).** A solution of crude **30** (~8 mmol) in EtOH (40 mL) was acidified with 2M aq HCl (7.7 mL), after which argon was passed through the solution for 15 min. Next, a catalytic amount of Pd/C (600 mg, 10 wt % on act. carbon) was added and the reaction mixture was shaken in a Parr-apparatus under 1 bar hydrogen pressure for 20 h. Pd/C was removed by filtration over a glass microfiber filter, followed by thorough rinsing with EtOH. The filtrate was concentrated and coevaporated with toluene. The residue was purified by silica gel column chromatography (5% » 15% MeOH in EtOAc with 0.5% NH_4OH) to give **4** (2.83 g, 7.1 mmol) as a colorless oil in 89% yield. R_F = 0.20 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD): δ = 3.86 (dd, J_{H6a-H5} = 2.7 Hz, $J_{H6a-H6b}$ = 12.1 Hz, 1H, H-6a), 3.82 (dd, J_{H6b-H5} = 2.7 Hz, $J_{H6b-H6a}$ = 12.1 Hz, 1H, H-6b), 3.46 (ddd, J_{H2-H1a} = 4.9, 9.1, 10.6 Hz, 1H, H-2), 3.38 (t, *J* = 6.3 Hz, 2H, OCH_2-5′ pentyl), 3.35 (dd, *J* = 9.4 Hz, 1H, H-4), 3.12 (dd, *J* = 9.1 Hz, 1H, H-3), 2.97 (dd, J_{H1a-H2} = 4.8 Hz, $J_{H1a-H1b}$ = 10.2 Hz, 1H, H-1eq), 2.96 (s, 2H, OCH_2-Ada), 2.79 (m, 1H, NC*H*H-1′ pentyl), 2.58 (m, 1H, NCH*H*-1′ pentyl), 2.17 (dd, *J* = 10.2, 10.6 Hz, 1H, H-1ax), 2.09 (dt, J_{H5-H4} = 9.4 Hz, $J_{H5-H6a/b}$ = 2.7 Hz, 1H, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77-1.66 (m, 6H, 3×CH_2 Ada), 1.58 (m, 2H, CH_2-4′pentyl), 1.55 (d, *J* = 2.8 Hz, 6H, 3×CH_2 Ada), 1.51 (m, 2H, CH_2-2′pentyl), 1.33 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (100 MHz, MeOD): δ = 83.6 (OCH_2-Ada), 79.1 (C-3), 71.1 (OCH_2-5′ pentyl), 70.6 (C-4), 69.3 (C-2), 65.8 (C-5), 58.0 (C-6), 56.3 (C-1), 52.3 (NCH_2-1′pentyl), 39.4 (3×CH_2 Ada), 36.9 (3×CH_2 Ada), 33.7 (C_q Ada), 29.1 (CH_2-4′ pentyl), 28.3 (3×CH Ada), 23.9 (CH_2-3′ pentyl), 23.6 (CH_2-2′ pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3317, 2901, 2847, 1448, 1360, 1344, 1259, 1217, 1188, 1155, 1088, 1036, 1011, 914, 812, 754, 665. $[\alpha]^{20}_D$: –10.6° (c = 2.30, MeOH). HRMS: found 398.29266 $[M+H]^+$, calculated for $[C_{22}H_{39}NO_5+H]^+$ 398.29010.

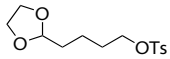


5-(Toluene-4-sulfonyloxy)-1-pentanol (22). To a cooled (0 °C) solution of pentane-1,5-diol (**17**, 9.76 kg, 93.71 mol), DMAP (390 g, 2.92 mol) and triethyl amine (4.88 kg, 51.72 mol) in MTBE (68.30 L) was added a cooled (0 °C) solution of TsCl (8.78 kg, 46.84 mol) in DCM (9.76 L) over a 2 hour period. The reaction mixture was kept at 0 °C for two hours after which it was warmed to 20 °C within a one hour period and stirred for an additional 18 hours. Water (39.04 L) was added to the reaction mixture over a 30 minute period, followed by 2M aq HCl (19.52 L). After stirring the mixture for 30 minutes, the organic layer was

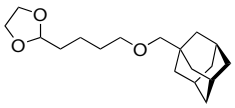
isolated and washed with saturated aq NaCl (2×19.52 L). The organic layer was concentrated using moderate heating (T_{max}< 40 °C: **22** slowly decomposes when heated) to produce a yellow oil. A solution of crude **22** in 2-propanol (24.4 L) was stirred for 1 hour at rt during which the ditosylate byproduct precipitated as a white solid. The mixture was cooled at –5 °C for 2 hours after which the precipitate was removed by centrifugation and washed with precooled 2-propanol (2×0.97 L; T = 0 °C). The mother liquor and washings were concentrated using moderate heating (T_{max}< 40 °C) and degassed at 30 °C under full vacuum for 2 hours to provide **22** (8.82 kg, 34.14 mol, 88.8 % area by HPLC) as a light yellow oil in 72.9% yield, which was stable when stored under inert atmosphere, below 5 °C in the dark. HPLC in-process control: Method A; Sample preparation: 50 µL reaction mixture in 25 mL CH_3CN; t_R: **22** = 13.7 min; ditosylate byproduct = 18.4 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3, 2H), 7.29 (d, *J* = 8.1, 2H), 3.96 (t, *J* = 6.4, 2H), 3.80 (s, 1H), 3.52 (t, *J* = 6.5, 2H), 2.38 (s, 3H), 1.65 – 1.56 (m, 2H), 1.49 – 1.40 (m, 2H), 1.37 – 1.27 (m, 2H).



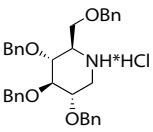
5-(Toluene-4-sulfonyloxy)-1-pentanal (23). To a solution of **22** (8.73 kg, 33.79 mol) and TEMPO (52.4 g, 0.33 mol) in DCM (43.65 L) was added a solution of KBr (0.43 kg) in water (1.74 L) and the mixture was cooled to 5 °C. Separately, sodium hypochlorite (~20.07 L; 12-15% in water; 30.69 mol) was diluted with enough aq $NaHCO_3$ (~20.07 L; 9%) to reach a pH between 8.5 and 9.5 and then cooled to 5 °C. Controlled addition of an equimolar amount of NaOCl was essential to prevent overoxidation of **22**. Therefore the exact concentration of the commercial NaOCl solution has to be determined. A portion (30.55 L) of the NaOCl/$NaHCO_3$ solution was added over a period of 2 hours at 5 °C to the mixture containing **22**, which caused initial orange coloration of the reaction mixture that slowly disappeared. The reaction mixture was stirred for an additional 30 minutes at 5 °C, after which the reaction progress was checked with HPLC by sampling the organic layer. Additional portions (1–2 L) of the NaOCl/$NaHCO_3$ solution were added over 15 minute periods with 30 minutes of additional stirring at 5 °C and intermittent HPLC analysis in between until less then 1% of **22** remained. The reaction mixture was warmed to 20 °C and the aq layer was separated and extracted with DCM (11.34 L). Aq 2.87M HCl (34.92 L) containing KI (87g) was slowly added to the combined organic layers. The aq layer was removed and the organic layer was successively extracted with aq $Na_2S_2O_3$ (34.9 L; 10%), saturated aq $NaHCO_3$ (34.9 L) and water (34.9 L). The organic layer was isolated, concentrated using moderate heating (T_{max}< 40 °C: **23** slowly decomposes when heated) and degassed at 30 °C under full vacuum for 2 hours to afford **23** (7.93 kg, 30.93 mol, 93.2 % area by HPLC) as a yellow oil in 91.5% yield, which was stable when stored under inert atmosphere, below 5 °C in the dark. HPLC in-process control: Method A; Sample preparation: 50 µL reaction mixture in 25 mL CH_3CN; t_R: **22** = 13.6 min; **23** = 13.8 min; ditosylate byproduct = 18.1 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (t, *J* = 1.3, 1H), 7.74 (d, *J* = 8.3, 2H), 7.31 (d, *J* = 8.0, 2H), 3.99 (t, *J* = 5.8, 2H), 2.44 – 2.37 (m, 5H), 1.68 – 1.58 (m, 4H).



2-(4-[Toluene-4-sulfonyloxy]-butyl)-1,3-dioxolane (24). To an emulsion of ethylene glycol (2.8 kg, 46.0 mol) and TsOH (171 g; 0.9 mol) in MTBE (27.27 L) was added a solution of **23** (7.79 kg, 30.39 mol) in MTBE (27.27 L) over a period of 30 minutes. The water liberated up to now was removed and the reaction mixture was refluxed (~56 °C) for 3 hours or until HPLC analysis indicated complete conversion. The reaction mixture was cooled to 20 °C and saturated aq $NaHCO_3$ (35.06 L) was added over a 30 minute period. The organic layer was washed with saturated aq NaCl (35.06 L), concentrated using moderate heating (T_{max}< 40 °C: **24** slowly decomposes when heated) and degassed at 30 °C under full vacuum for 2 hours. Compound **24** (8.81 kg, 29.33 mol, 91.0 % area by HPLC) was obtained as a light yellow oil in 96.5% yield, which was stable when stored under inert atmosphere, below 5 °C in the dark. HPLC in-process control: Method A; Sample preparation: 50 µL reaction mixture in 25 mL CH_3CN; t_R: **23** = 13.9 min; **24** = 15.6 min; ditosylate byproduct = 18.4 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3, 2H), 7.31 (d, *J* = 8.0, 2H), 4.76 (t, *J* = 4.6, 1H), 3.99 (t, *J* = 6.5, 2H), 3.95 – 3.84 (m, 2H), 3.84 – 3.75 (m, 2H), 2.41 (s, 3H), 1.71 – 1.61 (m, 2H), 1.61 – 1.54 (m, 2H), 1.46 – 1.36 (m, 2H).

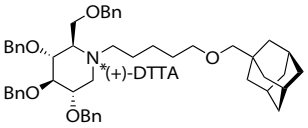


2-(4-[Adamantan-1-yl-methoxy]-butyl)-1,3-dioxolane (25). Water content of commercial adamantanemethanol (4.09 kg, 24.62 mol) was removed by azeotropic distillation with toluene (17.4 L) and the residue was dissolved in DMF (26.1 L) at 40 °C. Sodium hydride (1.97 kg, 60% in mineral oil, 49.23 mol) was suspended in DMF (26.1 L) and heated to 40 °C after which the adamantanemethanol solution was carefully added over a period of 1 hour. After additional stirring for 30 minutes a 40 °C solution of **24** (7.79 kg, 28.96 mol) in DMF (17.4 L) was added over a 1 hour period. The reaction mixture was stirred for 2 hours after which it was cooled to 20 °C and methanol (3.48 L) was carefully added over a 1 hour period keeping the temperature under 30 °C. Water (87 L) was added to the reaction mixture and after cooling to 20 °C the mixture was extracted with MTBE (2×87 L). The combined organic layers were washed with saturated aq NaCl (2×43.5 L) and concentrated using moderate heating (T_{max}<40 °C). The residue was dissolved in heptane (76.5 L) and extracted with a methanol/water mixture (4×84.2 L, 8/3 methanol/water, v/v). The heptane layer was isolated and concentrated (T_{max}<40 °C) to afford a light yellow oil. This residue was further purified by short path distillation at a temperature of 120 °C and a pressure below 0.1 mbar to afford **25** (5.84 kg, 19.83 mol; 92.3 % area by GC) in 80.5% yield as a colorless oil, which was stable when stored under inert atmosphere, below 5 °C in the dark. GC in-process control: Method: see general methods; Sample preparation: 100 µL reaction mixture is quenched with methanol and diluted with 1.4 mL DCM. t_R: adamantanemethanol = 4.78 min; 22 = 10.24 min, 21 = 10.80 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (t, *J* = 4.8, 1H), 3.98 – 3.88 (m, 2H), 3.87 – 3.77 (m, 2H), 3.35 (t, *J* = 6.5, 2H), 2.92 (s, 2H), 1.92 (s, 3H), 1.71 – 1.53 (m, 11H), 1.52 – 1.40 (m, 9H).



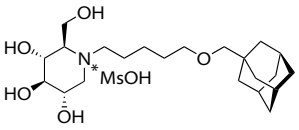
2,3,4,6-Tetra-*O*-benzyl-1-deoxynojirimycin hydrochloric acid salt (11*HCl). A solution (water content was verified to be KF < 0.05%) of DMSO (9.54 kg; 122.10 mol) in DCM (8.68 L) was slowly added to a cooled (–75 °C) solution of oxalylchloride (12.56 kg; 9.91 mol) in DCM (45.5 L; water content was verified to be KF < 0.03%) so the internal temperature of the reaction mixture did not exceed –65°C. The resulting mixture was stirred for 30 minutes at –75 °C, whereupon a solution of **28** (12.5 kg; 23.03 mol) in DCM (14.47 L) was slowly added so the internal temperature of the reaction mixture did not exceed –65 °C (**28** was dried by azeotropic distillation with DCM until water content was KF < 0.03%). After addition of **28**, the reaction mixture was stirred for 2 hours at –75 °C after which Et_3N (25.17 kg; 248.7 mol) was slowly added so the internal temperature of the reaction mixture did not exceed –65 °C. The resulting suspension was stirred for 4 hours, warming from –75 °C to –60 °C, and then transferred to a cooled (0–5 °C) mixture* of NH_4OAc (17.76 kg, 230.40 mol), Na_2SO_4 (9.81 kg, 69.06 mol) and $NaBH_3CN$ (5.79 kg, 92.10 mol) in methanol (207.3 L + 23.0 L for rinsing). The reaction mixture was stirred for 18 hours and allowed to warm to 20–25 °C. The reaction mixture was cooled to 5-10 °C and water (46.06 L) was slowly added over a 30 minute period so the internal temperature of the mixture did not exceed 35 °C.* An aq NaOH (18.3 L, 50 w%) solution was added to the mixture** followed by addition of water (414.6 L) over a one hour period (T < 35 °C). The two-phasic mixture was stirred for one hour at 18-25 °C after which the organic phase was isolated. The aq phase was back-extracted once with DCM (102.5 L). The combined organic phases were cooled to 5-10 °C and under vigorous stirring an aq NaOCl solution (131.1 L, 12 w%) was added over a one hour period (T < 35 °C). The two-phasic reaction mixture was vigorously stirred for one hour at 18-25 °C and then the organic phase was isolated and cooled to 5–10 °C. Aqueous 2M HCl (115.2 L) was added to the organic phase over a one hour period (T < 35 °C) after which the mixture was vigorously stirred for another hour at 18–25 °C. Isolation of **11** through precipitation was achieved by solvent exchange from DCM to acetone. The organic phase was isolated and DCM (~150 L) was evaporated until the residue reached 54–55 °C. Acetone (151.5 L) was added to the residue and the mixture was vigorously stirred (T < 35 °C) for 30 minutes during which **11*HCl** precipitated as white floccules. Residual DCM was removed by successively evaporating ~50 L of solvent and adding acetone (23.1 L). The suspension was vigorously stirred for one hour at ambient temperature and another hour whilst cooled at

0–5 °C. The product was isolated by centrifugation, washed twice with precooled acetone (T = 0–5 °C; portion 1 = 12.7 L; portion 2 = 6.5 L) and dried under vacuum at 35-40 °C to afford **11*HCl** (7.27 kg; 12.97 mol; 98.7% area by HPLC) as an off-white solid in 56% yield. Remaining impurities were removed through a reslurrying step in which a suspension of **11*HCl** (7.15 kg; 12.76) was vigorously stirred in acetone (46.3 L) for three hours at 20-25 °C and another hour at 0–5 °C. The solvent was removed by centrifugation and the product was washed with precooled acetone (T = 0–5 °C; 17.9 L) to afford, after drying under vacuum at 35–40 °C, **11*HCl** (6.66 kg; 11.89 mol; 98.8% area by HPLC) as a white solid with 93% recovery.*** HPLC in-process control: Method B; Sample preparation: 250 µL reaction mixture is added to a solution of 2 mL 2M aq H_3PO_4 in 15 mL CH_3CN and filled to 25 mL with CH_3CN; t_R: **11** = 15.6 min; **28** = 17.1 min; **29** = 17.5 min. ^{1}H NMR (400 MHz, *d6*-DMSO) δ 10.18 (s, 1H), 9.51 (s, 1H), 7.42 – 7.25 (m, 18H), 7.17 – 7.10 (m, 2H), 4.86 (d, *J* = 11.2, 1H), 4.77 – 4.67 (m, 3H), 4.62 (d, *J* = 11.7, 1H), 4.58 (d, *J* = 12.2, 1H), 4.50 (d, *J* = 12.2, 1H), 4.45 (d, *J* = 10.8, 1H), 3.91 (ddd, *J* = 5.0, 8.9, 11.0, 1H), 3.82 (dd, *J* = 2.3, 10.5, 1H), 3.79 – 3.62 (m, 3H), 3.41 (dd, *J* = 5.0, 12.1, 2H), 2.89 (dd, *J* = 11.6, 1H). DSC (50 °C » 300 °C; 10 °C/ min): 174.5 °C; 18.75 J/ g. *: Precautions should be taken for possible liberation of hydrogen cyanide gas from the mixture. **: The pH of the aq layer was checked to be above 10 to ensure fixation of hydrogen cyanide. ***: Solubility of **11*HCl** in acetone at ambient temperature was determined to be ~6 grams per liter.



2,3,4,6-Tetra-*O*-benzyl-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (+)DTTA salt (30*(+)DTTA). Aqueous 1M NaOH (65.0 L) was added to a suspension of **12*HCl** (6.50 kg, 11.60 mol) in EtOAc (65.0 L) over a 15 minute period. After stirring the two-phasic mixture for ten minutes, the organic phase was isolated and successively washed with aq 1M NaOH (19.5 L) and a saturated aq NaCl solution (19.5 L). The organic phase was concentrated (T < 40 °C) and coevaporated twice with ethanol (2×13.0 L) to produce free-base **11** as a light yellow oil. Crude **16** (4.50 kg, ~15.6 mol, 86.8 % area by GC) and Pd/C catalyst (650 g, slurry in ethanol) were successively added to a solution of **11** in ethanol (65.0 L)* and acetic acid (6.7 L). The reaction mixture was purged of oxygen by flushing it with nitrogen for 15 minutes. Hydrogen was bubbled through the vigorously stirred reaction mixture for 20 hours (initially with cooling to keep T < 30 °C). The reaction mixture was purged of hydrogen by flushing with nitrogen for 15 minutes and reaction progress was determined with GC and HPLC. If the amount of remaining **11** was still above 0.5% the reaction mixture was placed under hydrogen for a further 20 hours. *GC analysis* (consumption of **16**): Method: see general methods; Sample preparation: 100 µL reaction mixture was dissolved in 1.4 mL DCM; t_R: **16** = 8.4 min. *HPLC analysis* (consumption of **11**): Method B; Sample preparation: 250 µL reaction mixture is added to a solution of 2 mL 2M aq H_3PO_4 in 15 mL CH_3CN and filled to 25 mL with CH_3CN; t_R: Toluene = 14.0 min; **11** = 15.7 min; Partially debenzylated **30** = 17.7 and 17.8 min; **30** = 18.4 min. Celite (1.3 kg) was added to the nitrogen flushed reaction mixture when HPLC analysis indicated reaction completion. The reaction mixture was filtered, the filter cake was washed with ethanol (3×12.5 L) and the combined filtrate was concentrated (T < 40 °C). A methanolic hydrochloric acid solution was prepared separately by adding acetylchloride (3.7 L, 52.16 mol) over a 30 minute period to methanol (32.5 L) at 5–10 °C and stirring for an additional 30 minutes. The residue resulting from the concentrated filtrate was dissolved in methanol (32.5 L) and added to the methanolic hydrochloric acid solution over a 15 minute period at 20-25 °C. The combined methanolic solutions were washed with heptane (3 × 32.5 L) and subsequently concentrated (T < 40 °C). The residue was dissolved in MTBE (65.0 L) and washed successively with aq 1M NaOH (2×32.5 L) and a saturated aq NaCl solution (32.5 L). The organic phase was isolated and concentrated (T < 40 °C). The residue was dissolved in heptane (16.7 L) and added to a solution of (+)-di-*p*-toluoyl-L-tartaric acid (4.29 kg; 11.10 mol; exact amount should be equimolar to HPLC determined amount of **30** in the heptane solution) in ethanol (8.4 L) over a 15 minute period. The stirred solution was seeded with **30*(+)DTTA** that resulted in precipitation of **30*(+)DTTA** as a white solid. Heptane (25.1 L) was added and the mixture was stirred for 30 minutes at ambient temperature followed by one hour at 0–5 °C. The precipitate was isolated

by centrifugation and washed with a heptane/ethanol mixture (2×8.4 L; 5/1 v/v). After drying for 20 hours under vacuum (T < 40 °C), **30*(+)DTTA** (10.01 kg, 8.74 mol; 98.4% area by HPLC) was obtained as a white solid in 75% yield. HPLC Purity (area percent) = **30** = 85.3%; Partially debenzylated-1 **30** = 6.84; Partially debenzylated-2 **30** = 5.76%; Total = 98.43%; Palladium content (determined by ICP-MS) = < 5 ppm. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.89 (d, *J* = 8.2, 4H), 7.37 (d, *J* = 8.2, 4H), 7.35 – 7.22 (m, 18H), 7.19 – 7.14 (m, 2H), 5.79 (s, 2H), 4.85 (d, *J* = 11.3, 1H), 4.76 (d, *J* = 10.9, 1H), 4.72 (d, *J* = 11.3, 1H), 4.65 (d, *J* = 11.9, 1H), 4.58 (d, *J* = 11.8, 1H), 4.47 – 4.36 (m, 3H), 3.67 – 3.57 (m, 2H), 3.57 – 3.50 (m, 1H), 3.40 (dd, *J* = 8.2, 16.3, 2H), 3.27 (t, *J* = 6.2, 2H), 3.18 (dd, *J* = 4.5, 11.2, 1H), 2.89 (s, 2H), 2.79 – 2.69 (m, 1H), 2.56 – 2.48 (m, 2H), 2.38 (s, 6H), 2.25 (dd, *J* = 9.9, 1H), 1.90 (s, 3H), 1.62 (dd, *J* = 11.8, 30.6, 6H), 1.48 (d, *J* = 1.9, 6H), 1.46 – 1.33 (m, 4H), 1.23 – 1.10 (m, 2H). DSC (50 °C » 300 °C; 10 °C/ min): 105.7 °C, 36.8 J/ g; 160.7 °C, –13.6 J/g. *: Absence of acetaldehyde in used batch of ethanol should be verified beforehand otherwise significant formation of a 2,3,4,6-tetra-*O*-benzyl-*N*-ethyl-1-deoxynojirimycin byproduct is possible.



***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin methanesulfonic acid salt (4*MSA).** A solution of **30*(+)DTTA** (4.90 kg, 4.28 mol) in MTBE (49.0 L) was washed successively with aq 1M NaOH (1 × 24.5 L; then 1 × 12.3 L) and saturated aq NaCl (12.3 L). The organic phase was isolated, concentrated (T < 40 °C) to 5-10 L and coevaporated with ethanol (3 × 25 L; or until MTBE level < 2%) to quantitatively produce **30** (3.24 kg; 4.28 mol) as a colorless oil. The byproduct **31** contaminating **30** was debenzoylated by adding aq 6M NaOH (3.3 L) to a cooled (0–10 °C) solution of **30** (3.24 kg; 4.28 mol) in ethanol (63.7 L) over a 10 minute period (T < 10 °C) and stirring the resulting turbid reaction mixture for two hours at 20-25 °C. The reaction mixture was cooled (10 °C), aq 10.17M HCl (1.9 L) was added over a 10 minute period (altering the pH to 5-8) and subsequently aq 2M HCl (12.3 L) was added at 10-30 °C to produce a clear solution with acidic pH. Palladium on carbon (321 g; slurry in ethanol) was added to the solution and oxygen was purged by flushing the mixture for 15 minutes with nitrogen. Hydrogen was bubbled through the vigorously stirred reaction mixture for 6-12 hours (initially with cooling to keep T < 30 °C). The reaction mixture was purged of hydrogen by flushing with nitrogen for 15 minutes and reaction progress was determined by HPLC analysis (method B; sample preparation: 250 µL reaction mixture was added to a solution of 2 mL 2M aq H_3PO_4 in 15 mL CH_3CN and filled to 25 mL with CH_3CN; t_R: **4** = 14.1 min; **30** = 18.3 min). If the amount of **30** and partially debenzylated intermediates was higher then 1 area% compared to generated toluene the reaction mixture was placed under hydrogen for further 2-4 hour periods until complete. When HPLC analysis indicated reaction completion the mixture was filtered and the Pd/C filter cake was washed with ethanol (3×7.3 L). Ecosorb (172 g) was added to the combined filtrate whereupon the mixture was stirred for 1 hour at ambient temperature. The mixture was filtered and the Ecosorb filter cake was washed with ethanol (3×7.3 L). The combined filtrate was concentrated (T < 50 °C) to a volume of 5-10 L and coevaporated with ethanol (3×32 L). The remaining mixture was diluted to a volume of 34.3 L with ethanol (water content was verified to be KF < 2%) and 7M methanolic NH_3 (3.9–6.9 L) was added to the solution until the pH was adjusted to 8-9.5. The mixture was concentrated (T < 45 °C) to 5–10 L and coevaporated with DCM (5×122.5 L; or until ethanol level < 2%). The remaining mixture is diluted to a total volume of 24.5 L with DCM and the precipitated salts were removed by filtration. The precipitate was washed with DCM (3×2.5 L) and the combined filtrate concentrated (T < 45 °C) to 5–10 L. The residue could at this stage be further concentrated and degassed under vacuum for four hours at T < 45 °C to provide **4** as an off-white hygroscopic foam. (DSC (50 °C » 300 °C; 10 °C/ min) free base **5**: 126.1 °C, 12.0 J/ g; 171.1 °C, 1.8 J/g)). However for this preparation the solution of **5** in DCM was coevaporated with isopropanol (3×24.5 L; or until DCM level < 1%). Any remaining particulate was removed by a polish filtration step followed by additional rinsing with isopropanol (3×2.4 L) of the reaction vessel and filter. At ambient temperature a solution of methanesulfonic acid (473 g, 4.92 mol) in isopropanol (3.9 L + 2.45 rinse) was added to the isopropanol solution of **4**. The solution was heated to 70 °C and slowly cooled to ambient temperature over a 4-8 hour period during which at ~50 °C

seed crystals of **4*MSA** (5 g) were added. The solution slowly turned turbid and **4*MSA** precipitated as a course white solid. The mixture was stirred for 16 hours at ambient temperature, filtered and the collected solids were washed with isopropanol (3×2.4 L). Drying of the product under vacuum (T < 40 °C) provided **4*MSA** (1.38 kg, 2.80 mol) as a stable white solid in 65% yield. HPLC Purity (area percent): **4** = 99.9%; Benzoic acid = < 0.1%. Residual Solvents: Ethanol = < 0.01%; Toluene = < 0.005%; Isopropanol = < 0.05%; Methanol = < 0.02%; DCM = < 0.04%.; Palladium content (determined by ICP-MS) = <0.01 ppm; Water content (KF) = 0.12%; Loss on drying = 0.62%; Sulphated Ash = 0.03%. ^{1}H NMR (500 MHz, D_2O) δ 4.06 (dd, *J* = 1.4, 13.1, 1H, H-6a), 3.92 (dd, *J* = 2.5, 13.2, 1H, H-6b), 3.78 (ddd, *J* = 5.0, 9.5, 11.3, 1H, H-2), 3.63 (dd, *J* = 9.3, 10.5, 1H, H-4), 3.52 (dd, *J* = 5.0, 12.2, 1H H-1eq), 3.47 (dd, *J* = 9.3, 9.3, 1H, H-3), 3.44 (t, *J* = 6.5, 2H, OCH_2-5′ pentyl), 3.37 – 3.28 (m, 1H, NC*H*H-1′ pentyl), 3.24 – 3.16 (m, 1H, NCH*H*-1′ pentyl), 3.14 (m, 1H, H-5), 3.04 (dd, *J* = 11.3, 12.2, 1H, H-1ax), 3.02 (s, 2H, OCH_2-Ada), 2.75 (s, 3H, CH_3 MsOH), 1.92 (br s, 3H, 3×CH Ada), 1.81 – 1.56 (m, 10H, CH_2-4′ pentyl, 3×CH_2 Ada, CH_2-2′ pentyl), 1.50 (d, *J* = 1.5, 6H, 3×CH_2 Ada), 1.46 – 1.33 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (125 MHz, D_2O) δ 81.7 (OCH_2-Ada), 75.9 (C-3), 71.4 (OCH_2-5′ pentyl), 67.1 (C-4), 66.0 (C-2), 65.3 (C-5), 53.9 (C-6), 53.0 (C-1), 52.7 (NCH_2-1′ pentyl), 39.3 (3×CH_2 Ada), 38.5 (CH_3 MsOH), 36.9 (3×CH_2 Ada), 33.7 (Cq Ada), 28.2 (CH_2-4′ pentyl), 28.1 (3×CH Ada), 22.7 (CH_2-3′ pentyl), 22.3 (CH_2-2′ pentyl). DSC (50 °C » 300 °C; 10 °C/ min): 178.0 °C, 65.2 J/ g. $[\alpha]^{20}_D$ = -3.2 (*c* 1.02, H_2O). Found C: 55.9; H: 8.9; N: 2.8, calculated for $C_{23}H_{43}NO_8S$ = C: 56.0%; H: 8.8%; N: 2.8%. DSC (50 °C » 300 °C; 10 °C/ min): 178.0 °C, 65.2 J/ g.

Method for quantitative determination of residual solvents in **4*MSA** with GC analysis: *Column*: Rtx-624; L: 30 m × D: 320 µm; d_f: 1.8 µm; *Flow*: Helium at 3 mL/min*; Oven temperature*: 40 °C, 2 min; 10 °C/ min » 150 °C; 150 °C, 1 min; *Split*: 50; inlet: 180 °C; *Detection temperature*: 250 °C; *Split/flow*: 150; *Injection volume*: 2 µL*; Detection*: FID; *Runtime*: 14 min; *Sample preparation*: dissolve 80 mg in 1 mL of dimethylacetamide (DMA). t_R (min): methanol = 1.55; ethanol = 2.09; isopropanol = 2.56; CH_2Cl_2 = 2.81; EtOAc = 4.08 min; THF = 4.27; heptane = 5.05; acetic acid = 6.88; toluene = 6.99; DMA = > 9.

Method for qualitative control of **4*MSA** with HPLC: *Column*: C_{18}; D: 2.1 × L: 150 mm; d_P: 3 µm (Waters Atlantis) *Eluent A*: 0.01M aq phosphate buffer/MeOH/CH_3CN = 90:6:4; *Eluent B*: 0.01M aq phosphate buffer/MeOH/CH_3CN = 10:54:36; *Gradient*: (t in min; A/B (v/v); flow in mL/min) 0; 50/50; 0.30 » 4; 50/50; 0.30 » 12; 5/95; 0.30 » 24; 5/95; 0.30 » 25 ; 50/50; 0.30; *Injection volume*: 5 µL; *Temperature*: 30 °C; *Detection*: λ = 203 nm, *Runtime*: 33 min; *Sample preparation*: 4 mg of **4** is dissolved in 1 mL eluent B and filled to 25 mL with CH_3CN. t_R: Benzoic acid = 1.5 min; **4** = 13.7 min; **33** = 18.2 min (detector response of benzoic acid compared to **5** at 203 nm is approximately 100/1).

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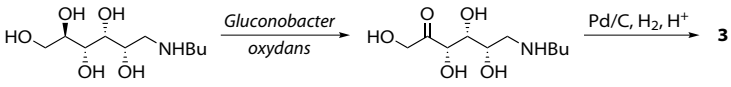

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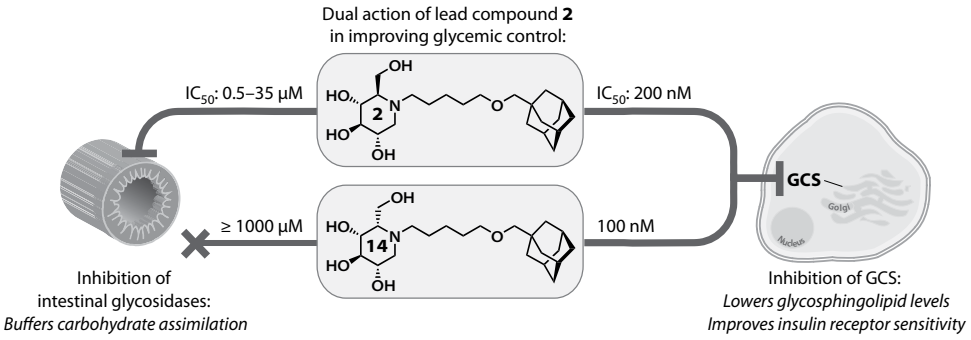
3 Improving Glycemic Control with Lipophilic Iminosugars

Influence of Iminosugar Stereochemistry on the Mode of Action

Abstract

This chapter presents analogues of lead lipophilic iminosugar **2** that vary in C-4/C-5 stereochemistry and functionalization of the nitrogen atom. From these analogues, **14** was identified as an equally potent but much more selective inhibitor of glucosylceramide synthase (GCS). The obtained GCS-selective inhibitor **14** was used to study the mechanism by which **2** improves glycemic control in type 2 diabetes rodent models. It was found that **2** exerts its beneficial effects on glycemic control via a dual action by both lowering of glycosphingolipids in tissues and buffering carbohydrate assimilation in the small intestine.

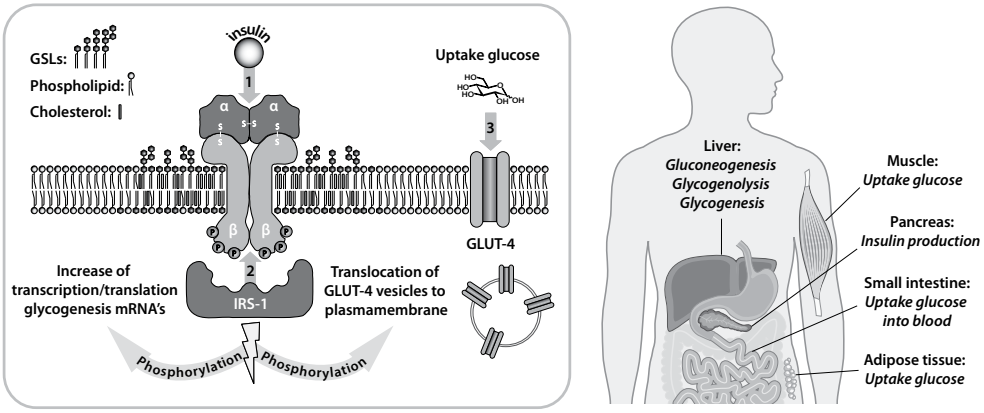


Introduction

Insulin Signaling and Glucose Metabolism.

Human energy metabolism starts with the extraction of carbohydrates (mainly glucose), amino acids and fats from food by the digestive system. An increase of blood glucose levels after eating triggers the increased release of insulin by β-cells of the pancreatic islets of Langerhans. The insulin hormone – a 51 amino acid polypeptide – binds the insulin receptor of insulin-responsive tissues mainly skeletal muscle and fat tissue but also hepatocytes of the liver. The insulin receptor is a dimeric transmembrane polypeptide with tyrosine kinase activity (Figure 1). Upon binding of insulin, the β-domains of the receptor inside the cell phosphorylate themselves, which is recognized by the insulin receptor substrate (IRS-1). IRS-1 binds the β-domains after which it is also phosphorylated and starts a signaling cascade. Amongst others, the signaling cascade may result in the translocation of the glucose transporter, GLUT-4, to the cell surface enabling the active uptake of glucose and thereby lowering/normalizing blood glucose levels – this is called glycemic control. Once inside the cell glucose is trapped by phosphorylation and is subsequently converted into energy by glycolysis. Insulin signaling also upregulates the cellular machinery for glycogenesis that results in the storage of glucose as glycogen – a process that occurs mainly in the liver. Glucose is also converted into fatty acids such as palmitate in the liver that are subsequently released as lipoproteins and absorbed by the fat tissues. Adipocytes in the fat tissues transform absorbed glucose into glycerol-1-phosphate that is esterified with absorbed fatty acids into triglycerides – also known as fat.[1]

Figure 1. Overview of cellular insulin signaling and its effect in the human body.



Obesity and Type 2 Diabetes.

An unhealthy diet with excessive intake of sugar and fat has become commonplace in many developed and developing countries. Combined with the often sedentary lifestyle (*e.g.* low physical activity) of many people nowadays this has led to a rapid increase in

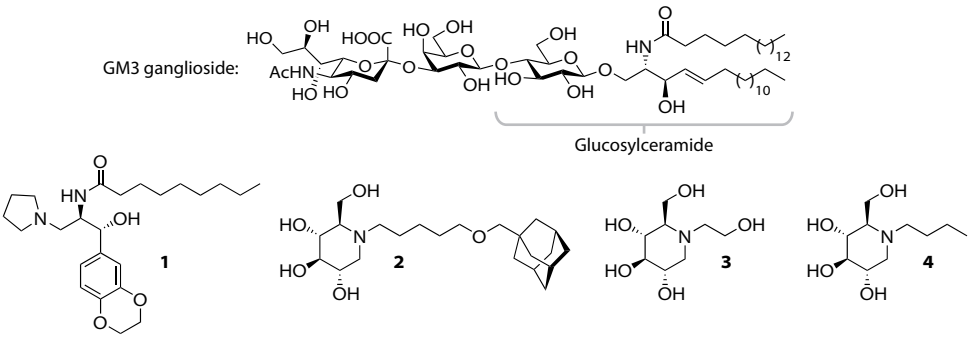
the occurrence of obesity. Coinciding with obesity, type 2 diabetes has reached epidemic proportions worldwide. Currently, 200 million people worldwide are believed to suffer from diabetes[2] – 23.6 million in the USA[3] and 1 million in the Netherlands[4] – and these figures are expected to have doubled in 2050.[5] Type 2 diabetes – also called non-insulin dependent diabetes – is the most common type of diabetes and accounts for ~90% of all cases. Insensitivity of the insulin receptor to insulin signaling, called insulin resistance, is one of the earliest detectable abnormalities during the development of type 2 diabetes. The lower responsiveness to insulin results in its overproduction and an increased glucose concentration in the blood (hyperglycemia) and a diminished ability of the liver, muscles and fat tissues to absorb this glucose. When the blood glucose rises above a certain level the kidneys are unable to resorb it back into the blood and glucose is secreted via excessive urination – hence the original Greek name *diabetes mellitus* meaning honeysweet excretion. The inability of the tissues to absorb glucose has side effects that in the liver cause glycogen degradation (glycolysis) and *de novo* glucose synthesis (gluconeogenesis). In the muscles protein synthesis is inhibited. Adipocytes start to degrade stored fat by oxidation which produces ketone bodies that cause the pH of the blood to drop (acidosis). In the long term these chronic symptoms will lead to damage of the β-cells (resulting in type 1 diabetes), blood vessels, nervous system, kidneys and retinas.[6]

Role of Glycosphingolipids in Insulin Resistance.

The precise cause for the rapidly increasing occurrence of insulin resistance has not been firmly established, but there is growing evidence that obesity and the associated lipotoxicity of excess fat (hyperlipidemia) play a crucial role.[7] Recent literature links insulin resistance to the presence of excessive amounts of a particular group of lipids, the so-called glycosphingolipids (GSLs). GSLs are located on the cell surface and together with cholesterol and specific proteins they congregate to form (detergent resistant) membrane microdomains also called lipid rafts. Recent reports indicate a close physical proximity of the insulin receptor to these microdomains.[8-10] A regulatory role for glycosphingolipids, in particular the ganglioside GM3 (see Figure 2), in insulin sensitivity is substantiated by a rapidly growing body of experimental evidence. Interaction of GSLs and the insulin receptor was originally described by Nojiri *et al.*, demonstrating the ganglioside-mediated inhibition of insulin-dependent cell growth of leukemic cell lines.[11] Tagami and co-workers were the first to demonstrate that addition of GM3 to cultured adipocytes suppresses phosphorylation of the insulin receptor and IRS-1, resulting in reduced glucose uptake.[12] Inokuchi and co-workers reported that exposure of cultured adipocytes to TNF-α increases the levels of GM3 and inhibits insulin receptor and IRS-1 phosphorylation. This was found to be counteracted by 1-phenyl-2-decanoylamino-3-morpholinopropanol (PDMP), an inhibitor of GSL biosynthesis.[13] Mutant mice lacking the capacity to synthesize GM3 have been reported to show an enhanced phosphorylation of the skeletal muscle insulin receptor after insulin binding and to be protected from

high-fat diet induced insulin resistance.[14] Consistent with this is the recent report on improved insulin sensitivity and glucose tolerance in mice with increased expression of the sialidase Neu3 that can degrade the terminal sialic acid of GM3.[15] Conversely, GM3 levels are elevated in the adipose tissue of certain obese, insulin resistant mouse and rat models.[12] Altered sphingolipid metabolism, reflected by increased GSL levels, has recently also been documented in relation to neuronal pathology in diabetic retinopathy.[16] Very recently Kabayami *et al.* provided evidence that the interaction of negatively charged sialic acid residues of GM3 with the insulin receptor is mediated by a specific lysine residue located just above the transmembrane domain of the receptor. Excess levels of GM3 appear to promote the dissociation of the insulin receptor from its membrane microdomain, a location which is essential for insulin signal transduction.[10]

Figure 2. Structure of GM3, glucosylceramide, **1**, **2**, miglitol (**3**) and miglustat (**4**).



Effect of Pharmacological Inhibition of Glucosylceramide Synthase.

The value of pharmacological lowering of excessive GSL levels to improve insulin sensitivity has recently been demonstrated.[17-19] Holland and co-workers reported that inhibition of the synthesis of ceramide, the precursor of GSLs, markedly improves glucose tolerance and prevents the onset of overt diabetes in obese rodents.[18] Zhao *et al.* demonstrated that inhibition of the first step in the biosynthesis of GSLs – catalyzed by glucosylceramide synthase (GCS) at the Golgi apparatus – improves insulin sensitivity. The GCS inhibitor and PDMP analogue **1** lowered blood glucose and HbA1c-hemoglobin[20,21] levels and improved glucose tolerance in insulin resistant rodents (*in vitro* IC_{50} of **1** for GCS is 14 nM).[19] Finally, it was recently shown that treatment of various rodent models of insulin resistance with the lipophilic iminosugar **2**, a well tolerated and potent inhibitor of GCS, very markedly lowered circulating glucose levels, improved oral glucose tolerance, reduced HbA1c, and improved insulin sensitivity in muscle and liver (description for HbA1c can be found in references section).[17]

The interpretation of the beneficial effect of **2** on glycemic control is hampered by the fact that **2** has a dual action and not only reduces GSL levels in tissues, but also reduces carbohydrate assimilation from food by inhibition of intestinal glycosidases.[22,23]

The latter effect is similar to the mode of action of registered anti-diabetics, including the iminosugar miglitol (**3**; Figure 2).[24] Furthermore, **2** also inhibits several other glycosidases among which glucocerebrosidase (GBA1) and β-glucosidase 2 (GBA2)[25] that are associated with glucosylceramide catabolism. To establish the relative importance of GSL lowering by GCS inhibition and reduction of carbohydrate assimilation in the small intestine with regard to insulin sensitivity, an analogue of **2** was needed that inhibits GCS more selectively.

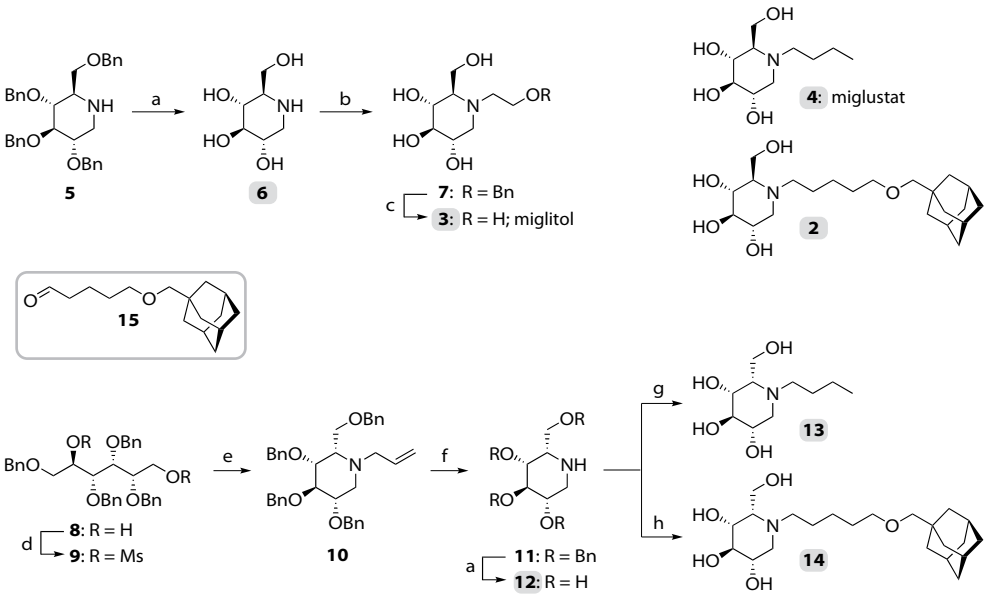
There is literature precedence for C-4/C-5 epimerized *N*-alkylated derivatives of 1-deoxynojirimycin as viable GCS inhibitors. For the research described in this chapter this fact was used as a guide for developing a more selective inhibitor of GCS. The design and synthesis of a panel of nine **2** derivatives is reported in which the D-*gluco*-stereochemistry at C-4 and C-5 of **2** and the type of substitution on the nitrogen atom were varied. All three C-4/C-5 epimers of 1-deoxynojirimycin (L-*ido,* D-*galacto* and L-*altro*) were prepared and the nitrogen in each case was either left unsubstituted, substituted with a butyl for analogues of miglustat (**4**)[26] – a commercial GCS inhibitor – or substituted with a 5-(adamantan-1-yl-methoxy)-pentyl (AMP) group. The selectivity profile of the synthesized inhibitors was assessed for a panel of enzymes that included GCS, GBA1, GBA2 and the intestinal glycosidases. This assay showed that L-*ido*-AMP derivative **14** (the C-5 epimer of **2**) was a more potent and selective inhibitor of GCS. With this result, the relative contributions of the dual action of **2** were further investigated in a subsequent animal study. Compound **2**, **14**, miglitol (**3**), miglustat (**4**) and **1** were compared head-to-head in *ob*/*ob* mouse and ZDF rat models of insulin resistance and type 2 diabetes.

Results

Synthesis of the Iminosugar Inhibitors.

1-Deoxynojirimycin (**6**) was obtained by Pd/C catalyzed hydrogenolysis of 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**5**; from Chapter 2). The synthesis of miglitol (**3**) started with the alkylation of the nitrogen atom in **6**, for which two methods were evaluated (see Scheme 1 on the next page). Chemoselective alkylation of **6** with 2-benzyloxy-1-bromoethane under the agency of potassium carbonate provided **7** in 65% yield. Reductive amination of **6** with commercially available 2-benzyloxyacetaldehyde with sodium cyanoborohydride provided **7** in 86% yield. Hydrogenolysis of **7** with catalytic Pd/C provided **3** in 81% yield over two steps. Formation of the hydrochloric acid salt of miglitol, **3*HCl**, provided a stable compound that was used as such in enzyme assay and animal studies. Lead compound **2** was synthesized starting from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose according to the procedure reported in Chapter 2.[27] Miglustat (**4**) is commercially available and was used in enzyme assay and animal studies as received.

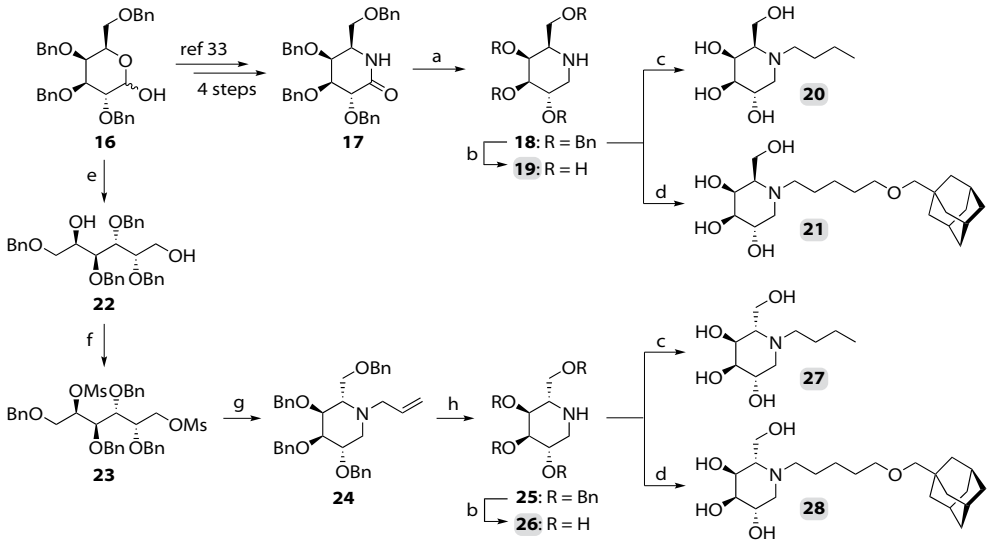
Scheme 1. Synthesis of iminosugars based on D-*gluco* and L-*ido* stereochemistry.



Reagents and conditions: [**a**] Pd/C, 4 bar H_2, EtOH, aq HCl, 20h, **6**: 93%; **12**: 86%. [**b**] Method A: 2-benzyloxy-1-bromoethane, K_2CO_3, DMF, 90 °C, 5h, 65%; Method B: 2-benzyloxyacetaldehyde, $NaCNBH_3$, MeOH/AcOH, 48h, 86%. [**c**] Pd/C, 4 bar H_2, MeOH/H_2O, aq HCl, 20h, 95%. [**d**] MsCl, pyridine, 0 °C, 2h, used crude. [**e**] Allylamine, reflux, 20h, 67% two steps. [**f**] i: KO*t*Bu, DMSO, 100 °C, 30 min; ii: 1M aq HCl, 15 min, 81%. [**g**] i: Butyraldehyde, $NaCNBH_3$, CH_3CN/AcOH, 20h; ii: BCl_3, DCM, 0 °C, 20h, 82% two steps. [**h**] i: **15**, Pd/C, 4 bar H_2, EtOH/AcOH, 20h; ii: Pd/C, 4 bar H_2, EtOH, aq HCl, 20h, 77% two steps.

The three L-*ido*-iminosugars (**12**, **13** and **14**) were synthesized starting from 2,3,4,6-tetra-*O*-benzyl-D-glucitol (**8**). Transformation of the two hydroxyl functions of **8** into their methanesulfonic esters and refluxing the obtained crude dimesylate **9** in allylamine provided **10** (Scheme 1).[28] Isomerization and cleavage of the allyl function in **10** by treatment with potassium *tert*-butoxide and subsequent acidic work-up provided **11**. Benzylamine was also evaluated in this protocol.[29] Although efficiently producing the L-*ido*-iminosugar, the excess benzylamine proved difficult to remove and the subsequent chemoselective cleavage of the *N*-benzyl group proved challenging. Hydrogenolysis of **11** with catalytic Pd/C provided L-*ido*-1-deoxynojirimycin (**12**). Reductive amination of **11** with butyraldehyde under the agency of $NaCNBH_3$ and subsequent deprotection of the crude intermediate with boron trichloride provided **13**.[30] Debenzylation with boron trichloride as opposed to Pd/C catalyzed hydrogenation proved more reproducible for the smaller scale synthesis of certain iminosugars. Synthesis of **14** was achieved by a selective Pd/C catalyzed hydrogenolysis of the intermediate imine between **11** and aldehyde **15** (from Chapter 2) in the presence of acetic acid. Deprotection of the crude intermediate by Pd/C catalyzed hydrogenolysis in the presence of hydrochloric acid produced **14** in a yield of 77% over two steps.[31]

Scheme 2. Synthesis of iminosugars with D-*galacto* and L-*altro* stereochemistry.



Reagents and conditions: [**a**] $LiAlH_4$, THF, reflux, 3h, 71%. [**b**] BCl_3, DCM, 0 °C, 20h, **19**: 96%; **26**: 77%. [**c**] i: Butyraldehyde, $NaCNBH_3$, CH_3CN/AcOH, 20h; ii: BCl_3, DCM, 0 °C, 20h, **20**: 74%; **27**: 91% two steps. [**d**] i: **15**, $NaCNBH_3$, CH_3CN/AcOH, 20h; ii: Pd/C, 4 bar H_2, EtOH, aq HCl, 20h, **21**: 61%; **28**: 89% two steps. [**e**] $NaBH_4$, MeOH, 20h, 81%. [**f**] MsCl, pyridine, 0 °C, 2h, used crude. [**g**] Allylamine, reflux, 20h, 82% two steps. [**h**] i: KO*t*Bu, DMSO, 100 °C, 30 min; ii: 1M aq HCl, 15 min, 73%.

The synthesis of the three D-*galacto*-iminosugars (**19**, **20** and **21**) commenced with the preparation and of 2,3,4,6-tetra-*O*-benzyl-D-galacto-pyranose **16**[32] and its transformation into **17** via a four step procedure as reported by Pandit *et al.* (Scheme 2).[33] Lactam **17** was reduced to **18** with $LiAlH_4$ in refluxing THF. Initially, an attempt was made to synthesize **18** from **22** via the three-step hemiacetal reduction/Swern oxidation/double reductive amination procedure described in Chapter 2. The first two steps of this procedure were successful, but the reductive amination yielded a complex mixture of products containing only trace amounts of **18**.[34] Next, deprotection of the benzyl ethers of **18** with boron trichloride provided **19**. Reductive amination of **18** with either butyraldehyde or 5-(adamantane-1-yl-methoxy)-1-pentanal (**15**) under the agency of $NaCNBH_3$ and subsequent deprotection of the crude *N*-alkylated intermediates produced **20** and **21**. The three L-*altro*-iminosugars (**26**, **27** and **28**) were synthesized starting from 2,3,4,6-tetra-*O*-benzyl-D-galactitol **22** via the same route as described for the L-*ido*-iminosugars **12**, **13** and **14** (Scheme 2).

Inhibition Profile of 2, 3, 4 and 6 and Effect on Glycemic Control in *ob*/*ob* Mice.

The three existing 1-deoxynojirimycin-based iminosugars, lead compound **2**, miglitol (**3**), miglustat (**4**), and 1-deoxynojirimycin (**6**) itself were comparatively investigated with respect to their ability to inhibit three intestinal glycosidases and GCS (see Table 1). To

further investigate their selectivity profile they were also assayed for the glycosidases GBA1, GBA2, lysosomal α-glucosidase and debranching enzyme. The lysosomal α-glucosidase was tested as it is known to be strongly inhibited by **2** and **4** and plays a critical role in lysosomal glycogen degradation during cellular turnover – also known as acid maltase it is the deficient enzyme in Pompe disease. The debranching enzyme is critical for cytosolic glycogen degradation (glycogenolysis) and it possesses both an α-1,4-transferase and α-1,6-glucosidase catalytic site for its substrate.

Table 1. Enzyme inhibition assay results: apparent IC_{50} values in μM (for GCS: % inhibition at μM).

Compound[a]	GCS[b] *in vivo* %	GCS[b] *in vivo* μM	GBA1	GBA2	Lysosomal α-glucosidase	Sucrase	Lactase	Maltase	Debranching enzyme
6: R = H	0	100	250	21	1.5	2	62	2	10
3: R = $(CH_2)_2OH$	0	100	200	9	2.0	0.5	50	6	-
7: R = $(CH_2)_2OBn$	50	360	11	-	3.7	-	-	-	> 10
4: R = Butyl	50	50	400	0.230	0.1	0.5	> 100	9	10
2: R = AMP	50	0.2	0.2	0.001	0.4	0.5	35	4	10
12: R = H	44	10	> 1000	400	> 1000	1000	> 1000	> 1000	> 100
13: R = Butyl	62	10	> 1000	0.25	> 1000	1000	> 1000	1000	> 100
14: R = AMP	75	0.1	2	0.03	> 1000	> 1000	> 1000	1000	> 100
19: R = H	0	10	350	100	6	0.26	1.5	50	10
20: R = Butyl	48	10	320	0.3	1.5	0.46	10	1000	10
21 R = AMP	50	0.5	0.2	< 0.001	0.5	3.5	15	375	4
26: R = H	0	10	> 1000	100	> 1000	220	> 1000	400	> 100
27: R = Butyl	< 10	10	> 1000	9	500	450	> 1000	> 1000	> 100
28: R = AMP	< 10	10	30	0.5	500	1000	> 1000	> 1000	> 100

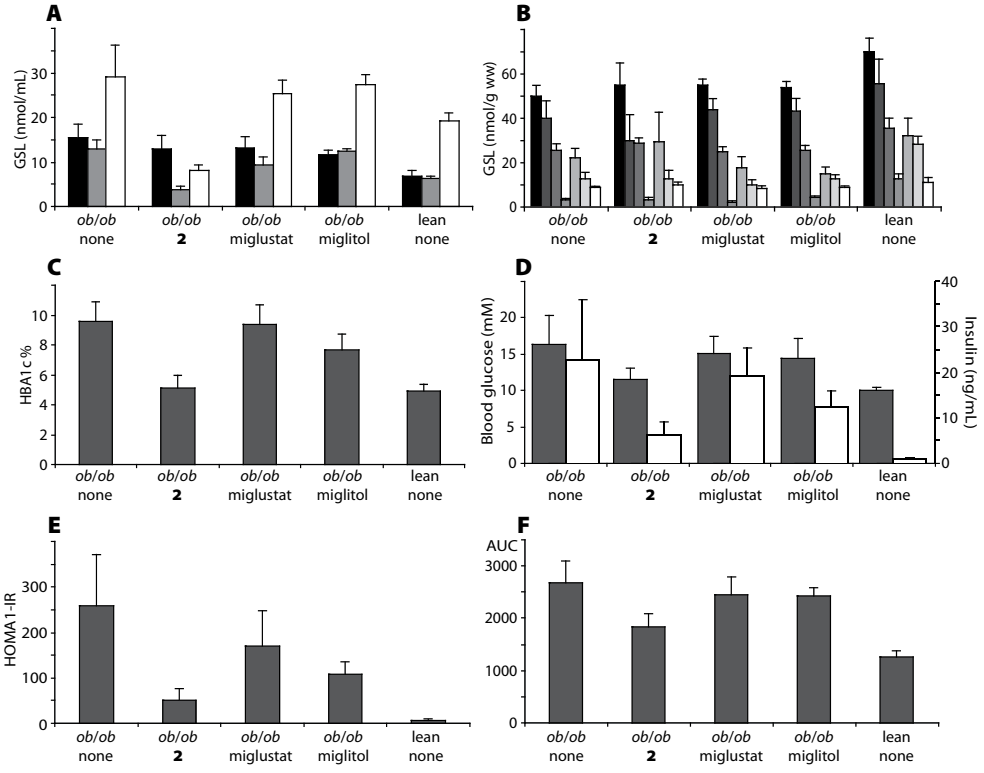
[a]AMP = 5-(adamantan-1-yl-methoxy)-pentyl; [b]Other enzyme assays are *in vitro*.

As expected, the anti-diabetic **3** is a potent inhibitor of the intestinal glycosidases maltase and sucrase. Compounds **2**, **4** and **6** also inhibit these enzymes at μM concentrations. Lead compound **2** in particular is a potent inhibitor of GCS (IC_{50} 0.2 μM), **4** is a weaker inhibitor (IC_{50} 50 μM), whilst **3** and **6** do not inhibit GSL biosynthesis at all. All compounds inhibited the lysosomal α-glucosidase. Debranching enzyme was only inhibited in the high μM range.

Next, the effects of **2**, miglitol (**3**) and miglustat (**4**) on obese, insulin resistant *ob*/*ob* mice were studied. *Ob*/*ob* mice lack the ability to produce the hormone leptin, which is excreted by adipocytes after consumption of sufficient food and suppresses appetite (satiety) and upregulates energy metabolism. This deficiency causes these mice to

become polyphagic (eat too much food), lethargic, obese and eventually develop insulin resistance and other type 2 diabetes-like symptoms. For this part of the study, 7-week old, C57Bl/6J mice (control group) and *ob*/*ob* mice were treated for 4 weeks with 100 mg/kg/day of **2**, **3** or **4**. Only in the case of **2** a significant lowering of plasma and liver GSLs was observed, without concomitant changes in ceramide content (Figure 3 A, B). Mice treated with **2** also showed a markedly lowered circulating blood glucose and insulin, improved HOMA and oral glucose tolerance (OGT), and reduced HbA1c (Figure 3 C-F). Treatment with **4** had marginal positive effects. Treatment with **3** resulted in some reduction of blood glucose and HbA1c, but did not, as expected, improve oral glucose tolerance (a description of Homeostatic Model Assessment (HOMA) can be found in references section).[35-37]

Figure 3. Effects of lead compound **2**, miglitol (**3**) and miglustat (**4**) treatment on GSLs and glycemic control in *ob*/*ob* mice and comparative values in untreated normal C57Bl/6J mice.



Animals were treated for 4 weeks daily with 100 mg compound per kg bodyweight. Panel **A**: plasma content (nmol/mL) of GSLs: ceramide (black); glucosylceramide (grey); total gangliosides (white). Panel **B**: liver content (nmol/g) of GSLs: (left to right) ceramide/10; glucosylceramide; lactosylceramide; GM3; GM2; GM2-glycol/10; GD1a. Panel **C**: HbA1c. Panel **D**: Blood glucose (grey) and insulin (white). Panel **E**: HOMA1-IR index. Panel **F**: Oral glucose tolerance (OGT; area under curve).

L-*Ido* 14, a Potent and More Selective Inhibitor of Glucosylceramide Synthase.

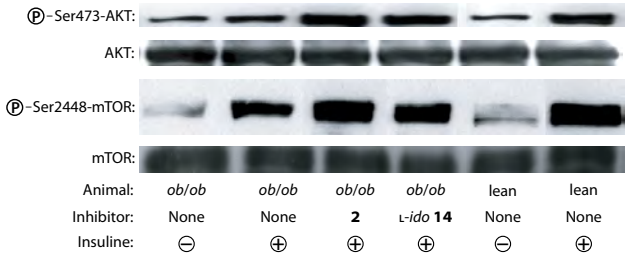
The piperidine rings of 1-deoxynojirimycin (**6**), miglitol (**3**), miglustat (**4**) and **2** possess D-*gluco* stereochemistry. It is a well established fact that structural mimicry of D-glucose is one of the causes for inhibition of intestinal glucosidases by these types of iminosugars. Therefore, changing the iminosugar stereochemistry could result in more selective GCS inhibitors. There is literature evidence that GCS allows manipulation of iminosugar inhibitors at the C-4 and C-5 position of the piperidine ring. Platt, Butters and co-workers have demonstrated previously that *N*-butyl-D-*galacto*-1-deoxynojirimycin (**20**), a C-4 epimer of **4**, still inhibits GCS.[38] The same has also been reported for *N*-pentyl-L-*ido*-1-deoxynojirimycin, a *N*-pentyl substituted C-5 epimer of **4**.[39] The synthesized nine C-4/C-5 analogues of **2** were analyzed for their inhibitory capacity towards the three intestinal glycosidases, GCS and the four other glycosidases (see Table 1).

Of the nine compounds only the three D-*galacto*-iminosugars (C-4 epimer; **19**, **20** and **21**) still substantially inhibit the intestinal glycosidases. This shows that D-glucose stereochemistry at the C-5 position is critical for binding of the active site of sucrase and maltase. Lactase binds and hydrolyzes a D-galactose from lactose and correspondingly **19**-**21** display potent inhibition of this enzyme. All three L-*altro*-iminosugars (C-4 and C-5 epimer; **26**, **27** and **28**) showed very weak to no inhibition of GCS or any of the enzymes except GBA2 – in fact **28** may be regarded as a lead towards the development of GBA2-selective inhibitors. In line with the literature reports, **20**, **21** and the L-*ido*-iminosugars (C-5 epimer; **13** and **14**) do inhibit GCS. The unsubstituted L-*ido*-iminosugar **12**, interestingly, also inhibits GCS to some extent and the D-*galacto*- and L-*ido*-miglustat analogues (**13** and **20**) are inhibitors of GCS in the micromolar range. For the D-*galacto*- and L-*ido*-iminosugars, a great increase in inhibitory potency for GCS is observed when switching from *N*-butyl substitution to *N*-AMP substitution, and a similar trend is seen for GBA1. Compared to **2**, the AMP-substituted D-*galacto*-iminosugar (**21**) is an only slightly less potent inhibitor of GCS, but it inhibits the debranching enzyme and as mentioned above the intestinal glycosidases. However, of particular interest was **14**, which did exhibit the required profile for a potent GCS-selective inhibitor. L-*Ido*-analogue **14** is slightly better than **2** with regard to inhibition of GCS (IC_{50} = 100 nM), but sharply contrasts from **2** in its much reduced capacity to inhibit intestinal glycosidases. Also, **14** is a much poorer inhibitor of GBA1 when compared to lead compound **2** (IC_{50} 1.0 μM *vs* 0.2 μM), acid α-glucosidase (IC_{50} > 1 mM *vs* 0.4 μM), and debranching enzyme (IC_{50} > 1 mM *vs* 10 μM), which further emphasizes its specificity in GCS inhibition. Exposure of various types of cultured cells to **2** and **14** resulted in comparable lowering of GSLs without concomitant increases in ceramide (data not shown). The pharmacokinetic properties of **2** and **14** were also found to be very similar (see Figure 8 in Experimental section).

Comparison of Effects of 2 and L-*ido*-Analogue 14 in *ob*/*ob* Mice and ZDF Rats.

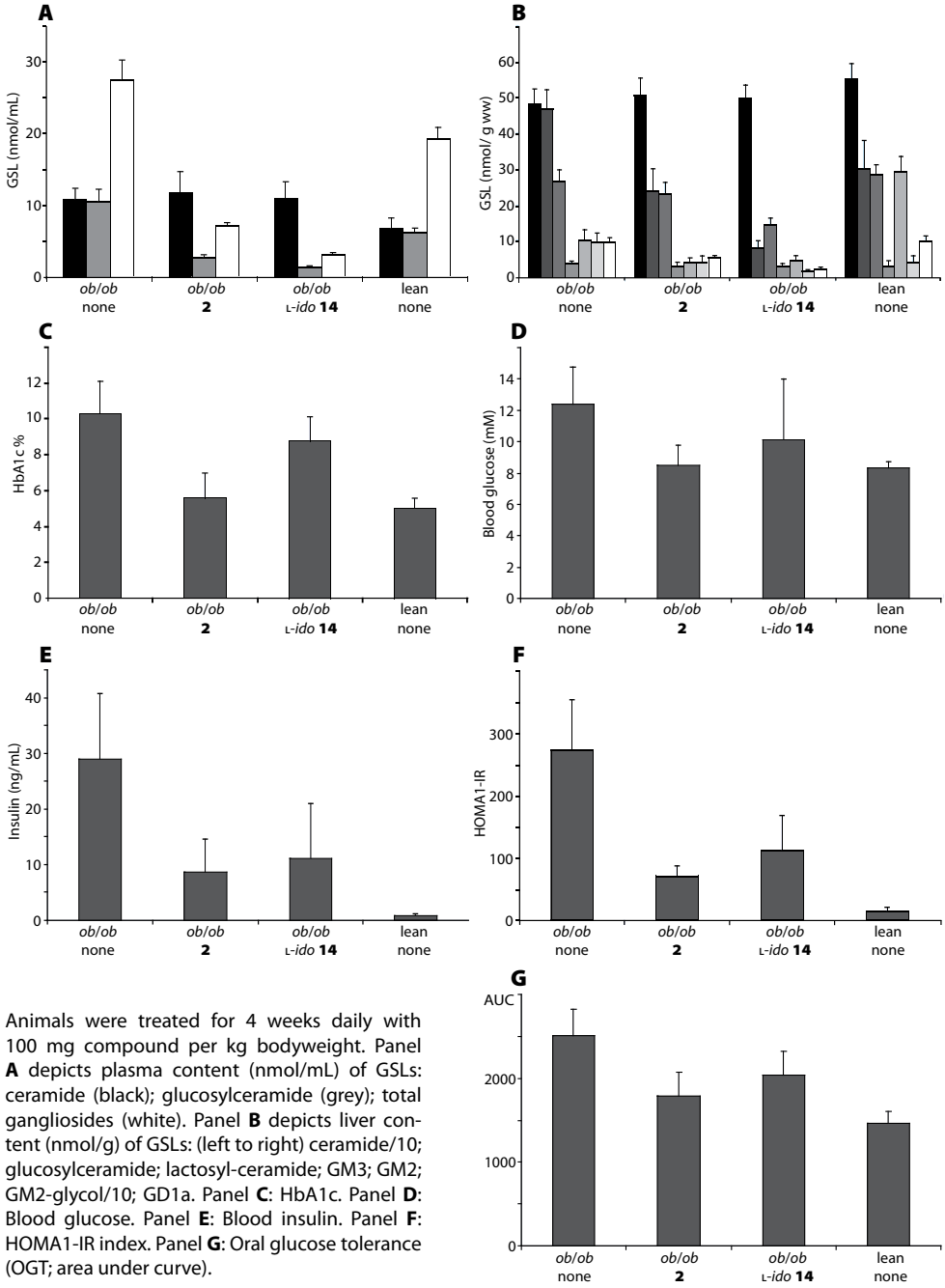
The effect of L-*ido* **14** and **2** on *ob*/*ob* mice was comparatively investigated. For this purpose, 7-week old animals were treated for 4 weeks with 100 mg/kg/day of inhibitor. Insulin signaling in the liver of **14** or **2** treated and untreated *ob*/*ob* mice and untreated lean mice was visualized on immunoblots. These showed comparable significant improvements in phosphorylation of mTor and AKT after insulin stimulation for both **14** and **2** treated *ob*/*ob* mice (Figure 4). mTor and AKT are kinases downstream from IRS-1 in the intracellular insulin initiated phosphorylation cascade. Both treatment with **14** and **2** resulted in significant reduction of GSLs in plasma and liver without affecting ceramide levels (Figure 5 A, B; page 92). No differences were noted in body weight gain or food intake between animals treated with both compounds (data not shown). Although, clear improvements in blood glucose concentration, insulin levels, HOMA and HbA1c were observed in L-*ido* **14** treated animals, these were significantly smaller than those detected in animals treated with **2** (Figure 5 C-F). Of note, oral glucose tolerance was strongly improved in animals treated with L-*ido* **14** (Figure 5 G) – an effect not observed for the intestinal glycosidase targeting miglitol **3** (data not shown).

Figure 4. Effect of **2** and L-*ido* **14** on phosphorylation of liver Ser473-AKT and Ser 2448-mTOR following insulin stimulus.



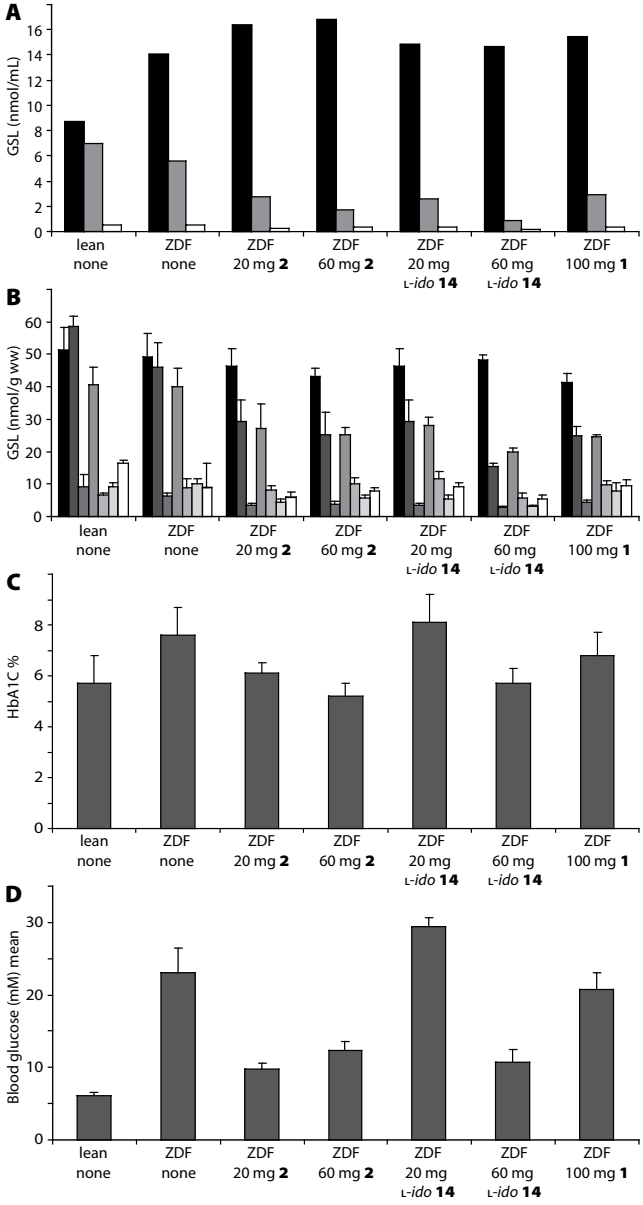
Next, the impact of treatment of obese ZDF rats with **2** and **14** was comparatively investigated. In addition, the effect of **1**[19], a (glucosyl)ceramide analogue and PDMP derivative that specifically inhibits GCS and not intestinal glycosidases (data not shown), was studied in this head-to-head comparison. The ZDF rats lack a receptor for leptin making them polyphagic (eating too much food), become obese and develop type 2 diabetes-like symptoms. All compounds resulted in significant lowering of plasma and liver GSL levels without changes in ceramide content (Figure 6 A, B; page 93). Similar to the findings with *ob*/*ob* mice, treatment of ZDF rats with **2** resulted in more prominent improvements in blood glucose concentration and HbA1c compared to treatment with **14** (Figure 6 C, D). Overall **1** was better in improving glycemic control compared to the lower dosage of **14**, but was outperformed by **2** and the higher dosage of **14**.

Figure 5. Effects of lead compound **2** and L-*ido* **14** on GSLs and glycemic control in *ob/ob* mice and comparative values in untreated normal C57Bl/6J mice.



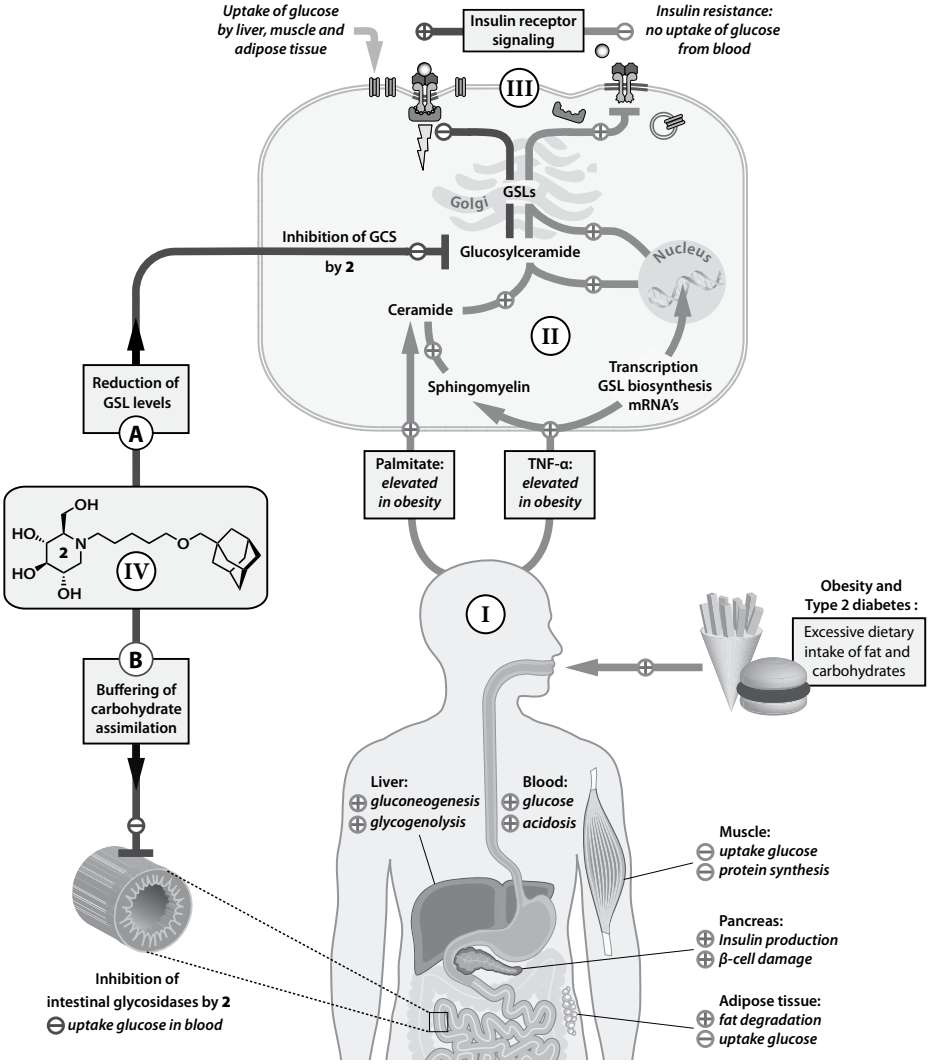
Animals were treated for 4 weeks daily with 100 mg compound per kg bodyweight. Panel **A** depicts plasma content (nmol/mL) of GSLs: ceramide (black); glucosylceramide (grey); total gangliosides (white). Panel **B** depicts liver content (nmol/g) of GSLs: (left to right) ceramide/10; glucosylceramide; lactosyl-ceramide; GM3; GM2; GM2-glycol/10; GD1a. Panel **C**: HbA1c. Panel **D**: Blood glucose. Panel **E**: Blood insulin. Panel **F**: HOMA1-IR index. Panel **G**: Oral glucose tolerance (OGT; area under curve).

Figure 6. Effects of **2**, L-*ido* **14** and **1** on GSLs and glycemic control in ZDF rats and comparative values for lean littermates.



Animals were treated for 4 weeks daily with indicated amount of compound per kg bodyweight. Panel **A** depicts plasma content (nmol/mL) of GSLs: ceramide (black); glucosylceramide (grey); total gangliosides (white). Panel **B** depicts liver content (nmol/g) of GSLs: (left to right) ceramide/10; glucosylceramide; lactosylceramide; GM3; GM2; GM2-glycol/10; GD1a. Panel **C**: HbA1c. Panel **D**: Blood glucose.

Figure 7. Proposed model for improved glycemic control by the dual action (**A**/**B**) of the lipophilic iminosugar **2** in type 2 diabetes.



Excessive dietary consumption of fats and carbohydrates leads to obesity and type 2 diabetes with their associated damaging symptoms (**I**). Obese individuals have elevated palmitate levels and are in a chronic inflammatory state[47] (TNF-α production). These factors together with heightened glucose levels stimulate GSL biosynthesis (**II**). The insulin receptor resides in lipid microdomains that also harbor most GSLs. Elevated GSL levels have been implicated in insulin receptor insensitivity and evidence exists that they bind with and dissociate the receptor from the microdomain, which renders it inactive (**III**). Inhibitor **2** downregulates GSL levels by inhibiting the enzyme GCS (**IV**; action **A**) at the base of GSL biosynthesis. Normalization of GSL levels in the microdomain results in a return of normal receptor functioning. Secondly, **2** improves glycemic control in type 2 diabetes by lowering blood glucose levels through inhibition of intestinal glycosidases (**IV**; action **B**), which limits the amount of glucose generated in the intestine from food. : effects of obesity/diabetes type 2; : effects of lipophilic iminosugar **2**; ⊕: increase of level or activity; ⊖: decrease of level or activity.

Discussion

In an earlier study with **2** it was demonstrated that it has dramatic beneficial effects on the insulin resistance and hyperglycemia seen in ZDF rats, *ob*/*ob* mice and high-fat diet–induced glucose-intolerant mice via a mechanism that does not require a reduction in food intake or loss of bodyweight.[17] In the ZDF type 2 diabetes model, protection of the pancreas by **2** was also observed. Given the ability of **2** to reduce GSLs in tissues as well as to buffer intestinal carbohydrate assimilation, it remained unclear how **2** was impacting glucose homeostasis. The study presented in this chapter dissects the two actions of **2** by the design, synthesis and use of L-*ido*-analogue **14** that inhibits GCS comparably to **2**, but shows greatly decreased inhibition of the intestinal glycosidases. Treatment of *ob*/*ob* mice and ZDF rats with **14** demonstrated that sole reduction of GSLs in tissues prominently contributes to improvements in blood glucose, HbA1c, oral glucose tolerance and insulin signaling in the liver. Improved pancreatic function in the ZDF diabetes model was also observed. These findings are consistent with observations made with **1**. This (glucosyl)ceramide-mimicking GCS inhibitor does not affect intestinal glycosidases and carbohydrate assimilation, but nevertheless helps to control hyperglycemia.

This study also reveals that the concomitant inhibition of intestinal carbohydrate assimilation by **2**, particularly at low concentrations, adds to its prominent beneficial effect on glycemic control in obesity induced type 2 diabetes models (see Figure 7 on page 94). The dual action of **2** is not surprising since the structurally related miglitol (**3**) positively affects glucose homeostasis via selective inhibition of intestinal glycosidases. Based on this mechanism of action, **3** is registered as anti-diabetic drug.[24] Miglitol itself does not inhibit glucosylceramide synthase as measured with cultured cells. Although its more lipophilic monobenzylated analogue (**7**) does slightly inhibit GCS (see Table 1). The present investigation rendered no indication that some metabolite of **3** is formed that causes reduction of GSLs. The development of **3** as anti-diabetic drug was stimulated by the ancient use in the Far East of iminosugar-rich mulberry leaves to control hyperglycemia.[40] Very recently, it has indeed been demonstrated that, compared with a placebo, co-ingestion of mulberry extract – containing 1-deoxynojirmycin (**6**) – with 75 g sucrose reduced the increase in blood glucose observed over the initial two hours of testing in control and type 2 diabetic subjects.[41,42]

Evaluation of known iminosugar-based inhibitors combined with the design and preparation of novel analogues has shown that the C-4/C-5 configuration of the iminosugar and the type of substitution on the nitrogen atom are critical for potent inhibition of GCS (Table 1). In general, iminosugars with D-*gluco*-, D-*galacto* and L-*ido*-stereochemistry in combination with a hydrophobic substituent on the nitrogen atom inhibit GCS. This finding is in agreement with recent unpublished data by Butters.[43] Substitution with a *N*-5-(adamantane-1-yl-methoxy)-pentyl (AMP) group provides the most potent inhibitors of GCS and this trend is also observed for GBA2 and to a lesser extent GBA1. This trend might reflect the lipohilicity of the natural substrates

and products (ceramide/glucosylceramide) of these enzymes. Epimerization of the C-5 position of **2** greatly reduced inhibition of intestinal glycosidases and slightly increased the inhibitory potency for GCS, making L-*ido* **14** the most potent iminosugar-based GCS-selective inhibitor reported to date.

A considerable drawback of compounds that buffer carbohydrate assimilation by virtue of inhibition of intestinal glycosidases is the associated intestinal complaints that lower drug compliance. Compound **14** does not affect intestinal glycosidases. In this respect, the compound is an appealing drug, particularly for conditions in which the exclusive lowering of GSL levels in tissues is desirable without the need for buffering of carbohydrate assimilation. Examples in this respect are the inherited glycosphingolipidoses, such as Gaucher disease, Sandhoff disease, Tay-Sachs disease and Fabry disease.[23] In all these disorders, a particular GSL accumulates in the lysosomes due to an inherited deficiency in a catabolic lysosomal glycosidase. Reduction of GSL biosynthesis by inhibition of GCS is envisioned to be beneficial in all these conditions.[23,44,45] Miglustat (**4**) has been registered as orphan drug for the treatment of mild to moderate type 1 Gaucher disease, and has proven to be efficacious.[26,46] Given the significantly improved features of **14** as compared to **4**, such as better bioavailability, specificity and potency of inhibition of GCS, it seems warranted to investigate its potential as therapeutic agent for inherited glycosphingolipidoses (*e.g.* Gaucher disease).

Conclusion

The analogues of lead lipophilic iminosugar **2** described in this chapter show that C-4 stereochemistry and the 5-(adamantane-1-yl-methoxy)-pentyl group in **2** are critical for potent inhibition of GCS. Epimerization of C-5 retains GCS inhibition and reduces or abolishes inhibition of most other enzymes except for GBA2. The more selective GCS inhibitor (**14**) obtained in this way was used together with **2** to study the mechanism by which **2** improves glycemic control in type 2 diabetes models. It was found that **2** exerts beneficial effects on glycemic control by virtue of its lowering of GSLs in tissues and buffering of carbohydrate assimilation in the small intestine. This dual action is desirable for control of hyperglycemia, a hallmark of type 2 diabetes. L-*Ido* analogue **14** specifically and potently inhibits GSL biosynthesis and may be of interest as an agent to intervene in inherited glycosphingolipidoses.

Experimental section

Animals. Experimental procedures were all approved by the appropriate Ethics Committee for Animal Experiments. C57Bl/6J and *ob*/*ob* mice (C57Bl/6J background) were obtained from Harlan (Horst, the Netherlands) and ZDF (ZDF/GMi-*fa*/*fa*) rats and lean litter mates from Charles River Laboratories (Wilmington, USA). Animals were housed in a light- and temperature controlled facility. Animals were fed a commercially available lab chow (RMH-B, Hope Farms BV, Woerden, the Netherlands) containing about 6% fat and ~0.01% cholesterol (w/w). To induce glucose intolerance in C57Bl/6J mice, animals were fed with a high fat diet (16.4 % protein, 25.5 % carbohydrates and 58.0% fat) for 4 weeks and glucose intolerant mice were selected using an intraperitoneal glucose tolerance test. The iminosugars were mixed in the food. In the case of experiments with ZDF rats the compounds were administered by oral gavage two times daily.

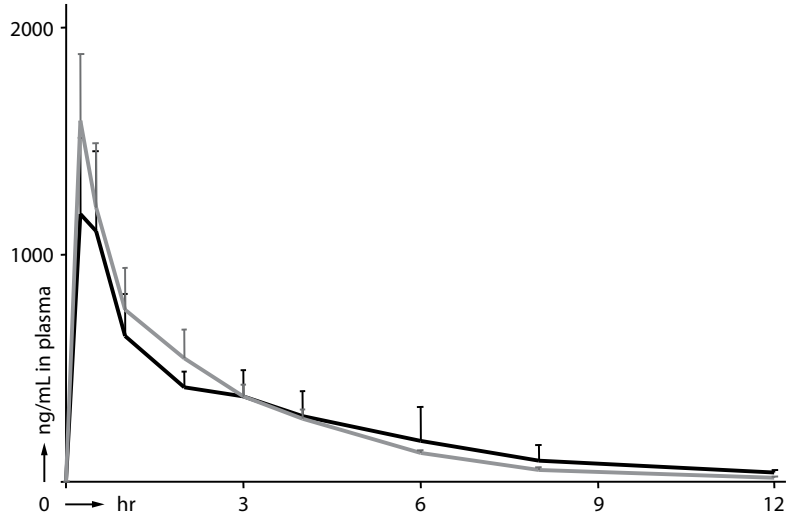
Plasma and tissue sampling. Blood samples were collected by either tail vein or retro orbital plexus puncture. Animals were sacrificed under isoflurane anaesthesia. A large blood sample was collected by cardiac puncture. Tissues were quickly removed and frozen for further analysis.

Analysis of lipids and measurement of enzyme activities. Lipids were extracted according to Folch *et al.*[48] Neutral GSLs were analyzed as described previously.[49] Ganglioside composition was determined as described previously.[50] IC_{50} values of the iminosugars for the various enzyme activities were determined by exposing cells or enzyme preparations to an appropriate range of iminosugar concentrations (DMSO stock solutions diluted with RPMI medium). *In vivo* glucosylceramide synthase assay: The mouse macrophage cell line RAW-267 was grown to 90-100 % confluence in growth medium at 37 °C in a 5% CO_2 incubator. The growth medium consisted of RPMI-1640 + 10% FCS + penicillin (150 µg/mL) and streptomycin (250 µg/mL) + 50 mM Hepes buffer (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid). The incubation flask was washed with RPMI medium without serum (3×5 mL) to remove serum. Cells were taken up in 3 mL RPMI + 50 mM Hepes + 300 µM conduritol B epoxide (10 mM stock in RPMI) + the inhibitor (0.1, 1, 10 µM (20 mM stock in DMSO diluted in RPMI) and 5 nmol C_6-NBD-ceramide/ BSA complex (*N*-[7-(4-nitrobenzo-2-oxa-1,3-diazole)]-6-aminocaproyl-D-*erythro*-sphingosine) were added successively to the cell culture. The cells were incubated for 1 hour at 37 °C in a 5% CO_2 incubator. At the end of incubation, the flask was inspected for potential cytotoxicity of the inhibitor and washed with medium without serum (5×5 mL). A 50 mM potassium phosphate buffer (KPi buffer, pH 5.8, 0.75 mL) was added and the flask was placed in ice. Cells were removed from the flask by scraping and the harvested cells were collected in a capped plastic vial and immediately immersed in liquid nitrogen. The frozen cell lysate (~0.75 mL) was suspended in methanol (3 mL) and extracted with chloroform (3 mL). After extraction a 0.73% NaCl solution (2.0 mL) was added to the biphasic. The aqueous phase was extracted once more with chloroform (1 mL). The combined chloroform layers were isolated and concentrated at 30-40 °C under a nitrogen flow. Lipids were separated by thin-layer chromatography (HP-TLC plates 20×10 silicagel 60 van Merck) using chloroform/ methanol/15 mM aq $CaCl_2$ (60:35:8, v/v/v) as the developing solvent. The C_6-NBD-labeled (glyco)sphingolipids were identified using standards, visualized with a Typhoon Trio Variable Mode Imager (λ_{ex} 488 nM, λ_{em} 520 nM) and quantified with ImageQuant TL software. Glucocerebrosidase activity was measured using recombinant enzyme and 4-methylumbelliferyl-beta-glucose as substrate.[51] GBA2 was measured using enzyme-containing membrane preparations from Gaucher spleen and 4-methylumbelliferyl-β-glucoside as substrate.[51] Lysosomal α-glucosidase was measured using purified enzyme from human urine and 4-methylumbelliferyl-α-glucoside as substrate.[51] Lactase, maltase and sucrase activities were determined with homogenates of freshly isolated rat intestine by measuring liberated glucose from the corresponding disaccharides.[52] The activity of debranching enzyme (α-1,6-glucosidase activity) was measured by determining liberated glucose from dextrin with an erythrocyte preparation as enzyme source.[53]

Pharmokinetic (PK) profiles. Plasma levels of **2** and **14** were determined by mass spectrometry following high pressure liquid chromatography (Xendo, Groningen, the Netherlands). C_{max} = maximum reached concentration in blood; Dose = mg compound divided by weight of animal in kg; $t_{½}$ = half life of compound in blood; AUC_{inf} =Area under the concentration time curve extrapolated to infinity; MRT = mean retention time in blood; F = % oral bioavailability of compound.

Figure 8. Pharmokinetic (PK) profiles of **2** and **14** in ZDF rats

Pharmokinetics	Lead compound **2**	L-*ido* compound **14**	units
C_{max}	1200 ± 400	1600 ± 300	ng·mL
C_{max}/dose	120 ± 40	160 ± 30	ng·mL/(mg/kg)
$t_{½}$	4.2 ± 1.8	2.9 ± 2.0	hr
AUC_{inf}	3400 ± 500	3300 ± 500	ng·hr/mL
AUC_{inf}/dose	340 ± 50	330 ± 50	ng·hr/mL/(mg/kg)
MRT	4.2 ± 0.9	3.0 ± 0.8	hr
F	41 ± 7	52 ± 7	%



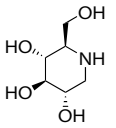
Analysis of insulin signaling in liver. Animals were treated for 4 weeks daily with 100 mg compound per kg bodyweight. Mice (*ob/ob* mice and untreated normal C57Bl/6J mice) were fasted for 4 h, and insulin (0.75 U/kg body weight) was administered intravenously (1 U = 6.00 pmol insulin). After 5 min, animals were killed and livers were quickly collected and lysed in modified radioimmunoprecipitation assay buffer. Lysates were clarified by centrifugation (13,000 rpm for 10min). Equal amounts of lysates were separated by SDS-PAGE, and immunoblots were performed in parallel using the appropriate antibodies; anti-pTyr1446 IR-β, anti-P-Ser473 AKT, anti-P-Ser2448 mTOR and anti-p-70S8K (Cell Signaling Technology Inc., US).

Oral Glucose Tolerance (OGT) test. The tolerance test was performed in fasted animals (> 6 h) with oral gavage of glucose (1 or 2 g of glucose per kg of body weight). Blood glucose values were measured immediately before and 10, 20, 30, 60, 90 and 120 min after glucose injection. AUCs (areas under the curve; arbitrary units per minute) were determined for individual animals.

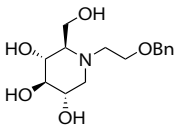
Blood glucose, insulin and HbA1c analysis. The concentrations of glucose, insulin and HbA1c levels in blood samples were determined as described previously.[17]

Statistical testing. Values presented in figures represent mean +/- SEM. Statistical analysis of two groups was assessed by Student's t-test (two-tailed) or ANOVA for repeated measurement. Level of significance was set at $p < 0.05$.

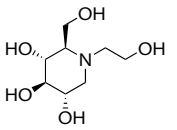
Synthesis of the iminosugars. *General methods and materials*: Lead compound **2** was synthesized as described in Chapter 2 and was used in enzyme assays and animal feeding experiments as its methanesulfonic acid salt (**2*MSA**). Miglustat (**4**) was obtained from Sigma (St Louis, USA). Compound **1** was obtained from Genzyme (Boston, USA) and used as its L-tartaric acid salt (Genz-123346). Reactions were executed at ambient temperature unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere and residual water was removed from the starting material by coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. All chemicals and solvents, unless indicated, were acquired from commercial sources and used as received. THF was distilled prior to use from $LiAlH_4$. EtOH was purged of acetaldehyde contamination by distillation from zinc/KOH. CH_2Cl_2 was distilled prior to use from P_2O_5. Reaction grade acetonitrile, dimethylsulfoxide, isopropanol and methanol were stored on 3Å molsieves. Other reaction grade solvents were stored on 4Å molsieves. Reactions were monitored by TLC analysis using silica gel coated aluminum plates (Schleichter & Schuell, F1500, LS254) and technical grade solvents. Compounds were detected during TLC analysis by UV absorption (254 nm) where applicable and/ or by spraying with a solution of $(NH_4)_6Mo_7O_{24}\times4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times2H_2O$ (10 g/L) in 10% sulfuric acid followed by charring at ~150 °C. Visualization of olefins was achieved by spraying with a solution of $KMnO_4$ (5 g/ L) and K_2CO_3 (25 g/ L) in water. Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at ~150 °C. Visualization of deprotected iminosugar compounds during TLC analysis was accomplished by exposure to molecular iodine vapor. Column chromatography was performed on silica gel (particle size: 40–63 µm) for all compounds. The ^1H and ^{13}C NMR, ^1H–^1H COSY and ^1H–^{13}C HSQC experiments were recorded on a 200/50 MHz, 300/75 MHz, 400/100 MHz, 500/125 MHz or 600/150 MHz spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard for all ^1H NMR measurements in $CDCl_3$ and the deuterated solvent signal for all other NMR measurements. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. All presented ^{13}C NMR spectra are proton decoupled ^{13}C-APT measurements. IR spectra were recorded on an apparatus fitted with a single bounce diamond crystal ATR-element and are reported in cm^{-1}. Optical rotations were measured on an automatic polarimeter (Sodium D-line, λ = 589 nm). Mass spectra were recorded an electronspray interface apparatus. High resolution mass spectra were recorded on a mass spectrometer equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 %, capillary temperature 275 °C) with resolution R = 100000 at *m/z* 400. The high resolution mass spectrometer was calibrated prior to measurements with a calibration solution (caffeine, MRFA, Ultramark 1621). Or high resolution mass spectra were recorded by direct injection (2 µL of a 2 µM solution in H_2O/CH_3CN; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at *m/z* 400 (mass range *m/z* = 150–2000) and dioctylpthalate (*m/z* = 391.28428) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan).



1-Deoxynojirimycin (6). A solution of **5** (1.06 g, 1.91 mmol) in EtOH (50 mL) was acidified to pH ~2 with 1M aq HCl and purged of oxygen by bubbling argon through the solution for 15 minutes. Pd/C (10 wt%, 100 mg) was added and the mixture was exposed to 4 bar of hydrogen for 20 hours. The reaction mixture was filtered over a glass microfiber filter and the filter cake was rinsed successively with MeOH (4×20 mL) and H_2O (2×20 mL). The combined filtrate was concentrated and coevaporated with MeOH (3×50 mL). The residue was purified by column chromatography with aluminum oxide (isocratic 16:3.7:0.3, *n*-propanol:H_2O:NH_4OH) to provide **6** (290 mg, 1.78 mmol) in 93% yield as a white foam. R_F = 0.24 (10:12:3; MeOH:EtOAc:NH_4OH). ^{1}H NMR (400 MHz, D_2O) δ 3.79 (dd, *J* = 3.0, 11.7, 1H, H-6a), 3.59 (dd, *J* = 6.3, 11.7, 1H, H-6b), 3.45 (ddd, *J* = 5.2, 9.1, 10.8, 1H, H-2), 3.28 (dd, *J* = 9.1, 1H, H-3), 3.22 – 3.16 (dd, *J* = 9.1, 9.4, 1H, H-4), 3.08 (dd, *J* = 5.2, 12.3, 1H, H-1a), 2.50 (ddd, *J* = 3.0, 6.2, 9.5, 1H, H-5), 2.42 (dd, *J* = 10.8, 12.3, 1H, H-1b). ^{13}C NMR (100 MHz, D_2O) δ 78.3 (C-3), 71.4 (C-4), 70.8 (C-2), 61.3 (C-6), 60.4 (C-5), 48.6 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3370, 2890, 1453, 1361, 1090, 1039, 1019, 841. $[\alpha]^{20}_D$: 49.5 (*c* 1.3, H_2O). HRMS: found 164.0918 $[M+H]^+$, calculated for $[C_6H_{13}O_4N_1+H]^+$ 164.0917.

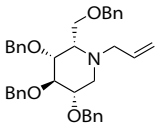


***N*-Benzyloxyethyl-1-deoxynojirimycin (7).** *Method A*: A dry suspension of potassium carbonate (995 mg, 7.2 mmol), **6** (782 mg, 4.8 mmol) and 2-benzyloxy-1-bromoethane (1. 24 g, 5.3 mmol; prepared via a literature procedure[54]) in DMF was heated to 90 °C for 5 h. The reactionmixture was filtered over a glas microfibre filter and the filtrate was concentrated. The residue was purified by silicagel column chromatography (0% » 20% MeOH in $CHCl_3$ + 1% NH_4OH) to provide **7** (929 mg, 3.1 mmol, 3.12 mmol) in 65% yield. *Method B*: Commercially available 2-benzyloxyacetaldehyde (1.18 mL, 8.4 mmol) and $NaCNBH_3$ (703 mg, 11.2 mmol) were successively added to a solution of the HCl salt of 1-deoxynojirimycin (**6**) (1.125 g, 5.6 mmol) in MeOH/AcOH (56 mL, 150/1 v/v). The resulting brown solution was stirred for 48 h and subsequently the pH was adjusted to 8 with saturated aq 1M NaOH. The reaction mixture was concentrated and coevaporated with toluene. The residue was dissolved in methanol, celite was added, and the resulting suspension was concentrated and purified by silicagel column chromatography (0 » 20% MeOH in $CHCl_3$ + 1% NH_4OH) to produce **7** (1.431 g, 4.8 mmol) in 86% yield as a white foam. R_F = 0.15 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (200 MHz, MeOD) δ 7.43 – 7.11 (m, 5H), 4.51 (s, 2H), 3.93 (dd, *J* = 1.9, 12.0, 1H), 3.83 (dd, *J* = 1.7, 12.1, 1H), 3.61 (t, *J* = 5.2, 2H), 3.54 – 3.33 (m, 2H), 3.25 – 2.98 (m, 3H), 2.74 (dt, *J* = 4.7, 14.4, 1H), 2.39 – 2.14 (m, 2H). ^{13}C NMR (50 MHz, MeOD) δ 137.8, 129.2, 128.9, 128.8, 78.2, 73.3, 69.8, 68.7, 66.1, 66.0, 57.2, 56.1, 51.5. IR ν_{max}(thin film)/ cm^{-1}: 3341, 2955, 2716, 1636, 1458, 1396, 1366, 1080, 1026, 748. $[\alpha]^{20}_D$: −0.6 (*c* 3.2, MeOH). HRMS: found 298.1664 $[M+H]^+$, calculated for $[C_{15}H_{23}O_5N_1+H]^+$ 298.1649.

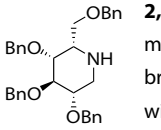


***N*-Hydroxyethyl-1-deoxynojirimycin (3).** A solution of **7** (2.39 g, 8.0 mmol) in MeOH/H_2O (100 mL/15 mL) was acidified to pH ~3 with 36% aq HCl. The solution was purged of oxygen by bubbling argon through the solution after which Pd/C (10 wt%, 400 mg) was added. The mixture was exposed to 4 bar of hydrogen for 20 h. The reaction mixture was filtered over a glass microfiber filter and the filter cake was rinsed successively with MeOH (4×20 mL) and H_2O (2×20 mL). The combined filtrate was concentrated and coevaporated with MeOH (3×50 mL). The residue was purified by silica gel column chromatography (8:2:0.05 » 6:4:0.05, *n*-propanol:H_2O:NH_4OH) to provide **3** (1.583 g, 7.6 mmol) in 95% yield as an off-white foam. R_F = 0.50 (6:4:0.05; *n*-propanol:H_2O:Et_3N). ^{1}H NMR (300 MHz, D_2O) δ 3.94 (dd, *J* = 2.5, 12.8, 1H, H-6a), 3.83 (dd, *J* = 3.0, 12.8, 1H, H-6b), 3.75 (t, *J* = 6.4, 2H, $HOCH_2$-2′), 3.55 (ddd, *J* = 3.8, 7.7, 14.0, 1H, H-2), 3.43 – 3.33 (dd, *J* = 9.1, 9.1, 1H), 3.27 (dd, *J* = 9.1, 9.1, 1H), 3.09 (dd, *J* = 4.8, 11.6, 1H, H-1a), 2.95 (dt, *J* = 6.5, 14.0, 1H, NC*H*H-1′), 2.72 (dt, *J* = 5.8, 14.0, 1H, NCH*H*-1′), 2.43 – 2.29 (m, 2H, H-1b, H-5).^{13}C NMR (50 MHz, D_2O) δ 81.1, 72.9, 71.7, 68.5, 60.9, 60.5, 58.9, 55.8. IR ν_{max}(thin film)/ cm^{-1}: 3333, 2924, 1636, 1420, 1358, 1265, 1080, 1026. $[\alpha]^{20}_D$: −6.5 (*c* 0.56, H_2O). HRMS: found 208.1182 $[M+H]^+$, calculated for $[C_8H_{17}O_5N_1+H]^+$ 208.1185. ***N*-Hydroxyethyl-1-**

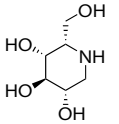
deoxynojirimycin hydrochloric acid salt (3*HCl). A solution of **3** (1.58 g, 7.6 mmol) in water (50 mL) was treated with Dowex OH^- resin for one hour. The resin was removed by filtration and the filtrate was coevaporated with water (3×50 mL). The residue was dissolved in water (50 mL) and treated with 1M aq HCl (8.4 mL, 8.4 mmol). The solution was concentrated, coevaporated with water (3×50 mL) and lyophilized to quantitatively yield **3** (1.865 g, 7.6 mmol) as hygroscopic white foam. ^{1}H NMR (300 MHz, D_2O/ MeOD 1/1) δ 4.15 – 4.04 (m, 2H, CH_2-6), 4.00 (t, *J* = 4.9, 2H, OCH_2-2′), 3.91 – 3.78 (m, 1H, H-2), 3.77 – 3.65 (m, 2H, H-1a, H-4), 3.65 – 3.57 (m, 1H, NC*H*H-1′), 3.53 (dd, *J* = 9.4, 1H, H-3), 3.45 – 3.36 (m, 1H, NCH*H*-1′), 3.33 – 3.25 (m, 1H, H-5), 3.16 (dd, *J* = 11.8, 1H, H-1b).



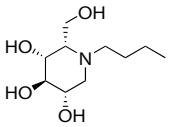
***N*-Allyl-2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (10).** Methanesulfonyl chloride (1.45 mL, 18.75 mmol) was added dropwise to a cooled (0 °C) solution of 2,3,4,6-tetra-*O*-benzyl-D-glucitol **8** (4.070 g, 7.50 mmol; for preparation see Chapter 2) in pyridine (30 mL). After TLC analysis indicated complete consumption of starting material (2 hours; R_F **8** = 0.25 in 2:1; PE:EtOAc), water (20 mL) was added and the reaction mixture was concentrated. The residue was dissolved in EtOAc (100 mL) and washed successively with 1M aq HCl (2×100 mL), sat aq $NaHCO_3$ (100 mL) and sat aq NaCl (100 mL). The organic phase was isolated, dried (Na_2SO_4) and concentrated to yield crude **9** (4.790g, 6.86 mmol) in ~91% yield as a yellow oil. R_F = 0.55 (2:1; PE:EtOAc). Crude **9** (4.790g, 6.86 mmol) was coevaporated with toluene, dissolved in allylamine (34 mL) and refluxed for 20 hours. The reaction mixture was concentrated, dissolved in EtOAc (100 mL) and washed successively with sat aq $NaHCO_3$ (2×100 mL) and sat aq NaCl (100 mL). The organic phase was isolated, dried (Na_2SO_4) and concentrated. The residue was purified by silicagel column chromatography (isocratic 15% EtOAc in PE) to produce **10** (2.591 g, 4.60 mmol) in 67% yield as an orange oil. R_F = 0.8 (2:1; PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.15 (m, 20H, H_{Ar} Bn), 5.84 – 5.70 (m, 1H, =CH allyl), 5.12 (dd, *J* = 1.3, 17.2, 1H, =C*H*H allyl), 5.07 (d, *J* = 10.2, 1H, =CH*H* allyl), 4.85 (d, *J* = 11.1, 1H, C*H*H Bn), 4.80 (d, *J* = 11.1, 1H, CH*H* Bn), 4.68 – 4.55 (m, 4H, 2×CH_2 Bn), 4.46 (s, 2H, CH_2 Bn), 3.83 (dd, *J* = 6.6, 10.2, 1H, H-6a), 3.76 – 3.66 (m, 2H, H-4, H-6b), 3.61 – 3.51 (m, 2H, H-2, H-3), 3.45 – 3.33 (m, 2H, H-5, C*H*H allyl), 3.18 (dd, *J* = 6.9, 14.1, 1H, CH*H* allyl), 2.92 (dd, *J* = 4.5, 11.8, 1H, H-1a), 2.58 – 2.53 (m, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.7, 138.6, 138.5 (4×C_q Bn), 136.2 (=CH allyl), 129.6, 129.2, 128.6, 128.3, 128.2, 128.2, 127.9, 127.7, 127.7, 127.5, 127.5, 127.4, 127.3, 127.1, 126.7 (CH_{Ar} Bn), 117.1 (=CH_2 allyl), 82.9, 80.1 (C-4), 78.7, 75.3, 73.2, 72.8, 72.6 (4×CH_2 Bn), 64.6 (C-6), 59.9 (C-5), 57.9 (NCH_2 allyl), 49.1 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3064, 3030, 2862, 1496, 1453, 1364, 1090, 1068, 914, 733. $[\alpha]^{20}_D$: −19.8 (*c* 18.8, $CHCl_3$). HRMS: found 564.3090 $[M+H]^+$, calculated for $[C_{37}H_{41}O_4N_1+H]^+$ 564.3108.



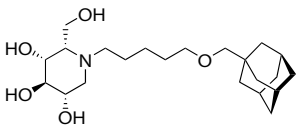
2,3,4,6-Tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (11). Potassium *tert*-butoxide (259 mg, 2.3 mmol) was added to a solution of **10** (2.60 g, 4.61 mmol) in DMSO (9.2 mL) and the resulting brown reaction mixture was heated at 100 °C for 30 minutes. The reaction mixture was charged with 1M aq HCl (9 mL) and stirred vigorously for 15 minutes. The mixture was poured into sat aq $NaHCO_3$ (100 mL) and extracted with Et_2O (3×100 mL). The organic phase was isolated, dried (Na_2SO_4) and concentrated. The residue was purified by silicagel column chromatography (33% » 66% EtOAc in PE) to furnish **11** (1.954 g, 3.73 mmol) in 81% yield as a yellow oil. R_F = 0.2 (1:1; PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 20H, H_{Ar} Bn), 4.67 – 4.50 (m, 8H, 4× CH_2 Bn), 3.67 (dd, *J* = 9.5, 9.5, 1H, H-6a), 3.64 – 3.59 (m, 2H, H-3, H-4), 3.55 (dd, *J* = 5.2, 9.5, 1H, H-6b), 3.44 (dd, *J* = 6.3, 10.5, 1H, H-2), 3.41 – 3.35 (m, 1H, H-5), 3.00 (dd, *J* = 4.1, 12.9, 1H, H-1a), 2.86 (dd, *J* = 6.7, 12.9, 1H, H-1b), 2.00 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.7, 138.6, 138.5 (4×C_q Bn), 128.6, 128.5, 128.5, 128.5, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7 (CH_{Ar} Bn), 78.1, 77.3, 77.1 (C-2), 74.2, 73.5, 72.8, 72.2 (4× CH_2 Bn), 67.4 (C-6), 54.8 (C-5), 44.4 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3064, 3030, 2863, 1496, 1453, 1364, 1092, 1068, 734. $[\alpha]^{20}_D$: −7.6 (*c* 3.3, $CHCl_3$). HRMS: found 524.2776 $[M+H]^+$, calculated for $[C_{34}H_{37}O_4N_1+H]^+$ 524.2795.



L-*Ido*-1-deoxynojirimycin (12). A solution of **11** (329 mg, 0.62 mmol) in EtOH (15 mL) was acidified to pH ~2 with 1M aq HCl and purged of oxygen by bubbling argon through the solution for 15 minutes. Pd/C (10 wt%, 50 mg) was added and the mixture was exposed to 4 bar of hydrogen for 20 hours. The reaction mixture was filtered over a glass microfiber filter and the filter cake was rinsed successively with MeOH (4×20 mL) and H_2O (2×20 mL). The combined filtrate was concentrated and coevaporated with MeOH (3×50 mL). The residue was purified by column chromatography with aluminum oxide (isocratic 16:3.7:0.3, *n*-propanol:H_2O:NH_4OH) to provide **12** (88 mg, 0.54 mmol) in 86% yield as a colorless oil. R_F = 0.18 (10:12:3; MeOH:EtOAc:NH_4OH). ^{1}H NMR (600 MHz, D_2O) δ 4.06 – 4.03 (m, 1H, H-2), 4.02 – 3.98 (m, 2H, H-3, H-4), 3.90 (dd, *J* = 5.0, 12.3, 1H, H-6a), 3.86 (dd, *J* = 9.0, 12.3, 1H, H-6b), 3.58 (ddd, *J* = 2.2, 4.9, 8.9, 1H, H-5), 3.42 (dd, *J* = 2.6, 13.6, 1H, H-1a), 3.34 (dd, *J* = 3.4, 13.6, 1H, H-1b). ^{13}C NMR (150 MHz, D_2O) δ 66.7 (C-4), 66.5 (C-3), 65.7 (C-2), 58.1 (C-6), 55.9 (C-5), 44.4 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3362, 3200, 2924, 2853, 1653, 1635, 1419, 1055, 963. $[\alpha]^{20}_D$: −2.8 (*c* 2.3, H_2O). HRMS: found 164.0912 $[M+H]^+$, calculated for $[C_6H_{13}O_4N_1+H]^+$ 164.0917.



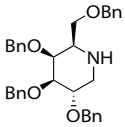
***N*-Butyl-L-*ido*-1-deoxynojirimycin (13).** Butyraldehyde (66 µL, 0.73 mmol) and $NaCNBH_3$ (27 mg, 0.44 mmol) were successively added to a solution of **10** (76 mg, 0.145 mmol) in CH_3CN/AcOH (1.45 mL, 30/1, v/v). The reaction mixture was stirred for 20 hours after which sat aq $NaHCO_3$ (5 mL) was added and the resulting mixture was extracted with Et_2O (3×5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to provide the crude *N*-butylated intermediate (R_F = 0.5 in 4:1; PE:EtOAc). The crude intermediate was coevaporated with dichloroethane and dissolved in DCM (1.5 mL). The solution was cooled to 0 °C and BCl_3 (1.74 mL, 1M in DCM) was added. After stirring for 20 hours at 0 °C MeOH (2 mL) was carefully added. The mixture was concentrated and coevaporated with toluene. The residue was purified by silicagel column chromatography (0% » 20% MeOH in $CHCl_3$ + 1% NH_4OH) to produce **13** (26 mg, 0.12 mmol) in 82% yield over two steps as a colorless oil. R_F = 0.18 (3:1; $CHCl_3$:MeOH + 1% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.06 – 3.96 (m, 3H, CH_2-6, H-4), 3.94 (d, *J* = 7.4, 1H, H-2), 3.83 (s, 1H, H-3), 3.51 (s, 1H, H-5), 3.44 (d, *J* = 12.8, 1H, H-1a), 3.36 – 3.28 (m, 3H, H-1b, CH_2-1 butyl), 1.87 – 1.65 (m, 2H, CH_2-2 butyl), 1.48 – 1.38 (m, 2H, CH_2-3 butyl), 1.01 (t, *J* = 7.4, 3H, CH_3-4 butyl). ^{13}C NMR (100 MHz, MeOD) δ 69.2, 63.8, 55.0, 21.1 (CH_2-3 butyl), 14.1 (CH_3-4 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3279, 2963, 2876, 1637, 1653, 1445, 1063, 979.4. $[\alpha]^{20}_D$: 12.2 (*c* 0.7, MeOH). HRMS: found 220.1538 $[M+H]^+$, calculated for $[C_{10}H_{21}O_4N_1+H]^+$ 220.1543.



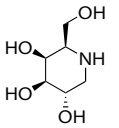
***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (14).** A solution of **10** (1.954 g, 3.73 mmol) and 5-(adamantane-1-yl-methoxy)-1-pentanal **15** (1.029 g, 4.11 mmol) in EtOH/AcOH (93 mL, 9/1, v/v) was purged of oxygen by bubbling argon through the solution. Pd/C (10 wt%, 329 mg,) was added to the solution and the reaction mixture was exposed to 4 bar of hydrogen for 20 hours. Removal of Pd/C by filtration over a glass microfiber filter and concentration of the filtrate provided the crude *N*-alkylated intermediate (R_F = 0.6 in 4:1; PE:EtOAc) as a light yellow oil. A solution of the crude intermediate in EtOH (50 mL) was acidified with 2M aq HCl (12 mL) and purged of oxygen by bubbling argon through the solution. Pd/C (10 wt%, 500 mg) was added to the solution and the reaction mixture was exposed to 4 bar of hydrogen for 20 hours. After removal of Pd/C and concentration, the residue was purified by silicagel column chromatography (0% » 10% MeOH in $CHCl_3$ + 1% NH_4OH) to afford **14** (1.146 g, 2.88 mmol) in 77% yield over two steps as white foam. R_F = 0.3 (3:1; $CHCl_3$:MeOH + 1% NH_4OH). ^{1}H NMR (400 MHz, MeOD, major conformation) δ 3.91 (d, *J* = 5.1, 2H, CH_2-6), 3.85 (s, 1H, , H-2/H-3/H-4), 3.74 (s, 1H, H-2/H-3/H-4), 3.63 (s, 1H, H-2/H-3/H-4), 3.40 (t, *J* = 6.2, 2H, OCH_2-5 pentyl), 3.31 – 3.27 (m, 1H, H-5), 3.23 – 2.97 (m, 4H, CH_2-1, NCH_2-1 pentyl), 2.97 (s, 2H, OCH_2), 1.95 (s, 3H, 3×CH Ada), 1.80 – 1.59 (m, 10H, CH_2-2′ CH_2-4′pentyl, 3×CH_2 Ada), 1.56 (d, *J* = 2.0, 6H, 3×CH_2 Ada), 1.47 – 1.38 (m, 2H, CH_2-3 pentyl).^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2), 72.5 (C-2/C-3/C-4), 72.5 (OCH_2-5 pentyl), 70.2(C-2/C-

3/C-4), 64.1 (C-5), 59.2 (C-6), 55.4 (NCH_2-1 pentyl), 53.6 (C-1), 41.0 (3×CH_2 Ada), 38.5 (3×CH_2 Ada), 35.3 (C_q Ada), 30.5 (CH_2 pentyl), 29.9 (3×CH Ada, CH_2 pentyl), 25.0 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3358, 2902, 2848, 1637, 1451, 1071. $[\alpha]^{20}_D$: 11.0 (*c* 0.4, MeOH). HRMS: found 398.2889 $[M+H]^+$, calculated for $[C_{22}H_{39}O_5N_1+H]^+$ 398.2901.

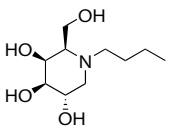
***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin hydrochloric acid salt (14*HCl).** A solution of compound **14** in dioxane/H_2O (~0.3M, 9/1, v/v) was treated with 1M aq. HCl (1.1 eq) and lyophilized to produce **14*HCl** as a white foam. ^{1}H NMR (600 MHz, MeOD, major conformation) δ 4.03 (s, 1H, H-2/H-3/H-4), 4.02 – 3.90 (m, 3H, CH_2-6, H-2/H-3/H-4), 3.87 (s, 1H, H-2/H-3/H-4), 3.52 (s, 1H, H-5), 3.51 – 3.32 (m, 6H, CH_2-1, NCH_2-1 pentyl, OCH_2-5 pentyl), 2.98 (s, 2H, OCH_2), 1.94 (s, 3H, 3×CH Ada), 1.92 – 1.59 (m, 10H, CH_2-2′ CH_2-4 pentyl, 3×CH_2 Ada), 1.56 (s, 6H, 3×CH_2 Ada), 1.47 (s, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD, major conformation) δ 83.2 (OCH_2), 72.4 (C-2/C-3/C-4), 72.3 (OCH_2-5′ pentyl), 69.1 4 (C-2/C-3/C-4), 68.2 4 (C-2/C-3/C-4), 63.9 (C-5), 61.5 (C-6), 55.3 (NCH_2-1′ pentyl), 54.6 (C-1), 41.0 (3×CH_2 Ada), 38.5 (3×CH_2 Ada), 35.3(C_q Ada), 30.3 (CH_2-4′ pentyl), 29.9 (3×CH Ada), 24.8 (CH_2-3′ pentyl), 23.5 (CH_2-2′ pentyl).



2,3,4,6-Tetra-*O*-benzyl-D-*galacto*-1-deoxynojirimycin (18). Lithium aluminumhydride (75 mg, 1.98 mmol) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-galactono-δ-lactam **17** (353 mg, 0.66 mmol, prepared via a literature procedure[33]) in THF (13 mL). The reaction mixture was refluxed for 3 hours or until TLC analysis indicated complete consumption of **17** (R_F = 0.25 in 2:1; PE:EtOAc). The reaction mixture was cooled to ambient temperature and EtOAc (6 mL) was carefully added. The mixture was poured into 1M aq NaOH (50 mL) and the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by silicagel column chromatography (20% » 66% EtOAc in PE) to furnish **18** (247 g, 0.47 mmol) in 71% yield as an orange crystalline solid. R_F = 0.1 (2:1; PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.18 (m, 20H, H_{Ar} Bn), 4.97 (d, *J* = 10.9, 1H, C*H*H Bn), 4.88 – 4.81 (m, 2H, CH*H* Bn, C*H*H Bn), 4.71 – 4.63 (m, 2H, CH_2 Bn), 4.51 – 4.38 (m, 3H, CH*H* Bn, CH_2 Bn), 3.66 (dd, *J* = 2.6, 9.0, 1H, H-6a), 3.58 – 3.45 (m, 3H, H-2, H-3, H-6b), 3.35 (dd, *J* = 8.9, 9.6, 1H, H-4), 3.24 (dd, *J* = 4.8, 12.3, 1H, H-1ax), 2.72 (ddd, *J* = 2.5, 5.9, 9.6, 1H, H-5), 2.50 (dd + br. s, *J* = 10.2, 12.2, 2H, H-1eq, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.6, 138.6, 138.1 (4×C_q Bn), 128.6, 128.5, 128.5, 128.5, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7 (CH_{Ar} Bn), 87.4 (C-3), 80.7 (C-2), 80.2 (C-4), 75.8, 75.3, 73.5, 72.9 (4× CH_2 Bn), 70.3 (C-6), 59.9 (C-5), 48.2 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2862, 1450, 1358, 1088, 1065, 1026, 841, 733. $[\alpha]^{20}_D$: 24.4 (*c* 13.6, $CHCl_3$). HRMS: found 524.2776 $[M+H]^+$, calculated for $[C_{34}H_{37}O_4N_1+H]^+$ 524.2795.

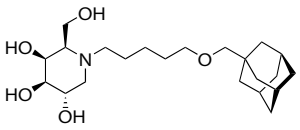


D-*Galacto*-1-deoxynojirimycin (19). Boron trichloride (1.2 mL, 1M in DCM) was added to a cooled (0 °C) solution of **18** (62 mg, 0.118 mmol) in DCM (2 mL). The reaction mixture was stirred for 20 hours at 0 °C after which MeOH (0.5 mL) was carefully added. The reaction mixture was concentrated and coevaporated with toluene. Column chromatography of the residue over aluminumoxide (1:2, MeOH:EtOAc » MeOH » 1:3, H_2O:MeOH) provided **19** (19 mg, 0.116 mmol) in 96% yield as a colorless oil. R_F = 0.24 (10:12:3; MeOH:EtOAc:NH_4OH). ^{1}H NMR (300 MHz, D_2O) δ 3.90 (dd, *J* = 3.2, 12.7, 1H, H-6a), 3.82 (dd, *J* = 5.2, 12.7, 1H, H-6b), 3.74 (ddd, *J* = 5.1, 9.1, 11.5, 1H, H-2), 3.59 – 3.42 (m, 3H, H-1a, H-3, H-4), 3.15 (ddd, *J* = 3.3, 5.1, 10.2, 1H, H-5), 2.92 (dd, *J* = 11.5, 12.3, 1H, H-1b).^{13}C NMR (75 MHz, D_2O) δ 76.9, 68.6, 67.7, 60.6, 58.5, 46.6. IR ν_{max}(thin film)/ cm^{-1}: 3242, 1651, 1405, 1094, 1022. $[\alpha]^{20}_D$: 24.7 (*c* 0.4, H_2O). HRMS: found 164.0912 $[M+H]^+$, calculated for $[C_6H_{13}O_4N_1+H]^+$ 164.0917.

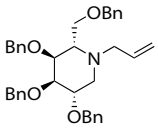


***N*-Butyl-D-*galacto*-1-deoxynojirimycin (20).** Compound **20** (31 mg, 0.14 mmol) was synthesized from **18** (100 mg, 0.19 mmol) in 74% yield as a colorless oil following the procedure as described for **13**. R_F *N*-butylated intermediate = 0.78 (1:1; PE:EtOAc); R_F **20** = 0.13 (3:1; EtOAc:MeOH + 1% NH_4OH). ^{1}H NMR (300 MHz, MeOD) δ 4.02 (dd, *J* = 2.0, 12.4, 1H,

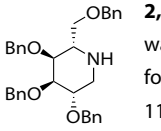
H-6a), 3.89 (dd, *J* = 3.0, 12.4, 1H, H6b), 3.65 (ddd, *J* = 4.9, 9.2, 11.0, 1H, H-2), 3.58 – 3.49 (m, 1H, H4), 3.35 – 3.27 (m, 2H, H-1a, H-3), 3.26 – 3.13 (m, 1H, NC*H*H-1 butyl), 3.08 – 3.00 (m, 1H, NCH*H*-1 butyl), 2.86 – 2.72 (m, 2H, H-1b, H-5), 1.73 – 1.59 (m, 2H, CH_2-2 butyl), 1.46 – 1.32 (m, 2H, CH_2-3 butyl), 0.98 (t, *J* = 7.3, 3H, CH_3-4 butyl).[13]C NMR (75 MHz, MeOD) δ 78.8 (C-3), 69.8 (C-4), 68.7 (C-2), 67.5 (C-5), 56.4 (C-6), 55.6 (C-1), 53.9 (NCH_2-1 butyl), 26.6 (CH_2-2 butyl), 21.3 (CH_2-3 butyl), 14.2 (CH_3-4 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3312, 2962, 2876, 1654, 1458, 1380, 1085, 1050, 1029. $[\alpha]^{20}_D$: −4.5 (*c* 0.6, MeOH). HRMS: found 220.1539 $[M+H]^+$, calculated for $[C_{10}H_{21}O_4N_1+H]^+$ 220.1543.



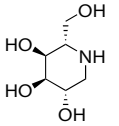
***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-D-*galacto*-1-deoxynojirimycin (21).** Compound **21** (45 mg, 0.11 mmol) was synthesized from **18** (94 mg, 0.18 mmol) and **15** (90 mg, 0.36 mmol) in 61% yield as a colorless oil following the reductive amination procedure as described for **13** and deprotected as described for compound **14**. Silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ + 1% NH_4OH). R_F *N*-alkylated intermediate = 0.68 (2:1; PE:EtOAc); R_F **21** = 0.19 (3:1; EtOAc:MeOH + 1% NH_4OH). [1]H NMR (400 MHz, MeOD, COSY) δ 3.97 (d, *J* = 12.0, 1H, H-6a), 3.88 (d, *J* = 12.0, 1H, H-6b), 3.63 – 3.54 (m, 1H, H-2), 3.50 – 3.46 (m, 1H, H-4), 3.41 (t, *J* = 6.1, 2H, CH_2-5 pentyl), 3.27 – 3.21 (m, 2H, H-1a, H-3), 3.12 – 3.04 (m, 1H, NC*H*H-1 pentyl), 2.98 (s, 2H, OCH_2), 2.95 – 2.86 (m, 1H, NCH*H*-1 pentyl), 2.65 – 2.54 (m, 2H, H-1b, H-5), 1.95 (s, 3H, 3×CH Ada), 1.80 – 1.59 (m, 10H, CH_2-2 CH_2-4 pentyl, 3×CH_2 Ada), 1.56 (s, 6H, 3×CH_2 Ada), 1.47 – 1.39 (m, 2H, CH_2-3 pentyl). [13]C NMR (100 MHz, MeOD) δ 83.3 (OCH_2), 79.5 (C-3), 72.5 (OCH_2-5 pentyl), 70.6 (C-4), 69.4 (C-2), 67.5 (C-5), 57.7 (C-6), 56.4 (C-1), 54.1 (NCH_2-1 pentyl), 41.0 (3×CH_2 Ada), 38.5 (3×CH_2 Ada), 35.3 (C_q Ada), 30.5 (CH_2-4 pentyl), 29.9 (3×CH Ada), 25.1 (CH_2-2 pentyl), 24.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3349, 2900, 2848, 1735, 1652, 1452, 1093, 1030. $[\alpha]^{20}_D$: 10.7 (*c* 0.28, MeOH). HRMS: found 398.2892 $[M+H]^+$, calculated for $[C_{22}H_{39}O_5N_1+H]^+$ 398.2901.



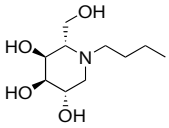
***N*-Allyl-2,3,4,6-tetra-*O*-benzyl-L-*altro*-1-deoxynojirimycin (24).** Compound **24** (1.970 g, 3.50 mmol) was synthesized starting from 2,3,4,6-tetra-*O*-benzyl-D-galactitol **22** (2.324 g, 4.28 mmol, prepared via a literature procedure[32]) in 82% yield over two steps following the procedure as described for **10**. R_F intermediate dimesylate **23** = 0.67 (1:1; PE:EtOAc); R_F **24** = 0.48 (5:1; PE:EtOAc). [1]H NMR (400 MHz, $CDCl_3$, major conformation) δ 7.34 – 7.21 (m, 20H, H_{Ar} Bn), 5.83 (dddd, *J* = 4.8, 7.7, 10.2, 15.0, 1H, =CH allyl), 5.10 (m, 2H, =CH_2 allyl), 4.73 (d, *J* = 11.9, 1H, C*H*H Bn), 4.60 – 4.41 (m, 7H, CH*H* Bn, 3×CH_2 Bn,), 4.07 (dd, *J* = 3.0, 6.7, 1H, H-3), 4.01 – 3.91 (m, 3H, H-2, H-5, H-6a), 3.75 (dd, *J* = 6.4, 10.6, 1H, H-6b), 3.69 – 3.60 (m, 1H, C*H*H allyl), 3.31 (dd, *J* = 5.3, 10.7, 1H, H-1a), 3.24 (dd, *J* = 4.6, 6.7, 1H, H-4), 2.99 (dd, *J* = 7.7, 14.2, 1H, CH*H* allyl), 2.39 (dd, *J* = 4.9, 10.7, 1H, H-1b). [13]C NMR (100 MHz, $CDCl_3$, major conformation) δ 139.2, 138.8, 138.2, 138.1 (4×C_q Bn), 136.0 (=CH allyl), 128.3, 128.2, 128.2, 128.1, 128.1, 127.6, 127.4, 127.4, 127.2, 127.1 (CH_{Ar} Bn), 116.4 (=CH_2 allyl), 83.9 (C-3), 82.1 (C-2), 78.6 (C-5), 73.0 (CH_2 Bn), 72.3 (C-6), 72.1 (CH_2 Bn), 71.3 (CH_2 Bn), 66.4 (C-4), 59.3 (NCH_2 allyl), 56.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3064, 3031, 2861, 1496, 1453, 1362, 1205, 1090, 1073, 1026, 914, 733. $[\alpha]^{20}_D$: −13.6 (*c* 3.1, $CHCl_3$). HRMS: found 564.3090 $[M+H]^+$, calculated for $[C_{37}H_{41}O_4N_1+H]^+$ 564.3108.



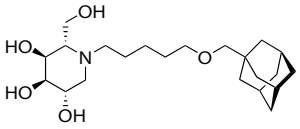
2,3,4,6-Tetra-*O*-benzyl-L-*altro*-1-deoxynojirimycin (25). Compound **25** (1.211 g, 2.31 mmol) was synthesized from **24** (1.793 g, 3.18 mmol) in 73% yield following the procedure as described for **11**. R_F = 0.10 (1:1; PE:EtOAc). [1]H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 20H, H_{Ar} Bn), 4.75 (d, *J* = 11.5, 1H, C*H*H Bn), 4.59 – 4.43 (m, 7H, CH*H* Bn, 3×CH_2 Bn), 4.10 (d, *J* = 3.9, 1H, H-5), 3.96 (dd, *J* = 2.2, 5.3, 1H, H-2), 3.94 – 3.83 (m, 2H, H-3, H-6a), 3.68 (dd, *J* = 4.8, 10.5, 1H, H-6b), 3.48 (dd, *J* = 3.9, 9.3, 1H, H-4), 3.33 (dd, *J* = 5.4, 12.2, 1H, H-1a), 2.92 (dd, *J* = 2.3, 12.2, 1H, H-1b), 1.95 (s, 1H, NH). [13]C NMR (75 MHz, $CDCl_3$) δ 139.2, 138.6, 138.4, 138.3, 128.6, 128.5, 128.5, 128.4, 127.9, 127.8, 127.7, 127.5, 82.4, 82.3, 77.6, 73.5, 72.4, 71.8, 71.4, 71.3, 62.2, 51.6. IR ν_{max}(thin film)/ cm^{-1}: 3064, 3030, 2862, 1486, 1453, 1359, 1206, 1092, 1026, 733. $[\alpha]^{20}_D$: −15.8 (*c* 2.0, $CHCl_3$). HRMS: found 524.2777 $[M+H]^+$, calculated for $[C_{34}H_{37}O_4N_1+H]^+$ 524.2795.



L-*Altro*-1-deoxynojirimycin (26). Compound **26** (449 mg, 0.86 mmol) was synthesized from **25** (108 mg, 0.66 mmol) in 77% yield following the procedure as described for **12**. R_F = 0.09 (10:12:3; MeOH:EtOAc:NH_4OH). ^1H NMR (400 MHz, D_2O) δ 4.40 – 4.38 (m, 2H, H-2, H-3), 4.13 (dt, *J* = 5.2, 8.8, 1H, H-5), 3.80 – 3.69 (m, 4H, H-1a, H-4, CH_2-6), 3.31 (d, *J* = 13.2, 1H, H-1b). ^{13}C NMR (100 MHz, D_2O) δ 75.0 (C-2/C-3), 74.1 (C-2/C-3), 67.3 (C-5), 63.7 (C-6), 62.6 (C-4), 51.9 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3326, 2925, 1590, 1454, 1088, 1043. $[\alpha]^{20}_D$: –27.9 (*c* 0.4, H_2O). HRMS: found 164.0913 $[M+H]^+$, calculated for $[C_6H_{13}O_4N_1+H]^+$ 164.0917.



***N*-Butyl-L-*altro*-1-deoxynojirimycin (27).** Compound **27** (19 mg, 87 µmol) was synthesized from **25** (50 mg, 96 µmol) in 91% yield as a colorless oil following the procedure as described for **13**. R_F *N*-butylated intermediate = 0.45 (4:1; PE:EtOAc); R_F **27** = 0.18 (3:1; EtOAc:MeOH + 1% NH_4OH). ^1H NMR (400 MHz, MeOD) δ 4.25 (dd, *J* = 2.4, 4.4, 1H, H-3), 4.12 – 4.09 (m, 1H, H-2), 4.03 (dd, *J* = 10.0, 14.8, 1H, H-5), 3.76 (ddd, *J* = 5.4, 11.2, 16.6, 2H, CH_2-6), 3.65 (dd, *J* = 4.8, 11.6, 1H, H-1a), 3.29 – 3.22 (m, 1H, H-4), 3.19 – 3.12 (m, 1H, NC*H*H-1 butyl), 2.74 – 2.72 (m, 2H, H-1b, NCH*H*-1 butyl), 1.65 – 1.58 (m, 2H, CH_2-2 butyl), 1.45 – 1.31 (m, 2H, CH_2-3 butyl), 0.96 (t, *J* = 7.3, 3H, CH_3-4 butyl). ^{13}C NMR (100 MHz, MeOD) δ 78.7 (C-3), 76.4 (C-2), 70.6 (C-5), 70.0 (C-4), 65.1 (C-6), 60.0 (C-1), 57.5 (NCH_2-1 butyl), 30.0 (CH_2-2 butyl), 21.3 (CH_2-3 butyl), 14.2 (CH_3-4 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3338, 2933, 1652, 1459, 1035. $[\alpha]^{20}_D$: –44.5 (*c* 0.2, MeOH). HRMS: found 220.1539 $[M+H]^+$, calculated for $[C_{10}H_{21}O_4N_1+H]^+$ 220.1543.



***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-L-*altro*-1-deoxynojirimycin (28).** Compound **28** (34 mg, 85 µmol) was synthesized from **25** (50 mg, 96 µmol) in 89% yield as a colorless oil following the reductive amination procedure as described for **13**, but now with 5-(adamantane-1-yl-methoxy)-1-pentanal **15** (48 mg, 0.19 mmol) and the deprotection procedure as described for **14**. Silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ + 1% NH_4OH). R_F *N*-alkylated intermediate = 0.60 (4:1; PE:EtOAc); R_F **28** = 0.27 (3:1; EtOAc:MeOH + 1% NH_4OH). ^1H NMR (400 MHz, MeOD) δ 4.21 (dd, *J* = 2.7, 4.8, 1H, H-3), 4.11 – 4.07 (m, 1H, H-2), 4.03 – 3.98 (m, 1H, H-5), 3.76 (d, *J* = 5.3, 2H, CH_2-6), 3.59 (dd, *J* = 5.1, 11.1, 1H, H-1a), 3.40 (t, *J* = 6.3, 2H, OCH_2-5 pentyl), 3.15 – 3.10 (m, 1H, H-4), 3.10 – 3.02 (m, 1H, NC*H*H-1 pentyl), 2.97 (s, 2H, OCH_2), 2.64-2.58 (m, 2H, H-1b, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.79 – 1.67 (m, 6H, 3×CH_2 Ada), 1.66 – 1.58 (m, 4H, CH_2-2, CH_2-4 pentyl), 1.56 (d, *J* = 2.5, 6H, 3×CH_2 Ada), 1.46 – 1.38 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (75 MHz, D_2O) δ 83.2 (OCH_2), 79.2 (C-3), 76.8 (C-2), 72.5 (OCH_2-5 pentyl), 71.3 (C-5), 69.6 (C-4), 65.3 (C-6), 60.0 (C-1), 57.7 (NCH_2-1 pentyl), 41.0 (3×CH_2 Ada), 38.5 (3×CH_2 Ada), 35.3 (C_q Ada), 30.6 (CH_2-4 pentyl), 29.9 (3×CH Ada), 28.2 (CH_2-2 pentyl), 25.1 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3360, 2902, 2849, 1652, 1452, 1110. $[\alpha]^{20}_D$: –28.8 (*c* 0.3, MeOH). HRMS: found 398.2888 $[M+H]^+$, calculated for $[C_{22}H_{39}O_5N_1+H]^+$ 398.2901.

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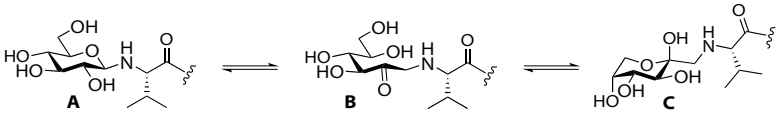

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Note: Attempted benzyl deprotection of **14** with BCl_3 at 0 °C for 20 h resulted in concomitant cleavage of the adamantane-1-yl-methoxy ether.

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(34) Note on synthesis of **18**: Double reductive aminations of C-1/C-5 diketone intermediates selectively provide β-aza-*C*-D-galactosides in good yields as reported by van Boom[55] and Mootoo.[56]

(35) *Note on HOMA values*: The homeostatic model assessment (HOMA)[36] of β-cell function and insulin resistance (IR) was first described in 1985. The physiological basis of the HOMA model is a predictable feedback loop between the liver and the β-cell during a fasting period. The blood glucose concentration in a fastening state is regulated by the rate of *de novo* glucose synthesis by the liver (gluconeogenesis), which is insulin and insulin receptor sensitivity dependent. The blood insulin concentration is dependent on β-cell response to the blood glucose concentration. Insulin levels regulate the uptake of glucose by fat tissue and skeletal muscles, which is dependant on insulin receptor sensitivity in these tissues. Uptake of glucose in the brain (~50% turnover of total fastening glucose) and disposal by the kidneys is only dependant on glucose concentration. In this study the adapted model of Matthews (HOMA1-IR)[36] was used; the HOMA1-IR = fasting blood insulin concentration (mU/L) × fasting blood glucose concentration (mmol/L) / 22.5 – a lower value means less insulin resistance and better glycemic control.

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Note on C-4/ C-5 epimerized miglustat (**4**) derivatives: Page 255 of Chapter 11 by Butters lists the following GCS IC_{50} values as unpublished data: **4**: 20 μM; **13** (L-*ido*): 27 μM; **20** (D-*galacto*): 40 μM; **27** (L-*altro*): 70 μM. A recently discovered patent[57] by Butters and coworkers lists the following GCS IC_{50} values: **4**: 15 μM; **13** (L-*ido*): 10.6 μM; **20** (D-*galacto*): 32.5 μM; **27** (L-*altro*): 73.1 μM. The patent also lists a GCS IC_{50} value for *N*-pentyl-L-*ido*-1-deoxynojirimycin[39] of 4.0 μM. Especially, the trend in the values from the patent corresponds well with the IC_{50}'s determined for the study described in this chapter. Differences can be caused by the fact that all the values from Butters were determined with an *in vitro* assay[38] on HL-60 cell microsomal preparations.

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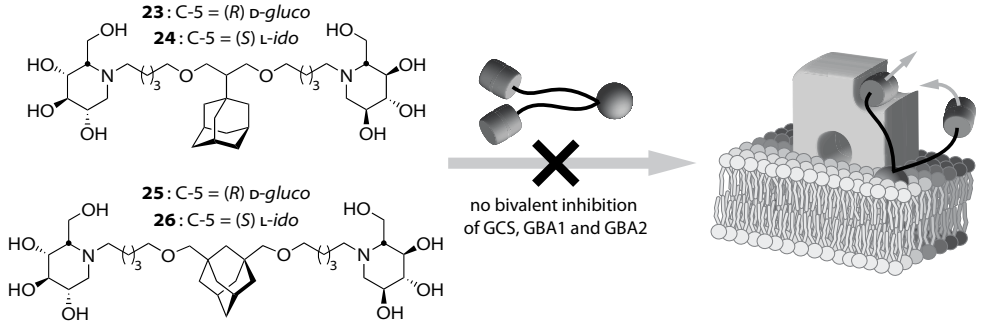
4 Dimeric Lipophilic Iminosugars

Evaluation as Bivalent Glucosylceramide Metabolism Inhibitors

Abstract

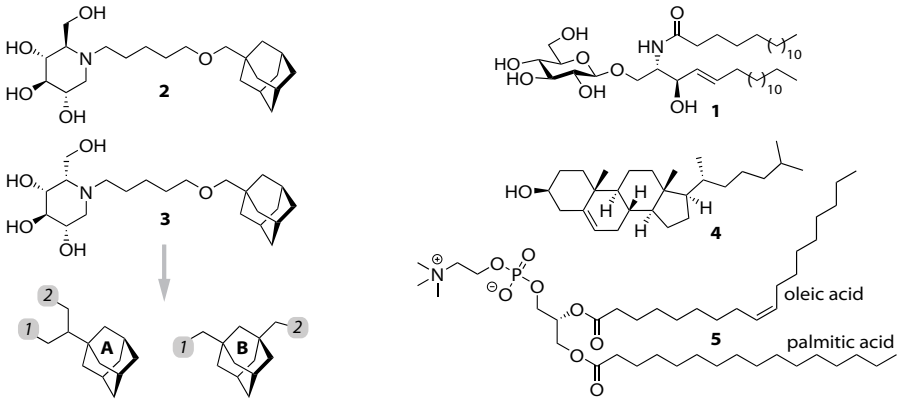
This chapter describes the design, synthesis and evaluation of dimeric lipophilic iminosugars **23**, **24**, **25** and **26**. Compounds **23**–**26** were evaluated for inhibition of the three glucosylceramide metabolism related enzymes, GBA1, GBA2 and GCS and the glycosidases, lysosomal α-glucosidase and sucrase. Comparison of the enzyme assay results of **23**–**26** and their monomeric equivalents showed that the dimeric iminosugars do not inhibit any of the tested enzymes with greater potency.



Introduction

Glucosylceramide (**1**; Figure 1) and its more complexly glycosylated derivatives are called glycosphingolipids (GSLs). They are components of the outer cellular membrane and are involved in many (patho)physiological processes in humans, such as intercellular recognition, signaling processes (e.g. insulin signaling, see Chapter 3) and interactions with pathogens.[1,2] In the metabolism of GSLs, glucosylceramide (**1**) functions as the crucial precursor for the biosynthesis of most complex glycosphingolipids. The biosynthesis of **1** takes place at the cytosolic side of the Golgi apparatus by the membrane-bound enzyme – glucosylceramide synthase (GCS). This glycosyltransferase catalyzes the glycosylation of α-UDP-D-glucopyranoside with ceramide to produce **1**. The main pathway for catabolism of **1** occurs in the lysosome where glucocerebrosidase (GBA1), with assistance of activator protein saposin C, catalyzes the hydrolysis of the β-glycosidic bond between ceramide and glucose in **1**. A third enzyme, the membrane bound β-glucosidase 2 (GBA2) has recently been identified as being capable of hydrolyzing **1** and is thought to be located on the outside of the plasmembrane.[3,4]

Figure 1. Left: inhibitors **2** and **3** and the general design of the dimeric inhibitors; Right: membrane components glucosylceramide (**1**), cholesterol (**4**) and phosphatidylcholine lipid (**5**).

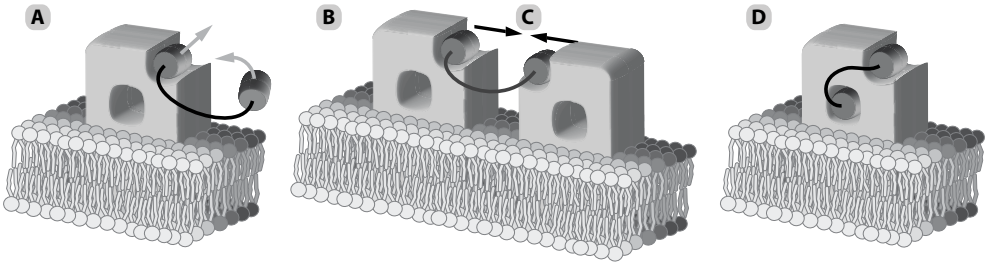


The research described in this thesis aims to develop selective inhibitors for each of these three enzymes. Potent and selective inhibitors of these enzymes can be used as tools to further investigate the diverse functions of GSLs, but also hold potential as therapeutics for diseases associated with abnormal GSL metabolism such as lysosomal sphingolipidoses[5,6] and type 2 diabetes.[7] The lipophilic iminosugar **2**, which is a known inhibitor of all three enzymes, was chosen as a lead compound (Figure 1).[8,9] The structure of **2** can be divided in three parts, the iminosugar core, a pentyl spacer and the adamantan-1-yl-methoxy hydrophobic moiety. Modification of the stereochemistry of the iminosugar core has shown that epimerization of C-5 to L-*ido*-analogue **3** leads to a slightly more potent inhibitor of GCS and increases the selectivity for this enzyme (see Chapter 3). The results from chapter 3 and previous studies have also shown the importance of the adamantane

moiety in achieving potent inhibition of GCS, GBA1 and GBA2. Both GCS and GBA2 are membrane-bound and the role of the hydrophobic adamantane might be to concentrate the iminosugar inhibitor at the location of these enzymes. If this hypothesis holds true, then appending a second iminosugar to the adamantane could increase the local concentration of the iminosugar at the enzyme's active site even further, with an altered inhibitory potency as a result.

In nature, related bivalent or indeed multivalent interactions are often encountered as a way of improving the interactions between receptor and ligand.[10] Multivalancy has also been adopted as a strategy in pharmaceutical research as a way of improving interactions of natural receptors with designed ligands.[10,11] The most basic form of multivalency is bivalency and in general a bivalent ligand can bind to its target receptor in four ways that all cause increased specificity and/or strength of binding (Figure 2).[11]

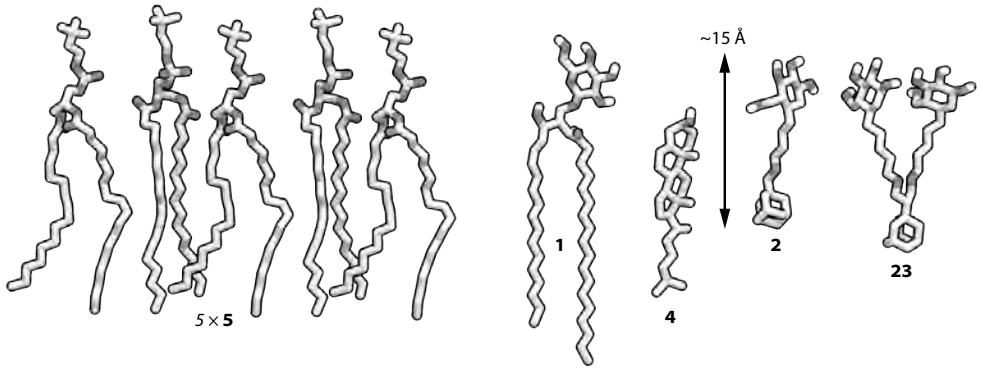
Figure 2. Overview of mechanisms of bivalent ligand binding.



A: Favored rebinding of inhibitor by the high local concentration of "free" ligand; **B**: Simultaneous inhibition of two neighboring copies of the receptor; **C**: Dimerisation/clustering of the two copies of the receptor; **D**: Increased binding specificity and strength by additional binding at a sub site.

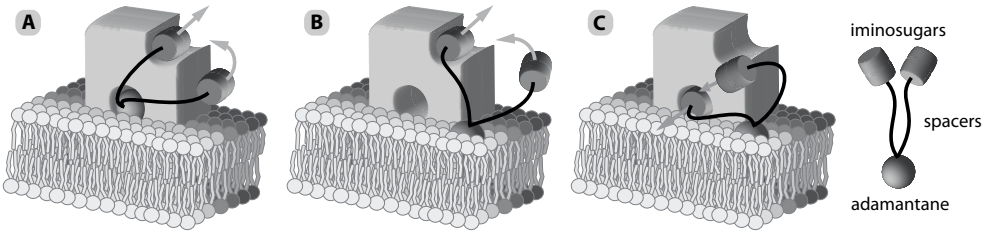
There is no evidence that carbohydrate-processing enzymes group together, dimerize or possess sub sites for binding. Therefore a bivalent inhibitor of these enzymes would operate via mechanism A in Figure 2. As mentioned, two of the target enzymes for a bivalent lipophilic iminosugar based on **2** reside in the cellular membrane. The majority of the lipid composition of cellular membranes in humans is represented by phospholipids and cholesterol (**4**) (Figure 1 and 3). The most common phospholipid is phosphatidylcholine that contains two fatty acid tails that are often both palmitic acid or in combination with oleic acid (**5**; Figure 1 and 3). The *cis*-double bond in oleic acid creates a bend in the acyl chain of **5** that confers fluidity to the membrane by preventing tight packing of the lipid acyl chains whilst cholesterol "vertically" fits in between the lipids and promotes tight packing leading to membrane rigidity (gel or liquid crystalline phase). Inhibitors **2** and **3** have molecular dimensions comparable to cholesterol so they should fit in between the lipids. The adamantane moiety occupies a sphere-like molar volume of ~6 Å^{12} and could occupy the pockets in between the lipids created by the "bent" *cis*-acyl chains and thereby stabilize the inhibitor in the membrane (see Figure 3) making the iminosugar more available for inhibition of the enzyme – GBA2 and GCS.

Figure 3. 3D structures of common membrane lipid **5** (subset of five taken from a molecular simulation of a lipid bilayer),[13] glucosylceramide (**1**),[14] cholesterol (**4**) , lead compound **2** and target bivalent inhibitor **23**.



Although the multivalency approach has been extensively utilized in optimization of receptor ligand interactions it is relatively unexplored for carbohydrate-processing enzymes. A literature search uncovered only a few examples of previous studies with iminosugar based multivalent inhibitors of carbohydrate-processing enzymes of which none found bivalent inhibition.[15-18] Madsen *et al.* developed a tetravalent 1-aza-fagomine that inhibited almond β-glucosidase and glycogen phosphorylase, but was not more potent compared to a monovalent analogue.[17] A difference of these reports with the here presented case is that the multimeric inhibitors developed in those studies all target solubilized enzymes and the enzymes here are membrane-bound.

Figure 4. Mechanisms for binding and bivalent inhibition of GCS by the proposed dimeric iminosugars.



A: Specific targeting of the two iminosugar inhibitors to the glucose binding pocket by the binding of the adamantane-spacer in the ceramide pocket; **B**: General targeting of the inhibitor to the membrane via the adamantane and GCS inhibition by binding of the iminosugars at the glucose (**B**) or ceramide pocket (**C**).

Due to the difficulty in crystallizing membrane-associated proteins, no crystal structures of GBA2 and GCS have been reported, impeding inhibitor design. However, two models exist for the inhibition of GCS by lipophilic iminosugars. Extensive previous studies on the inhibition of glycosidases by iminosugars point toward the binding of the iminosugar core at the (UDP)-glucose binding pocket of GCS with the lipophilic tail either in the ceramide pocket or in the membrane.[19,20] However other studies indicate that lipophilic iminosugars are competitive inhibitors of ceramide and not glucose and therefore inhibit GCS by binding the ceramide binding pocket.[21,22] Based on these two models a bivalent

inhibitor of GCS based on **2** or **3** could operate via either of three distinct mechanisms as depicted in Figure 4.

A critical aspect in the design of the bivalent inhibitors is the type and distance of separation between the two iminosugars. For inhibitor **2** it has already been ascertained that lengthening or shortening the pentyl spacer dramatically decreases inhibition of the targeted enzymes. Removal of the ether function in the hydrophobic *N*-alkyl tail of iminosugars increases their cytotoxicity.[23] Also, removal of the ether function in **2** decreases inhibition of GCS. Therefore it was decided to minimize the amount of change in the general structure of the inhibitor. The orientation of the two binding elements in a bivalent inhibitor can also be critical. In this respect the adamantane moiety, besides targeting the inhibitors to the membrane, also functions as a rigid scaffold.[24] If the adamantane moiety indeed binds in hydrophobic bilayer pockets then the two pentyl spaced iminosugars should be oriented in the same direction in order to cause bivalent inhibition as depicted in Figure 4. To this end difunctionalized adamantane **A** (Figure 1) was designed. One of the target bivalent inhibitors (**23**) based on orientation **A** is depicted in Figure 3. Scaffold **A** however does introduce an additional methylene in between the adamantane and the iminosugar. Therefore a second difunctionalized adamantane (**B**) was designed. Scaffold **B** minimizes the change to the general design of the original inhibitor (**2** and **3**), but its orientation of the two iminosugars could be less monodirectional.

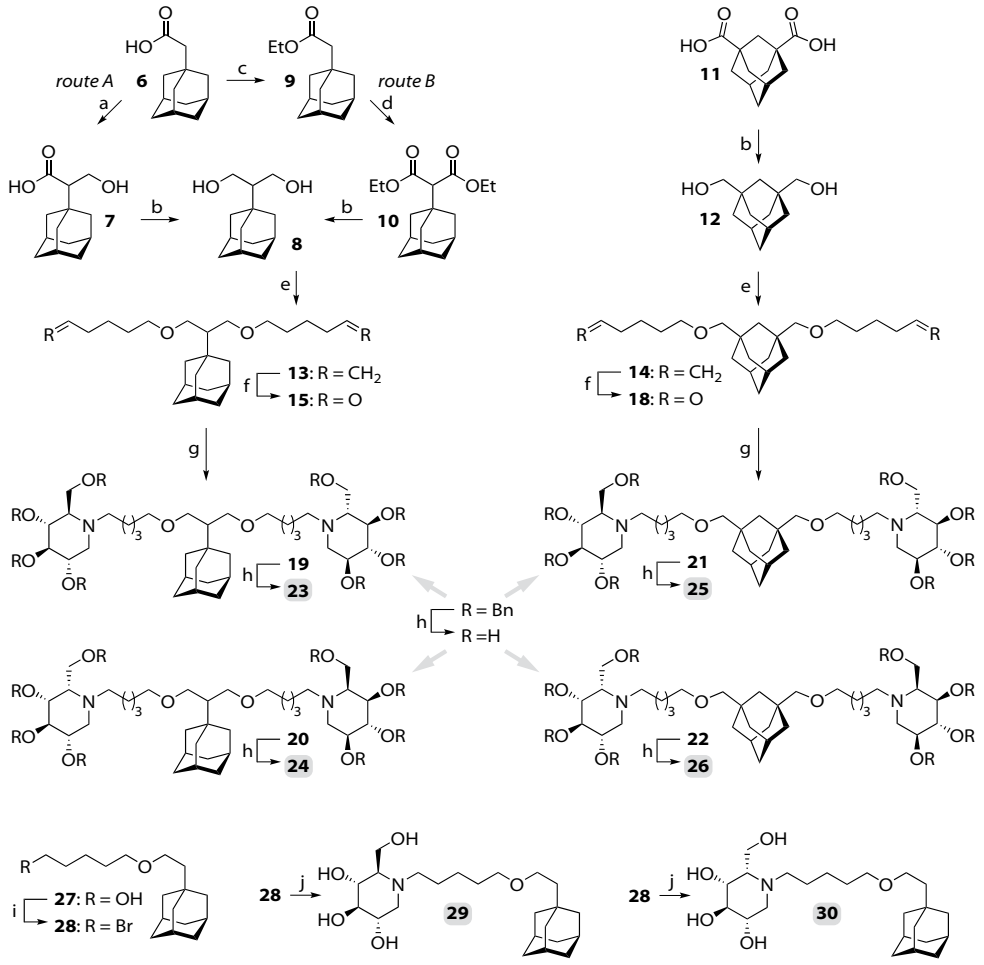
This chapter describes the synthesis of the two types of dimeric scaffolds functionalized with two 1-deoxynojirmycin or L-*ido*-1-deoxynojirimycin iminosugars. To investigate the effect of the added methylene in scaffold **A** the monomeric analogues of this scaffold were also prepared. The resulting six compounds were evaluated in an enzyme assay for inhibition of GBA1, GBA2, GCS. The compounds were also evaluated for inhibition of lysosomal α-glucosidase and sucrase to assess their selectivity for the three target enzymes and evaluate the scope of the dimeric approach .

Results and Discussion

A reductive amination was chosen as the means for condensation of the iminosugar cores to the bisfunctionalized adamantanes scaffold. This entailed the synthesis of dipentanal derivatized adamantanes that in turn could be obtained by ozonolysis of dihex-1-ene precursors. Synthesis of the target compounds started with the preparation of the two types of adamantanes. Generation of the enolate of commercially available 1-adamantaneacetic acid (**6**) and condensation with formaldehyde produced **7** in 27% yield with 68% recovery of **6** (Scheme 1).[25] Reduction of **7** with $LiAlH_4$ provided **8**. Upon increasing the scale of the aldol condensation with **6** the yield of **7** decreased due to the difficult handling of gaseous formaldehyde. Therefore a different route was developed. The ethyl ester (**9**) of **6** was prepared and deprotonated with LDA. Reaction of this enolate with ethyl chloroformate produced malonate derivative **10** in 82% yield

that upon reduction with $LiAlH_4$ also gave **8**. The other bisfunctionalized adamantane could be prepared in a straightforward manner by reduction of commercially available 1,3-adamantane-diacetic acid (**11**) to give **12**.

Scheme 1. Synthesis of dimeric lipophilic iminosugars **23**–**26** and reference monomeric analogues **29** and **30**.



Reagents and conditions: [**a**] i: LDA (2 eq) THF, –30 °C, 1h; ii: HMPA (1 eq), –30 °C; iii: formaldehyde gas, –30 °C, 20 min, scale: 3 mmol: 27% **7** and 68% **6**; 39 mmol: 11% **7** and 88% **6**. [**b**] $LiAlH_4$, THF, 0 °C » rt, 20h, **8** from **7**: 86%; **8** from **10**: 96%; **12**: used crude. [**c**] EtOH, 18M H_2SO_4, reflux, 5h, 93%. [**d**] i: LDA (1 eq) THF, –30 °C, 1h; ii: HMPA (1 eq), –30 °C; iii: Ethyl chloroformate, –30 °C , 1h, 82%. [**e**] i: 6-bromo-1-hexene, NaH, TBAI, DMF, 0 °C to rt, 2h; ii: 6-bromo-1-hexene, NaH, 20h, **13**: 72%; **14**: 65%. [**f**] i: O_3, DCM, –30 °C, 30 min,; ii: PMe_3, rt, 4h, **15**: 80%; **18**: 72%. [**g**] 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin or 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (3 eq), $NaCNBH_3$ (6 eq), Na_2SO_4 (5 eq), EtOH/AcOH (20/1), 20h, 0 °C » rt, **19**: 60%; **20**: 55%; **21**: 62%; **22**: 64%. [**h**] Pd/C, H_2 4 bar, *n*-propanol/EtOAc, HCl, 20h, **23**: 79%; **24**: 73%; **25**: 60%. **26**: 55%. [**i**] CBr_4, PPh_3, CH_3CN, reflux, 3h, 87%. [**j**] 1-deoxynojirimycin or L-*ido*-1-deoxynojirimycin (0.66 eq), K_2CO_3 (2 eq), DMF, 90 °C, 48h, **29**: 58% ; **30**: 43%.

Williamson etherification of **8** and **12** with excess 6-bromo-1-hexene produced almost no dialkylation, but instead yielded the mono-alkylated products – especially in case of

8. Successively performing the deprotonation and bromide addition twice in one pot did produce dienes **13** and **14**. Ozonolysis of **13** and work up with dimethylsulfide produced a mixture of products. Isolation and characterization of the major product (~30%) showed it was not dialdehyde **15** but an intermediate ozonide (**16** or **17**[26]). Ozonolylis of **13** and **14** and treatment of the intermediate ozonides with trimethylphosphine did provide dialdehydes **15** and **18**. Reductive amination of the dialdehydes with either 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin or 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (synthesis described in Chapters 2 and 3) provided the penultimate **19**, **20**, **21** and **23**. Palladium catalyzed hydrogenation at 4 bar produced the dimeric compounds **23**, **24**, **25** and **26**. The two monomeric reference analogues **29** and **30** were prepared by selective nitrogen alkylation of 1-deoxynojirmycin and L-*ido*-1-deoxynojirimycin (synthesis described in Chapter 3) with bromide **28**.

Biological evaluation

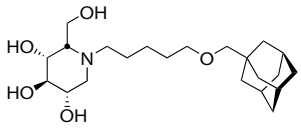
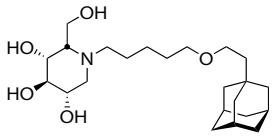
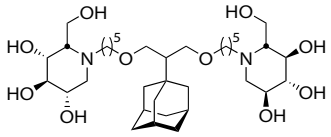
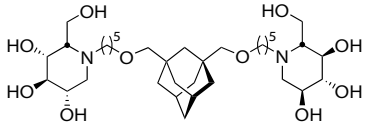
The six compounds were evaluated and compared to **2** and **3** in an enzyme assay for inhibition of the three glucosylceramide metabolism related enzymes, GCS, GBA1 and GBA2 (see Table 1 on the next page). The results for the two monomeric analogues **29** and **30** of scaffold type **A** show that the introduction of an additional methylene between the ether and adamantane is allowed. This modification does not affect the inhibition profile when compared to **2** and **3** – a moderate decrease in inhibition of GCS is observed. The dimeric derivatives **23** and **24** also still inhibit GBA1 and GBA2 comparable to the monomeric iminosugars, but are markedly less potent for GCS. The second type of dimeric iminosugars (**25** and **26**) again showed little change in inhibitory potency for GBA1 and GBA2. For this type of dimeric iminosugar the inhibition of GCS also decreases considerably upon introduction of a second pentyl-spaced iminosugar moiety.

Besides the steric implications of attaching a second iminosugar-pentyl moiety to the adamantane there is also a marked effect upon the overall polarity of the molecule – the number of hydroxyls is doubled. This phenomenon was already observed during purification of the bivalent end products during synthesis. Lead compound **2** has an R_F of 0.3 upon elution (25% MeOH and 5% NH_4OH in $CHCl_3$) from a silica gel column as opposed to almost complete retention for **23** (R_F = 0–0.05). The increased polarity of the dimeric compounds could negatively affect their cell permeability as well as their concentration in the Golgi membranes were GCS resides. The cell permeability of compounds **23**–**26** was investigated by testing them in an *in vitro* assay for GCS inhibition. All four compounds showed comparable IC_{50} values to the *in vivo* assay indicating that cell permeability is probably not the cause for the decreased GCS inhibition.

Although GCS inhibition decreases for all tested compounds when compared with **2** and **3**, they are still more or equally potent as the commercial GCS inhibitor, miglustat, *N*-butyl-1-deoxynojirimycin (*in vivo* IC_{50} = 50 μM). A trend observed in the GCS

inhibitory data is that the L-*ido* analogues are more potent and selective inhibitors of GCS then their D-*gluco* equivalents. This corresponds with the finding of Chapter 3 were **3** was identified as a more potent and selective inhibitor of GCS than **2**.

Table 1. Enzyme inhibition assay results (GCS: % inhibition at μM; other four enzymes: apparent IC_{50} in μM).

Compound		GCS[a] *in vivo*		GCS[b] *in vitro*		GBA1 *in vitro*	GBA2 *in vitro*	Lysosomal α-glucosidase *in vitro*	Sucrase *in vitro*
		%[a]	μM	%[b]	μM				
	**2**: C-5 = (*R*) D-*gluco*	50	0.2	36	0.5	0.2	0.001	0.4	0.5
	3: C-5 = (*S*) L-*ido*	75	0.1	-	-	2	0.03	> 100	> 100
	**29**: C-5 = (*R*) D-*gluco*	55	1	40	5	0.19	0.005	0.8	0.35
	30: C-5 = (*S*) L-*ido*	43	1	68	5	2	0.006	> 100	200
	**23**: C-5 = (*R*) D-*gluco*	30	20	64	40	0.38	0.008	0.35	0.4
	24: C-5 = (*S*) L-*ido*	69	20	52	10	5	0.150	700	200
	**25**: C-5 = (*R*) D-*gluco*	35	20	47	40	0.34	0.010	0.5	0.5
	26: C-5 = (*S*) L-*ido*	46	5	59	10	6	0.013	> 100	> 100

[a] average of 3 measurements; [b] 1 measurement.

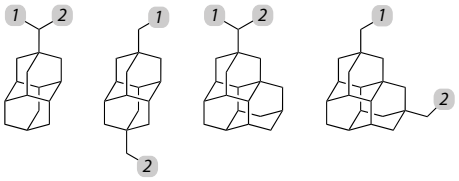
GBA2 and GCS are both membrane-bound enzymes that together with GBA1 process membrane localized lipophilic substrates. To further test the bivalent properties of **23**–**26** they were also evaluated as inhibitors of the non-membrane bound lysosomal α-glucosidase and the intestinal membrane-bound sucrase. Both enzymes process non-lipophilic substrates and are potently inhibited by lead compound **2**, but not L-*ido*-analogue **3**. The results of the enzyme assay confirm the fact that iminosugar-type inhibitors of lysosomal α-glucosidase and sucrase require D-glucose stereochemistry. Both dimeric iminosugars **23** and **25** show similar inhibition of the enzymes and are comparable to lead compound **2**. Dimeric **23** is twice as potent as its monomeric derivative (**29**) for lysosomal α-glucosidase but this trend is not observed for inhibition of sucrase.

Conclusion

This chapter describes the design, synthesis and evaluation of four dimeric lipophilic iminosugars **23**–**26**. Evaluation of two monomeric analogues showed that the structure–activity relationship (SAR) of GBA1, GBA2 and GCS inhibition tolerates the introduction of an additional methylene between the ether function and the adamantane. The four dimeric iminosugars **23**–**26** inhibited GBA1 and GBA2 to an equal extent compared to their monomeric analogues **2**, **3**, **29** and **30**. However inhibition of GCS decreased markedly for all four compounds. This was observed in both *in vivo* and *in vitro* GCS assays that ruled out cell permeability of the more polar dimeric iminosugars as a cause for the decrease.

These results indicate that dimeric lipophilic iminosugars with the here presented design do not inhibit GBA1, GBA2, GCS or lysosomal α-glucosidase and sucrase in a bivalent fashion. However, the retained inhibitory potency for GBA1, GBA2 and GCS does show that the SAR tolerates the attachment of second pentyl-spaced iminosugar, with no clear difference between the two types of adamantane scaffold.

Figure 5. Dimeric designs based on diamantane and triamantane.



It could also be possible that the length of the pentyl spacer is impeding bivalent binding modes therefore variation of its length is worth investigating in future analogues. The much increased polarity of the here presented bivalent inhibitors might make them less lipophilic and thereby less available for the membrane bound enzymes. Targeting to the membrane bound enzymes and stabilization inside the membrane could therefore perhaps be improved in future dimeric analogues of **2** and **3** by basing the scaffold on the more hydrophobic diamondoids, diamantane and triamantane (Figure 5). Synthetic procedures exist for the functionalization of these diamondoids.[27-30]

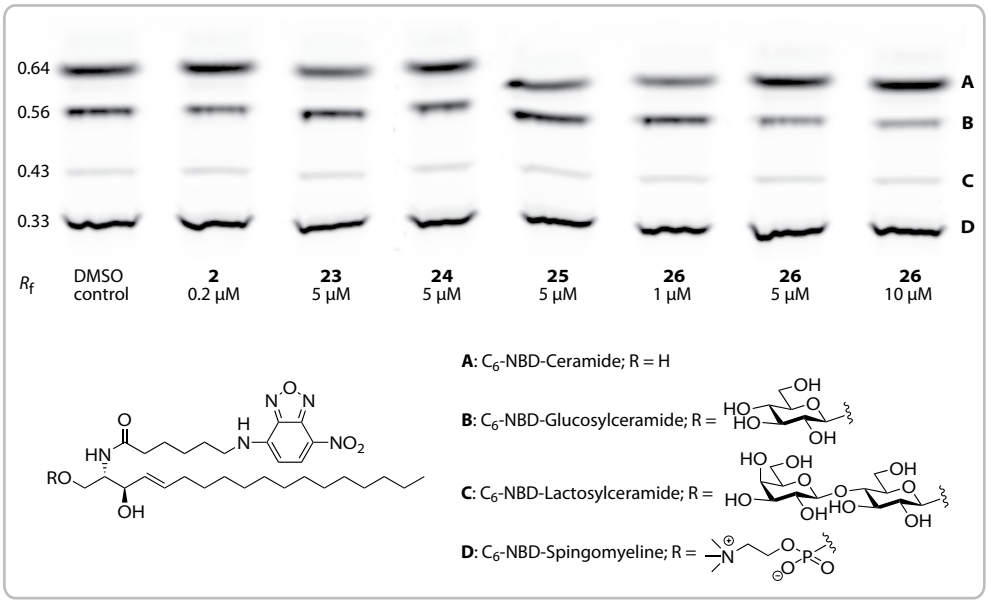
Experimental section

General methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at ambient temperatures unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere. Residual water was removed from starting compounds by repeated coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. Reaction grade acetonitrile, *n*-propanol and methanol were stored on 3Å molecular sieves. Other reaction grade solvents were stored on 4Å molecular sieves. THF was distilled prior to use from $LiAlH_4$. Ethanol was purged of acetaldehyde contamination by distillation from zinc/KOH. DCM was distilled prior to use from P_2O_5. Disopropylamine was distilled from KOH and stored over KOH. Paraformaldehyde was dried

prior to use in a P_2O_5 containing desiccator for 7 days. R_F values were determined from TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by spraying with a solution of $(NH_4)_6Mo_7O_{24}\times4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times2H_2O$ (10 g/L) in 10% sulfuric acid or a solution of phosphomolybdic acid hydrate (7.5 wt% in ethanol) followed by charring at ~150 °C. Visualization of all deprotected iminosugar compounds during TLC analysis was accomplished by exposure to iodine vapor. Column chromatography was performed on silica gel (40–63 μm). ^{1}H and ^{13}C-APT NMR spectra were recorded on a Bruker DMX 600 (600/150 MHz), Bruker DMX 500 (500/125 MHz), or Bruker AV 400 (400/100 MHz) spectrometer in $CDCl_3$ or MeOD. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard (^{1}H NMR in $CDCl_3$) or the signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. All presented ^{13}C-APT spectra are proton decoupled. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150–2000) and dioctylpthalate (m/z = 391.28428) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Optical rotations were measured on a Propol automatic polarimeter (Sodium D-line, λ = 589 nm). ATR-IR spectra were recorded on a Shimadzu FTIR-8300 fitted with a single bounce Durasample IR diamond crystal ATR-element and are reported in cm^{-1}.

Enzyme Assays: The enzyme assays used for determining the inhibition of activity of glucosylceramide synthase (GCS), glucocerebrosidase (GBA1), β-glucosidase 2 (GBA2), lysosomal α-glucosidase and sucrase are described in the experimental section of Chapter 3. In vitro assay GCS in spleen microsomes. Compounds **23**–**26** were tested as their dihydrochloric acid salt and **29** and **30** were assayed as their TFA-salt. Figure 6 shows an example of a TLC plate from the *in vivo* GCS inhibition assay with C_6-NBD-ceramide as substrate (1 h incubation with inhibitor and substrate). After developing the TLC plate ($CHCl_3$/MeOH/15mM $CaCl_2$; 60/35/8; v/v/v), fluorescently labelled sphingolipids were visualized with a Typhoon Imager (λ_{ex} 488 nM, λ_{em} 520 nM).

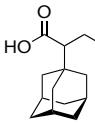
Figure 6. Fluorescent scan of TLC plate with fluorescent sphingolipids from the *in vivo* GCS assay with **23**–**26**.



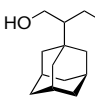
*General method A – Reductive amination of dialdehydes **15** and **18***: A dry and cooled (0 °C) mixture of the dialdehyde (1 eq), Na_2SO_4 (5 eq) and 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (3 eq; synthesis in Chapter 2) or 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (3 eq; synthesis in Chapter 3) in EtOH/AcOH (20/1, v/v, 0.1M) was charged with $NaCNBH_3$ (6 eq). The reaction mixture was stirred for 20 h and allowed to warm to rt. The reaction mixture was diluted with EtOAc (100 mL) and washed with sat aq $NaHCO_3$ (2×100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column purification (1:5 EtOAc:PE » 1:1 EtOAc:PE) to afford the product. TLC- analysis: R_F **15** = 0.55; **18** = 0.60 (2:3; EtOAc:PE).

General procedure B – Pd/C catalyzed hydrogenolysis: A solution of compound (~300–400 µmol) in *n*-propanol/EtOAc (50 mL, 8/1, v/v) was acidified to pH ~2 with 1M aq HCl (1 mL). Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C (50 mg, 10 wt % on act. carbon) and Pd black (5 mg) was added. The reaction vessel was placed under vacuum and subsequently ventilated with hydrogen gas. This cycle was repeated one more time after which the vessel was placed under 4 bar of hydrogen gas and mechanically shaken for 20 h. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene. The residue was purified by silica gel column purification (3:1 EtOAc:MeOH+5%NH_4OH » 19:1 MeOH:NH_4OH) to give the product. Silica gel residue in the purified product was removed by dissolving the product in MeOH/$CHCl_3$ (1/9, v/v), passing the solution over a filter (0.5 µM) and concentrating the filtrate.

Numbering of adamantane:

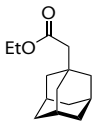


(*R*/*S*)-2-(Adamantan-1-yl)-3-hydroxypropanoic acid (7). Butyllithium (4.25 mL, 6.8 mmol; 1.6M in hexane) was added to a dry and cooled (−30 °C) solution of diisopropylamine (0.95 mL, 6.8 mmol) in THF (20 mL). After 10 min, a dry solution of 1-adamantaneacetic acid (**6**: 602 mg, 3.1 mmol) in THF (15 mL) was added over a 1 min period at −30 °C, a yellow/orange turbid reaction mixture was formed. After 20 min, HMPA (0.56 mL, 3.1 mmol) was added that resulted in a clear orange reaction mixture. Paraformaldehyde (3-4 g) was decomposed at 200 °C and the resulting formaldehyde vapours were passed by a N_2 flow over the surface of the cooled (−30 °C) reaction mixture. After complete depolymerization of the paraformaldehyde the reaction mixture was stirred for an additional 30 min. The reaction mixture was quenched by addition of water (1 mL). Ethylacetate (50 mL) was added and the mixture was extracted with aq 0.1M HCl (4×50 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (2:1 EtOAc:PE » 19:1 EtOAc:AcOH) to produce **7** (185 mg, 0.82 mmol) as white solid in 27% yield with 68% recovery of 1-adamantaneacetic acid. R_F = 0.65 (19:1; EtOAc:AcOH); R_F 1-adamantaneacetic acid = 0.85 (19:1; EtOAc:AcOH). ^{1}H NMR (200 MHz, MeOD) δ 3.92 – 3.71 (m, 2H, CH_2-3), 2.23 (dd, *J* = 4.5, 9.9, 1H, CH-2), 1.95 (s, 3H, 3×CH Ada), 1.88 – 1.45 (m, 12H, 6×CH_2 Ada). ^{13}C NMR (50 MHz, MeOD) δ 177.6 (C(O)-1), 61.5 (CH-2), 60.6 (CH_2-3), 41.7 (CH_2 Ada), 38.1 (CH_2 Ada), 35.0 (C_q Ada), 30.2 (CH Ada). IR ν_{max}(thin film)/ cm^{-1}: 3332, 2902, 2851, 1698, 1445, 1257, 1223, 1008, 808, 652, 618. HRMS: found 225.1485 $[M+H]^+$, calculated for $[C_{13}H_{20}O_3+H]^+$ 225.1485.

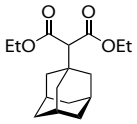


2-(Adamantan-1-yl)propane-1,3-diol (8). *Reduction of **7***: A dry and cooled (0 °C) solution of **7** (424 mg, 2.0 mmol) in THF (20 mL) was charged with $LiAlH_4$ (5 mL, 5.0 mmol; 1M in THF) and stirred for 20 h, warming to rt. The reaction was quenched (1st EtOAc 30 min, 2nd water) and aq 1M HCl (30 mL) was added. The mixture was extracted with EtOAc (2×50 mL) and the resulting combined organic phase was washed with sat aq $NaHCO_3$ (100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (2:1 EtOAc:PE » 4:1 EtOAc:MeOH) to furnish **8** (339

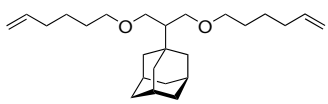
mg, 1.73 mmol) as white solid in 86% yield. *Reduction of **10***: Compound **10** (1.07 g, 3.64 mmol) was subjected to same procedure as described above, but with 4.1 eq of $LiALH_4$ to produce **8** (685 mg, 3.49 mmol) in 96% yield after purification. R_F = 0.52 (19:1; EtOAc:AcOH). ^{1}H NMR (200 MHz, MeOD) δ 3.84 (dd, *J* = 4.0, 10.7, 2H, C*H*H-1,3), 3.66 (dd, *J* = 7.3, 10.8, 2H, CH*H*-1,3), 1.94 (s, 3H, 3×CH Ada), 1.84 – 1.59 (m, 12H, 6×CH_2 Ada), 1.26 – 1.12 (m, 1H, CH-2). ^{13}C NMR (50 MHz, MeOD) δ 61.5 (CH_2-1,3), 54.2 (CH-2), 41.7 (CH_2 Ada), 38.4 (CH_2 Ada), 35.2 (C_q Ada), 30.3 (CH Ada). IR ν_{max}(thin film)/ cm^{-1}: 3235, 2900, 2846, 1447, 1344, 1034, 1009, 973. HRMS: found 211.1694 $[M+H]^+$, calculated for $[C_{13}H_{22}O_2+H]^+$ 211.1693.



Ethyl (adamantan-1-yl)acetate (9). Sulphuric acid (1 mL, 98%/18M) was added to a solution of 1-adamantaneacetic acid (**6**: 10 g, 51.5 mmol) in ethanol (200 mL). The reaction mixture was refluxed for 5h after which it was neutralized by addition of 4M aq NaOH (~4.5 mL). The reaction mixture was concentrated to a quarter of its volume and EtOAc (100 mL) was added. The mixture was washed with sat aq $NaHCO_3$ (4×50 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (100% PE » 1:9 EtOAc:PE) to furnish **9** (2.07 g, 9.3 mmol) as a colorless oil in 93% yield. R_F = 0.65 (1:12.5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.1, 2H, CH_2 ethyl), 2.05 (s, 2H, CH_2-COOEt), 1.97 (s, 3H, 3×CH Ada), 1.72 – 1.62 (m, 12H, 6×CH_2 Ada), 1.26 (t, *J* = 7.1, 3H, CH_3 ethyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C=O), 59.9 (CH_2 Et), 49.1 (*C*H_2-COOEt), 42.5 (CH_2 Ada), 36.9 (CH_2 Ada), 35.9 (C_q Ada), 28.7 (CH Ada), 14.5 (CH_3 Et). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2848, 1731, 1451, 1323, 1255, 1196, 1135, 1033, 700. HRMS: found 222.1694 $[M+H]^+$, calculated for $[C_{14}H_{22}O_2+H]^+$ 222.1693.



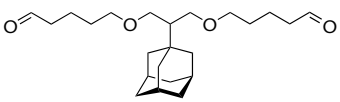
Diethyl 2-(adamantan-1-yl)malonate (10). Butyllithium (3.75 mL, 6.0 mmol; 1.6M in hexane) was added to a dry and cooled (−30 °C) solution of diisopropylamine (0.84 mL, 6.0 mmol) in THF (10 mL). After 10 min, a dry solution of **9** (1.20 g, 5.4 mmol) in THF (10 mL) was added over a 1 min period at −50 °C, a yellow turbid reaction mixture was formed. After 20 min, HMPA (0.95 mL, 5.4 mmol) was added that resulted in a clear yellow reaction mixture. Ethyl chloroformate (0.62 mL, 6.4 mmol) was added and the reaction mixture was stirred at (−30 °C for 1 h. The reaction mixture was quenched with water and EtOAc (100 mL) was added. The mixture was extracted with aq 0.1M HCl (4×50 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (1:19 EtOAc:PE » 1:9 EtOAc:PE) to produce **10** (1.30 g, 4.41 mmol) as a colorless oil in 82% yield. R_F = 0.45 (1:12.5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.1, 4H, 2×CH_2 Et), 3.08 (s, 1H, CH-2), 1.99 (s, 3H, 3×CH Ada), 1.79 (d, *J* = 2.7, 6H, 3×CH_2 Ada), 1.72 – 1.62 (m, 6H, 3×CH_2 Ada), 1.27 (t, *J* = 7.1, 6H, 2×CH_3 Et). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (C(O)-1,3), 62.7 (CH-2), 60.9 (CH_2 Et), 40.0 (CH_2 Ada), 36.9 (CH_2 Ada), 36.1 (C_q Ada), 28.7 (CH Ada), 14.4 (CH_3 Et). IR ν_{max}(thin film)/ cm^{-1}: 2904, 2850, 1753, 1726, 1449, 1368, 1319, 1250, 1221, 1201, 1142, 1032. MS (ESI): found 295.3 $[M+H]^+$, calculated for $[C_{17}H_{26}O_4+H]^+$ 295.2.



1,1'-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy)dihex-5-ene (13). A dry cooled (0 °C) solution of **8** (210 mg, mmol) and TBAI (50 mg, 0.14 mmol) in DMF (5 mL) was charged with NaH (120 mg, 3 mmol; 60% in mineral oil). The reaction mixture was stirred for 1 h at after which 6-bromo1-hexene (0.4 mL, 3 mmol) was added. The reaction mixture was stirred for 2 h, warming to rt. The reaction mixture was cooled to and additional NaH (120 mg) was added. After stirring for 15 min, additional 6-bromo1-hexene (0.4 mL) was added and the reaction mixture was stirred for 20 h, warming to rt. The reaction mixture was quenched with water. The mixture was diluted with Et_2O (100 mL) and washed with water (3×100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (100% PE » 1:9 EtOAc:PE) to produce **13** (270 mg, 0.72 mmol) as a colorless oil in 72% yield. R_F = 0.85 (1:5; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 6.7, 10.2, 17.0, 2H, 2×=CH-5 hexenyl), 5.04 – 4.98 (m, 2H, 2×=C*H*H-6 hexenyl), 4.97 – 4.91 (m, 2H,

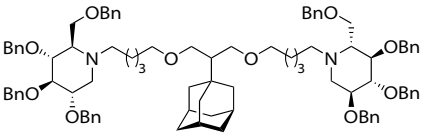
2×=CH*H*-6 hexenyl), 3.52 (dd, *J* = 4.2, 9.4, 2H, 2×C*H*H-1,3 propyl), 3.45 – 3.33 (m, 6H, 2×CH*H*-1,3 propyl, 2×CH_2-1 hexenyl), 2.07 (dd, *J* = 7.2, 14.5, 4H, 2×CH_2-4 hexenyl), 1.93 (s, 3H, 3×CH Ada), 1.71 – 1.60 (m, 12H, 6×CH_2 Ada), 1.60 – 1.54 (m, 4H, 2×CH_2-2 hexenyl), 1.49 – 1.42 (m, 4H, 2×CH_2-3 hexenyl), 1.32 – 1.26 (m, 1H, CH-2 propyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1 (=CH-5 hexenyl), 114.6 (=CH_2-6 hexenyl), 70.9 (CH_2-1 hexenyl), 68.3 (CH_2-1,3 propyl), 49.5 (CH-2 propyl), 40.8 (CH_2 Ada), 37.4 (CH_2 Ada), 34.1 (C_q Ada), 33.7 (CH_2-4 hexenyl), 29.4 (CH_2-2 hexenyl), 29.0 (CH Ada), 25.8 (CH_2-3 hexenyl). IR ν_{max}(thin film)/ cm^{-1}: 2902, 2849, 1640, 1450, 1366, 1110, 992, 908. HRMS: found 375.3259 $[M+H]^+$, calculated for $[C_{25}H_{42}O_2+H]^+$ 375.3258. **(*R*/*S*)-2-(Adamantan-1-yl)-3-(hex-5-enyloxy)propan-1-ol.** If in the above procedure no additional NaH and 6-bromo-1-hexene were added, the monoalkyalted analogue was isolated as the major product in ~50–60% after extraction and silica gel column purification. R_F = 0.38 (1:5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 6.7, 10.1, 17.1, 1H, =CH-5 hexenyl), 5.00 (dd, *J* = 1.7, 17.1, 1H, =C*H*H-6 hexenyl), 4.95 (dd, *J* = 0.8, 10.1, 1H, =C*H*H-6 hexenyl), 3.85 (dd, *J* = 7.7, 8.0, 1H, C*H*H-1 propyl), 3.76 (dd, *J* = 1.2, 4.0, 1H, C*H*H-3 propyl), 3.69 (dd, *J* = 9.1, 10.2, 1H, CH*H*-1 propyl), 3.54 (dd, *J* = 9.0, 9.1, 1H, CH*H*-3 propyl), 3.43 (t, *J* = 6.3, 2H, CH_2-1 hexenyl), 3.24 (d, *J* = 6.6, 1H, OH-1), 2.09 – 2.04 (m, 2H, CH-4 hexenyl), 1.94 (s, 3H, 3×CH Ada), 1.71 – 1.51 (m, 14H, 6×CH_2 Ada, CH_2-2 hexenyl), 1.50 – 1.41 (m, 3H, CH-2 propyl, CH_2-3 hexenyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (=CH-5 hexenyl), 114.6 (=CH_2-6 hexenyl), 72.3 (CH_2-3 propyl), 63.3 (CH_2-1 propyl), 50.0 (CH-2 propyl), 40.1 (CH_2 Ada), 40.0 (CH_2 Ada), 33.6 (C_q Ada), 33.4 (CH_2-4 hexenyl), 29.0 (CH_2-2 hexenyl), 28.5 (CH Ada), 25.4 (CH_2-3 hexenyl). MS (ESI): found 295.4 $[M+H]^+$, calculated for $[C_{19}H_{32}O_2+H]^+$ 293.3.

1,1′-[Adamantan-1,3-diylbis(methylene)]bis(oxy)dihex-5-ene (14). *Synthesis of 1,3-adamantane-dimethanol (**12**)*: A dry and cooled (0 °C) solution of 1,3-adamantane-diacetic acid (**11**: 1 g, 4.46 mmol) in THF (45 mL) was charged with $LiAlH_4$ (678 mg, 17.8 mmol) and stirred for 20 h, warming to rt. The reaction was quenched (1st EtOAc 30 min, 2nd water) and aq 1M HCl (100 mL) was added. The mixture was extracted with EtOAc (3×100 mL) and the resulting combined organic phase was washed with sat aq $NaHCO_3$ (100 mL). The organic phase was dried (Na_2SO_4) and concentrated to produce 1,3-adamantane-dimethanol (**12**: 863 mg, ~4.4 mmol) as an off-white solid, which was used crude in the next reaction. R_F 1,3-adamantane-dimethanol = 0.52; R_F 1,3-adamantane-diacetic acid = 0.80 (19:1; EtOAc:AcOH). ^{1}H NMR (400 MHz, $CDCl_3$/MeOD) δ 2.96 (s, 4H, 2×OCH_2-Ada), 1.87 (s, 2H, CH-5,7 Ada), 1.43 (s, 2H, CH_2-6 Ada), 1.35 – 1.15 (m, 8H, CH_2-4,8,9,10 Ada), 1.04 (s, 2H, CH_2-2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$/MeOD) δ 72.6 ($HOCH_2$-Ada), 40.2 (CH_2-2 Ada), 38.5 (CH_2-4,8,9,10 Ada), 36.5 (CH_2-6 Ada), 34.7 (C_q-1,3 Ada), 28.1 (CH-5,7 Ada). *Synthesis of **14***: A dry cooled (0 °C) solution of **12** (196 mg, mmol) and TBAI (50 mg, 0.14 mmol) in DMF (5 mL) was charged with NaH (120 mg, 3 mmol; 60% in mineral oil). The reaction mixture was stirred for 1 h at after which 6-bromo1-hexene (0.4 mL, 3 mmol) was added. The reaction mixture was stirred for 2 h, warming to rt. The reaction mixture was cooled to and additional NaH (120 mg) was added. After stirring for 15 min, additional 6-bromo1-hexene (0.4 mL) was added and the reaction mixture was stirred for 20 h, warming to rt. The reaction mixture was quenched with water. The mixture was diluted with Et_2O (100 mL) and washed with water (3×100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (100% PE » 1:9 EtOAc:PE) to produce **14** (233 mg, 0.65 mmol) as a colorless oil in 65% yield. R_F = 0.90 (1:4; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 6.7, 10.2, 17.1, 2H, 2×=CH-5 hexenyl), 5.00 (d, *J* = 17.2, 2H, 2×=C*H*H-6 hexenyl), 4.94 (d, *J* = 10.3, 2H, 2×=CH*H*-6 hexenyl), 3.39 – 3.35 (m, 4H, 2×CH_2-1 hexenyl), 2.99 (s, 4H, 2×OCH_2-Ada), 2.11 – 2.05 (m, 4H, 2×CH_2-4 hexenyl), 2.03 (s, 2H, CH-5,7 Ada), 1.65 – 1.60 (m, 2H, CH_2-6 Ada), 1.60 – 1.53 (m, 4H, 2×CH_2-3 hexenyl), 1.46 (ddd, *J* = 9.4, 17.9, 23.5, 12H, CH_2-4,8,9,10 Ada, 2×CH_2-2 hexenyl), 1.31 (s, 2H, CH_2-2 Ada). ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1 (=CH-5 hexenyl), 114.6 (=CH_2-6 hexenyl), 81.8 (OCH_2-Ada), 71.6 (CH_2-1 hexenyl), 42.0 (CH_2-2 Ada), 39.6 (CH_2-4,8,9,10 Ada), 37.0 (CH_2-6 Ada), 34.7 (C_q-1,3 Ada), 33.8 (CH_2-4 hexenyl), 29.2 (CH_2-2 hexenyl), 28.5 (CH-5,7 Ada), 25.7 (CH_2-3 hexenyl). IR ν_{max}(thin film)/ cm^{-1}: 2899, 2848, 1640, 1455, 1366, 1108, 993, 908. HRMS: found 361.3102 $[M+H]^+$, calculated for $[C_{24}H_{40}O_2+H]^+$ 361.3101.

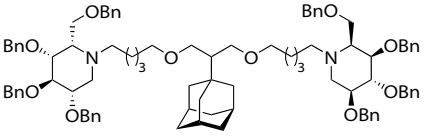


5,5′-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy)dipentanal (15). A solution of **13** (400 mg, 1.1 mmol) in DCM (70 mL; EtOH stabilized) was cooled to −80 °C. Ozone gas was generated and bubbled through the reaction mixture (reaction gas outlet was passed over silica gel blue for detection of ozone generation). After the reaction mixture had turned blue, ozone flow was continued for a further 15 min. Ozone generation was stopped and oxygen was bubbled through the reaction mixture for ~15 min or until blue colouration had completely disappeared. Trimethylphosphine (5 mL, 1M in toluene) was added and the mixture was stirred for 3 h at rt. The mixture was concentrated and the resulting residue was purified by silica gel column purification (1:5 EtOAc:PE » 1:3 EtOAc:PE) to produce **15** (323 mg, 0.85 mmol) as a colorless oil in 80% yield. R_F = 0.25 (1:3; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.7, 2H, 2×CH(O)-1 pentanal), 3.51 (dd, *J* = 4.2, 9.4, 2H, 2×OC*H*H-1,3 propyl), 3.45 – 3.34 (m, 6H, 2×OCH*H*-1,3 propyl, 2×CH_2-5 pentanal), 2.46 (dt, *J* = 1.7, 7.3, 4H, 2×CH_2-2 pentanal), 1.93 (s, 3H, 3×CH Ada), 1.76 – 1.55 (m, 20H, 6×CH_2 Ada, 4×CH_2 pentanal), 1.31 – 1.25 (m, 1H, CH-2 propyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4 (CH(O)-1 pentanal), 70.3 (CH_2-5 pentanal), 68.1 (OCH_2-1,3 propyl), 49.3 (CH-2 propyl), 43.6 (CH_2-2 pentanal), 40.6 (CH_2 Ada), 37.2 (CH_2 Ada), 33.9 (C_q Ada), 29.1 (CH_2-3 pentanal), 28.7 (CH Ada), 19.1 (CH_2-3 pentanal). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2848, 1723, 1451, 1367, 1109. HRMS: found 379.2843 $[M+H]^+$, calculated for $[C_{23}H_{38}O_4+H]^+$ 379.2843. **3,3′-{4,4′-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy)bis(butane-4,1-diyl)} bis(1,2,4-trioxolane) (16) or 3,8-bis{4,4′-[2-(Adamantane-1-yl)propane-1,3-diyl]bis(oxy)bis(butane-4,1-diyl)}-1,2,4,6,7,9-hexaoxecane (17).** *See reference 26:* Treatment of the ozonolysis reaction mixture with DMS (0.5 mL, 6.8 mmol) for 1 h at rt resulted in a complex mixture of products from which **16** or **17** could be isolated in ~30% yield after concentration and silica gel column purification (1:5 EtOAc:PE » 1:3 EtOAc:PE). Pure **16**/**17** in DCM proved stable to DMS treatment (0.5 mL; 15 min). Combination of **16**/**17** and other minor products and treatment with PMe_3 provided **15** in good yields (70%-80%). R_F = 0.55 (1:5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (s, 2H, CH_2-5/5′ trioxolane), 5.13 (t, *J* = 4.9, 2H, 2×CH-3 trioxolane), 5.03 (s, 2H, CH_2-5/5′ trioxolane), 3.51 (dd, *J* = 4.2, 9.4, 2H, 2×C*H*H-1,3 propyl), 3.44 – 3.33 (m, 6H, 2×CH*H*-1,3 propyl, 2×CH_2-4 butane), 1.93 (s, 3H, 3×CH Ada), 1.79 – 1.72 (m, 4H, 2×CH_2-1 butane), 1.72 – 1.63 (m, 6H, 3×CH_2 Ada), 1.63 – 1.46 (m, 16H, 3×CH_2 Ada, 2×CH_2-3 butane), 1.55 – 1.49 (m, 4H, 2×CH_2-2 butane), 1.31 – 1.25 (m, 1H, CH-2 propyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.9 (CH-3 trioxolane), 94.1 (CH_2-5/5′ trioxolane), 70.5 (CH_2-4 butane), 68.3 (CH_2-1,3 propyl), 49.5 (CH-2 propyl), 40.7 (CH_2 Ada), 37.4 (CH_2 Ada), 34.1 (C_q Ada), 31.0 (CH_2-1 butane), 29.6 (CH_2-3 butane), 28.9 (CH Ada), 20.9 (CH_2-2 butane).

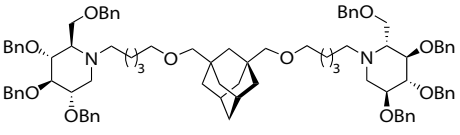
5,5′-[Adamantan-1,3-diylbis(methylene)]bis(oxy)dipentanal (18). A solution of **14** (658 mg, 1.8 mmol) in DCM (75 mL; EtOH stabilized) was cooled to −80 °C. Ozone gas was generated and bubbled through the reaction mixture (reaction gas outlet was passed over silica gel blue for detection of ozone generation). After the reaction mixture had turned blue, ozone flow was continued for a further 15 min. Ozone generation was stopped and oxygen was bubbled through the reaction mixture for ~15 min or until blue colouration had completely disappeared. Trimethylphosphine (7.5 mL, 1M in toluene) was added and the mixture was stirred for 20 h at 5 °C. The mixture was concentrated and the resulting residue was purified by silica gel column purification (1:5 EtOAc:PE » 1:3 EtOAc:PE) to produce **18** (479 mg, 1.30 mmol) as a colorless oil in 72% yield. R_F = 0.30 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.7, 2H, 2×CH(O)-1 pentanal), 3.38 (t, *J* = 6.2, 4H, 2×CH_2-5 pentanal), 2.98 (s, 4H, 2×OCH_2-Ada), 2.47 (dt, *J* = 1.7, 7.2, 4H, 2×CH_2-2 pentanal), 2.07 – 1.99 (m, 2H, CH-5,7 Ada), 1.74 –1.67 (m, 4H, 2×CH_2-3 pentanal), 1.63 – 1.55 (m, 6H, CH_2-6 Ada, 2×CH_2-4 pentanal), 1.53 – 1.38 (m, 8H, CH_2-4,8,9,10 Ada), 1.30 (s, 2H, CH_2-2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7 (CH(O)-1 pentanal), 81.6 (OCH_2-Ada), 70.9 (CH_2-5 pentanal), 43.6 (CH_2-2 pentanal), 41.8 (CH_2-2 Ada), 39.4 (CH_2-4,8,9,10 Ada), 36.8 (CH_2-6 Ada), 34.5 (C_q-1,3 Ada), 29.0 (CH_2-4 pentanal), 28.3 (CH-5,7 Ada), 19.0 (CH_2-3 pentanal). IR ν_{max}(thin film)/ cm^{-1}: 2898, 2847, 1722, 1454, 1366, 1126, 1103. HRMS: found 365.2693 $[M+H]^+$, calculated for $[C_{22}H_{36}O_4+H]^+$ 365.2686.



***N,N'*-{5,5'-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy) bis(pentane-5,1-diyl)}-bis(2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin) (19).** Dialdehyde **15** (159 mg, 0.42 mmol) was subjected to General procedure A with 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin to provide **19** (343 mg, 0.25 mmol) in 60% yield as a colorless oil after silica gel column purification. R_F = 0.58 (2:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 36H, CH_{Ar} Bn), 7.15 – 7.09 (m, 4H, CH_{Ar} Bn), 4.95 (d, *J* = 11.1, 2H, 2×*CH*H Bn), 4.87 (d, *J* = 10.9, 2H, 2×*CH*H Bn), 4.81 (d, *J* = 11.1, 2H, 2×CH*H* Bn), 4.68 (d, *J* = 11.6, 2H, 2×*CH*H Bn), 4.64 (d, *J* = 11.6, 2H, 2×CH*H* Bn), 4.46 (s, 4H, 2×CH_2 Bn), 4.40 (d, *J* = 10.9, 2H, 2×CH*H* Bn), 3.70 – 3.62 (m, 4H, 2×H-2, 2×H-6a), 3.59 (dd, *J* = 9.3, 9.5, 2H, 2×H-4), 3.56 – 3.38 (m, 8H, 2×H-3, 2×H-6b, 2×CH_2-1,3 propyl), 3.38 – 3.27 (m, 4H, 2×CH_2-5 pentyl), 3.08 (dd, *J* = 4.8, 11.1, 2H, 2×H-1a), 2.72 – 2.63 (m, 2H, 2×NC*H*H-1 pentyl), 2.63 – 2.54 (m, 2H, 2×NCH*H*-1 pentyl), 2.30 (dt, *J* = 2.1, 9.5, 2H, 2×H-5), 2.23 (dd, *J* = 10.5, 11.1, 2H, 2×H-1b), 1.94 (s, 3H, 3×CH Ada), 1.73 – 1.59 (m, 12H, 6×CH_2 Ada), 1.56 – 1.46 (m, 4H, 2×CH_2-4 pentyl), 1.45 – 1.17 (m, 9H, CH-2 propyl, 2×CH_2-2 pentyl, 2×CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.8, 138.8, 138.0 (4×C_q Bn), 128.6, 128.6, 128.5, 128.0, 128.0, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 87.6 (C-3), 78.8, 78.7 (C2, C-4), 75.5, 75.3, 73.6, 72.9 (4×CH_2 Bn), 71.1, 71.0 (CH_2-5,5' pentyl), 68.5 (CH_2-1,3 propyl), 65.5 (C-6), 63.9 (C-5), 54.7 (C-1), 52.6 (NCH_2-1,1' pentyl), 49.5 (CH-2 propyl), 40.8 (CH_2 Ada), 37.5 (CH_2 Ada), 34.2 (C_q Ada), 29.9 (CH_2-4,4' pentyl), 29.0 (CH Ada), 24.5, 24.4 (CH_2-3,3' pentyl), 23.6, 23.5 (CH_2-2,2' pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2903, 2853, 1495, 1454, 1361, 1274, 1208, 1093, 1027, 734, 697. $[\alpha]^{20}_D$: –2.4 (*c* 3.7, $CHCl_3$). HRMS: found 1393.8394 $[M+H]^+$; 697.4230 $[M+2H]^{2+}$, calculated for $[C_{91}H_{112}N_2O_{10}+H]^+$ 1393.8390 ; $[C_{91}H_{112}N_2O_{10}+2H]^{2+}$ 697.4231.

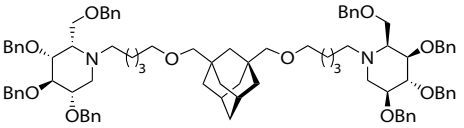


***N,N'*-{5,5'-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy) bis(pentane-5,1-diyl)}-bis(2,3,4,6-tetra-*O*-benzyl-L-ido-1-deoxynojirimycin) (20).** Dialdehyde **15** (159 mg, 0.42 mmol) was subjected to General procedure A with 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin to provide **20** (322 mg, 0.23 mmol) in 55% yield as a colorless oil after silica gel column purification. R_F = 0.70 (2:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 40H, CH_{Ar} Bn), 4.85 (d, *J* = 11.0, 2H, 2×*CH*H Bn), 4.79 (d, *J* = 11.0, 2H, 2×CH*H* Bn), 4.70 (d, *J* = 11.4, 2H, 2×*CH*H Bn), 4.67 – 4.59 (m, 6H, 2×CH*H* Bn, CH_2 Bn), 4.51 (d, *J* = 12.2, 2H, 2×*CH*H Bn), 4.47 (d, *J* = 12.2, 2H, 2×CH*H* Bn), 3.80 (dd, *J* = 6.4, 10.1, 2H, 2×H-6a), 3.72 – 3.63 (m, 4H, 2×H-4, 2×H-6b), 3.57 – 3.38 (m, 8H, 2×H-2, 2×H-3, 2×CH_2-1,3 propyl), 3.38 – 3.30 (m, 6H, 2×H-5, 2×CH_2-5 pentyl), 2.86 (dd, *J* = 5.2, 11.8, 2H, 2×H-1a), 2.75 – 2.64 (m, 2H, 2×NC*H*H-1 pentyl), 2.58 – 2.46 (m, 4H, 2×H-1b, 2×NCH*H*-1 pentyl), 1.93 (s, 3H, 3×CH Ada), 1.71 – 1.58 (m, 12H, 6×CH_2 Ada), 1.58 – 1.49 (m, 4H, 2×CH_2-4 pentyl), 1.49 – 1.35 (m, 4H, 2×CH_2-2 pentyl), 1.35 – 1.26 (m, 5H, CH-2 propyl, 2×CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.9, 138.8, 138.7 (4×C_q Bn), 128.5, 128.5, 128.4, 128.1, 127.9, 127.7, 127.7, 127.6, 127.5 (CH_{Ar} Bn), 83.3 (C-3), 80.5 (C-4), 79.1 (C-2), 75.5, 73.4, 73.2, 72.8 (4×CH_2 Bn), 71.1 (CH_2-5,5' pentyl), 68.4 (CH_2-1,3 propyl), 64.6 (C-6), 59.9 (C-5), 54.9 (NCH_2-1 pentyl), 50.0 (C-1), 49.5 (CH-2 propyl), 40.8 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 29.9 (CH_2-4 pentyl), 29.0 (CH Ada), 28.0 (CH_2-2 pentyl), 24.2 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2902, 2851, 1496, 1454, 1364, 1093, 1027, 734, 697. $[\alpha]^{20}_D$: –21.8 (*c* 1.8, $CHCl_3$). HRMS: found 1393.8392 $[M+H]^+$; 697.4230 $[M+2H]^{2+}$, calculated for $[C_{91}H_{112}N_2O_{10}+H]^+$ 1393.8390 ; $[C_{91}H_{112}N_2O_{10}+2H]^{2+}$ 697.4231.

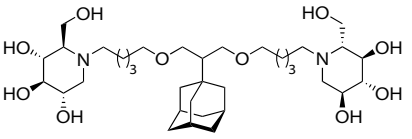


***N,N'*-{5,5'-[Adamantan-1,3-diylbis(methylene)] bis(oxy)bis(pentane-5,1-diyl)}-bis(2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin) (21).** Dialdehyde **18** (119 mg, 0.33 mmol) was subjected to General procedure A with 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin to provide **21** (282 mg, 0.20 mmol) in 62% yield as a colorless oil

after silica gel column purification. R_F = 0.57 (2:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 36H, CH_{Ar} Bn), 7.15 – 7.10 (m, 4H, CH_{Ar} Bn), 4.95 (d, *J* = 11.1, 2H, 2×*CH*H Bn), 4.87 (d, *J* = 10.8, 2H, 2×*CH*H Bn), 4.81 (d, *J* = 11.1, 2H, 2×CH*H* Bn), 4.69 (d, *J* = 11.6, 2H, 2×*CH*H Bn), 4.64 (d, *J* = 11.6, 2H, 2×CH*H* Bn), 4.49 (d, *J* = 12.3, 2H, 2×*CH*H Bn), 4.45 (d, *J* = 12.3, 2H, 2×CH*H* Bn), 4.41 (d, *J* = 10.8, 2H, 2×CH*H* Bn), 3.70 – 3.63 (m, 4H, 2×H-2, 2×H-6a), 3.60 (dd, *J* = 9.3, 2H, 2×H-4), 3.53 (dd, *J* = 2.1, 10.3, 2H, 2×H-6b), 3.45 (dd, *J* = 9.1, 2H, 2×H-3), 3.33 (t, *J* = 6.5, 4H, 2×CH_2-5 pentyl), 3.09 (dd, *J* = 4.8, 11.1, 2H, 2×H-1a), 2.99 (s, 4H, 2×OCH_2-Ada), 2.72 – 2.63 (m, 2H, 2×NC*H*H-1 pentyl), 2.62 – 2.52 (m, 2H, 2×NCH*H*-1 pentyl), 2.29 (dt, *J* = 2.1, 9.6, 2H, 2×H-5), 2.23 (t, *J* = 10.8, 2H, 2×H-1b), 2.05 (s, 2H, CH-5,7 Ada), 1.62 (s, 2H, CH_2-6 Ada), 1.56 – 1.43 (m, 12H, CH_2-4,8,9,10 Ada, 2×CH_2-4 pentyl), 1.43 – 1.33 (m, 4H, 2×CH_2-2 pentyl), 1.31 (s, 2H, CH_2-2 Ada), 1.28 – 1.12 (m, 4H, 2×CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.7, 138.7, 137.9 (4×C_q Bn), 128.6, 128.5, 128.4, 128.4, 128.0, 127.9, 127.7, 127.6, 127.5 (CH_{Ar} Bn), 87.5 (C-3), 81.8 (OCH_2-Ada), 78.8, 78.7 (C-2, C-4), 75.4, 75.3, 73.6, 72.9 (4×CH_2 Bn), 71.7 (CH_2-5 pentyl), 65.4 (C-6), 63.8 (C-5), 54.6 (C-1), 52.5 (NCH_2-1 pentyl), 42.0 (CH_2-2 Ada), 39.6 (CH_2-4,8,9,10 Ada), 36.9 (CH_2-6 Ada), 34.7 (C_q-1,3 Ada), 29.6 (CH_2-4 pentyl), 28.5 (CH-5,7 Ada), 24.2 (CH_2-3 pentyl), 23.5 (CH_2-2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3030, 2900, 2849, 1495, 1454, 1360, 1208, 1094, 1027, 734, 696. $[\alpha]^{20}_D$: –3.0 (*c* 2.4, $CHCl_3$). HRMS: found 1379.8234 $[M+H]^+$; 690.4150 $[M+2H]^{2+}$, calculated for $[C_{90}H_{110}N_2O_{10}+H]^+$ 1379.8233 ; $[C_{90}H_{110}N_2O_{10}+2H]^{2+}$ 690.4153.

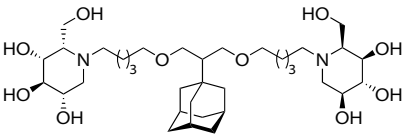


***N,N'*-{5,5'-[Adamantan-1,3-diylbis(methylene)] bis(oxy)bis(pentane-5,1-diyl)}-bis(2,3,4,6-tetra-*O*-benzyl-L-ido-1-deoxynojirimycin) (22).** Dialdehyde **18** (119 mg, 0.33 mmol) was subjected to General procedure A with 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin to provide **22** (293 mg, 0.21 mmol) in 64% yield as a colorless oil after silica gel column purification. R_F = 0.69 (2:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 40H, CH_{Ar} Bn), 4.85 (d, *J* = 11.0, 2H, 2×*CH*H Bn), 4.79 (d, *J* = 11.0, 2H, 2×CH*H* Bn), 4.70 (d, *J* = 11.5, 2H, 2×*CH*H Bn), 4.67 – 4.60 (m, 6H, 2×CH*H* Bn, CH_2 Bn), 4.52 (d, *J* = 12.2, 2H, 2×*CH*H Bn), 4.48 (d, *J* = 12.2, 2H, 2×CH*H* Bn), 3.80 (dd, *J* = 6.4, 10.1, 2H, 2×H-6a), 3.70 (dd, *J* = 2.4, 10.1, 2H, 2×H-6b), 3.66 (dd, *J* = 5.9, 9.4, 2H, 2×H-4), 3.58 – 3.52 (m, 2H, 2×H-2), 3.52 – 3.46 (m, 2H, 2×H-3), 3.38 – 3.31 (m, 5H, , 2×H-5, 2×CH_2-5 pentyl), 2.98 (s, 4H, 2×OCH_2-Ada), 2.86 (dd, *J* = 5.3, 11.9, 2H, 2×H-1a), 2.70 (ddd, *J* = 6.5, 8.7, 12.5, 2H, 2×NC*H*H-1 pentyl), 2.56 – 2.48 (m, 4H, 2×H-1a, 2×NCH*H*-1 pentyl), 2.03 (s, 2H, CH-5,7 Ada), 1.68 – 1.35 (m, 18H, CH_2-4,6,8,9,10 Ada, 2×CH_2-2 pentyl, 2×CH_2-4 pentyl), 1.35 – 1.22 (m, 6H, CH-2 Ada, 2×CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.8, 138.8, 138.7 (4×C_q Bn), 128.5, 128.5, 128.4, 128.4, 128.1, 127.9, 127.7, 127.7, 127.6, 127.5 (CH_{Ar} Bn), 83.3 (C-3), 81.8 (OCH_2-Ada), 80.5 (C-4), 79.1 (C-2), 75.5, 73.4, 73.2, 72.8 (4×CH_2 Bn), 71.8 (CH_2-5 pentyl), 64.5 (C-6), 59.9 (C-5), 54.8 (NCH_2-1 pentyl), 50.0 (C-1), 42.1 (CH_2-2 Ada), 39.6 (CH_2-4,8,9,10 Ada), 36.9 (CH_2-6 Ada), 34.7 (C_q-1,3 Ada), 29.6 (CH_2-4 pentyl), 28.5 (CH-5,7 Ada), 28.0 (CH_2-2 pentyl), 24.0 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3030, 2900, 2849, 1496, 1454, 1363, 1207, 1094, 1027, 734, 697. $[\alpha]^{20}_D$: –25.9 (*c* 2.1, $CHCl_3$). HRMS: found 1379.8236 $[M+H]^+$; 690.4151 $[M+2H]^{2+}$, calculated for $[C_{90}H_{110}N_2O_{10}+H]^+$ 1379.8233 ; $[C_{90}H_{110}N_2O_{10}+2H]^{2+}$ 690.4153.

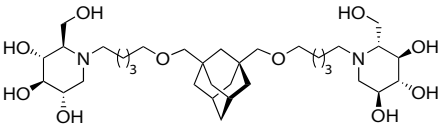


***N,N'*-{5,5'-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy) bis(pentane-5,1-diyl)}-bis(1-deoxynojirimycin) (23).** Compound **19** (377 mg, 0.27 mmol) was subjected to General procedure B to provide **23** (144 mg, 0.21 mmol) in 79% yield as a colorless oil after silica gel column purification. R_F = 0.40 (19:1; EtOAc:NH_4OH); R_F = 0.05 (1:1; EtOAc:MeOH+5%NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.93 (dd, *J* = 2.4, 12.1, 2H, 2×H-6a), 3.88 (dd, *J* = 2.7, 12.1, 2H, 2×H-6b), 3.59 – 3.53 (m, 4H, 2×H-2, 2×C*H*H-1,3 propyl), 3.49 – 3.37 (m, 8H, 2×H-4, 2×CH*H*-1,3 propyl, 2×CH_2-5 pentyl), 3.22 (dd, *J* = 9.1, 9.1, 2H, 2×H-3), 3.14 (dd, *J* = 4.8, 11.5, 2H, 2×H-1a), 3.03 – 2.93 (m, 2H, 2×NC*H*H-1 pentyl), 2.84 – 2.74 (m, 2H, 2×NCH*H*-1 pentyl), 2.49 – 2.40 (m, 4H, 2×H-1b, 2×H-5), 1.94 (s, 3H, 3×CH Ada), 1.78 – 1.64 (m, 12H, 6×CH_2 Ada), 1.64 – 1.56 (m, 8H, 2×CH_2-2 pentyl, 2×CH_2-3 pentyl), 1.45

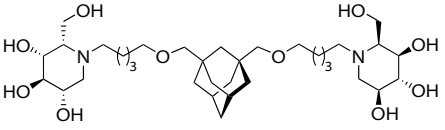
– 1.35 (m, 4H, 2×CH_2-3 pentyl), 1.31 – 1.25 (m, 1H, CH-2 propyl). ^{13}C NMR (100 MHz, MeOD) δ 79.9 (C-3), 71.9 (CH_2-5 pentyl), 71.1 (C-4), 69.9 (C-2), 69.4 (CH_2-1,3 propyl), 67.5 (C-5), 58.2 (C-6), 56.9 (C-1), 54.0 (NCH_2-1 pentyl), 50.8 (CH-2 propyl), 41.9 (CH_2 Ada), 38.4 (CH_2 Ada), 35.2 (C_q Ada), 30.7 (CH_2-4 pentyl), 30.3 (CH Ada), 25.3 (CH_2-3 pentyl), 24.8 (CH_2-2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3344, 2902, 2849, 1448, 1370, 1108, 1032. $[\alpha]^{20}_D$: –8.8 (*c* 1.9, MeOH). HRMS: found 673.4633 $[M+H]^+$, calculated for $[C_{35}H_{64}N_2O_{10}+H]^+$ 673.4634.



***N,N'*-{5,5'-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy) bis(pentane-5,1-diyl)}-bis(L-*ido*-1-deoxynojirimycin) (24).** Compound **20** (435 mg, 0.31 mmol) was subjected to General procedure B to provide **24** (153 mg, 0.23 mmol) in 73% yield as a colorless oil after silica gel column purification. R_F = 0.45 (19:1; EtOAc:NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.05 – 3.95 (m, 6H, 2×CH_2-6, 2×H-4), 3.95 – 3.90 (m, 2H, 2×H-2), 3.84 – 3.79 (m, 2H, 2×H-3), 3.55 (dd, *J* = 4.2, 9.5, 2H, 2×C*H*H-1,3 propyl), 3.50 (s, 2H, 2×H-5), 3.48 – 3.36 (m, 8H, 2×CH*H*-1,3 propyl, 2×CH_2-5 pentyl), 3.34 – 3.24 (m, 4H, 2×CH_2-1, 2×CH_2-1 pentyl), 1.94 (s, 3H, 3×CH Ada), 1.90 – 1.76 (m, 4H, 2×CH_2-2 pentyl), 1.76 – 1.59 (m, 16H, 6×CH_2 Ada, 2×CH_2-4 pentyl), 1.51 – 1.41 (m, 4H, 2×CH_2-3 pentyl), 1.31 – 1.25 (m, 1H, CH-2 propyl). ^{13}C NMR (100 MHz, MeOD) δ 72.0 (C-4), 71.7 (CH_2-5 pentyl), 69.4 (CH_2-1,3 propyl), 69.2 (C-2, C-3), 63.7 (C-5), 60.2 (C-6 collapsed), 55.2 (CH_2-1 pentyl), 53.9 (C-1), 50.8 (CH-2 propyl), 41.8 (CH_2 Ada), 38.4 (CH_2 Ada), 35.2 (C_q Ada), 30.4 (CH_2-4 pentyl), 30.3 (CH Ada), 24.8 (CH_2-3 pentyl), 24.3 (CH_2-2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3314, 2902, 2849, 1447, 1065. $[\alpha]^{20}_D$: 11.4 (*c* 2.6, MeOH). HRMS: found 673.4633 $[M+H]^+$, calculated for $[C_{35}H_{64}N_2O_{10}+H]^+$ 673.4634.

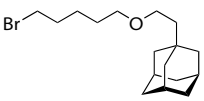


***N,N'*-{5,5'-[Adamantan-1,3-diylbis(methylene)]bis(oxy) bis(pentane-5,1-diyl)}-bis(1-deoxynojirimycin) (25).** Compound **21** (624 mg, 0.45 mmol) was subjected to General procedure B to provide **25** (177 mg, 0.27 mmol) in 60% yield as a colorless oil after silica gel column purification. R_F = 0.40 (19:1; EtOAc:NH_4OH).^{1}H NMR (400 MHz, MeOD) δ 4.04 (dd, *J* = 1.7, 12.5, 2H, 2×H-6a), 3.92 (dd, *J* = 2.7, 12.5, 2H, 2×H-6a), 3.72 (ddd, *J* = 4.9, 9.3, 10.9, 2H, 2×H-2), 3.57 (dd, *J* = 9.1, 9.6, 2H, 2×H-4), 3.47 – 3.33 (m, 8H, 2×CH_2-5 pentyl, 2×H-1a, 2×H-3), 3.27 – 3.15 (m, 2H, 2×NC*H*H-1 pentyl), 3.14 – 3.03 (m, 2H, 2×NCH*H*-1 pentyl), 3.02 (s, 4H, 2×OCH_2-Ada), 2.86 (d, *J* = 9.8, 2H, 2×H-5), 2.81 (dd, *J* = 10.5, 11.5, 2H, 2×H-1b), 2.02 (s, 2H, 2×CH-5,7 Ada), 1.72 (s, 4H, 2×CH_2-2 pentyl), 1.67 – 1.58 (m, 6H, CH_2-6 Ada, 2×CH_2-4 pentyl), 1.56 – 1.37 (m, 12H, CH_2-4,8,9,10 Ada, 2×CH_2-3 pentyl), 1.32 (s, 2H, CH_2-2 Ada). ^{13}C NMR (100 MHz, MeOD) δ 82.8 (OCH_2-Ada), 78.6 (C-3), 72.3 (CH_2-5 pentyl), 69.8 (C-4), 68.7 (C-2), 67.4 (C-5), 56.6 (C-6), 55.6 (C-1), 54.1 (NCH_2-1 pentyl), 43.0 (CH_2-2 Ada), 40.6 (CH_2-4,8,9,10 Ada), 38.0 (CH_2-6 Ada), 35.7 (C_q-1,3 Ada), 30.3 (CH_2-4 pentyl), 29.8 (CH-5,7 Ada), 24.8 (CH_2-3 pentyl), 24.3 (CH_2-2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3296, 2899, 2848, 1453, 1369, 1102, 1029. $[\alpha]^{20}_D$: –3.6 (*c* 3.6, MeOH). HRMS: found 659.4475 $[M+H]^+$, calculated for $[C_{34}H_{62}N_2O_{10}+H]^+$ 659.4477.

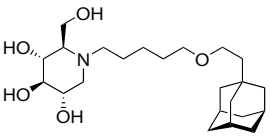


***N,N'*-{5,5'-[Adamantan-1,3-diylbis(methylene)]bis(oxy) bis(pentane-5,1-diyl)}-bis(L-*ido*-1-deoxynojirimycin) (26).** Compound **22** (611 mg, 0.44 mmol) was subjected to General procedure B to provide **26** (159 mg, 0.24 mmol) in 55% yield as a colorless oil after silica gel column purification. R_F = 0.45 (19:1; EtOAc:NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.08 – 3.99 (m, 6H, 2×CH_2-6, 2×H-4), 3.99 – 3.93 (m, 2H, 2×H-2), 3.91 – 3.81 (m, 2H, 2×H-3), 3.59 – 3.50 (m, 2H, 2×H-5), 3.49 – 3.32 (m, 12H, 2×NCH_2-1 pentyl, 2×CH_2-5 pentyl, 2×CH_2-1), 3.01 (s, 4H, 2×OCH_2-Ada), 2.02 (s, 2H, 2×CH-5,7 Ada), 1.92 – 1.71 (m, 4H, 2×CH_2-2 pentyl), 1.69 – 1.58 (m, 6H, CH_2-6 Ada, 2×CH_2-4 pentyl), 1.57 – 1.41 (m, 12H, CH_2-4,8,9,10 Ada, 2×CH_2-3 pentyl), 1.32 (s, 2H, CH_2-2 Ada). ^{13}C NMR (100 MHz, MeOD) δ 82.9 (OCH_2-Ada),

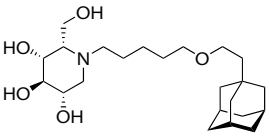
72.3 (CH_2-5 pentyl), 71.7 (C-4), 68.9 (C-2, C-3), 63.7 (C-5), 60.5 (C-6 collapsed), 55.2 (CH_2-1 pentyl), 54.0 (C-1), 43.0 (CH_2-2 Ada), 40.6 (CH_2-4,8,9,10 Ada), 38.0 (CH_2-6 Ada), 35.7 (C_q-1,3 Ada), 30.2 (CH_2-4 pentyl), 29.8 (CH-5,7 Ada), 24.7 (CH_2-3 pentyl), 24.1 (CH_2-2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3312, 2899, 2848, 1450, 1101, 1027. $[\alpha]^{20}_D$: 13.2 (*c* 3.1, MeOH). HRMS: found 659.4476 $[M+H]^+$, calculated for $[C_{34}H_{62}N_2O_{10}+H]^+$ 659.4477.



5-(Adamantan-1-yl-ethoxy)-1-bromo-pentane (28). A solution of PPh_3 (5.53 g, 21.1 mol) in CH_3CN (50 mL) was added to a solution of 5-(adamantan-1-yl-ethoxy)-1-pentanol (**27**: 1.87 g, 7.0 mmol) and carbontetrabromide (4.66 g, 14.1 mmol) in CH_3CN (150 mL). The reaction mixture was refluxed for 3 h and subsequently concentrated. The residue was purified by silica gel column purification (100% PE » 1:19 EtOAc:PE) to provide **28** (2.01 g, 6.13 mmol) in 87% yield as a colorless oil. 5-(Adamantan-1-yl-ethoxy)-1-pentanol was obtained via the same route as described for 5-(adamantan-1-yl-methoxy)-1-pentanol (route A) in Chapter 2, but now with commercially available 2-adamantaneethanol. R_F = 0.15 (1:9; toluene:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (dt, *J* = 6.9, 13.2, 6H, CH_2-1 pentyl, CH_2-5 pentyl, OCH_2 ethoxy), 1.93 (s, 3H, 3×CH Ada), 1.92 – 1.84 (m, 2H, CH_2-2 pentyl), 1.73 – 1.61 (m, 6H, 3×CH_2 Ada), 1.61 – 1.54 (m, 2H, CH_2-4 pentyl), 1.54 – 1.45 (m, 8H, 3×CH_2 Ada, CH_2-3 pentyl), 1.37 (t, *J* = 7.5, 2H, CH_2-Ada ethoxy). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.6 (CH_2-5 pentyl), 66.9 (OCH_2 ethoxy), 43.8 (CH_2-Ada ethoxy), 42.9 (CH_2 Ada), 37.3 (CH_2 Ada), 33.9 (CH_2-1 pentyl), 32.8 (CH_2-2 pentyl), 31.8 (C_q Ada), 29.1 (CH_2-4 pentyl), 28.8 (CH Ada), 25.2 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2897, 2845, 1728, 1450, 1362, 1344, 1271, 1109, 968.



***N*-[5-(Adamantan-1-yl-ethoxy)-pentyl]-1-deoxynojirimycin (29).** Bromide **28** (148 mg, 0.45 mmol) was added to a mixture of 1-deoxynojirimycin (49 mg, 0.3 mmol; see Chapter 3 for synthesis) and K_2CO_3 (124 mg, 0.9 mmol) in DMF (1.5 mL). The mixture was heated at 90 °C for 48 h. The mixture was filtered over a glass microfibre filter and the filtrate was concentrated. Silica gel column purification (100% EtOAc » 3:1 EtOAc:MeOH+5%NH_4OH) of the residue provided **29** (70 mg, 0.17 mmol) in 58% yield as a colorless oil. R_F = 0.45 (1:2; MeOH:EtOAc+NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.88 – 3.83 (m, 2H, CH_2-6), 3.51 – 3.45 (m, 3H, H-2, OCH_2 ethoxy), 3.42 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 3.36 (dd, *J* = 9.3, 1H, H-4), 3.14 (dd, *J* = 9.1, 1H, H-3), 3.01 (dd, *J* = 4.8, 11.2, 1H, H-1a), 2.86 – 2.79 (m, 1H, C*H*H-1 pentyl), 2.65 – 2.58 (m, 1H, CH*H*-1 pentyl), 2.21 (dd, *J* = 10.8, 1H, H-1b), 2.15 (d, *J* = 7.6, 1H, H-5), 1.93 (s, 3H, 3×CH Ada), 1.71 (dd, *J* = 11.6, 41.9, 6H, 3×CH_2 Ada), 1.62 – 1.56 (m, 2H, CH_2-4 pentyl), 1.56 (d, *J* = 2.6, 6H, 3×CH_2 Ada), 1.55 – 1.49 (m, 2H, CH_2-2 pentyl), 1.39 – 1.31 (m, 4H, CH_2-3 pentyl, CH_2-Ada ethoxy). ^{13}C NMR (150 MHz, MeOD) δ 80.6 (C-3), 72.0 (C-4), 71.9 (CH_2-5 pentyl), 70.7 (C-2), 67.9 (OCH_2 ethoxy), 67.5 (C-5), 59.3 (C-6), 57.7 (C-1), 53.9 (CH_2-1 pentyl), 44.9 (CH_2-Ada ethoxy), 44.0 (CH_2 Ada), 38.3(CH_2 Ada), 32.9 (C_q Ada), 30.8 (CH_2-4 pentyl), 30.3 (CH Ada), 25.4 (CH_2-3 pentyl), 25.1 (CH_2-2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3360, 2899, 2844, 1673, 1456, 1097, 1013, 980. $[\alpha]^{20}_D$: –16.6 (*c* 0.8, MeOH). HRMS: found 412.3058 $[M+H]^+$, calculated for $[C_{23}H_{41}NO_5+H]^+$ 412.3057.



TFA salt of *N*-[5-(Adamantan-1-yl-ethoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (30*TFA). Bromide **28** (148 mg, 0.45 mmol) was added to a mixture of L-Ido-1-deoxynojirimycin (49 mg, 0.3 mmol; see Chapter 3 for synthesis) and K_2CO_3 (124 mg, 0.9 mmol) in DMF (1.5 mL). The mixture was heated at 90 °C for 48 h. The mixture was filtered over a glass microfibre filter and the filtrate was concentrated. Silica gel column purification (100% EtOAc » 3:1 EtOAc:MeOH+5%NH_4OH) of the residue provided **30** (53 mg, 0.13 mmol) in 43% yield as a colorless oil. R_F = 0.35 (2:3; MeOH:EtOAc+NH_4OH). ^{1}H NMR (400 MHz, D_2O) δ 4.06 – 3.46 (m, 4H, CH_2-6, H-2, H-3, H-4), 3.46 – 3.36 (m, 1H, H-5), 3.36 – 3.16 (m, 6H, CH_2-5 pentyl, CH_2-1 pentyl, OCH_2 ethoxy), 3.16 – 3.03 (m, 2H, CH_2-1), 1.74 (s, 3H, 3×CH Ada), 1.69 – 1.27 (m, 8H, 6×CH_2 Ada, 2×CH_2

pentyl), 1.27 – 1.04 (m, 3H, CH_2 pentyl, CH_2-Ada ethoxy). ^{13}C NMR (100 MHz, D_2O) δ 162.5, 162.1, 161.8, 161.4 (C=O TFA), 120.2, 117.3, 114.4, 111.5 (CF_3 TFA), 70.2 (CH_2-5 pentyl), 69.4, 67.2, 66.5 (C-2, C-3, C-4), 66.4 (OCH_2 ethoxy), 61.3 (C-5), 58.5 (C-6), 53.5 (C-1), 52.2 (CH_2-1 pentyl), 42.9 (CH_2-Ada ethoxy), 42.3 (CH_2 Ada), 36.9 (CH_2 Ada), 31.2 (C_q Ada), 28.6 (CH_2 Ada, CH_2 pentyl), 22.7, 22.1 (2×CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3362, 2902, 2848, 1670, 1450, 1182, 1139, 1067, 1024, 837. $[\alpha]^{20}_D$: 11.9 (*c* 0.8, MeOH). HRMS: found 412.3055 $[M+H]^+$, calculated for $[C_{23}H_{41}NO_5+H]^+$ 412.3057.

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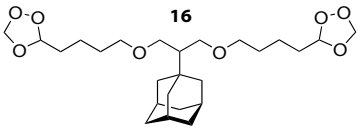
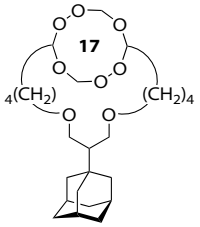
(26) *Note on the isolated ozonide **16** or **17***: Isolation and NMR analysis of the major product after ozonolysis and DMS treatment of **13** confirms the general ozonide structure. However ozonide **16** is the standard ozonide obtained after ozonolysis of a terminal alkene and should be susceptible to DMS treatment. There is precedent by Odinokov *et al.*[32] for the formation of a bis-substituted 1,2,4,6,7,9-hexaoxecane like **17** after ozonolysis of terminal alkenes and **17** might be less susceptible to DMS treatment.





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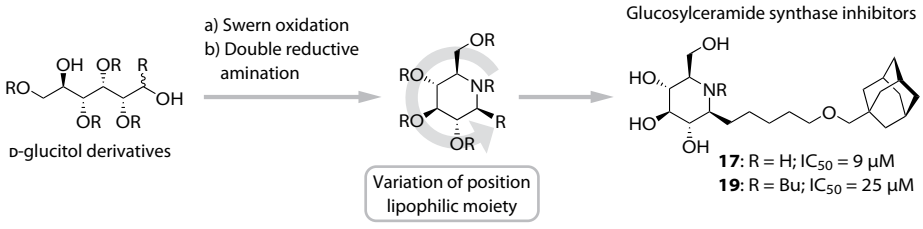
5 Location of the Lipophilic Moiety on the Iminosugar

Influence on Inhibition of Glucosylceramide Metabolism

Abstract

This chapter deals with the influence on inhibition of glucosylceramide metabolism when changing the position of the lipophilic moiety on the 1-deoxynoijirimycin core. D-Glucitol derivatives for each target position were synthesized and transformed into a library of fifteen lipophilic iminosugars. Evaluation of these compounds as inhibitors proved that positioning of the lipophilic moiety on the ring nitrogen atom – as in lead compound **2** – produces the most potent inhibitor of glucosylceramide synthase. However, two β-aza-*C*-glycoside derivatives (**17** and **19**) still considerably inhibited glucosylceramide biosynthesis. Three other compounds (**5**, **6** and **8**) proved to be potent and selective inhibitors of glucocerebrosidase.



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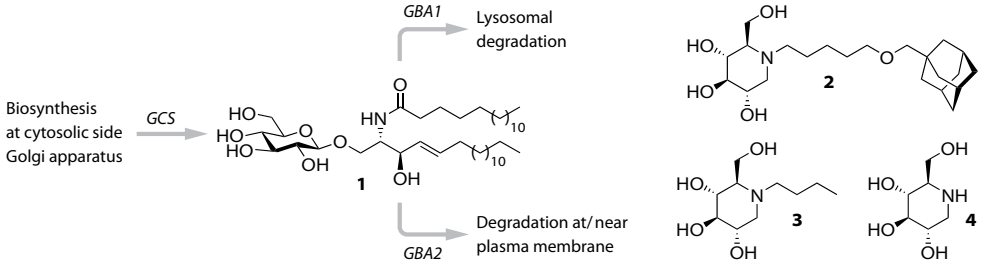
Introduction

Glucosylceramide (**1**) and its additionally glycosylated derivatives are called glycosphingolipids (GSLs). They are components of the outer cellular membrane and are involved in many (patho)physiological processes in humans, such as intercellular recognition, signaling processes (*e.g.* insulin signaling, see Chapter 3)[1] and interactions with pathogens.[2-6] In the metabolism of GSLs, **1** functions as the crucial precursor for the biosynthesis of the majority of the GSLs. The metabolism of **1** itself is summarized in Scheme 1 and involves three enzymes.[7-9] Glucosylceramide synthase (GCS) is responsible for its biosynthesis while glucocerebrosidase (GBA1) carries out its degradation. In a rare recessively inherited disorder – called Gaucher disease – glucosylceramide accumulates inside the lysosomes because of the deficient activity of a mutated GBA1.[10] Furthermore, β-glucosidase 2 (GBA2) has recently been unequivocally identified as being capable of hydrolyzing **1**, although **1** is not its exclusive substrate.[11,12] The biological function of this activity remains unclear.

Scheme 1. The metabolism of glucosylceramide (**1**) (left); Structures of iminosugars **2**, **3** and **4** (right).



In 1998, Aerts *et al.* reported a set of lipophilic GBA2 inhibitors.[13] The most potent of these, **2** (see Scheme 1), proved to be a nanomolar inhibitor of both GBA2, GCS and GBA1. Previously, the work of Platt and Butters had already shown that GCS – to a lesser extent – could be inhibited by **3**.[14] Both these compounds are *N*-alkylated derivatives of the naturally occurring iminosugar – and known glycosidase inhibitor – 1-deoxynojirimycin (**4**).

Selective inhibitors of the enzymes of glucosylceramide metabolism can find an application as tools in the continuing study of the functions of glucosylceramide, complex GSLs and their metabolism.[15,16] Additionally, the crucial role of glucosylceramide synthase (GCS) in glycosphingolipid biosynthesis makes it a interesting drug target for treating diseases in which excessive GSL levels play a role the in the pathology (*e.g.* Gaucher disease and type 2 diabetes, see Chapter 1, section 1.3).[17-20] In 2000, compound **3** received an orphan drug status as a GCS inhibitor for the treatment of Gaucher disease via substrate reduction therapy (see Chapter 1, section 1.3).[21]

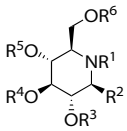
In view of these applications compound **2** is interesting, but also poses a challenge. Besides already inhibiting both GCS, GBA1 and GBA2, **2** also inhibits a number of other

glycosidases not related to the metabolism of **1**. Consequently, more selective inhibitors for each of the targeted three enzymes are needed. In the case of GCS, this search for potent *and* selective inhibitors is hampered by the fact that no structural information of the enzyme and its binding site is available.[22]

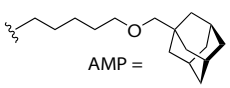
As outlined in Chapter 1, the strategy presented in this thesis for developing inhibitors of glucosylceramide metabolism and a structure–activity–relationship model for GCS inhibition is based on **2** as a lead compound. The structure of **2** can be regarded as possessing a polyhydroxylated iminosugar core to which a hydrophobic group is attached via an aliphatic spacer. The influence on inhibition of the stereochemistry of the iminosugar core and the necessity and nature of the hydrophobic group has been investigated and is described in Chapter 3 – both proved to play an important role.

Table 1. Structures of the lipophilic iminosugar library of Chapter 5.

1-Deoxynojirimycin core:



5-(Adamantan-1-yl-methoxy)-pentyl lipophilic group–spacer moiety:



Compound	R^1	R^2	R^3	R^4	R^5	R^6
2 (lead):	AMP	H	H	H	H	H
5–**7**:	H, Me or Bu	H	H	H	H	AMP
8–**10**:	H, Me or Bu	H	AMP	H	H	H
11–**13**:	H, Me or Bu	H	H	H	AMP	H
14–**16**:	H, Me or Bu	H	H	AMP	H	H
17–**19**:	H, Me or Bu	AMP	H	H	H	H

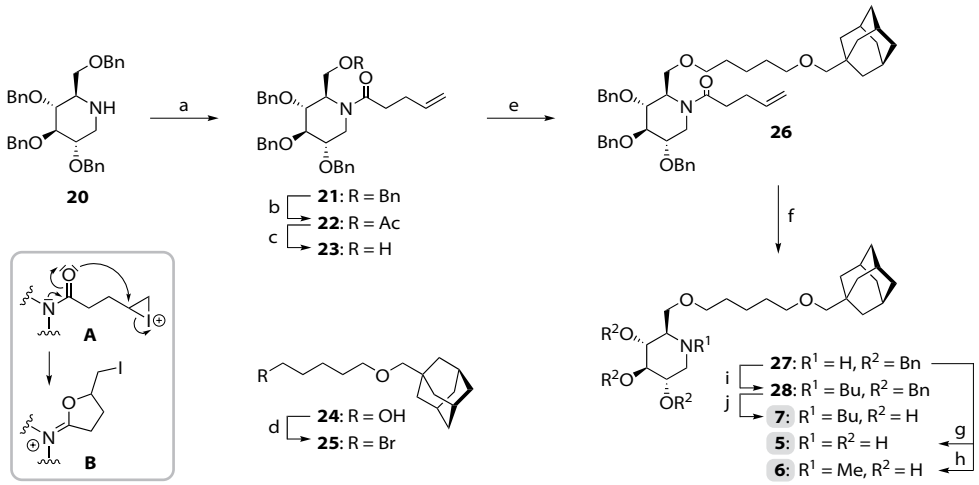
In the research presented in this chapter the attachment site of the hydrophobic moiety on the iminosugar core is varied. The synthesis and biological evaluation of a set of 1-deoxynojirimycin derivatives having the adamantan-1-yl-methoxy-pentyl moiety appended to either the C1 (as a β-aza-*C*-glycoside), O2, O3, O4 or O6 position is reported (see Table 1). Furthermore, in order to assess the influence of the substitution on the endocyclic nitrogen atom, both *N*-methylated and *N*-butylated analogues of each modification were prepared. This library of fifteen lipophilic iminosugars was screened for inhibitory potency against GCS, GBA1 and GBA2. In order to better assess the selectivity of the compounds they were also tested for inhibitory activity against several relevant human glycosidases not related to glucosylceramide metabolism.

Results and Discussion

The general strategy towards the *O*-alkylated iminosugars was to synthesize orthogonally protected 1-deoxynojirimycin derivatives for these four positions via the tandem Swern oxidation/ double reductive amination procedure reported in Chapter 2. Subsequent

selective deprotection followed by alkylation of the free hydroxyl with a suitably activated adamantan-1-yl-methoxy-pentyl moiety would produce the target compounds in protected form. This synthetic strategy would also provide building blocks suitable for straightforward derivitization in the future by alkylation with different lipophilic moieties.

Scheme 2. Synthesis of lipophilic bromide **25** and O6-functionalized iminosugars **5**–**7**.

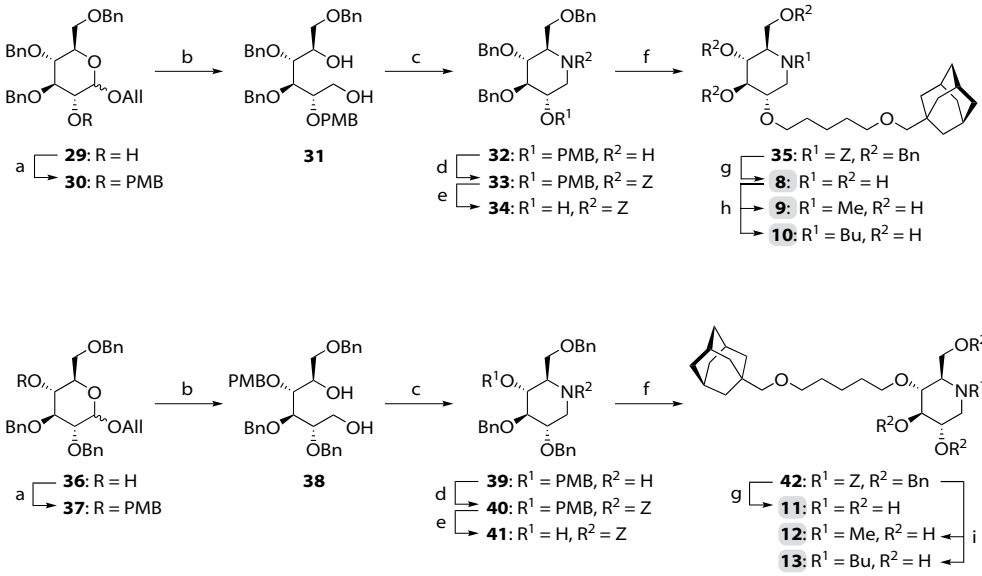


Reagents and conditions: [**a**] 1.5 eq pent-4-enoic anhydride, pyridine, 3h, quantitative. [**b**] $ZnCl_2$, AcOH/Ac_2O (1/2), 20h, 83%. [**c**] cat. NaOMe, MeOH, 90 min, 86%. [**d**] PPh_3, CBr_4, CH_3CN, reflux, 2h, 94%. [**e**] **25**, NaH, DMF, 0 °C to rt, 6h, 92%. [**f**] I_2, THF/H_2O (3/2), 30 min, 81%. [**g**] Pd/C, H_2 atm, EtOH, HCl, 20h, **5**: 75%. [**h**] i: formaldehyde, $NaBH_3CN$, AcOH, ACN, 20h; ii: Pd/C, H_2 atm, EtOH, HCl, 20h, **6**: 83% 2 steps. [**i**] butyraldehyde, $NaBH_3CN$, EtOH/AcOH, 20h, 82%. [**j**] Pd/C, H_2 atm, EtOH, HCl, 20h, **7**: 93%. Bottom left insert: deprotection mechanism of the pent-4-enamide in **26**.

The already optimized synthesis of **20** (see Chapter 2) combined with the possibility of selective deprotection of its primary 6'-benzyl ether made it the starting material of choice for the synthesis of the O6-functionalized iminosugars **5**–**7**. Their synthesis started with protection of the free amine of **20** as a pent-4-enamide to give **21** (see Scheme 2).[23,24] Protection of the amine as a carbamate – *e.g.* Boc or Z – is unfavorable due to their propensity to react intramolecularly upon activation or deprotonation of the 6'-hydroxyl to form a cyclic carbamate/oxazolidinone.[25-31] Next, the primary benzyl ether was selectively cleaved and *in situ* acetylated to **22** by treatment of **21** with zinc chloride in acetic acid/ acetic anhydride.[32] Zemplén deacetylation of **22** thereafter provided **23**. The hydroxyl function of **23** was alkylated by Williamson etherification with bromide **25** to provide protected O6-analogue **26** in 92% yield. Bromide **25** was prepared by subjecting alcohol **24** – from Chapter 2 – to Appel bromination conditions. The pent-4-enoyl group was cleaved by treatment of **26** with excess molecular iodine in THF/water to provide free amine **27**. Deprotection of the pent-4-enoyl group occurs via a cascade of ionic intermediates (see Scheme 2). First the molecular iodine coordinates with the π-bond of

26 and forms iodonium ion **A**. This cyclizes to oxoiminium species **B** and is subsequently hydrolized to the free amine.[23] Deprotection of **27** by Pd-catalyzed hydrogenolysis furnished O6-analogue **5**. Subjecting **27** to formaldehyde and sodium cyanoborohydride treatment followed by hydrogenolysis of the crude intermediate gave *N*-methylated O6-analogue **6**. Reductive amination of **27** with butyraldehyde in the presence of sodium cyanoborohydride and subsequent catalytic hydrogenation of product **28** provided the *N*-butylated O6-analogue **7**.

Scheme 3. Synthesis of O2-functionalized **8**–**10** and O4-functionalized iminosugars **11**–**13**.



Reagents and conditions: [**a**] PMBCl, NaH, DMF, 4h, **30**: 83%; **37**: 90%. [**b**] from **30**: i: $RhCl(PPh_3)_3$, DABCO, EtOH/H_2O, refluxing, 2 days; ii: I_2, THF/H_2O, 6h; iii: $LiAlH_4$, THF, 20h, **31**: 79% 2 steps; from **37**: i: 0.5 eq. KO*t*Bu, DMSO, 100 °C, 30 min; ii: I_2, THF/H_2O, 6h; iii: $LiAlH_4$, THF, 20h, **38**: 82% 2 steps. [**c**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: Et_3N, –75 °C to rt, 1h; iii: $NaBH_3CN$, $HCOONH_4$, 3Å mol. sieves, MeOH, 0 °C to rt, 20h, **32**: 68%; **39**: 48%. [**d**] BnOC(O)Cl, dioxane, aq $NaHCO_3$, 20h, **33**: 99%; **40**: quantitative. [**e**] 2% TFA, DCM, 60 min, **34**: 90%; **41**: 98%. [**f**] **25**, NaH, DMF, 0 °C to rt, 4h, **35**: 91%; **42**: 91%. [**g**] Pd/C, H_2 atm, EtOH, HCl, 20h, **8**: 72%; **11**: 83%. [**h**] Pd/C, H_2 atm, formaldehyde or butyraldehyde, EtOH, HCl, 20h, **9**: quantitative; **10**: 90%. [**i**] i: Pd/C (Degussa-type), H_2 atm, EtOH, 90 min; ii: formaldehyde or butyraldehyde, 90 min; iii: Pd/C, H_2 atm, EtOH, HCl, 20h, **12**: 94%; **13**: 83%.

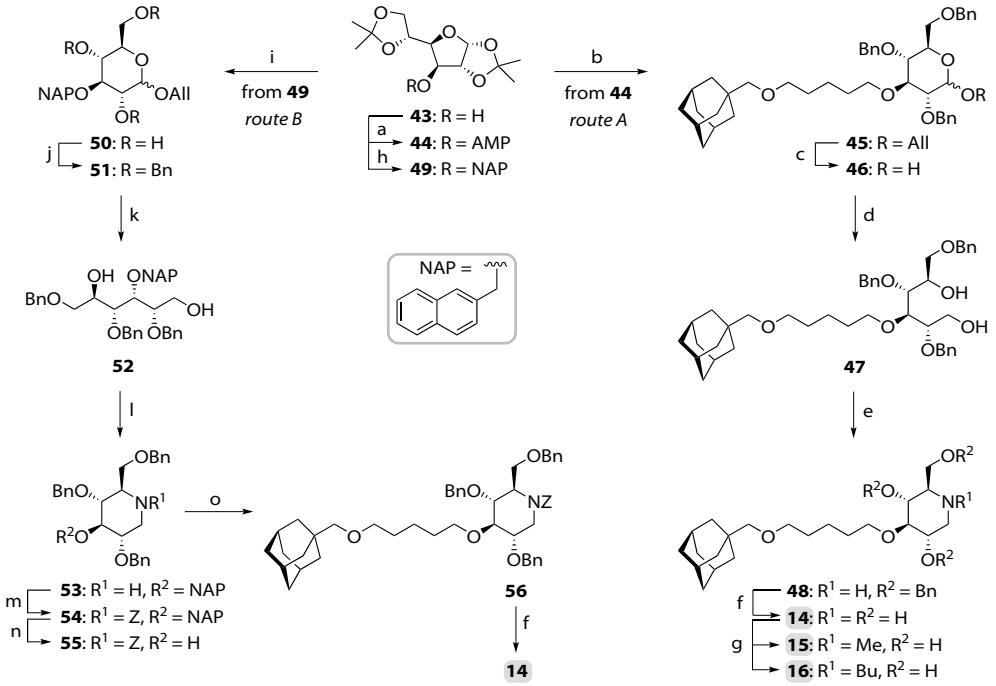
Construction of the O2- and O4-functionalized iminosugars was accomplished following a similar synthetic strategy that entailed the synthesis of O2/O4-orthogonally protected D-glucitol derivates. First the free hydroxyl function of known benzylated allyl glucopyranosides **29**[33]and **36**[34] was protected as a *p*-methoxybenzyl ether (Scheme 3). Next, deallylation of the anomeric position was achieved by isomerization with Wilkinson's catalyst for O2-PMB **30** and KO*t*Bu/DMSO for O4-PMB **37**. For both compounds the generated vinyl-ether was hydrolyzed using molecular iodine in THF/H_2O. The resulting hemiacetal products were not isolated but immediately subjected to $LiAlH_4$ mediated reduction to provide the O2-PMB (**31**) and O4-PMB (**38**) D-glucitol

derivatives. Sequential Swern oxidation and double reductive amination produced orthogonally PMB-protected 1-deoxynojirimycins **32** and **39**. Protection of the amine as a Z-carbamate (**33** and **40**) and subsequent deprotection of the PMB-ethers with 2% TFA provided free 2'-OH **34** and 4'-OH **41**. The liberated hydroxyl functions were alkylated by Williamson etherification with bromide **25** to afford the protected O2-analogue **35** and O4-analogue **42**. Deprotection of the benzyl ethers provided **8** and **11**. *N*-methylated (**9**) and *N*-butylated (**10**) O2-analogues were obtained by Pd-catalyzed hydrogenolysis of **8** in the presence of aqueous HCl and either formaldehyde or butyraldehyde. The *N*-methylated (**12**) and *N*-butylated (**13**) O4-functionalized iminosugars were prepared by a one-pot Z-deprotection and *N*-alkylation with formaldehyde or butyraldehyde, followed by deprotection to yield **12** in **13**.

The synthetic route for the O3-functionalized iminosugars **14**–**16** started with diacetoneglucose **43** (see Scheme 4). Introduction of the adamantane-spacer moiety at the beginning of the route by alkylation of **43** with bromide **25** provided **44**. Consecutive isopropylidene hydrolysis/Fisher glycosidation with allyl alcohol and benzylation of **44** produced **45**. Isomerization and cleavage of the allyl group in **45** was followed by $LiAlH_4$ mediated reduction of the crude hemiacetal (**46**) to produce **47**. Swern oxidation of **47** produced the hexosulose that was subjected to reductive amination conditions to produce the iminosugar **48**. Hydrogenolysis of **48** with Pd/C and H_2 produced O3-analogue **14**. Reductive amination of **48** with either formaldehyde or butyraldehyde, followed by benzyl ether hydrogenolysis produced *N*-methylated **15** and *N*-butylated O3-analogue **16**.

An O3-orthogonally protected 1-deoxynojirimycin has however not been reported yet and would provide a valuable building block for future research. Initial attempts to produce an O3-orthogonally protected glucitol derivative from **43** were hampered by partial cleavage of most established protecting groups during the initial isopropylidene hydrolysis/Fisher glycosidation steps. The O3 PMB-, TBDPS-, MOM-ethers and pivaloyl ester all proved to be to labile under these conditions. To this end the relatively new 2'-naphthylmethylether protecting group was evaluated. It can be cleaved under similar oxidative conditions as the PMB group, but it is more acid stabile.[35-37] Consequently, **43** was protected by alkylation with commercially available 2'-naphthylmethylbromide to produce **49**[35] (see Scheme 4). In a one-pot procedure under the agency of Amberlite H^+ resin the isopropylidene acetals of **49** could be successfully hydrolyzed with concomitant Fischer glycosidation with allyl alcohol to provide **50** in 50% yield. Consecutive benzylation of **50**, cleavage of the anomeric allyl ether, reduction to **52** and transformation into the iminosugar provided **53**. Protection of endocyclic amine as a Z-carbamate (**54**) made it possible to selectively cleave the O3-NAP ether with DDQ to give **55** in 85% yield.[37] The free OH-3 function in **55** could be alkylated with **25** to give **56**. Penultimate **56** can be exploited via the same procedures as described for the synthesis of the O2- and O4-functionalized iminosugars to give **14**–**16**, albeit via a lengthier route when starting from **43**.

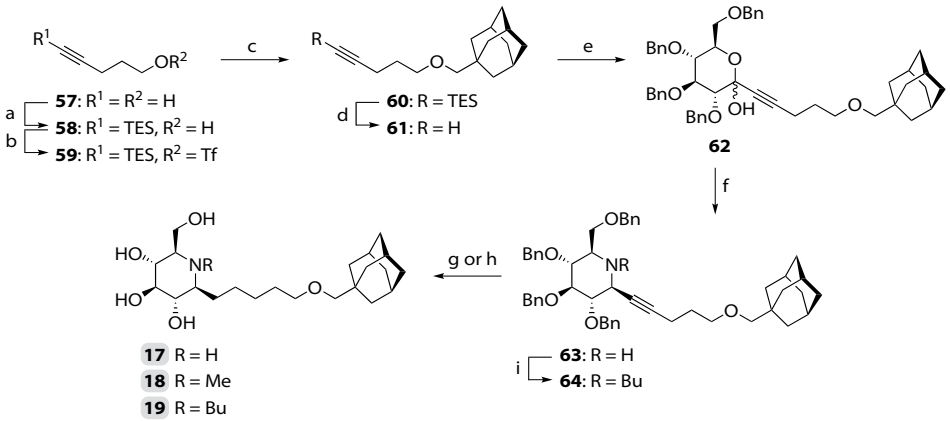
Scheme 4. Synthesis of O3-functionalized iminosugars **14**–**16** via route A and B.



Reagents and conditions: [**a**] **25**, NaH, DMF, 0 °C to rt, 4h, 98%. [**b**] i: AcOH/H_2O, 100 °C, 5h; ii: AllOH, 5 mol% AcCl, reflux, 24h; iii: BnBr, NaH, DMF, 0 °C to rt, 20h, 56% 3 steps. [**c**] i: 0.5 eq. KO*t*Bu, DMSO, 100 °C, 35 min; ii: I_2, THF/H_2O, 6h, 75%. [**d**] $LiAlH_4$, THF, 20h, quantitative. [**e**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: Et_3N, –75 °C to –10 °C, 3h; iii: $NaBH_3CN$, $HCOONH_4$, Na_2SO_4, MeOH, 0 °C to rt, 20h, 67% 2 steps. [**f**] Pd/C, H_2 atm, EtOH, HCl, 20h, from **48**: 86%; **56**: quantitative. [**g**] i: Pd/C (Degussa-type), H_2 atm, 10 eq formaldehyde or butyraldehyde, EtOH, 1h; ii: Pd/C, H_2 atm, EtOH, HCl, 20h, **15**: 83%; **16**: 99%. [**h**] NAP–Br, NaH, DMF, 0 °C to rt, 20h, 98%. [**i**] AllOH, H_2O, Amberlite H^+, 102 °C, 20h, 50%, [**j**] BnBr, NaH, DMF, 0 °C to rt, 20h, 90%. [**k**] i: 0.5 eq. KO*t*Bu, DMSO, 100 °C, 35 min; ii: I_2, THF/H_2O, 20h; iii: $LiAlH_4$, THF, 20h, 68% 2 steps. [**l**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: Et_3N, –75 °C to –10 °C, 3h; iii: $NaBH_3CN$, NH_4HCO_2, Na_2SO_4, MeOH, 0 °C to rt, 20h, 53% 2 steps. [**m**] BnOC(O)Cl, dioxane, aq. $NaHCO_3$, 20h, 81%. [**n**] DDQ, DCM/MeOH (4/1), 5h, 85%. [**o**] **25**, NaH, DMF, 0 °C to rt, 4h, quantitative.

For the preparation of the C1-functionalized iminosugars **17**–**19** established β-aza-*C*-glycoside chemistry could be used. For a concise overview of this class of compounds and their chemistry see Chapter 6. The synthesis of β-aza-*C*-glucosides **17**–**19** commenced with the preparation of alkyne **61** (see Scheme 5 on the next page). Formation of the dianion of pent-4-yn-1-ol **57** with butyllithium followed by successive treatment with triethylsilylchloride and 2M HCl produced **58**. Alkynol **58** was treated with triflic anhydride and triethylamine in DCM to provide triflate **59**. Reaction of the triflate with adamantanemethanol under the agency of potassium carbonate in DCM afforded compound **60**.[38] Installation of various other sulfonate leaving groups on either **58** or adamantanemethanol and alkylations with these under various conditions failed to reproducibly provide **60**. Next, removal of the silyl protective group was accomplished by treatment of **60** with excess NaOMe in MeOH at 90 °C to give alkyne **61**.

Scheme 5. Synthesis of C1-functionalized iminosugars **17**–**18**.



Reagents and conditions: [**a**] i: BuLi, THF, –68 °C, 1h; ii: TESCl, –68 °C to rt, 20h; iii: 2M HCl, 48h, 83%. [**b**] Tf_2O, Et_3N, DCM, –40 °C, 1h. [**c**] adamantanemethanol, K_2CO_3, DCM, reflux, 3 days, 88%. [**d**] 4 eq. NaOMe, THF/MeOH (1/1), 90 °C, 20h, 99%. [**e**] i: BuLi, THF, –50 °C, 1h; ii: 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[39], –50 °C, 2h, 77%. [**f**] i: $NaBH_4$, MeOH/DCM (5/1), 2h; ii: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; iii: Et_3N, –75 °C to rt, 0.5; iv: $NaBH_3CN$, $HCOONH_4$, 3Å mol. sieves, MeOH/DCM (5/1), 0 °C to rt, 20h, 56% 3 steps. [**g**] Pd/C, H_2 atm, EtOH, HCl, 20h, 85% from **63** to **17**; 91% from **64** to **19**. [**h**] i: Pd/C (Degussa-type), H_2 atm, formaldehyde, *n*-propanol, 1h; ii: Pd/C, H_2 atm, EtOH, HCl, 20h, 94% two steps from **63** to **18**. [**i**] Butyraldehyde, $NaBH_3CN$, EtOH/AcOH (3/1), 20h, 80%.

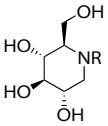
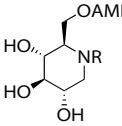
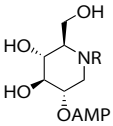
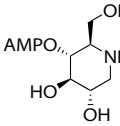
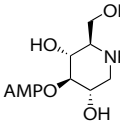
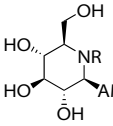
Conversion of **61** into the acetylenic anion with butyllithium in THF at –60 °C was followed by addition of excess 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[39] to produce ketose **62** as an α/β mixture. Reduction of **62** with sodium borohydride in MeOH/DCM was followed by Swern oxidation to give a diketone. The crude diketone was subjected to excess ammonium formate and sodium cyanoborohydride in MeOH/DCM at 0 °C to produce β-aza-*C*-analogue **63** as a single stereoisomer[40,41] in 58% yield over the three steps. Deprotection of the benzyl ethers and reduction of the triple bond under Pd/C catalyzed hydrogenolysis conditions provided C1-analogue **17**. Reductive amination of formaldehyde with the endocyclic amine in **63** with Pd/C (Degussa-type) and subsequent hydrogenolysis after addition of HCl to the reaction mixture yielded *N*-methylated **18** in 94% over the two steps. Sodium cyanoborohydride mediated reductive amination of **63** with butyraldehyde yielded **64**, which was deprotected to produce *N*-butylated **19**.

Biological evaluation

The inhibitory potency and selectivity of the synthesized iminosugars **5**–**19** were assessed by testing the compounds in assays for the three enzymes involved in glucosylceramide metabolism, namely, glucosylceramide synthase (GCS), glucocerebrosidase (GBA1) and β-glucosidase 2 (GBA2) (see Table 2). To further establish the inhibitory profile of iminosugars **5**–**19**, they were also tested for inhibition of the lysosomal α-glucosidase, debranching enzyme, sucrase, lactase and maltase. The lysosomal α-glucosidase was tested as it is known to be strongly inhibited by **3** as well as the lead compound

2 and plays a critical role in lysosomal glycogen degradation during cellular turnover. Debranching enzyme is involved in cytosolic glycogen degradation and it possesses both an α-1,4-transferase and α-1,6-glucosidase catalytic site for its substrate. The intestinal glucosidases are located in the outer membrane of epithelial cells lining the small intestine. The enzymes sucrase, lactase and maltase are responsible for degrading the glucose containing disaccharides (sucrose, lactose and maltose) derived from food and as a side-effect are also inhibited in Gaucher patients receiving substrate deprivation therapy with **3**.[42,43]

Table 2. Enzyme inhibition assay results: apparent IC_{50} values in μM for compounds **2**–**19**.[a,b]

Compound		GCS *in vivo*	GBA1	GBA2	Lysosomal α-gluco-sidase	Sucrase	Lactase	Maltase	De-branching enzyme
	**4**: R = H	> 100	250	21	1.5	2	62	2	10
	3: R = Bu	50	400	0.230	0.1	0.5	> 100	9	10
	2: R = AMP	0.2	0.2	0.001	0.4	4.5	> 100	19	10
	**5**: R = H	> 100	0.5	10	120	25	> 100	> 100	> 100
	6: R = Me	> 100	0.3	250	> 2000	> 100	> 100	> 100	> 100
	7: R = Bu	> 100	2	40	630	39	> 100	> 100	> 100
	**8**: R = H	> 100	0.3	60	~50	57	> 100	> 100	> 100
	9: R = Me	> 100	6	> 100	27	63	> 100	> 100	> 100
	10: R = Bu	> 100	6	5	156	> 100	> 100	> 100	> 100
	**11**: R = H	> 100	25	55	190	50	> 100	> 100	> 100
	12: R = Me	> 100	18	20	1000	50	> 100	> 100	> 100
	13: R = Bu	> 100	250	100	1500	25	> 100	> 100	> 100
	**14**: R = H	> 100	11	60	18	17	> 100	50	> 100
	15: R = Me	> 100	50	50	120	30	> 100	> 100	> 100
	16: R = Bu	> 100	100	40	150	35	> 100	> 100	> 100
	**17**: R = H	9	3	0.04	6.25	> 100	> 100	> 100	> 100
	18: R = Me	> 100	25	1.4	48	> 100	> 100	> 100	> 100
	19: R = Bu	25	40	10	255	> 100	> 100	> 100	> 100

[a]AMP = 5-(adamantan-1-yl-methoxy)-pentyl; [b]Except for GCS all other enzyme assays are *in vitro*.

The apparent IC_{50} values of the newly synthesized iminosugars **5**–**19** for the various enzymes were compared to the values obtained for **2**, **3** and 1-deoxynojirimycin (**4**). When compared to **2**, O6-analogue **5** shows strongly decreased inhibition of GCS and

GBA2, but remains a potent inhibitor of GBA1. The five other human glucose processing enzymes are also inhibited less strongly by this analogue. Its *N*-methylated derivative **6** is even more selective towards GBA1 (IC_{50}: 0.3 μM) as opposed to its *N*-butylated counterpart **7**. O2-analogue **8** has an inhibition profile similar to O6-analogue **5**. Again, both *N*-methylated (**9**) and *N*-butylated (**10**) O2-functionalized iminosugars show a general reduction in inhibitory capacity for all measured enzymes. The inhibitory potency for GCS of both O4-functionalized iminosugars (**11**–**13**) and O3-functionalized iminosugars (**14**–**16**) is very low and a general decrease in inhibition for all the measured enzymes for these compounds is observed. The β-aza-*C*-glycosides **17**–**19** also did not improve upon the potency of GCS inhibition compared to lead compound **2**.

However, compound **17** still shows strong inhibition of GCS, with an *in vivo* IC_{50} of 9 μM. However, it lacks improvement in selectivity for this enzyme when compared to **2**. *N*-methylated analogue **18** showed strongly decreased inhibition of GCS and all other enzymes. Although *N*-butyl analogue **19** also showed decreased inhibition of all tested enzymes, it did show a marked improvement of inhibition of GCS when compared to **18**. Analogue **17** has a fifty times lower potency for GCS inhibition compared to lead compound **2**, but is still a more potent and selective inhibitor than **3**. In a recent paper by Boucheron *et al*., derivatives of **3** were synthesized bearing one or two additional alkyl chains on the C1, O2 or O4 positions.[44] The outcome of this study corroborates our results in that lipophilic entities are best attached to the endocyclic nitrogen atom.

Conclusion

In this chapter a collection of adamantan-1-yl-methoxy functionalized 1-deoxynojirimycin derivatives is presented in which the attachment site of the hydrophobic moiety is altered compared to lead compound **2**. Determination of their IC_{50} values for the three enzymes involved in glucosylceramide metabolism and comparison with **2** demonstrated that relocating the hydrophobic moiety from the endocyclic nitrogen atom to other positions on the 1-deoxynojirimycin ring system does not lead to a more potent or selective inhibitor of GCS. However, the most potent iminosugar derivative in the presented series, β-aza-*C*-glycoside **17**, still inhibits GCS in the low μM range and shows decreased inhibition of intestinal glucosidases. When combined with the marked improvement of GCS inhibition when lengthening the *N*-alkyl moiety from methyl (**18**) to butyl (**19**), the aza-*C*-glycoside derivatives of **2** may hold potential for development of improved inhibitors of GCS. In chapter 6, the potential and structure–activity relationship of this class of compounds is further explored via the synthesis and evaluation of a diverse library of aza-*C*-glycoside derivatives based on **2**.

Iminosugars **5**, **6** and **8**, although being poor inhibitors of GCS, did show potent and selective inhibition of GBA1. As such, these compounds may find application as potential pharmacological chaperones of the Gaucher disease associated deficient GBA1 (see section 1.3.4 in Chapter 1).[45]

Experimental section

General methods and materials: Reactions were executed at ambient temperature unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere and residual water was removed from the starting material by coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. All chemicals and solvents, unless indicated, were acquired from commercial sources and used as received. THF was distilled prior to use from $LiAlH_4$. EtOH was freed of acetaldehyde contamination by distillation from zinc/KOH. DCM was distilled prior to use from P_2O_5. Reaction grade acetonitrile, dimethylsulfoxide, isopropanol and methanol were stored on 3Å molecular sieves. Other reaction grade solvents were stored on 4Å molecular sieves. Reactions were monitored by TLC analysis using silica gel coated aluminum plates (Schleichter & Schuell, F1500, LS254) and technical grade solvents. Compound were detected during TLC analysis by UV absorption (254 nm) where applicable and/ or by spraying with a solution of $(NH_4)_6Mo_7O_{24}\times4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times2H_2O$ (10 g/L) in 10% sulfuric acid followed by charring at ~150 °C. Visualization of olefins was achieved by spraying with a solution of $KMnO_4$ (5 g/ L) and K_2CO_3 (25 g/ L) in water. Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at ~150 °C. Visualization of deprotected iminosugar compounds during TLC analysis was accomplished by exposure to molecular iodine vapor. Column chromatography was performed on silica gel (particle size: 40–63 µm) for all compounds. The ^{1}H- and ^{13}C-NMR, ^{1}H–^{1}H COSY and ^{1}H–^{13}C HSQC experiments were recorded on a 200/50 MHz, 300/75 MHz, 400/100 MHz, 500/125 MHz or 600/150 MHz spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard for all ^{1}H NMR measurements in $CDCl_3$ and the deuterated solvent signal for all other NMR measurements. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. All presented ^{13}C NMR spectra are proton decoupled ^{13}C-APT measurements. IR spectra were recorded on an apparatus fitted with a single bounce diamond crystal ATR-element and are reported in cm^{-1}. Optical rotations were measured on an automatic polarimeter (Sodium D-line, λ = 589 nm). Mass spectra were recorded an electronspray interface apparatus. High resolution mass spectra were recorded on a mass spectrometer equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 %, capillary temperature 275 °C) with resolution R = 100000 at *m/z* 400. The high resolution mass spectrometer was calibrated prior to measurements with a calibration solution (caffeine, MRFA, Ultramark 1621). Of High resolution mass spectra were recorded by direct injection (2 µL of a 2 µM solution in H_2O/CH_3CN; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at *m/z* 400 (mass range *m/z* = 150–2000) and dioctylpthalate (*m/z* = 391.28428) as a "lock mass".[46] The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

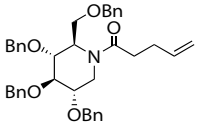
Enzyme Assays: IC_{50} values of compounds for the various enzyme activities were determined by exposing cells or enzyme preparations to an appropriate range of iminosugar concentrations. All iminosugars were tested as their HCl-salt from DMSO stock solutions. IC_{50} values for glucosylceramide synthase were measured using living cells with C_6-NBD-ceramide as substrate.[13] Glucocerebrosidase activity was measured using recombinant enzyme and 4-methylumbelliferyl-beta-glucose as substrate.[13] GBA2 was measured using enzyme-containing membrane preparations from Gaucher spleen and 4-methylumbelliferyl-beta-glucose as substrate.[13] Lysosomal α-glucosidase was measured using purified enzyme from human urine and 4-methylumbelliferyl-alpha-glucoside as substrate.[13] Lactase, maltase and sucrase activities were determined with homogenates of freshly isolated rat intestine by measuring liberated glucose from the corresponding disaccharides.[43] The activity of debranching enzyme (α-1,6-glucosidase activity) was measured by determining liberated glucose from dextrin with an erythrocyte preparation as enzyme source.[47]

General procedure A – $LiAlH_4$ mediated reduction of hemiacetal intermediates.
$LiAlH_4$ (3.5 eq) was added in portions to a cooled (0 °C) and dry solution of the hemiacetal intermediate in THF (0.15 M). The reaction mixture was stirred for 20 h, allowing it to warm to rt. The excess $LiAlH_4$ was quenched with water at 0 °C. The mixture was diluted with EtOAc and washed with sat aq NH_4Cl (3×). The organic phase was dried ($MgSO_4$) and concentrated.

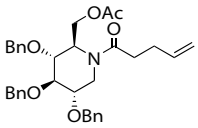
General procedure B – Swern oxidation and double reductive amination:
Swern oxidation: A solution of oxalylchloride (4 eq) in DCM (1 M) was cooled to –78 °C. After dropwise addition of a solution of DMSO (5 eq) in DCM (2 M) over 10 min, the reaction mixture was stirred for 40 min while being kept below –70 °C. Next, a dry solution of the glucitol intermediate in DCM (0.5M) was added dropwise to the reaction mixture over a 15 min period, while keeping the reaction mixture below –70 °C. After stirring the reaction mixture for 2 h below –65 °C, Et_3N (12 eq) was added dropwise over a 10 min period, while keeping the reaction mixture below –65 °C. After addition, the reaction mixture was allowed to warm to –5 °C over 2 h.
Double reductive amination method A: $NaBH_3CN$ (4 eq) and Na_2SO_4 (4 eq) were added to a solution of NH_4HCO_2 (20 eq) in MeOH (0.02M relative to starting compound). The methanolic mixture was cooled to 0 °C, after which the crude Swern oxidation reaction mixture (still at 0 °C) was added under vigorous stirring. The combined mixture was kept at 0 °C for 1 h, after which cooling was ceased and the reaction mixture was stirred for 20 h at rt. The pH of the reaction mixture was adjusted to ~10 by addition of a 1M aq. NaOH solution and the mixture was poured into water (3-fold volume to reaction MeOH). The aqueous phase was extracted repeatedly with DCM (3×), after which the combined organic layers were dried ($MgSO_4$) and concentrated.
Double reductive amination method B: The Swern reaction mixture was concentrated at a moderate temperature (~30 °C) with simultaneous coevaporation of toluene (3×). The residue was dissolved in MeOH (0.05 M relative to starting compound) and NH_4HCO_2 (20 eq) was added. The mixture was cooled to 0 °C and stirred until all NH_4HCO_2 had dissolved. Activated 3Å molsieves (10 g/mmol) were added and reaction mixture was stirred for 15 min, after which $NaBH_3CN$ (4 eq) was added. The reaction mixture was kept at 0 °C for one h after which the cooling source was removed and the reaction was stirred for an additional 20 h. After removal of the molsieves over a glass microfibre filter, the filtrate was concentrated, dissolved in EtOAc and washed with sat aq $NaHCO_3$. The aqueous phase was back-extracted with EtOAc (3×) and the combined organic layers were dried ($MgSO_4$) and concentrated.

*General procedure C – Alkylation with bromide **25***: A combined dry solution of the starting compound and bromide **25** (1.5 eq) in DMF (0.5 M) was cooled to 0 °C. NaH (1.5 eq, 60% wt in mineral oil) was added and the reaction was stirred for 3 h, allowing it to warm to rt. If TLC analysis indicated incomplete conversion, the reaction mixture was cooled to 0 °C and a solution of additional bromide **25** (0.5 eq) in a small amount of DMF and NaH (1 eq, 60% wt in mineral oil) were added. The reaction mixture was stirred for another 3 h at rt, after which it was quenched by addition of water. The mixture was poured into water and extracted repeatedly with Et_2O (3×), after which the combined organic layers were dried ($MgSO_4$) and concentrated.

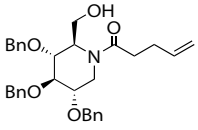
General procedure D – Pd/C catalyzed hydrogenolysis: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (4 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 min, after which a catalytic amount of Pd/C (50 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 min and the reaction was stirred for 20 h under atmospheric hydrogen pressure. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene.



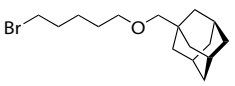
2,3,4,6-Tetra-*O*-benzyl-*N*-pent-4′-enoyl-1-deoxynojirimycin (21)[#]. A dry solution of **20** (1.05 g, 2.0 mmol) in pyridine was charged with pent-4-enoic anhydride (548 µL, 3.0 mmol) and stirred for 3 h. The reaction mixture was concentrated and coevaporated with toluene. The residue was dissolved in EtOAc (50 mL) and washed with sat aq $NaHCO_3$ (100 mL) and sat aq NaCl (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to quantitatively provide **21** (1.212 mg, 2.0 mmol) as a colorless oil. R_F = 0.71 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, T = 320 K, COSY) δ 7.30 – 7.15 (m, 20H, H_{Ar} Bn), 5.79 (m, 1H CH vinyl), 5.05 – 4.89 (m, 2H, CH_2 vinyl), 4.70 – 4.33 (m, 9H, 4×CH Bn, CH), 3.38 – 2.47 (m, 6H), 2.45 – 2.36 (m, 5H, 2×CH_2 pen-4′-enoyl, CH). ^{13}C NMR (75 MHz, $CDCl_3$, T = 320 K) δ 160.9, (C=O), 138.1 (4×C_q Bn), 137.5 (CH vinyl), 128.1, 127.7, 127.6, 127.5, 127.4, 127.1 (CH_{Ar} Bn), 114.7 (CH_2 vinyl), 74.5 (CH), 73.0, 68.4, 32.1, 29.0 (4×CH_2 Bn, 2×CH_2 pent-4-enoyl, C-1, C-6). IR ν_{max}(thin film)/ cm^{-1}: 3395, 2870, 2106, 1720, 1620, 1450, 1366, 1265, 1211, 1065, 910, 741, 694, 633. $[\alpha]^{20}_D$: 4.6 (*c* 3.9, $CHCl_3$). HRMS: found *m/z* 606.3250 $[M+H]^+$, calcd for $[C_{39}H_{43}NO_5+H]^+$ 606.3214. [#]: NMR characterization suffered from collapsed/multiple signals and severe peak broadening due to rotamers of the *N*-pent-4-enoyl amide.



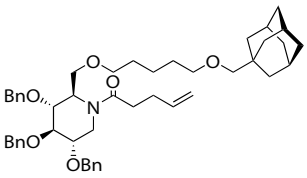
6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-*N*-pent-4′-enoyl-1-deoxynojirimycin (22)[#]. A dry solution of **21** (1.090 g, 1.80 mmol) in a mixture of AcOH (6 mL) and Ac_2O (12 mL) was charged with anhydrous $ZnCl_2$ (2.46 g, 18.0 mmol) and stirred for 20 h. The reaction was quenched (water, 5 mL) and stirred for 30 min. The reaction mixture was poured into sat aq Na_2CO_3 (100 mL) and extracted with DCM (3×50 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to afford **22** (832 mg, 1.49 mmol) in 83% yield as a colorless oil. R_F = 0.62 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.35 – 7.17 (m, 15H, H_{Ar} Bn), 5.76 (m, 1H, CH vinyl), 4.99 (d, *J* = 17.4, 1H, C*H*H vinyl), 4.93 (d, *J* = 10.4, 1H, CH*H* vinyl), 4.85 – 4.45 (m, 8H, 3×CH_2 Bn, 2×CH), 4.35 – 4.05 (m, 2H), 3.73 – 3.65 (m, 3H), 3.48 (m, 1H), 2.50 – 2.37 (m, 4H, 2×CH_2 pen-4′-enoyl), 1.95 (s, 3H, CH_3 Ac). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.9 (2×C=O; Ac, pent-4′-enoyl), 137.7, 137.3 (3×C_q Bn), 137.1 (CH vinyl), 128.0, 127.9, 127.6, 127.2 (CH_{Ar} Bn), 114.5 (CH_2 vinyl), 79.0, 76.9, 74.7, 55.7, 51.5 (C-2, C-3, C-4, C-5), 72.5, 72.0, 71.3, 70.7, 70.0, 61.5, 42.7, 34.9, 32.7, 31.8, 31.3, 28.6 (3×CH_2 Bn, 2×CH_2 pent-4-enoyl, C-1, C-6), 20.3 (CH_3 Ac). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2862, 1720, 1643, 1450, 1366, 1312, 1265, 1211, 1096, 1072, 910, 741, 702, 617. $[\alpha]^{20}_D$: 2.3 (*c* 6.8, $CHCl_3$). HRMS: found *m/z* 558.2882 $[M+H]^+$, calcd for $[C_{34}H_{39}NO_6+H]^+$ 558.2850. [#]: NMR characterization suffered from collapsed/multiple signals and severe peak broadening due to rotamers of the *N*-pent-4-enoyl amide.



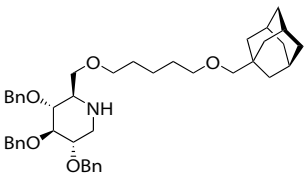
2,3,4-Tri-*O*-benzyl-*N*-pent-4′-enoyl-1-deoxynojirimycin (23)[#]. NaOMe (20 mg, 0.37 mmol) was added to a dry solution of **22** (810 mg, 1.45 mmol) in MeOH (14.5 mL). The reaction was stirred for 90 min and was subsequently quenched by addition of Amberlite resin (H^+-form) until neutral pH was achieved. The resin was removed by filtration and the filtrate was concentrated. The residue was purified by silica gel column chromatography (33% » 66% EtOAc in PE) to afford **23** (644 mg, 1.25 mmol) in 86% yield as a colorless oil. R_F = 0.15 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.17 (m, 15H, H_{Ar} Bn), 5.76 (m, 1H, CH vinyl), 5.01 – 4.92 (m, 2H, CH_2 vinyl), 4.75 – 4.39 (m, 7H, 3×CH_2 Bn, CH), 3.95 – 3.44 (m, 7H), 2.60 – 2.34 (m, 4H, 2×CH_2 pen-4′-enoyl). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (C=O), 137.9, 137.8 (3×C_q Bn), 137.2 (CH vinyl), 128.2, 128.1, 127.5, 127.4 (CH_{Ar} Bn), 114.8 (CH_2 vinyl), 75.0 (CH), 72.9 (CH_2), 72.9 (CH_2), 61.4 (CH_2), 32.4 (CH_2), 28.9 (CH_2). IR ν_{max}(thin film)/ cm^{-1}: 3395, 2870, 2106, 1720, 1620, 1450, 1366, 1265, 1211, 1065, 910, 741, 694, 633. $[\alpha]^{20}_D$: –12.5 (*c* 12.6, $CHCl_3$). HRMS: found *m/z* 516.2780 $[M+H]^+$, calcd for $[C_{32}H_{37}NO_5+H]^+$ 516.2745. [#]: NMR characterization suffered from collapsed/multiple signals and severe peak broadening due to rotamers of the *N*-pent-4-enoyl amide.



5-(Adamantan-1-yl-methoxy)-1-bromo-pentane (25). A dry solution of **24** (1.651 g, 6.58 mmol; synthesis described in chapter 2) in acetonitrile (150 mL) was charged with CBr_4 (4.378 g, 13.2 mmol). The solution was heated to reflux at which point a dry solution of PPh_3 (5.194 g, 19.8 mmol) in acetonitrile (50 mL) was added dropwise over 15 min. After addition the reaction mixture was refluxed for 2 h. Next, the solution was concentrated and toluene (100 mL) and sat aq $NaHCO_3$ (100 mL) were added to the residue. The resulting two phase system was vigorously stirred and small portions of molecular iodine were added until the toluene phase obtained a permanent brown color. The mixture was washed with 1M aq $Na_2S_2O_3$ (2×200 mL) after which the organic phase was dried ($MgSO_4$) and concentrated. The residue was dissolved in acetone (5 mL) followed by addition of PE (100 mL). The solids were removed by filtration, washed with PE (2×50 mL) and the combined filtrates were concentrated. The residue was purified by silica gel column chromatography (0% » 10% EtOAc in PE) to provide **25** (1.951 g, 6.21 mmol) in 94% yield as a colorless oil. R_F = 0.89 (1:4; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.44 – 3.36 (m, 4H, CH_2-1, CH_2-5 pentyl), 2.95 (s, 2H, OCH_2-Ada), 1.95 (br s, 3H, 3×CH Ada), 1.89 (m, 2H, CH_2-2 pentyl), 1.74 – 1.62 (m, 6H, 3×CH_2 Ada), 1.61 – 1.48 (m, 10H, 3×CH_2 Ada, CH_2-3, CH_2-4 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 81.9 (OCH_2-Ada), 71.1 (CH_2-5 pentyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 33.8 (C_q Ada), 33.4 (CH_2-1 pentyl), 32.4, 28.5 (CH_2-2, CH_2-4 pentyl), 28.0 (3×CH Ada), 24.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1450, 1358, 1250, 1188, 1157, 1111, 1049, 1011, 910, 810, 733, 640. HRMS: found *m/z* 315.1571 $[M+H]^+$, calcd for $[C_{16}H_{27}OBr+H]^+$ 315.1318.

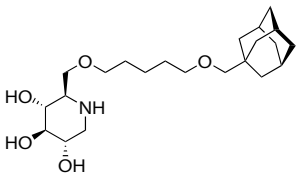


2,3,4-Tri-*O*-benzyl-*N*-pent-4′-enoyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (26)#. General procedure C was applied on compound **23** (322 mg, 0.63 mmol). The resulting residue was purified by silica gel column chromatography (15% » 30% EtOAc in PE) to provide **26** (431 mg, 0.58 mmol) in 92% yield as a colorless oil. R_F = 0.35 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.30 – 7.25 (m, 15H, H_{Ar} Bn), 5.81 (m, 1H CH vinyl), 5.00 (d, *J* = 17.2, 1H, C*H*H vinyl), 4.94 (d, *J* = 10.1, 1H, CH*H* vinyl), 4.80 – 4.40 (m, 7H, 3×CH Bn, CH), 4.07 – 3.94 (m, 1H), 3.70 – 3.45 (m, 6H), 3.36 – 3.30 (m, 4H, 2×OCH_2 pentyl), 2.94 (s, 2H, OCH_2-Ada), 2.50 – 2.30 (m, 4H, 2×CH_2 pen-4′-enoyl), 1.94 (br s, 3H, 3×CH Ada), 1.72 – 1.62 (m, 6H, 3×CH_2 Ada), 1.57 – 1.50 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.34 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) 138.1 (3×C_q Bn), 137.2 (CH vinyl), 128.3, 127.9, 127.7 (CH_{Ar} Bn), 114. 9 (CH_2 vinyl), 82.0 (OCH_2-Ada), 74.4 (CH), 71.5 (CH_2), 39.8 (3×CH_2 Ada), 37.3 (3×CH_2 Ada), 34.1 (C_q Ada), 29.6, 29.4 (2×CH_2 pentyl), 28.3 (3×CH Ada), 22.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2901, 2847, 1643, 1450, 1366, 1211, 1096, 1034, 910, 810, 741, 694, 617. $[\alpha]^{20}_D$: 5.2 (*c* 8.5, $CHCl_3$). MS (ESI): *m/z* 750.5 $[M+H]^+$; 772.6 $[M+Na]^+$. #: NMR characterization suffered from collapsed/multiple signals and severe peak broadening due to rotamers of the *N*-pent-4-enoyl amide.

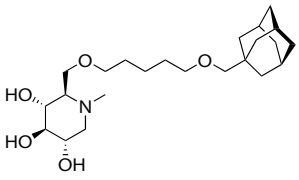


2,3,4-Tri-*O*-benzyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (27). Water (2 mL) was added to a solution of compound **26** (345 mg, 0.46 mmol) in THF (5.5 mL). The solution was charged with molecular iodine (351 mg, 1.38 mmol) and stirred for 30 min when TLC analysis indicated conversion into a lower running product. 1M aq $Na_2S_2O_3$ (10 mL) was added and the mixture was vigorously stirred for 30 min. The suspension was poured into a mixture of 1M aq $Na_2S_2O_3$/sat aq NaCl (100 mL, 1/1) and extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (isocratic 25% EtOAc in PE) to yield **27** (246 mg, 0.37 mmol) as a colorless oil in 81% yield. R_F **27** = 0.31; (*R*/*S*)-γ-Iodomethyl-gamma-butyrolactone = 0.45 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.35 – 7.24 (m, 15H, H_{Ar} Bn), 5.97 (d, *J* = 10.9, 1H, C*H*H Bn), 4.88 (d, *J* = 11.0, 1H, C*H*H Bn), 4.83 (d, *J* = 10.9,

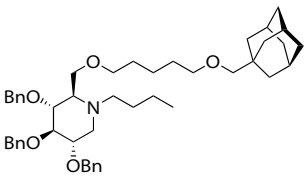
1H, CH*H* Bn), 4.69 (d, *J* = 11.7, 1H, C*H*H Bn), 4.66 (d, *J* = 11.7, 1H, CH*H* Bn), 4.56 (d, *J* = 11.0, 1H, CH*H* Bn), 3.59 (dd, *J* = 2.5, *J* = 9.1, 1H, H-6a), 3.55 – 3.30 (m, 8H, H-2, H-3, H-4, H-6b, 2×OCH_2 pentyl), 3.25 (dd, $J_{H1a\text{-}H2}$ = 4.7, $J_{H1a\text{-}H1b}$ = 12.2, 1H, H-1a), 2.93 (s, 2H, OCH_2-Ada), 2.68 (m, 1H, H-5), 2.51 (dd, $J_{H1b\text{-}H2}$ = 10.2, $J_{H1b\text{-}H1a}$ = 12.2, 1H, H-1b), 2.03 (br s, 1H, NH), 1.94 (br s, 3H, 3×CH Ada), 1.72 – 1.62 (m, 6H, 3×CH_2 Ada), 1.58 – 1.51 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.37 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 138.2 (3×C_q Bn), 128.2, 127.7, 127.6, 127.4, 127.3 (CH_{Ar} Bn), 87.1 (C-3), 81.7 (OCH_2-Ada), 80.4, 79.9 (C-2, C-4), 75.5, 75.0, 72.6, 71.2, 71.1(3×CH_2 Bn, 2×OCH_2 pentyl), 70.4 (C-6), 59.5 (C-5), 47.9 (C-1), 39.5 (3×CH_2 Ada), 37.0 (3×CH_2 Ada), 33.8 (C_q Ada), 29.2 (2×CH_2 pentyl), 28.1 (3×CH Ada), 22.6 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2901, 2847, 1450, 1358, 1258, 1211, 1096, 1065, 903, 741, 694, 610. $[\alpha]^{20}_D$: 18.8 (*c* 4.1, $CHCl_3$). HRMS: found *m/z* 668.4334 $[M+H]^+$, calcd for $[C_{43}H_{57}NO_5+H]^+$ 668.4310.



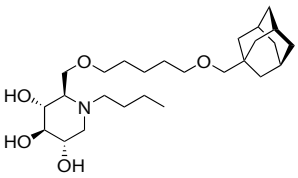
6-*O*-[1-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (5). Compound **27** (56 mg, 84 µmol) was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **5** (25 mg, 63 µmol) as a colorless oil in 75% yield. R_F = 0.48 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.76 – 3.70 (m, 2H, CH_2-6), 3.56 – 3.43 (m, 3H, H-2, OCH_2 pentyl), 3.39 – 3.34 (m, 3H, H-4 or H-3, OCH_2 pentyl), 3.17 (m, 1H, H-3), 3.02 (m, 1H, H-1a), 2.96 (s, 2H, OCH_2-Ada), 2.49 (br s, 2H, 2×OH), 2.32 (m, 1H, H-5), 2.21 (m, 1H, H-1b), 1.94 (br s, 3H, 3×CH Ada), 1.77-1.55 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.44 (m, 2H, CH_2 pentyl). ^{13}C NMR (50 MHz, MeOD) δ 83.1 (OCH_2-Ada), 80.6, 73.3 (C-2, C-3, C-4), 72.5, 71.7 (C-6, 2×OCH_2 pentyl), 61.3 (C-5), 51.0 (C-1), 40.8 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.2 (C_q Ada), 30.5 (2×CH_2 pentyl), 29.8 (3×CH Ada), 24.0 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3333, 2901, 2847, 1674, 1450, 1366, 1319, 1258, 1103, 1042, 671, 610. $[\alpha]^{20}_D$: 16.4 (*c* 0.2, MeOH). HRMS: found *m/z* 398.2910 $[M+H]^+$, calcd for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.



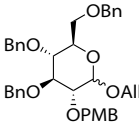
***N*-Methyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (6).** A dry solution of compound **27** (60 mg, 90 µmol) and formaldehyde (100 µL, 1 mmol; 37 wt % in water) in acetonitrile (0.5 mL) was charged with $NaBH_3CN$ (19 mg, 0.3 mmol) and stirred for 15 min, after which AcOH (13 µL) was added. The reaction mixture was stirred for 20 h (R_F intermediate = 0.68 in EtOAc:PE; 1:2), subsequently poured into sat aq $NaHCO_3$ (50 mL) and extracted with Et_2O (3×50 mL). The organic phase was concentrated and coevaporated with EtOH. The crude intermediate product was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **6** (31 mg, 75 µmol) as a colorless oil in 83% yield. R_F = 0.54 (1:2; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.73 (dd, $J_{H6a\text{-}H5}$ = 2.1, $J_{H6a\text{-}H6b}$ = 10.5, 1H, CH-6a), 3.63 (dd, $J_{H6b\text{-}H5}$ = 3.4, $J_{H6b\text{-}H6a}$ = 10.5, 1H, CH-6b), 3.53-3.43 (m, 3H, H-2, OCH_2 pentyl), 3.37 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.32- 3.28 (m, 1H, H-4), 3.12 (dd, *J* = 9.0, 9.0, 1H, H-3), 2.96 (s, 2H, OCH_2-Ada), 2.89 (dd, *J* = 4.8, 11.1, 1H, H-1a), 2.35 (s, 3H, NCH_3), 2.09 (dd, *J* = 10.9, H-1b), 1.98 – 1.88 (m, 4H, H-5, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.60 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.42 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.1 (OCH_2-Ada), 80.5 (C-3), 72.6, 72.4 (2×OCH_2 pentyl), 71.8 (C-4), 70.4 (C-2), 69.2 (C-5), 68.7 (C-6), 62.1 (C-1), 42.7 (NCH_3), 40.9 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.2 (C_q Ada), 30.5, 30.4 (2×CH_2 pentyl), 29.8 (3×CH Ada), 24.1 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3325, 2901, 2847, 2800, 2091, 1612, 1450, 1366, 1250, 1103, 1034, 833, 748. $[\alpha]^{20}_D$: –37.1 (*c* 0.6, MeOH). HRMS: found *m/z* 412.3063 $[M+H]^+$, calcd for $[C_{23}H_{42}NO_5+H]^+$ 412.3058.



2,3,4-Tri-*O*-benzyl-*N*-butyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (28). A dry solution of compound **27** (64 mg, 96 µmol) and butyraldehyde (100 µL, 1 mmol) in EtOH (0.75 mL) and AcOH (0.25 mL) was charged with $NaBH_3CN$ (13 mg, 0.2 mmol). The reaction mixture was stirred for 20 h and subsequently coevaporated with toluene. The residue was dissolved in little EtOAc, poured into sat aq $NaHCO_3$ (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 30% EtOAc in PE) to provide **28** (57 mg, 79 µmol) as a colorless oil in 82% yield. R_F = 0.71 (1:2 EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 15H, H_{Ar} Bn), 4.95 (d, *J* = 11.2, 1H, C*H*H Bn), 4.93 (d, *J* = 11.2, 1H, C*H*H Bn), 4.83 (d, *J* = 11.2, 1H, CH*H* Bn), 4.69 (d, *J* = 11.6, 1H, C*H*H Bn), 4.65 (d, *J* = 11.6, 1H, CH*H* Bn), 4.59 (d, *J* = 11.2, 1H, CH*H* Bn), 3.68 – 3.56 (m, 4H, H-2, H-4, CH_2-6), 3.49 – 3.41 (m, 2H, H-3, OC*H*H pentyl), 3.37 – 3.32 (m, 3H, OCH*H* pentyl, OCH_2 pentyl), 3.09 (dd, $J_{H1a\text{-}H2}$ = 4.8, $J_{H1a\text{-}H1b}$ = 11.2, 1H, CH-1a), 2.92 (s, 2H, OCH_2-Ada), 2.71 – 2.64 (m, 2H, NCH_2 butyl), 2.30 (d, *J* = 9.2 1H, H-5), 2.25 (dd, *J* = 10.4, 1H, H-1b), 1.93 (br s, 3H, 3×CH Ada), 1.71 – 1.51 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.43 – 1.24 (m, 6H, CH_2 pentyl, 2×CH_2 butyl), 0.92 (t, *J* = 7.2, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 139.0, 138.7, 138.6 (3×C_q Bn), 128.3, 128.2, 127.82, 127.76, 127.71, 127.54, 127.48, 127.3 (CH_{Ar} Bn), 87.3 (C-3), 81.9 (OCH_2-Ada), 78.8, 78.6 (C-2, C-4), 75.3, 75.2 72.7 (3×CH_2 Bn), 71.5 (2×OCH_2 pentyl), 66.5 (C-6), 63.8 (C-5), 54.6 (C-1), 52.1 (NCH_2 butyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 29.4, 29.3 (2×CH_2 pentyl), 28.3 (3×CH Ada), 25.7 (CH_2 butyl), 22.9 (CH_2 pentyl), 20.7 (CH_2 butyl), 14.0 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2901, 2847, 1497, 1458, 1366, 1312, 1265, 1096, 1034, 903, 810, 733, 694. $[\alpha]^{20}_D$: –0.4 (*c* 1.1, $CHCl_3$). HRMS: found *m/z* 724.4905 $[M+H]^+$, calcd for $[C_{47}H_{65}NO_5+H]^+$ 724.4936.

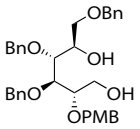


***N*-Butyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (7).** Compound **28** (57 mg, 79 µmol) was subjected to General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **7** (33 mg, 74 µmol) as a colorless oil in 93% yield. R_F = 0.68 (1:2; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.74 (d, $J_{H6a\text{-}H6b}$ = 10.5, 1H, CH-6a), 3.62 (dd, $J_{H6b\text{-}H5}$ = 3.7, $J_{H6b\text{-}H6a}$ = 10.5, 1H, CH-6b), 3.45 – 3.43 (m, 3H, H-2, OCH_2 pentyl), 3.37 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.24 (dd, *J* = 9.1, 9.1, 1H, H-4), 3.11 (dd, *J* = 9.1, 9.1, 1H, H-3), 2.98 – 2.93 (m, 3H, H-1a, OCH_2-Ada), 2.78 (m, 1H, NC*H*H butyl), 2.55 (m, 1H, NCH*H* butyl), 2.24 – 2.22 (m, 1H, H-5), 2.16 (dd, *J* = 11.0, 1H, H-1b), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.65 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.48 – 1.43 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.31 (m, 2H, CH_2 butyl), 0.94 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.1 (OCH_2-Ada), 80.6 (C-3), 72.6, 72.3 (2×OCH_2 pentyl), 72.2 (C-4), 70.6 (C-2), 69.4 (C-6), 66.4 (C-5), 57.7 (C-1), 53.9 (NCH_2 butyl), 40.9 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.2 (C_q Ada), 30.5 (2×CH_2 pentyl), 29.8 (3×CH Ada), 27.5 (CH_2 butyl), 24.1 (CH_2 pentyl), 21.8 (CH_2 butyl), 14.4 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3364, 2901, 2847, 2106, 1828, 1651, 1458, 1366, 1258, 1103, 1018, 810. $[\alpha]^{20}_D$: –21.8 (*c* 0.7, MeOH). HRMS: found *m/z* 454.3531 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

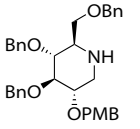


Allyl 3,4,6-tri-*O*-benzyl-2-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (30). A dry solution of compound **29**[33] (112 mg, 0.23 mmol) in DMF (1.5 mL) was cooled to 0 °C, followed by addition of NaH (10 mg, 60% wt in mineral oil, 0.25 mmol). After stirring for 20 min at rt, PMBCl (35 µL, 0.25 mmol) was added and the reaction was stirred for 4 h. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 50% EtOAc in PE) yielded **30** (116 mg, 0.19 mmol) in 83% as a colorless oil. R_F = 0.76 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25

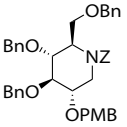
(m, 15H, H_{Ar} Bn), 6.90 – 6.81 (m, 4H, H_{Ar} PMB), 6.01 – 5.93 (m, 1H, CH vinyl; All), 5.38 – 5.19 (m, 2H, CH_2 vinyl; All), 4.95 – 4.39 (m, 8H, 4×CH_2 Bn/PMB), 4.17 – 4.13 (m, 1H), 3.84 – 3.50 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (*p*-C_q PMB), 138.6, 138.0 (3×C_q Bn), 134.0 (CH vinyl; All), 130.5 (C_q PMB), 129.9, 129.8, 129.6, 129.3, 129.2, 128.2, 127.8, 127.7, 127.6, 127.5 (CH_{Ar} Bn, 2× CH_{Ar} PMB), 117.0 (CH_2 vinyl; All), 113.6 (2×CH_{Ar} PMB), 102.6 (C-1), 84.6, 81.7, 77.7, 74.7 (C-2, C-3, C-4, C-5), 75.5, 74.8, 74.4, 71.2, 70.1, 68.8 (CH_2 All, 3×CH_2 Bn, CH_2 PMB, C-6), 55.1 (OCH_3 PMB). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2862, 1720, 1612, 1512, 1458, 1358, 1304, 1242, 1173, 1065, 1034, 926, 818, 741, 694. $[\alpha]^{20}_D$: 7.2 (*c* 3.0, $CHCl_3$). HRMS: found *m/z* 633.2868 $[M+Na]^+$, calcd for $[C_{38}H_{42}O_7+Na]^+$ 633.2823.



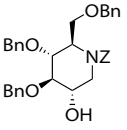
3,4,6-Tri-*O*-benzyl-2-*O*-*p*-methoxybenzyl-D-glucitol (31). Compound **30** (486 mg, 0.8 mmol) and DABCO (29 mg, 0.26 mmol) were combined, dissolved in EtOH/water (12.7 mL/ 0.6 mL) and argon was passed through the solution for 15 min. Wilkinson's catalyst (56 mg, 0.06 mmol) was added and the reaction mixture was refluxed for 48 h. The reaction mixture was concentrated with coevaporation of dioxane and redissolved in THF/water (6 mL/ 1 mL). Molecular iodine (407 mg, 1.6 mmol) was added to the solution and the reaction was stirred for 6 h's, after which TLC indicated the appearance of a lower running hemiacetal product mixture (R_F = 0.49; 0.42 in EtOAc:PE; 1:1). 1M aq $Na_2S_2O_3$ (4 mL) was added to the reaction, stirred for 15 min and poured into a mixture of sat aq NaCl/ 1M aq $Na_2S_2O_3$ (40 mL; 1/1). The aqueous phase was extracted with EtOAc (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude hemiacetal was used in General procedure A. The resulting residue was purified by silica gel column chromatography (20% » 50% EtOAc in PE) to give **31** (362 mg, 0.63 mmol) in 79% over two steps as a colorless oil. R_F = 0.56 (2:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.47 – 7.24 (m, 17H, H_{Ar} Bn, H_{Ar} PMB), 6.87 (m, 2H, H_{Ar} PMB), 4.74 (d, *J* = 11.3, 1H, C*H*H Bn/PMB), 4.68 (d, *J* = 11.3, 1H, CH*H* Bn/PMB), 4.66 – 4.52 (m, 6H, 3×CH_2 Bn/PMB), 4.05 (m, 1H, H-5), 3.89 (dd, *J* = 3.6, 6.3, 1H, H-3), 3.85 – 3.78 (m, 5H, H-2, H-4, OCH_3 PMB), 3.74 (dd, J_{H1a-H2} = 4.5, $J_{H1a-H1b}$ = 11.8, 1H, H-1a), 3.70 – 3.66 (m, 2H, CH_2-6), 3.58 (dd, J_{H1b-H2} = 4.8, $J_{H1b-H1a}$ = 11.8, 1H, H-1b), 3.01 (br s, 1H, OH), 2.11 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (*p*-C_q PMB), 138.0, 137.9, 137.8 (3×C_q Bn), 130.2 (C_q PMB), 130.0, 129.9, 129.8, 129.7, 129.6, 129.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.91, 127.88, 128.82, 127.76 (CH_{Ar} Bn, 2×CH_{Ar} PMB), 113.9 (2×CH_{Ar} PMB), 79.1, 79.0 (C-2, C-3), 77.5 (C-4), 74.4, 73.5, 73.3, 72.7 (3×CH_2 Bn, CH_2 PMB), 71.1 (C-6), 70.7 (C-5), 61.9 (C-1), 55.3 (OCH_3 PMB). IR ν_{max}(thin film)/ cm^{-1}: 3410, 2870, 1713, 1612, 1512, 1458, 1250, 1072, 1034, 826, 741, 702, 625. $[\alpha]^{20}_D$: 10.0 (*c* 0.2, $CHCl_3$). MS (ESI): *m/z* 573.3 $[M+H]^+$; 595.3 $[M+Na]^+$.



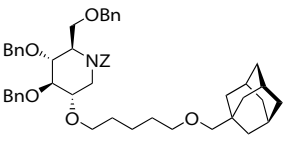
3,4,6-Tri-*O*-benzyl-2-*O*-*p*-methoxybenzyl-1-deoxynojirimycin (32). Compound **31** (994 mg, 1.74 mmol) was used in General procedure B with double reductive amination method B. The resulting residue was purified by silica gel column chromatography (25% » 75% EtOAc in PE) to provide **32** (654 mg, 1.18 mmol) in 68% yield as a light yellow crystalline solid. R_F = 0.19 (2:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.36 – 7.18 (m, 17H, H_{Ar} Bn, H_{Ar} PMB), 6.85 (m, 2H, H_{Ar} PMB), 4.96 (d, *J* = 11.0, 1H, C*H*H Bn/PMB), 4.85 (d, *J* = 11.2, 1H, C*H*H Bn/PMB), 4.82 (d, *J* = 11.2, 1H, CH*H* Bn/PMB), 4.62 (d, *J* = 11.3, 1H, C*H*H Bn/PMB), 4.58 (d, *J* = 11.3, 1H, CH*H* Bn/PMB), 4.48 (d, *J* = 11.0, 1H, CH*H* Bn/PMB), 4.47 (d, *J* = 11.8, 1H, CH*H* Bn/PMB), 4.42 (d, *J* = 11.8, 1H C*H*H Bn/PMB), 3.79 (s, 3H, OCH_3 PMB), 3.67 (dd, J_{H6a-H5} = 2.5, $J_{H6a-H6b}$ = 9.0, 1H, H-6a), 3.55 – 3.45 (m, 3H, H-2, H-3, H-6b), 3.35 (dd, *J* = 8.9, 8.9, 1H, H-4), 3.22 (dd, J_{H1a-H2} = 4.8, $J_{H1a-H1b}$ = 12.2, 1H, H-1a), 2.72 (ddd, *J* = 2.5, 5.9, 9.0, 1H, H-5), 2.48 (dd, J_{H1b-H2} = 10.3, $J_{H1b-H1a}$ = 12.2, 1H, H-1b), 2.06 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 159.2 (*p*-C_q PMB), 139.0, 138.4, 137.9 (3×C_q Bn), 130.6 (C_q PMB), 129.4, 128.4, 128.35, 128.33, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{Ar} Bn, 2×CH_{Ar} PMB), 113.8 (2×CH_{Ar} PMB), 87.2 (C-3), 80.2, 80.0 (C-2, C-4), 75.6, 75.2, 73.4, 72.5 (3×CH_2 Bn, CH_2 PMB), 70.2 (C-6), 59.7 (C-5), 55.2 (OCH_3 PMB), 48.1 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 2932, 2862, 1728, 1612, 1512, 1458, 1358, 1250, 1096, 1072, 1034, 818, 741, 702, 633. $[\alpha]^{20}_D$: 18.8 (*c* 1.1, $CHCl_3$). HRMS: found *m/z* 554.2930 $[M+H]^+$, calcd for $[C_{35}H_{39}NO_5+H]^+$ 554.2901.



3,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-2-*O*-*p*-methoxybenzyl-1-deoxynojirimycin (33). To a solution of compound **32** (654 mg, 1.18 mmol) in dioxane (12 mL), 10 wt % aq $NaHCO_3$ (4 mL) was added. Next, benzyloxychloroformate (253 µL, 1.77 mmol) was added and the reaction was stirred for 20 h. The reaction mixture was poured into water (40 mL) and extracted with Et_2O (3×50mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 33% EtOAc in PE) to provide **33** (808 mg, 1.17 mmol) in 99% yield as a colorless oil. R_F = 0.69 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.32 – 7.19 (m, 22H, H_{Ar} Bn, H_{Ar} Z, H_{Ar} PMB), 6.81 (d, *J* = 8.6, 2H, H_{Ar} PMB), 5.14 (d, *J* = 12.3, 1H, C*H*H Z), 5.08 (d, *J* = 12.3, 1H, CH*H* Z), 4.72 (d, *J* = 11.6, 1H, C*H*H Bn/PMB), 4.62 – 4.55 (m, 3H, 3×CH Bn/PMB), 4.51 (d, *J* = 11.6, 1H, CH*H* Bn/PMB), 4.43 (d, *J* = 12.1, 1H, C*H*H Bn/PMB), 4.39 (d, *J* = 11.5, 1H, CH Bn/PMB), 4.33 (d, *J* = 12.1, 1H, CH*H* Bn/PMB), 4.20 – 4.18 (m, 1H, H-5), 4.13 (br d, $J_{H1a\text{-}H1b}$ = 14.4, 1H, H-1a), 3.90 (dd, *J* = 6.5, 1H, H-4), 3.78 (s, 3H, OCH_3 PMB), 3.71 (dd, *J* = 4.4, *J* = 6.9, 1H, H-3), 3.73 – 3.60 (m, 3H, H-2, CH_2-6), 3.32 (dd, $J_{H1b\text{-}H2}$ = 3.4, $J_{H1b\text{-}H1a}$ = 14.4, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 159.1 (*p*-C_q PMB), 155.8 (C=O Z), 138.3, 138.2, 136.6 (3×C_q Bn, C_q Z), 130.1 (C_q PMB), 129.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.57, 127.49, 127.46 (CH_{Ar} Bn, 2×CH_{Ar} PMB, CH_{Ar} Z), 113.7 (2×CH_{Ar} PMB), 81.8 (C-3), 77.8 (C-2), 74.1 (C-4), 73.2, 72.9, 72.8, 70.2 (3×CH_2 Bn, CH_2 PMB), 68.4 (C-6), 67.2 (CH_2 Z), 55.7 (C-5), 55.2 (OCH_3 PMB), 41.3 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2862, 1697, 1612, 1512, 1420, 1358, 1304, 1242, 1072, 1026, 910, 818, 740, 694. $[\alpha]^{20}_D$: 7.0 (*c* 1.5, $CHCl_3$). HRMS: found *m/z* 688.3298 $[M+H]^+$, calcd for $[C_{43}H_{45}NO_7+H]^+$ 688.3269.

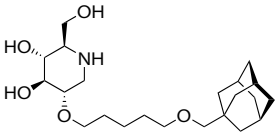


3,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-1-deoxynojirimycin (34)#. Trifluoroacetic acid (600 µL) was slowly added to a dry solution of compound **33** (601 mg, 0.87 mmol) in DCM (29 mL), under rapid stirring. The reaction mixture was stirred for 60 min, after which it was poured into sat aq $NaHCO_3$ (50 mL) and extracted with DCM (3×50mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (20% » 33% EtOAc in PE) to provide **34** (446 mg, 0.79 mmol) in 90% yield as a colorless oil. R_F = 0.51 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.60 – 7.28 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.32 (d, *J* = 12.8, 1H, C*H*H Z), 5.27 (d, *J* = 12.8, 1H, CH*H* Z), 5.08 (m, 1H), 4.79 – 4.53 (m, 6H, 3×CH_2 Bn), 3.31 (m, 1H, H-1a), 3.98 (m, 1H), 3.92 – 3.81 (m, 5H), 3.37 (d, *J* = 14.0 , 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 156.6 (C=O Z), 138.0, 137.4, 136.7, 136.6 (3×C_q Bn, C_q Z), 128.32, 128.28, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3 (CH_{Ar} Bn, CH_{Ar} Z), 74.3, 72.5, 66.5 (C-2, C-3, C-4, C-5), 72.6, 71.9, 71.4, (CH_2 Bn), 67.1 66.8 (CH_2 Z, C-6), 42.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3503, 3032, 2870, 1697, 1605, 1450, 1427, 1358, 1319, 1250, 1172, 1072, 1026, 818, 733, 694. $[\alpha]^{20}_D$: –35.6 (*c* 1.3, $CHCl_3$). HRMS: found *m/z* 568.2668 $[M+H]^+$, calcd for $[C_{35}H_{37}NO_6+H]^+$ 568.2694. #: NMR characterization suffered from collapsed signals and peak broadening due to rotamers of the benzyloxycarbamate.

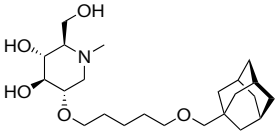


3,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-2-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (35). Compound **34** (148 mg, 0.26 mmol) was alkylated with bromide **25** using General procedure C. The resulting residue was purified by silica gel column chromatography (5% » 33% EtOAc in PE) to provide **35** (186 mg, 0.24 mmol) in 91% yield as a colorless oil. R_F = 0.50 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.31 – 7.25 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.14 (d, *J* = 12.4, 1H, C*H*H Z), 5.07 (d, *J* = 12.4, 1H, CH*H* Z), 4.74 (d, *J* = 11.6, 1H, C*H*H Bn), 4.65 (s, 2H, CH_2 Bn), 4.51 (d, *J* = 11.6, 1H, CH*H* Bn), 4.42 (d, *J* = 12.0, 1H, C*H*H Bn), 4.32 (d, *J* = 12.0, 1H, CH*H* Bn), 4.13 (m, 1H, H-5), 3.99 (dd, *J* = 14.2, 4.6, 1H, H-1a), 3.91 (dd, *J* = 6.7, 6.7, 1H, H-4), 3.67 – 3.54 (m, 4H, H-2, H-3, CH_2-6), 3.38 – 3.31 (m, 5H, H-1b, 2×OCH_2 pentyl), 2.93 (s, 2H, OCH_2-Ada), 1.94 (br s, 3H, 3×CH Ada), 1.72 – 1.52 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.36 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.7 (C=O Z), 138.2, 136.6 (3×C_q Bn, 1×C_q Z), 128.4, 128.2, 127.9, 127.7, 127.5, 127.4 (CH_{Ar} Bn, CH_{Ar} Z), 82.4, 79.5, 74.3 (C-2, C-3, C-4), 81.9 (OCH_2-Ada), 73.2, 72.9, 72.8, 71.5, 70.0, 68.5, 67.1 (CH_2

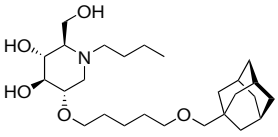
Z, 3×CH_2 Bn, 2×OCH_2 pentyl, C-6), 55.8 (C-5), 41.7 (C-1), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 29.7, 29.4 (2×CH_2 pentyl), 28.2 (3×CH Ada), 22.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1697, 1450, 1420, 1358, 1312, 1250, 1219, 1088, 1026, 910, 810, 733, 694, 617. $[\alpha]^{20}_D$: –3.7 (*c* 3.7, $CHCl_3$). HRMS: found *m/z* 802.4694 $[M+H]^+$, calcd for $[C_{51}H_{63}NO_7+H]^+$ 802.4677.



2-*O*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (8). Compound **35** (94 mg, 236 µmmol) was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **8** (72 mg, 181 µmol) as an off-white solid in 72% yield. R_F = 0.35 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.82 (dd, J_{H6a-H5} = 2.8, $J_{H6a-H6b}$ = 10.9, 1H, H-6a), 3.65 – 3.56 (m, 3H, H-6b, OCH_2 pentyl), 3.37 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.28 – 3.22 (m, 2H, H-3, H-1a), 3.18 – 3.12 (m, 2H, H-2, H-4), 2.96 (s, 2H, OCH_2-Ada), 2.44 (m, 1H, H-5), 2.35 (dd, *J* = 10.2, 10.2, 1H, H-1b), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.63 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.42 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.0 (OCH_2-Ada), 80.8 79.6 (C-2, C-3), 73.4 (C-4), 72.6, 71.7 (2×OCH_2 pentyl), 63.0 (C-6), 62.7 (C-5), 48.6 (C-1), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.1 (C_q Ada), 31.0, 30.5 (2×CH_2 pentyl), 29.7 (3×CH Ada), 23.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3333, 2901, 2847, 2476, 1450, 1366, 1258, 1096, 1049, 880, 841, 710. $[\alpha]^{20}_D$: 28.2 (*c* 1.4, $CHCl_3$). HRMS: found *m/z* 398.2921 $[M+H]^+$, calcd for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.

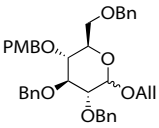


***N*-Methyl-2-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (9).** A solution of compound **8** (36 mg, 90 µmol) and formaldehyde (0.5 mL, 6.2 mmol; 37 wt % in water) in EtOH (4 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 min, after which a catalytic amount of Pd/C (30 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 10 min and stirring was continued under atmospheric hydrogen pressure for 20 h. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH. The filtrate was concentrated and coevaporated with toluene. The residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **9** (37 mg, 90 µmol) as a light yellow oil in quantitative yield. R_F = 0.49 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.84 – 3.83 (m, 2H, CH_2-6), 3.40 – 3.36 (m, 3H, H-4, OCH_2 pentyl), 3.25 – 3.17 (m, 2H, H-2, H-3), 3.04 (dd, J_{H1a-H2} = 4.4, $J_{H1a-H1b}$ = 11.3, 1H, H-1a), 2.96 (s, 2H, OCH_2-Ada), 2.35 (s, 3H, NCH_3), 2.00 (dd, *J* = 9.0, 12.2, H-1b), 1.95 – 1.93 (m, 4H, H-5, 3×CH Ada), 1.79 – 1.66 (m, 6H, 3×CH_2 Ada), 1.61 – 1.53 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.43 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.0 (OCH_2-Ada), 79.5, 78.8 (C-2, C-3), 72.6, 71.9 (2×OCH_2 pentyl), 71.6, 70.3 (C-4, C-5), 59.6, 59.2 (C-6, C-1), 42.5 (NCH_3), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.0, 30.5 (2×CH_2 pentyl), 29.7 (3×CH Ada), 23.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3302, 2901, 2847, 2353, 2106, 1659, 1612, 1450, 1366, 1234, 1234, 1096, 1049, 910, 826. $[\alpha]^{20}_D$: 6.3 (*c* 0.8, $CHCl_3$). HRMS: found *m/z* 412.3076 $[M+H]^+$, calcd for $[C_{23}H_{41}NO_5+H]^+$ 412.3058.

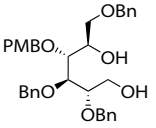


***N*-Butyl-2-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (10).** Compound **8** (24 mg, 60 µmol) was transformed into **10** using the procedure as described for **9**, but substituting formaldehyde for butyraldehyde (0.1 mL, 1.1 mmol). The crude product was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **10** as a light yellow oil (24 mg, 54 µmol) in 90% yield. R_F = 0.59 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.84 – 3.83 (m, 2H, CH_2-6), 3.65 – 3.56 (m, 2H, OCH_2 pentyl), 3.40 – 3.33 (m, 3H, H-4, OCH_2 pentyl),

3.24 – 3.15 (m, 2H, H-2, H-3), 3.08 (dd, $J_{H1eq-H2}$ = 4.2, $J_{H1eq-H1ax}$ = 11.2, 1H, H-1a), 2.96 (s, 2H, OCH_2-Ada), 2.78 (m, 1H, NC*H*H butyl), 2.59 (m, 1H, NCH*H* butyl), 2.12 – 2.07 (m, 2H, H-1b, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.63 – 1.53 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.50 – 1.40 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.30 (m, 2H, CH_2 butyl), 0.94 (t, *J* = 7.4, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.0 (OCH_2-Ada), 79.6, 79.2 (C-2, C-3), 72.6 (OCH_2 pentyl), 72.1 (C-4), 71.7 (OCH_2 pentyl), 67.1 (C-5), 59.4 (C-6), 55.2 (C-1), 53.6 (NCH_2 butyl), 40.9 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.1 (C_q Ada), 31.0, 30.7 (2×CH_2 pentyl), 29.8 (3×CH Ada), 27.3 (CH_2 butyl), 23.9 (CH_2 pentyl), 21.8 (CH_2 butyl), 14.4 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3371, 2901, 2847, 2091, 1690, 1458, 1366, 1150, 1103, 903, 826, 664. $[\alpha]^{20}_D$: 28.1 (*c* 0.3, $CHCl_3$/MeOH; 2/1). HRMS: found *m/z* 454.3551 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

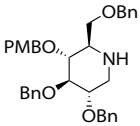


α/β-Mixture of allyl 2,3,6-tri-*O*-benzyl-4-*O*-*p*-methoxybenzyl-D-glucopyranoside (37). Compound **36**[34] (2.328 g, 4.75 mmol) was protected with a PMB-group using the same procedure as described for the synthesis of **30**. The crude product was purified by silica gel column chromatography (15% » 33% EtOAc in PE) to yield **37** (2.617 g, 4.29 mmol) in 90% as a crystalline solid. R_F = 0.68 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) α/β mixture δ 7.38 – 7.23 (m, 15H, H_{Ar} Bn), 7.07 – 7.02 (m, 2H, H_{Ar} PMB), 6.78 – 6.76 (m, 2H, H_{Ar} PMB), 5.97 – 5.87 (m, 1H, CH vinyl; All), 5.35 – 5.17 (m, 2H, CH_2 vinyl; All), 5.01 – 4.39 (m, 8H, 4×CH_2 Bn/PMB), 4.16 – 4.10 (m, 1H), 4.03 – 3.97 (m, 1H), 3.81 – 3.42 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) α/β mixture δ 159.0 (*p*-C_q PMB), 138.7, 138.4, 138.2, 138.0, 137.0 (3×C_q Bn α+β), 133.9, 133.5 (CH vinyl; All α+β), 130.2, 130.0 (C_q PMB α+β) 129.4, 129.3, 128.1, 127.9, 127.8, 127.63, 127.60, 127.56, 127.53, 127.50, 127.4, 127.3 (CH_{Ar} Bn, 2×CH_{Ar} PMB; α+β), 117.8, 116.8 (CH_2 vinyl; All α+β), 113.6 (2×CH_{Ar} PMB α+β), 102.5(C-1 β), 95.4 (C-1 α), 84.5, 82.0, 81.9, 79.7, 77.3, 77.2, 74.6, 70.0 (C-2, C-3, C-4, C-5; α+β), 75.4, 74.6, 74.4, 73.2, 72.9, 69.9, 68.7, 68.2, 67.9 (CH_2 All, 3×CH_2 Bn, CH_2 PMB, C-6; α+β), 54.9 (OCH_3 PMB; α+β). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2862, 1720, 1612, 1512, 1458, 1358, 1304, 1250, 1157, 1065, 1034, 926, 818, 741, 694. $[\alpha]^{20}_D$: 15.6 (c = 5.5, $CHCl_3$). HRMS: *M/Z* found 633.2883 $[M+Na]^+$, calcd for $[C_{38}H_{42}O_7+Na]^+$ 633.2823.

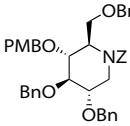


2,3,6-Tri-*O*-benzyl-4-*O*-*p*-methoxybenzyl-D-glucitol (38). A dry solution of **37** (1.221 mg, 2.00 mmol) in DMSO (4 mL) was charged with KO*t*Bu (112 mg, 1.00 mmol) and heated at 100 °C for 30 min, after which it was quenched by addition of water (1 mL). The reaction mixture was poured into water (150 mL) and extracted with Et_2O (3×100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in THF/water (8.5 mL/ 1.5 mL). Molecular iodine (1 g, 4 mmol) was added to the solution and the reaction was stirred for 6 h, after which TLC indicated the appearance of a lower running hemiacetal product mixture (R_F = 0.67; 0.60 in EtOAc:PE; 1:1). 1M aq $Na_2S_2O_3$ (10 mL) was added to the reaction, stirred for 15 min and poured into a mixture of sat aq NaCl/ 1M aq $Na_2S_2O_3$ (80 mL; 1/1). The aqueous phase was extracted with EtOAc (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude hemiacetal intermediate was reduced to **38** using General procedure A. The resulting residue was purified by silica gel column chromatography (25% » 66% EtOAc in PE) to give **38** (940 mg, 1.64 mmol) in 82% over two steps as a colorless oil. R_F = 0.40 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.35 – 7.23 (m, 15H, H_{Ar} Bn), 7.13 (dd, *J* = 3.9, 11.4, 2H, H_{Ar} PMB), 6.80 (dd, *J* = 3.0, 11.4, 2H, H_{Ar} PMB), 4.71 (d, *J* = 11.3, 1H, C*H*H Bn/PMB), 4.66 (d, *J* = 11.6, 1H, C*H*H Bn/PMB), 4.64 (d, *J* = 11.3, 1H, CH*H* Bn/PMB), 4.61 (d, *J* = 11.6, 1H, CH*H* Bn/PMB), 4.55 (d, *J* = 11.9, 1H, C*H*H Bn/PMB), 4.51 (d, *J* = 11.0, 1H, C*H*H Bn/PMB), 4.50 (d, *J* = 11.9, 1H, CH*H* Bn/PMB), 4.46 (d, *J* = 11.0, 1H, CH*H* Bn/PMB), 4.02 (m, 1H, H-5), 3.87 (dd, *J* = 3.6, 6.4, 1H, H-3), 3.80 – 3.74 (m, 5H, H-2, H-4, OCH_3 PMB), 2.71 (dd, J_{H1a-H2} = 4.3, $J_{H1a-H1b}$ = 11.9, 1H, H-1a), 3.66 – 3.58 (m, 2H, CH_2-6), 3.55 (dd, J_{H1b-H2} = 4.5, $J_{H1b-H1a}$ = 11.9, 1H, H-1b), 2.98 (br s, 1H, OH), 2.16 (br. s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 159.3 (*p*-C_q PMB), 138.1, 137.9, 137.8 (3×C_q Bn), 129.9 (C_q PMB), 129.8, 128.4, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{Ar} Bn, 2×CH_{Ar} PMB), 113.8 (2×CH_{Ar} PMB), 79.4 (C-2), 79.1 (C-3), 76.8 (C-4), 74.4, 73.4, 73.0, 72.8 (3×CH_2 Bn, CH_2 PMB), 71.1 (C-6),

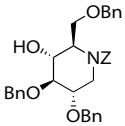
70.7 (C-5), 61.8 (C-1), 55.2 (OCH_3 PMB). IR ν_{max}(thin film)/ cm^{-1}: 3433, 3032, 2924, 2870, 1713, 1612, 1512, 1458, 1358, 1288, 1250, 1065, 1034, 918, 818, 733, 694. $[\alpha]^{20}_D$: 4.3 (*c* 13.1, $CHCl_3$). HRMS: found *m/z* 573.2698 $[M+H]^+$, calcd for $[C_{35}H_{40}O_7+H]^+$ 573.2666.



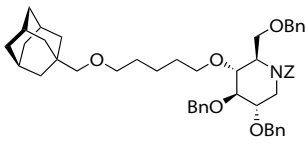
2,3,6-Tri-*O*-benzyl-4-*O*-*p*-methoxybenzyl-1-deoxynojirimycin (39). Compound **39** was synthesized from **38** (469 mg, 0.82 mmol) using General procedure B with double reductive amination method B. The crude product was purified by silica gel column chromatography (25% » 75% EtOAc in PE) to provide **39** (218 mg, 0.39 mmol) in 48% yield as a light yellow crystalline solid. R_F = 0.14 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.38 – 7.24 (m, 15H, H_{Ar} Bn), 7.09 (m, 2H, H_{Ar} PMB), 6.80 (m, 2H, H_{Ar} PMB), 4.98 (d, *J* = 11.0, 1H C*H*H Bn/PMB), 4.85 (d, *J* = 11.0, 1H CH*H* Bn/PMB), 4.78 (d, *J* = 10.5, 1H CH Bn/PMB), 4.66 (m, 2H, CH_2 Bn/PMB), 4.51 – 4.39 (m, 3H, 3×CH Bn/PMB), 3.73 (s, 3H, OCH_3 PMB), 3.64 (dd, *J* = 2.3, 8.9, 1H, H-6a), 3.57 – 3.43 (m, 3H, H-2, H-3, H-6b), 3.33 (dd, *J* = 8.8, 9.3, 1H, H-4), 3.21 (dd, $J_{H1a\text{-}H2}$ = 4.6, $J_{H1a\text{-}H1b}$ = 12.2, 1H, H-1a), 2.69 (m, 1H, H-5), 2.48 (dd, $J_{H1b\text{-}H2}$ = 10.2, $J_{H1b\text{-}H1a}$ = 12.2, 1H, H-1b), 2.00 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (*p*-C_q PMB), 138.8, 138.4, 137.8 (3×C_q Bn), 130.4 (C_q PMB), 129.5, 128.2, 127.7, 127.6, 127.5, 127.3 (CH_{Ar} Bn, 2×CH_{Ar} PMB), 113.6 (2×CH_{Ar} PMB), 87.2, 80.5, 79.6 (C-2, C-3, C-4), 75.5, 74.6, 73.2, 72.6, 70.1 (3×CH_2 Bn, CH_2 PMB, C-6), 59.6 (C-5), 55.1 (OCH_3 PMB), 48.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2862, 1612, 1512, 1458, 1358, 1304, 1250, 1096, 1034, 910, 818, 741, 702. $[\alpha]^{20}_D$: 17.4 (*c* 2.6, $CHCl_3$). HRMS: found *m/z* 554.2954 $[M+H]^+$, calcd for $[C_{35}H_{39}NO_5+H]^+$ 554.2901.



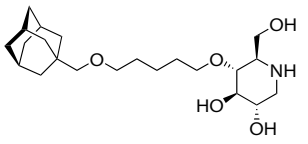
2,3,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-4-*O*-*p*-methoxybenzyl-1-deoxynojirimycin (40). Compound **39** (218 mg, 0.39 mmol) was protected with a Z-carbamate function using the same procedure as described for the synthesis of **33**. The crude product was purified by silica gel column chromatography (15% » 33% EtOAc in PE) to provide **40** (268 mg, 0.39 mmol) quantitatively as a colorless oil. R_F = 0.78 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.33 – 7.20 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 7.14 (d, *J* = 8.5, 2H, H_{Ar} PMB), 6.77 (d, *J* = 8.5, 2H, H_{Ar} PMB), 5.09 (d, *J* = 12.4, 1H C*H*H Z), 5.03 (d, *J* = 12.4, 1H CH*H* Z), 4.65 – 4.38 (m, 7H, 7×CH Bn/PMB), 4.29 (d, *J* = 12.0, 1H, CH Bn/PMB), 4.19 – 4.11 (m, 2H, H-5, H-1a), 3.88 (dd, *J* = 6.3, 6.3, 1H, H-4), 3.75 – 3.62 (m, 7H, H-2, H-3, CH_2-6, OCH_3 PMB), 3.30 (dd, *J* = 2.9, 14.4, 1H, H-1b). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9 (*p*-C_q PMB), 155.7 (C=O Z), 138.0, 137.9, 137.8, 136.3 (3×C_q Bn, C_q Z), 130.0 (C_q PMB), 129.5, 128.1, 127.6, 127.5, 127.3, 127.2, 127.1, 126.6 (CH_{Ar} Bn, 2×CH_{Ar} PMB, CH_{Ar} Z), 113.5 (2×CH_{Ar} PMB), 81.4, 77.8, 73.3 (C-2, C-3, C-4), 72.6, 72.5, 70.3, 68.0, 67.1, 64.6 (3×CH_2 Bn, CH_2 PMB, CH_2 Z, C-6), 55.4 (C-5), 54.9 (OCH_3 PMB), 41.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 2932, 2870, 1697, 1612. 1512, 1450, 1358, 1250, 1072, 1034, 826, 741, 694. $[\alpha]^{20}_D$: 5.7 (*c* 2.0, $CHCl_3$). HRMS: found *m/z* 688.3287 $[M+H]^+$, calcd for $[C_{43}H_{45}NO_7+H]^+$ 688.3269.



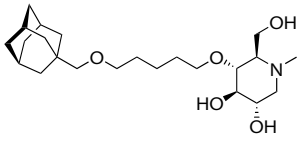
2,3,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-1-deoxynojirimycin (41)#. The PMB-function in **40** (268 mg, 0.39 mmol) was cleaved using the same procedure as described for the synthesis of **34**. The crude product was purified by silica gel column chromatography (20% » 33% EtOAc in PE) to provide product **41** (217 mg, 0.38 mmol) in 98% yield as a colorless oil. R_F = 0.71 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.19 (d, *J* = 12.5, 1H, C*H*H Z), 5.14 (d, *J* = 12.5, 1H, CH*H* Z), 4.75 – 4.65 (m, 2H), 4.70 – 4.37 (m, 6H, 3×CH_2 Bn), 3.96 (m, 1H), 3.81 – 3.63 (m, 5H), 3.15 (d, *J* = 14.7, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.5, 136.9 (C_q Bn), 128.4, 128.3, 128.2, 127.9, 127.8, 127.5, 127.4 (CH_{Ar} Bn, CH_{Ar} Z), 75.2, 66.0 (CH), 72.6, 72.2, 70.8, 67.3, 67.0 (CH_2). IR ν_{max}(thin film)/ cm^{-1}: 3502, 3032, 2870, 1697, 1504, 1450, 1427, 1358, 1312, 1250, 1096, 1026, 741, 694. $[\alpha]^{20}_D$: 19.3 (*c* 2.1, $CHCl_3$). HRMS: found *m/z* 568.2725 $[M+H]^+$, calcd for $[C_{35}H_{37}NO_6+H]^+$ 568.2694. #: NMR characterization suffered from collapsed signals and peak broadening due to rotamers of the benzyloxycarbamate.



2,3,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-4-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (42). Compound **41** (102 mg, 0.18 mmol) was alkylated with bromide **25** using General procedure C. The resulting residue was purified by silica gel column chromatography (5% » 33% EtOAc in PE) to provide product **42** (132 mg, 0.16 mmol) in 91% yield as a colorless oil. R_F = 0.60 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.32 – 7.21 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.13 (d, *J* = 12.4, 1H, C*H*H Z), 5.08 (d, *J* = 12.4, 1H, CH*H* Z), 4.68 (d, *J* = 11.6, 1H, C*H*H Bn), 4.64 – 4.61 (m, 3H, 2×CH Bn), 4.51 (d, *J* = 12.0, 1H, C*H*H Bn), 4.43 (d, *J* = 11.7, 1H, CH Bn), 4.42 (d, *J* = 12.0, 1H, CH*H* Bn), 4.12 – 4.05 (m, 2H, H-1a, H-5), 3.75 (dd, *J* = 6.7, 6.7, 1H, H-4), 3.69 – 3.65 (m, 5H, H-2, H-3, CH_2-6, OC*H*H pentyl), 3.42 (m, 1H, OCH*H* pentyl), 3.36 – 3.31 (m, 3H, H-1b, OCH_2 pentyl), 2.93 (s, 2H, OCH_2-Ada), 1.94 (br s, 3H, 3×CH Ada), 1.71 – 1.62 (m, 6H, 3×CH_2 Ada), 1.55 – 1.47 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.32 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 (C=O Z), 138.3, 138.0, 136.6 (3×C_q Bn, 1×C_q Z), 128.3, 128.3, 127.79, 127.76, 127.69, 127.59, 127.53, 127.46 (CH_{Ar} Bn, CH_{Ar} Z), 82.2, 78.6, 75.0 (C-2, C-3, C-4), 81.8 (OCH_2-Ada), 73.0, 72.9, 71.6, 71.4, 70.5, 68.5, 67.1 (CH_2 Z, 3×CH_2 Bn, 2×OCH_2 pentyl, C-6), 56.0 (C-5), 41.4 (C-1), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 29.8, 29.4 (2×CH_2 pentyl), 28.2 (3×CH Ada), 22.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1697, 1497, 1450, 1420, 1358, 1312, 1219, 1096, 1026, 910, 741, 694. $[\alpha]^{20}_D$: 5.8 (*c* 2.5, $CHCl_3$). HRMS: found *m/z* 802.4639 $[M+H]^+$, calcd for $[C_{51}H_{63}NO_7+H]^+$ 802.4677.

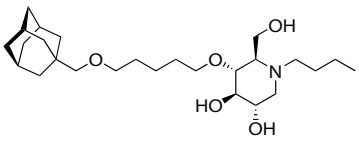


4-*O*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (11). Compound **42** (132 mg, 164 µmol) was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in EtOAc with 0.5% NH_4OH) to give **11** (54 mg, 136 µmol) as an off-white solid in 83% yield. R_F = 0.22 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.89 – 3.85 (m, 1H, OC*H*H pentyl), 3.79 (dd, *J* = 2.5, 10.8, 1H, H-6a), 3.62 – 3.52 (m, 2H, H-6b, OCH*H* pentyl), 3.42 – 3.36 (m, 3H, H-2, OCH_2 pentyl), 3.28 (dd, *J* = 9.4, 9.4, 1H, H-3), 3.07 (dd, J_{H1a-H2} = 5.1, $J_{H1a-H1b}$ = 12.2, 1H, H-1a), 3.00 (dd, *J* = 9.4, 9.4, 1H, H-4), 2.96 (s, 2H, OCH_2-Ada), 2.47 (ddd, *J* = 2.5, 5.6, 9.6, 1H, H-5), 2.40 (dd, J_{H1b-H2} = 10.8, $J_{H1b-H1a}$ = 12.2, 1H, H-1b), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.64 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.43 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.0 (OCH_2-Ada), 81.2 (C-4), 80.6 (C-3), 72.8 (C-2), 73.9, 72.6 (2×OCH_2 pentyl), 62.4 (C-6), 62.3 (C-5), 50.8 (C-1), 40.4 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.1 (C_q Ada), 31.2, 30.5 (2×CH_2 pentyl), 29.7 (3×CH Ada), 23.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3371, 2901, 2847, 2476, 2068, 1674, 1450, 1366, 1258, 1196, 1096, 1049, 980, 880, 841, 718. $[\alpha]^{20}_D$: 16.9 (*c* 1.1, MeOH). HRMS: found *m/z* 398.2905 $[M+H]^+$, calcd for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.

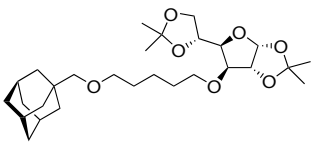


***N*-Methyl-4-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (12).** Argon was passed through a solution of compound **42** (54 mg, 67 µmol) in MeOH (3 mL) for 15 min, after which a catalytic amount of Pd/C Degussa type (50 mg, 5 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 30 min. After stirring the reaction under atmospheric hydrogen pressure for 60 min, TLC analysis indicated full conversion to the Z-deprotected intermediate product (R_F = 0.04 in 3:1; PE:EtOAc). At this point a solution of formaldehyde (0.7 mL; 37 wt % in water) in MeOH (1.4 mL), through which argon had been passed for 5 min, was added to the reaction mixture. After stirring under a hydrogen atmosphere for another 90 min, TLC analysis indicated full conversion to the *N*-methylated intermediate (R_F intermediate = 0.36 in PE:EtOAc; 2:1). The Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH. The filtrate was concentrated and coevaporated once with toluene. The crude intermediate product was deprotected using General procedure

D. The resulting residue was purified by silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **12** (26 mg, 63 µmol) as a colorless oil in 94% yield. R_F = 0.42 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^1H NMR (400 MHz, MeOD, COSY) δ 3.94 – 3.89 (m, 1H, OC*H*H pentyl), 3.82 (dd, $J_{H6a\text{-}H5}$ = 2.3, $J_{H6a\text{-}H6b}$ = 11.9, 1H, CH-6a), 3.74 (dd, $J_{H6b\text{-}H5}$ = 2.1, $J_{H6b\text{-}H6a}$ = 11.9, 1H, CH-6b), 3.65 – 3.60 (m, 1H, OCH*H* pentyl), 3.47 (m, 1H, H-2), 3.38 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.23 – 3.21 (m, 2H, H-3, H-4), 2.96 (s, 2H, OCH_2-Ada), 2.89 (dd, *J* = 4.8, 11.1, 1H, H-1a), 2.33 (s, 3H, NCH_3), 2.03 (dd, *J* = 10.8, 1H, H-1b), 1.93 (br s, 3H, 3×CH Ada), 1.76 – 1.65 (m, 7H, H-5, 3×CH_2 Ada), 1.63 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.44 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.1 (OCH_2-Ada), 80.7, 79.5 (C-3, C-4), 74.1, 72.6 (2×OCH_2 pentyl), 70.7, 69.8 (C-2, C-5), 62.1, 58.5 (C-1, C-6), 42.3 (NCH_3), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.2, 30.6 (2×CH_2 pentyl), 29.6 (3×CH Ada), 23.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3387, 2901, 2847, 2793, 2106, 1666, 1458, 1358, 1250, 1096, 1042, 988, 918, 826. $[\alpha]^{20}_D$: 11.5 (*c* 0.4, $CHCl_3$/MeOH; 2/1). HRMS: found *m/z* 412.3074 $[M+H]^+$, calcd for $[C_{23}H_{42}NO_5+H]^+$ 412.3058.

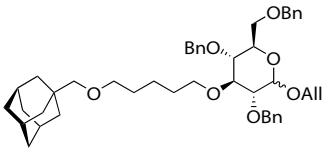


***N*-Butyl-4-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (13).** Compound **42** (83 mg, 104 µmol) was *N*-butylated and deprotected using the same procedure as described above for the synthesis of **12**, but substituting formaldehyde for butyraldehyde (200 µL, 2 mmol). The crude product was purified by silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **13** (39 mg, 86 µmol) as a colorless oil in 83%. R_F = 0.72 (1:3; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^1H NMR (400 MHz, MeOD) δ 3.94 – 3.89 (m, 1H, OC*H*H pentyl), 3.83 (dd, $J_{H6a\text{-}H5}$ = 2.1, $J_{H6a\text{-}H6b}$ = 11.8, 1H, CH-6a), 3.75 (dd, $J_{H6b\text{-}H5}$ = 2.2, $J_{H6b\text{-}H6a}$ = 11.8, 1H, CH-6b), 3.65 – 3.59 (m, 1H, OCH*H* pentyl), 3.44 (ddd, *J* = 4.7, 10.0, 14.6, 1H, H-2), 3.38 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.24 – 3.19 (m, 2H, H-3, H-4), 2.97 – 2.93 (m, 3H, H-1a, OCH_2-Ada), 2.76 (m, 1H, NC*H*H butyl), 2.58 (m, 1H, NCH*H* butyl), 2.15 – 2.07 (m, 2H, H-1b, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.55 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.48 – 1.41 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.30 (m, 2H, CH_2 butyl), 0.94 (t, *J* = 7.2, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.0 (OCH_2-Ada), 80.7, 79.9 (C-3, C-4), 74.0, 72.6 (2×OCH_2 pentyl), 71.0 (C-2), 66.6 (C-5), 58.5 (C-6), 57.5 (C-1), 53.3 (NCH_2 butyl), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.2, 30.6 (2×CH_2 pentyl), 29.8 (3×CH Ada), 27.3 (CH_2 butyl), 23.9 (CH_2 pentyl), 21.8 (CH_2 butyl), 14.4 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3364, 2901, 2847, 1666, 1458, 1366, 1250, 1103, 1042, 903, 818. $[\alpha]^{20}_D$: –2.5 (*c* 0.4, $CHCl_3$/MeOH; 1/1). HRMS: found *m/z* 454.3539 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

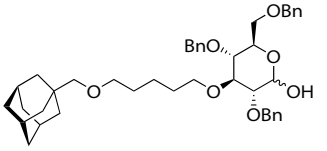


1,2:5,6-Di-*O*-isopropylidene-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-α-D-glucofuranoside (44). 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**43**: 222 mg, 0.85 mmol) was alkylated with bromide **25** using General procedure C. The resulting residue was purified by silica gel column chromatography (0% » 20% EtOAc in PE) to furnish **44** (413 mg, 0.84 mmol) in 98% yield as a colorless oil. R_F = 0.61 (1:4; EtOAc:PE). ^1H NMR (600 MHz, $CDCl_3$, COSY) δ 5.87 (d, *J* = 3.7, 1H, H-1), 4.53 (d, $J_{H2\text{-}H1}$ = 3.7, 1H, H-2), 4.30 (m, 1H, H-5), 4.12 (dd, *J* = 3.0, 7.6, 1H, H-4), 4.08 (dd, $J_{H6a\text{-}H6b}$ = 8.5, $J_{H6a\text{-}H5}$ = 6.3, 1H, H-6a), 3.99 (dd, $J_{H6b\text{-}H6a}$ = 8.5, $J_{H6b\text{-}H5}$ = 6.0, 1H, H-6b), 3.85 (d, *J* = 3.0, 1H, H-3), 3.61 (m, 1H, OC*H*H pentyl), 3.52 (m, 1H, OCH*H* pentyl), 3.40 (m, 2H, OCH_2 pentyl), 3.00 (s, 2H, OCH_2-Ada), 1.95 (br s, 3H, 3×CH Ada), 1.68 (m, 6H, 3×CH_2 Ada), 1.58 (m, 4H, 2×CH_2 pentyl) 1.52 (br d, 6H, 3×CH_2 Ada), 1.50 (s, 3H, CH_3 isopropylidene), 1.43 (s, 3H, CH_3 isopropylidene), 1.40 (m, 2H, CH_2-3 pentyl), 1.35 (s, 3H, CH_3 isopropylidene), 1.32 (s, 3H, CH_3 isopropylidene). ^{13}C NMR (150 MHz, $CDCl_3$) δ 111.6, 108.8 (2×C_q isopropylidene), 105.1 (C-1), 82.5, 82.0, 81.1 (C-2, C-3, C-4), 81.8 (OCH_2-Ada), 72.4 (C-5), 71.3, 70.4 (2×OCH_2 pentyl), 67.1 (C-6), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 34.0 (C_q Ada), 29.5, 29.3 (2×CH_2 pentyl), 28.2 (3×CH Ada), 26.7, 26.6, 26.1, 25.3 (4×CH_3 isopropylidene), 22.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1454, 1369, 1254, 1215, 1157, 1072, 1018, 957, 914, 849, 637. $[\alpha]^{20}_D$:

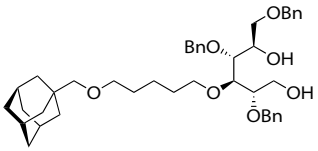
–16.7 (*c* 0.5, $CHCl_3$). HRMS: found *m/z* 495.3341 $[M+H]^+$; 512.3598 $[M+NH_4]^+$, calcd for $[C_{28}H_{46}O_7+H]^+$ 495.3316; $[C_{28}H_{46}O_7+NH_4]^+$ 512.3582.



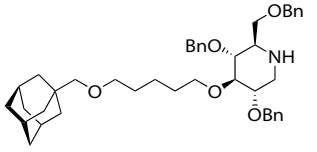
α/β-Mixture of allyl 2,4,6-tri-*O*-benzyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-D-glucopyranoside (45). Compound **44** (383 mg, 0.77 mmol) was dissolved in AcOH (6 mL) and water (2 mL). The resulting solution was refluxed for 5 h at 105 °C. The reaction mixture was concentrated and coevaporated with allyl alcohol. The residue was dissolved in allyl alcohol (1.6 mL), which contained 5 mol % HCl (generated by prior addition of AcCl). The reaction mixture was refluxed for 24 h, after which TLC analysis showed disappearance of the starting material (R_F = 0.07 in EtOAc:PE; 3:1) and the appearance two products (R_F = 0.85; 0.76 in MeOH:EtOAc; 1:4). The reaction was quenched (Et_3N, 0.3 mL), concentrated and coevaporated with toluene. The residue was dissolved in DMF (4 mL) and BnBr (380 µL, 3.2 mmol) was added. The reaction mixture was cooled to 0 °C and NaH (128 mg; 60% wt in mineral oil, 3.2 mmol) was added. The reaction was stirred for 20 h, warming to rt, after which TLC analysis indicated incomplete conversion. Additional BnBr (48 µL, 0.40 mmol) was added, the reaction mixture was cooled to 0 °C and additional NaH was added (16 mg; 60% wt in mineral oil, 0.40 mmol). After stirring for 20 h at rt, the reaction was quenched (water, 1 mL) and poured into water (100 mL). The aqueous layer was extracted repeatedly with Et_2O (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 15% EtOAc in PE) yielding **45** (313 mg, 0.43 mmol) as an α/β mixture in 56% over three steps as a colorless oil. R_F = 0.37; 0.33 (1:10; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) α/β mixture δ = 7.48 – 7.17 (m, 15H, H_{Ar} Bn), 5.97 – 5.85 (m, 1H, CH vinyl), 5.35 – 5.17 (m, 3H), 4.93 – 4.38 (m, 6H, 3×CH_2 Bn), 4.13 – 3.20 (m, 13H), 2.96 – 2.89 (m, 3H), 1.93 (br s, 3H, 3×CH Ada), 1.71 – 1.21 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) α/β mixture δ = 138.4, 138.2, 138.1, 137.7 (3×C_q Bn, α/β), 133.9, 133.6 (CH vinyl, α/β), 128.2, 128.0, 127.8, 127.7, 127.6, 127.5 (CH_{Ar}, Bn), 117.9, 116.9 (CH_2 vinyl, α/β), 102.5, 95.7 (C-1, α/β), 84.6, 82.0, 79.6, 77.6, 70.0 (CH, α/β), 81.7 (OCH_2-Ada), 77.6, 74.8, 73.6, 73.5, 73.3, 73.1, 71.3, 68.8, 68.3, 67.9 (CH_2, α/β), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 30.3, 29.4 (2×CH_2 pentyl), 28.1 (3×CH Ada), 22.8 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1724, 1497, 1454, 1362, 1312, 1273, 1150, 1092, 1069, 1030, 930, 748, 698. $[\alpha]^{20}_D$: 26.1 (*c* 0.4, $CHCl_3$). HRMS: found *m/z* 747.4255 $[M+Na]^+$, calcd for $[C_{46}H_{60}O_7+Na]^+$ 747.4231.



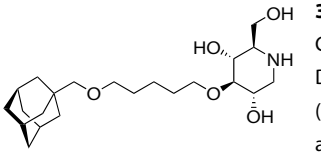
α/β-Mixture of 2,4,6-tri-*O*-benzyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-D-glucopyranose (46). The allyl-function in compound **45** (295 mg, 0.41 mmol) was cleaved using the same procedure as described for the synthesis of **38**. The crude product was purified by silica gel column chromatography (10% » 40% EtOAc in PE) to furnish **46** (211 mg, 0.31 mmol) as an α/β mixture in 75% yield as a colorless oil. R_F = 0.20 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) major α-anomer δ = 7.36 – 7.17 (m, 15H, H_{Ar} Bn), 5.15 (d, $J_{H1\text{-}H2}$= 3.2, 1H, H-1), 4.84 – 4.42 (m, 6H, 3×CH_2 Bn), 3.86 – 3.31 (m, 10H, H-2, H-3, H-4, H-5, CH_2-6, 2×OCH_2 pentyl), 2.93 (s, 2H, OCH_2-Ada), 1.93 (br s, 3H, 3×CH Ada), 1.71 – 1.38 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) α/β mixture δ = 138.4, 138.2, 138.0, 137.7 (3×C_q Bn, α+β), 128.3, 128.2, 127.9, 127.8, 127.6 (CH_{Ar}, Bn), 97.3, 91.2 (C-1 α+β), 84.6, 82.9, 81.6, 79.7, 77.7, 74.4, 70.0 (CH, α+β), 81.8 (OCH_2-Ada), 74.8, 74.6, 73.6, 73.3, 73.1, 71.3, 68.8, 68.5 (CH_2, α+β), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 34.0 (C_q Ada), 30.4, 29.5 (2×CH_2 pentyl), 28.2 (3×CH Ada), 22.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1724, 1497, 1454, 1362, 1315, 1258, 1207, 1153, 1073, 911, 733, 698. $[\alpha]^{20}_D$: 26.0 (*c* 0.2, $CHCl_3$). HRMS: found *m/z* 707.3930 $[M+Na]^+$, calcd for $[C_{43}H5_6O_7+Na]^+$ 707.3918.



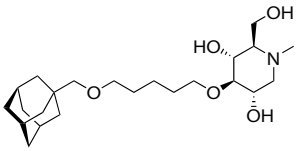
2,4,6-Tri-*O*-benzyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-D-glucitol (47). Compound **46** (211 mg, 0.31 mmol) was subjected to General procedure A. The resulting residue was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to give **47** (211 mg, 0.31 mmol) in quantitative yield as a colorless oil. R_F = 0.15 (1:3; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 15H, H_{Ar} Bn), 4.69 – 4.49 (m, 6H, 3×CH_2 Bn), 4.04 (m, 1H, H-5), 3.73 – 3.51 (m, 9H, CH_2-1, H-2, H-3, H-4, CH_2-6, OCH_2 pentyl), 3.32 (t, J = 6.5, 2H, OCH_2 pentyl), 2.93 (s, 2H, OCH_2-Ada), 2.44 (br s, 2H, OH-1, OH-5), 1.94 (br s, 3H, 3×CH Ada), 1.72 – 1.28 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.8, 137.7 (3×C_q Bn), 128.2, 128.0, 127.8, 127.7, 127.6 (CH_{Ar}, Bn), 81.8 (OCH_2-Ada), 80.1, 79.1, 76.9 (C-2, C-3, C-4), 73.3, 73.0, 72.9, 72.7, 71.3, 71.1 (3×CH_2 Bn, 2×OCH_2 pentyl, C-6), 70.6 (C-5), 61.7 (C-1), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 29.9, 29.3 (2×CH_2 pentyl), 28.2 (3×CH Ada), 22.5 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3464, 2901, 2847, 1497, 1454, 1358, 1315, 1207, 1088, 1026, 910, 814, 733, 694. $[\alpha]^{20}_D$: 1.3 (*c* 1.2, $CHCl_3$). HRMS: found *m/z* 687.4270 $[M+H]^+$; 709.4063 $[M+Na]^+$, calcd for $[C_{43}H_{58}O_7+H]^+$ 687.4255; $[C_{43}H_{58}O_7+Na]^+$ 709.4075.



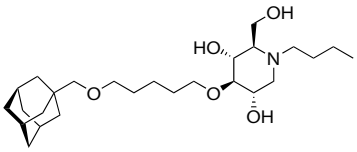
2,4,6-Tri-*O*-benzyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (48). Compound **47** (132 mg, 0.20 mmol) was treated according to General procedure B and double reductive amination method A. The crude product was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to provide **48** (89 mg, 0.13 mmol) in 67% yield as a colorless oil. R_F = 0.32 (1:2; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.53 – 7.23 (m, 15H, H_{Ar} Bn), 4.86 (d, J = 10.9, 1H, C*H*H Bn), 4.70 (d, J = 11.7, 1H, C*H*H Bn), 4.63 (d, J = 11.7, 1H, CH*H* Bn), 4.49 (d, J = 10.9, 1H, CH*H* Bn), 4.42 (d, J = 11.8, 1H, CH Bn), 4.40 (d, J = 11.8, 1H, CH Bn), 3.90 (dt, J = 9.0, 6.8, 1H, OC*H*H pentyl), 3.78 (dt, J = 9.0, 6.8, 1H, OCH*H* pentyl), 3.64 (dd, $J_{H6a\text{-}H5}$ = 2.4, $J_{H6a\text{-}H6b}$ = 9.0, 1H, H-6a), 3.49 (dd, $J_{H6b\text{-}H5}$ = 5.9, $J_{H6b\text{-}H6a}$ = 9.0, 1H, H-6b), 3.43 – 3.23 (m, 5H, H-2, H-3, H-4, OCH_2 pentyl), 3.19 (dd, $J_{H1a\text{-}H2}$ = 4.8, $J_{H1a\text{-}H1b}$ = 12.1, 1H, H-1a), 2.92 (s, 2H, OCH_2-Ada), 2.67 (ddd, $J_{H5\text{-}H6a}$ = 2.4, $J_{H5\text{-}H6b}$ = 5.9, $J_{H5\text{-}H4}$ = 9.2, 1H, H-5), 2.45 (dd, $J_{H1b\text{-}H2}$ = 10.2, $J_{H1b\text{-}H1a}$ = 12.1, 1H, H-1b), 2.40 (br s, 1H, NH), 1.93 (br s, 3H, 3×CH Ada), 1.72 – 1.35 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.4, 137.9 (3×C_q Bn), 128.3, 128.0, 127.8, 127.6, 127.5 (CH_{Ar}, Bn), 87.3, 80.4, 80.0 (C-2, C-3, C-4), 81.8 (OCH_2-Ada), 75.1, 73.7, 73.3, 72.8, 71.5, 70.2 (3×CH_2 Bn, 2×OCH_2 pentyl, C-6), 59.6 (C-5), 48.1 (C-1), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 30.5, 29.6 (2×CH_2 pentyl), 28.3 (3×CH Ada), 22.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1724, 1497, 1454, 1362, 1265, 1096, 1069, 1026, 733, 698. $[\alpha]^{20}_D$: 19.9 (*c* 1.8, $CHCl_3$). HRMS: found *m/z* 668.4319 $[M+H]^+$, calcd for $[C_{43}H_{57}NO_5+H]^+$ 668.4310.



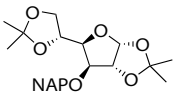
3-*O*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (14). Compound **48** (53 mg, 80 µmol) was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in EtOAc with 0.5% NH_4OH) to give **14** (28 mg, 69 µmol) as an off-white solid in 86% yield. R_F = 0.22 (1:3; MeOH:EtOAc + 0.5% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$:MeOD; 2:1, COSY) δ 3.93 – 3.80 (m, 4H, CH_2-6, OCH_2 pentyl), 3.76 (m, 1H, H-2), 3.57 (dd, J = 9.1, 9.1, 1H, H-4), 3.42 (t, J = 6.5, 2H, OCH_2 pentyl), 3.31 (dd, $J_{H1a\text{-}H2}$ = 4.4, $J_{H1a\text{-}H1b}$ = 12.4, 1H, H-1a), 3.19 (m, 1H, H-3), 2.99 (s, 2H, OCH_2-Ada), 2.98 (m, 1H, H-5), 2.78 (dd, J = 11.9, 1H, H-1b), 1.96 (br s, 3H, 3×CH Ada), 1.75 – 1.57 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.54 (br d, J = 2.3, 6H, 3×CH_2 Ada), 1.42 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$:MeOD; 2:1) δ 84.2 (C-3), 81.5 (OCH_2-Ada), 72.8, 71.2 (2×OCH_2 pentyl), 67.7, 67.0 (C-2, C-4), 60.3 (C-5), 57.7 (C-6), 46.0 (C-1), 39.1 (3×CH_2 Ada), 36.6 (3×CH_2 Ada), 33.6 (C_q Ada), 29.4, 28.7 (2×CH_2 pentyl), 27.8 (3×CH Ada), 21.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3358, 2901, 2847, 1674, 1597, 1448, 1344, 1186, 1103, 1026, 733, 623. $[\alpha]^{20}_D$: 17.4 (*c* 0.5, MeOH). HRMS: found *m/z* 398.2892 $[M+H]^+$, calcd for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.



***N*-Methyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-nojirimycin (15).** Argon was passed through a solution of compound **48** (42 mg, 63 µmol) and formaldehyde (160 µL, 2 mmol; 37 wt % in water) in MeOH (2 mL) for 5 min, after which a catalytic amount of Pd/C Degussa type (30 mg, 5 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 10 min. After stirring the reaction under atmospheric hydrogen pressure for 1 h, TLC analysis full conversion to the intermediate product (R_F = 0.54 in PE:EtOAc; 1:1). The Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH. The filtrate was concentrated and coevaporated once with toluene. The crude intermediate product was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in EtOAc with 0.5% NH_4OH) to give **15** (22 mg, 52 µmol) as an off-white solid in 83% yield. R_F = 0.38 (1:3; MeOH:EtOAc + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 4.04 (d, $J_{H6a\text{-}H6b}$ = 12.2, 1H, H-6a), 3.88 (dd, $J_{H6b\text{-}H6a}$ = 12.2, $J_{H6b\text{-}H5}$ = 2.7, 1H, H-6b), 3.85 (m, 2H, OCH_2 pentyl), 3.70 (m, 1H, H-2), 3.60 (dd, J = 9.4, 9.4, 1H, H-4), 3.38 (t, J = 6.4, 2H, OCH_2 pentyl), 3.32 (dd, $J_{H1a\text{-}H2}$ = 4.7, $J_{H1a\text{-}H1b}$ = 12.1, 1H, H-1a), 3.15 (dd, J = 9.4, 9.4, 1H, H-3), 2.96 (s, 2H, OCH_2-Ada), 2.95 – 2.83 (m, 5H, H-1b, NCH_3, H-5), 1.93 (br s, 3H, 3×CH Ada), 1.7 – 1.63 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.60-1.55 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.44 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 86.6 (C-3), 83.1 (OCH_2-Ada), 74.5, 72.7 (2×OCH_2 pentyl), 69.3, 68.7, 68.0 (C-2, C-4, C-5), 58.9 (C-6 and C-1 overlap), 41.3 (NCH_3), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.1, 30.5 (2×CH_2 pentyl), 29.7 (3×CH Ada), 23.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3351, 2903, 2847, 1657, 1454, 1358, 1101, 1040, 1020, 959, 611. $[\alpha]^{20}_D$: 6.9 (*c* 0.6, MeOH). HRMS: found *m/z* 412.3047 $[M+H]^+$, calcd for $[C_{23}H_{42}NO_5+H]^+$ 412.3058.

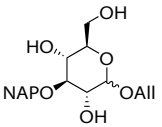


***N*-Butyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-nojirimycin (16).** Compound **48** (42 mg, 63 µmol) was *N*-butylated and deprotected using the same procedure as described above for the synthesis of **15**, but substituting formaldehyde for butyraldehyde (80 µL, 1 mmol). The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in EtOAc with 0.5% NH_4OH) to give **16** (28 mg, 63 µmol) as an off-white solid in 99% yield. R_F = 0.74 (1:3; MeOH:EtOAc + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD:acetone-*d6*; 3:1) δ 4.09 (m, 1H, H-6a), 3.90 (m, 1H, H-6b), 3.83 (m, 2H, OCH_2 pentyl), 3.77 (m, 1H, H-2), 3.66 (m, 1H, H-4), 3.43 (m, 1H, H-1a), 3.38 (m, 3H, OCH_2 pentyl, NC*H*H butyl), 3.24 – 3.20 (m, 2H, H-3, NCH*H* butyl), 3.09 (m, 1H, H-5), 3.01 (m, 1H, H-1b), 2.96 (s, 2H, OCH_2-Ada), 1.94 (br s, 3H, 3×CH Ada), 1.76 – 1.64 (m, 10H, 3×CH_2 Ada, CH_2 pentyl, CH_2 butyl), 1.58 – 1.55 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.43 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.00 (t, J = 7.1, 3H, CH_3 butyl). ^{13}C NMR (150 MHz, $CDCl_3$:MeOD; 2:1) δ 81.6 (OCH_2-Ada), 71.3 (OCH_2 pentyl), 66.8, 65.8 (2×CH), 39.2 (3×CH_2 Ada), 36.7 (3×CH_2 Ada), 33.7 (C_q Ada), 29.5, 28.8 (2×CH_2 pentyl), 27.9 (3×CH Ada), 22.0 (CH_2), 19.4 (CH_2), 12.8 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3341, 2903, 2847, 1672, 1456, 1364, 1103, 1030, 1030, 608. $[\alpha]^{20}_D$: 2.8 (*c* 0.5, MeOH). HRMS: found *m/z* 454.3509 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

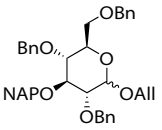


1,2:5,6-Di-*O*-isopropylidene-3-*O*-(2-naphthylmethyl)-α-D-glucofuranoside (49). A dry solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**43**: 2.140 g, 8.22 mmol) in DMF (16.4 mL) was cooled to 0 °C. The solution was charged with NaH (362 mg, 60% wt in mineral oil, 9.04 mmol) and stirred at 0 °C for 30 min after which 2-bromomethylnaphthalene (2 g, 9.04 mmol) was added. The reaction mixture was stirred for 20 h, warming to rt. The reaction mixture was quenched (water, 1 mL), concentrated and redissolved in Et_2O (100 mL). The organic layer was washed successively with water (50 mL) and sat aq NaCl (50 mL), dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 25% EtOAc in PE) to furnish **49**[35] (3.224 g, 8.06 mmol) in 98% yield as a colorless

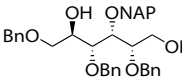
oil. R_F = 0.74 (1:6; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.77 – 7.75 (m, 4H, H_{Ar} NAP), 7.45 – 7.39 (m, 3H, H_{Ar} NAP), 5.91 (d, *J* = 3.7, 1H, H-1), 4.78 (d, *J* = 12.1, 1H, C*H*H NAP), 4.71 (d, *J* = 12.1, 1H, CH*H* NAP), 4.59 (d, $J_{H2\text{-}H1}$ = 3.7, 1H, H-2), 4.43 (m, 1H, H-5), 4.18 (dd, *J* = 3.1, 7.8, 1H, H-4), 4.13 (dd, $J_{H6a\text{-}H6b}$ = 8.5, $J_{H6a\text{-}H5}$ = 6.3, 1H, H-6a), 4.06 (d, *J* = 2.5, 1H, H-3), 4.04 (dd, $J_{H6b\text{-}H6a}$ = 8.5, $J_{H6b\text{-}H5}$ = 5.8, 1H, H-6b), 1.47 (s, 3H, CH_3 isopropylidene), 1.42 (s, 3H, CH_3 isopropylidene), 1.37 (s, 3H, CH_3 isopropylidene), 1.26 (s, 3H, CH_3 isopropylidene). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 134.9, 133.0, 132.8 (3×C_q NAP), 127.9, 127.6, 127.4, 126.1, 125.9, 125.7, 125.4 (7×H_{Ar} NAP), 111.4, 108.7 (2×C_q isopropylidene), 105.1 (C-1), 82.4 (C-2), 81.4 (C-3), 81.1 (C-4), 72.3 (C-5), 72.0 (CH_2 NAP), 67.1 (C-6), 26.6, 26.5, 26.0, 25.2 (4×CH_3 isopropylidene). IR ν_{max}(thin film)/ cm^{-1}: 2986, 2932, 1454, 1369, 1339, 1254, 1211, 1165, 1126, 1069, 1015, 953, 887, 845, 818, 748, 637. [α]$^{20}_D$: –30.0 (*c* 4.1, $CHCl_3$). HRMS: found *m/z* 401.1951 [M+H]$^+$, calcd for [$C_{23}H_{28}O_6$+H]$^+$ 401.1959.



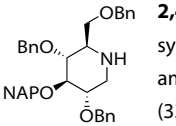
α/β-Mixture of allyl 3-*O*-(2-naphthylmethyl)-D-glucopyranoside (50). To a solution of compound **49** (404 mg, 1.01 mmol) in allylalcohol (10 mL), water (37 µL, 2.02 mmol) and Amberlite resin (170 mg, IR-120 H$^+$-form) were added. The reaction mixture was heated at 102 °C for 20 h. The reaction was filtered and the resin was washed with MeOH. The filtrate was concentrated and the resulting residue was purified by silica gel column chromatography (50% » 100% EtOAc in PE) yielding a 2:1 α/β mixture of **50** (182 mg, 0.51 mmol) in 50% as a white solid. R_F = 0.29; 0.23 (3:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) α/β mixture δ = 7.78 – 7.76 (m, 4H, H_{Ar} NAP, α/β), 7.49 – 7.40 (m, 3H, H_{Ar} NAP, α/β), 5.92 – 5.81 (m, 1H, CH vinyl, α/β), 5.29 – 5.16 (m, 2H, CH_2 vinyl, α/β), 5.08 (d, *J* = 11.7, 1H, C*H*H NAP, α), 5.06 (d, *J* = 11.7, 1H, C*H*H NAP, β), 4.92 (d, *J* = 11.7, 1H, CH*H* NAP, β), 4.90 (d, *J* = 11.7, 1H, CH*H* NAP, α), 4.82 (s, 1H, H-1, α), 4.28 (m, 1H, OC*H*H Allyl, β), 4.26 (d, *J* = 7.6, 1H, H-1, β), 4.12 (dd, *J* = 5.3, 12.8, 1H, OC*H*H Allyl, α), 4.12 (dd, *J* = 6.3, 12.8, 1H, OCH*H* Allyl, β), 3.94 (dd, *J* = 6.3, 12.8, 1H, OCH*H* Allyl, α), 3.80 – 3.70 (m, 4H, CH_2-6, α+β), 3.64 – 3.60 (m, 5H, H-2, H-3, H-4, H-5, α; H-4, β), 3.51 (dd, 1H, H-2, β), 3.42 (m, 1H, H-3, β), 3.21 (m, 1H H-5, β), 3.04 – 2.59 (3×br s, 3H, OH). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) α/β mixture δ = 135.9, 135.8, 133.2, 132.9 (3×C_q NAP, α/β), 133.6, 133.4 (CH vinyl, α/β), 128.2, 128.1, 127.8, 127.6, 126.7, 126.5, 126.2, 126.0, 125.8 (CH_{Ar} NAP, α/β), 117.9 (CH_2 vinyl, α/β), 101.8 (C-1, β), 97.6 (C-1, α), 83.6 (C-3, β), 82.6 (C-3, α), 75.3, 74.1 (C-2, C-5, β), 74.9 (CH_2 NAP, α), 74.6 (CH_2 NAP, β), 72.5 (C-2, α), 71.3, 69.7 (C-4, C-5, α), 70.3 (OCH_2 Allyl, β), 68.4 (OCH_2 Allyl , α), 61.9 (C-6, β), 61.7 (C-6, α). IR ν_{max}(thin film)/ cm^{-1}: 3387, 2924, 2874, 1508, 1458, 1346, 1273, 1026, 926, 895, 857, 814, 748, 621. [α]$^{20}_D$: 62.6 (*c* 3.6, $CHCl_3$). HRMS: found *m/z* 383.1447 [M+Na]$^+$, calcd for [$C_{20}H_{24}O_6$+Na]$^+$ 383.1465.



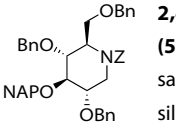
α/β-Mixture of allyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-naphthylmethyl)-D-glucopyranoside (51). A dry solution of compound **50** (182 mg, 0.51 mmol) in DMF (5 mL) was charged with BnBr (198 µL, 1.67 mmol). The reaction mixture was cooled to 0 °C and NaH (67 mg; 60% wt in mineral oil, 1.67 mmol) was added. The reaction was stirred for 20 h, warming to rt, after which TLC analysis indicated complete conversion and the reaction was quenched (water, 0.2 mL). The mixture was poured into water (50 mL) and the aqueous layer was extracted repeatedly with Et_2O (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 15% EtOAc in PE) giving an α/β mixture of **51** (286 mg, 0.45 mmol) in 90% as a colorless oil. R_F = 0.62; 0.58 (1:3; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) α/β mixture δ 7.75 – 7.67 (m, 4H, H_{Ar} NAP, α/β), 7.47 – 7.07 (m, 18H, H_{Ar} Bn/NAP, α/β), 5.98 – 5.87 (m, 1H, CH vinyl, α/β), 5.35 – 4.41 (m, 11H, α/β), 4.15 – 4.31 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) α/β mixture δ 139.3, 139.2, 138.9, 137.4, 135.1, 134.8, 134.7, 134.4, 133.9, 129.2, 128.5, 127.0, 126.7, 119.1, 118.1, 104.4, 103.7, 97.7, 96.7, 85.7, 83.3, 83.1, 82.9, 81.0, 80.2, 79.6, 78.9, 78.8, 76.7, 76.6, 76.1, 76.0, 75.9, 75.8, 74.4, 74.0, 71.3, 71.2, 70.7, 69.5, 69.3, 69.2, 63.7. IR ν_{max}(thin film)/ cm^{-1}: 2866, 1497, 1454, 1362, 1269, 1207, 1069, 1026, 930, 856, 818, 733, 694. [α]$^{20}_D$: 19.4 (*c* 0.4, $CHCl_3$). HRMS: found *m/z* 653.2828 [M+Na]$^+$, calcd for [$C_{41}H_{42}O_6$+Na]$^+$ 653.2874.



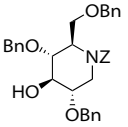
2,4,6-Tri-*O*-benzyl-3-*O*-(2-naphthylmethyl)-D-glucitol (52). The allyl-function in **51** (397 mg, 0.63 mmol) was cleaved using the same procedure as described for the synthesis of **38**. The crude hemiacetal intermediate was reduced with $LiALH_4$ using General procedure A (R_F hemiacetal = 0.21; 0.15 in EtOAc:PE; 1:4). The resulting residue was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to give product **52** (254 mg, 0.43 mmol) over two steps in 68% yield as a colorless oil. R_F = 0.1 (1:2; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.70 (m, 4H, H_{Ar} NAP), 7.48 – 7.41 (m, 3H, H_{Ar} NAP), 7.34 – 7.17 (15H, H_{Ar} Bn), 4.86 (d, *J* = 11.5, 1H, C*H*H Bn/NAP), 4.80 (d, *J* = 11.5, 1H, CH*H* Bn/NAP), 4.66 (d, *J* = 11.6, 1H, CH Bn/NAP), 4.63 – 4.50 (m, 4H, 4×CH Bn), 4.46 (d, *J* = 11.9, 1H, CH Bn/NAP), 4.05 (m, 1H, H-5), 3.95 (dd, *J* = 3.7, 6.3, 1H), 3.84 – 3.72 (m, 3H), 3.68 – 3.55 (m, 3H), 3.04 (br s, 1H, OH-1 or OH-5), 2.22 (br s, 1H, OH-1 or OH-5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.9, 137.8, 135.3, 133.1, 132.9 (3×C_q Bn, 3×C_q NAP), 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.1, 126.2, 126.1, 125.9 (CH_{Ar} Bn/NAP), 79.5, 79.2, 77.3 (C-2, C-3, C-4), 74.6, 73.4, 73.2, 73.0 (3×CH_2 Bn, CH_2 NAP), 71.1 (C-6), 70.7 (C-5), 61.8 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3445, 3032, 2870, 1497, 1454, 1362, 1207, 1065, 1026, 952, 895, 856, 818, 733, 694. $[\alpha]^{20}_D$: 10.5 (*c* 2.7, $CHCl_3$). HRMS: found *m/z* 593.2872 $[M+H]^+$, calcd for $[C_{38}H_{40}O_6+H]^+$ 593.2898.



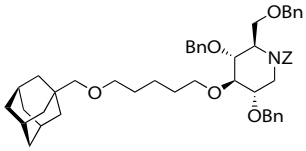
2,4,6-Tri-*O*-benzyl-3-*O*-(2-naphthylmethyl)-1-deoxynojirimycin (53). Compound **53** was synthesized from **52** (142 mg, 0.24 mmol) via General procedure B with double reductive amination method A. The crude product was purified by silica gel column chromatography (33% » 75% EtOAc in PE) to provide **53** (89 mg, 0.13 mmol) in 53% yield as a crystalline solid. R_F = 0.61 (2:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.82 – 7.71 (m, 4H, H_{Ar} NAP), 7.48 – 7.42 (m, 3H, H_{Ar} NAP), 7.34 – 7.16 (15H, H_{Ar} Bn), 5.13 (d, *J* = 11.2, 1H, C*H*H Bn/NAP), 4.97 (d, *J* = 11.2, 1H, CH*H* Bn/NAP), 4.87 (d, *J* = 11.0, 1H, CH Bn/NAP), 4.71 (d, *J* = 12.0, 1H, C*H*H Bn/NAP), 4.67 (d, *J* = 12.0, 1H, CH*H* Bn/NAP), 4.56 – 4.41 (m, 3H, 3×CH Bn), 3.69 (dd, $J_{H6a\text{-}H5}$ = 2.2, $J_{H6a\text{-}H6b}$ = 9.0, 1H, H-6a), 3.61 (dd, *J* = 9.0, 9.0, 1H, H-3), 3.57 – 3.53 (m, 2H, H-2, H6b), 3.41 (dd, *J* = 9.1, 9.1, 1H, H-4), 3.29 (dd, $J_{H1a\text{-}H2}$ = 4.6, $J_{H1a\text{-}H1b}$ = 12.2, 1H, H-1a), 2.76 (ddd, $J_{H5\text{-}H6a}$ = 2.4, $J_{H5\text{-}H6b}$ = 5.7, $J_{H5\text{-}H4}$ = 9.8, 1H, H-5), 2.53 (dd, $J_{H1b\text{-}H2}$ = 10.2, $J_{H1b\text{-}H1a}$ = 12.1, 1H, H-1b), 2.23 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.3, 137.9, 135.3, 133.0 (3×C_q Bn, 3×C_q NAP), 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 126.4, 126.1, 125.9, 125.7 (CH_{Ar} Bn/NAP), 87.1, 80.3, 79.8 (C-2, C-3, C-4), 75.7, 75.2, 73.4, 72.8 (3×CH_2 Bn, CH_2 NAP), 69.9 (C-6), 59.7 (C-5), 47.9 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3028, 2858, 1497, 1454, 1362, 1269., 1207, 1092, 1061, 1026, 949, 895, 856, 818, 733, 694. $[\alpha]^{20}_D$: 10.0 (*c* 0.1, $CHCl_3$). HRMS: found *m/z* 574.2928 $[M+H]^+$, calcd for $[C_{38}H_{39}NO_4+H]^+$ 574.2952.



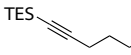
2,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-3-*O*-(2-naphthylmethyl)-1-deoxynojirimycin (54). Compound **53** (89 mg, 0.13 mmol) was protected with a Z-carbamate function using the same procedure as described for the synthesis of **33**. The resulting residue was purified by silica gel column chromatography (15% » 25% EtOAc in PE) to provide **54** (72 mg, 0.10 mmol) in 81% yield as a colorless oil. R_F = 0.35 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.82 – 7.65 (m, 4H, H_{Ar} NAP), 7.48 – 7.34 (m, 3H, H_{Ar} NAP), 7.32 – 7.22 (20H, H_{Ar} Bn, H_{Ar} Z), 5.13 (d, *J* = 12.4, 1H, C*H*H Bn/NAP/Z), 5.08 (d, *J* = 12.4, 1H, CH*H* Bn/NAP/Z), 4.78 – 4.42 (m, 7H, 7×CH Bn/NAP/Z), 4.34 (d, *J* = 12.0, 1H, CH Bn/NAP/Z), 4.23 – 4.14 (m, 2H, H-1a, H-5), 3.94 (dd, *J* = 6.3, 1H, H-4), 3.79 (dd, *J* = 4.3, 6.5, 1H, H-3), 3.71-3.62 (m, 3H, H-2, CH_2-6), 3.36 (dd, $J_{H1b\text{-}H2}$ = 3.3, $J_{H1b\text{-}H1a}$ = 14.4, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (C=O Z), 138.3, 138.2, 138.0, 136.6, 135.6, 133.1 (3×C_q Bn, 3×C_q NAP, C_q Z), 128.4, 128.3, 128.0, 127.8, 127.6, 127.5, 127.4, 126.4, 126.0, 125.8, 125.7 (CH_{Ar} Bn, CH_{Ar} NAP, CH_{Ar} Z), 81.6, 78.1, 74.1 (C-2, C-3, C-4), 73.1, 72.9, 70.6 (3×CH_2 Bn, CH_2 NAP), 68.4 (C-6), 67.2 (CH_2 Z), 55.7 (C-5), 41.2 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 2858, 1693, 1497, 1455, 1424, 1354, 1312, 1250, 1219, 1069, 1026, 964, 910, 856, 818, 733, 694. $[\alpha]^{20}_D$: 4.3 (*c* 0.1, $CHCl_3$). HRMS: found *m/z* 708.3288 $[M+H]^+$, calcd for $[C_{46}H_{45}NO_6+H]^+$ 708.3320.



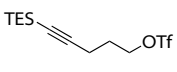
2,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-1-deoxynojirimycin (55). A dry solution of compound **54** (72 mg, 102 µmol) in a mixture of DCM (4.8 mL) and MeOH (1.2 mL) was charged with DDQ (69 mg, 306 µmol). The reaction mixture was stirred for 5 h, after which TLC analysis showed complete consumption of **54**. The reaction mixture was diluted with DCM (15 mL) and washed successively with sat aq $NaHCO_3$ (20 mL) and sat aq NaCl (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (20% » 50% EtOAc in PE) to furnish **55** (49 mg, 86 µmol) in 85% yield as a colorless oil. R_F = 0.25 (1:3; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$, COSY) δ 7.33 – 7.23 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.12 (d, *J* = 12.3, 1H, C*H*H Z), 5.07 (d, *J* = 12.3, 1H, CH*H* Z), 4.67 – 4.51 (m, 4H, 4×CH Bn), 4.47 (d, *J* = 11.8, 1H, C*H*H Bn), 4.38 (d, *J* = 11.8, 1H, CH*H* Bn), 4.16 (br s, 1H, H-5), 4.09 (d, *J* = 14.0, 1H, H-1a), 3.87 (m, 1H, H-3), 3.75 – 3.56 (m, 3H, H-2, CH_2-6), 3.44 (dd, J_{H1b-H2} = 3.9, $J_{H1b-H1a}$ = 14.3, 1H, H-1b), 3.10 (br s, 1H, OH-3). ^{13}C NMR (125 MHz, $CDCl_3$, HSQC) δ 155.7 (C=O Z), 138.2, 138.0, 137.4, 136.5 (3×C_q Bn, C_q Z), 128.5, 128.4, 128.3, 127.9, 127.7, 127.6, 127.5 (CH_{Ar} Bn, CH_{Ar} Z), 78.4 (C-2), 77.4 (C-4), 73.3 (C-3), 73.4, 73.2, 70.8 (3×CH_2 Bn), 70.2 (C-6), 67.2 (CH_2 Z), 56.2 (C-5), 42.5 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3418, 3032, 2866, 1670, 1497, 1454, 1427, 1354, 1250, 1215, 1069, 1026, 910, 733, 694. $[\alpha]^{20}_D$: –14.0 (*c* 0.1, $CHCl_3$). HRMS: found *m/z* 568.2671 $[M+H]^+$, calcd for $[C_{35}H_{37}NO_6+H]^+$ 568.2694.



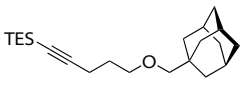
2,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (56). Compound **55** (45 mg, 0.08 mmol) was alkylated with bromide **25** using General procedure C. The resulting residue was purified by silica gel column chromatography (5% » 33% EtOAc in PE) to provide product **56** (64 mg, 0.08 mmol) in quantitative yield as a colorless oil. Compound **56** could be deprotected using General procedure D to quantitatively yield **14**. R_F = 0.78 (1:2; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 20H, H_{Ar} Bn/ Z), 5.11 (d, *J* = 12.3, 1H, C*H*H Z), 5.08 (d, *J* = 12.3, 1H, CH*H* Z), 4.72 (d, *J* = 11.6, 1H, C*H*H Bn), 4.68 – 4.64 (m, 1H, C*H*H Bn), 4.55 (d, *J* = 11.6, 1H, CH*H* Bn), 4.49 – 4.31 (m, 3H, CH*H* Bn, CH_2 Bn), 4.28 – 4.07 (m, 3H), 3.82 (dd, *J* = 6.0, 6.0, 1H), 3.63 (s, 1H), 3.60 – 3.49 (m, 4H, OCH_2 pentyl, 2×CH), 3.32 (t, *J* = 6.5, 2H, OCH_2 pentyl), 3.29 (dd, *J* = 2.9, 14.5, 1H), 2.93 (s, 2H, OCH_2-Ada), 1.94 (s, 3H, 3×CH Ada), 1.66 (dd, *J* = 11.9, 34.5, 6H, 3×CH_2 Ada), 1.57 – 1.48 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.40 – 1.22 (m, 2H, CH_2-3 pentyl).^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0 (C(O) Z), 138.5, 138.3, 136.8 (C_q Bn/ Z), 128.6, 128.5, 128.1, 128.0, 127.7, 127.7 (CH_{Ar} Bn/ Z), 82.1, 78.3, 74.3, 73.3, 73.1, 71.6, 71.2, 70.8, 68.5, 68.3, 67.4, 55.7, 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.3 (C_q Ada), 30.1, 29.6 (2×CH_2 pentyl), 28.5 (CH Ada), 23.0 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2900, 2847, 1697, 1497, 1450, 1421, 1359, 1310, 1219, 1096, 1026, 910, 741, 694 cm^{-1}. MS (ESI): *m/z* 802.5 $[M+H]^+$.



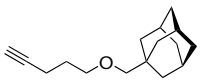
5-(Triethylsilyl)pent-4-yn-1-ol (58). A dry and cooled (–68 °C) solution of pent-4-yn-1-ol (**57**:1.85 mL, 20 mmol) in THF (20 mL) was charged with BuLi (27.5 mL, 44 mmol, 1.6M in toluene) and stirred at –68 °C for 1 h. Triethylsilylchloride (10 mL, 59.5 mmol) was added dropwise to the reaction and the mixture was stirred at –68 °C for 1 h, after which cooling was ceased and the solution was stirred for 18 h. 2M aq HCl (100 mL) was added and the reaction mixture was stirred for 48 h. The mixture was extracted with Et_2O (2×100 mL) and the combined organic layers were washed with water (2×100 mL). The organic phase was dried ($MgSO_4$), concentrated and the resulting residue was purified by silica gel column chromatography (5% » 25% EtOAc in PE) to provide product **58** (3.276 g, 16.50 mmol) in 83% yield as a colorless oil. R_F = 0.53 (3:7; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.75 (t, *J* = 6.2, 2H, $HOCH_2$-1 pent-4-yn), 2.44 (m, 1H, OH-1), 2.36 (t, *J* = 7.3, 2H, CH_2-3 pent-4-yn), 1.77 (m, 2H, CH_2-4 pent-4-yn), 0.98 (t, *J* = 8.0, 9H, 3×CH_3 $SiEt_3$), 0.57 (m, 6H, 3×CH_2 $SiEt_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 107.5, 81.4 (2×C_q pent-4-yn), 60.6 (OCH_2-1 pent-4-yn), 31.2 (CH_2-2 pent-4-yn), 16.0 (CH_2-3 pent-4-yn), 7.0 (3×CH_3 $SiEt_3$), 4.2 (3×CH_2 $SiEt_3$). IR ν_{max}(thin film)/ cm^{-1}: 3319, 2953, 2936, 2912, 2876, 2172, 1458, 1414, 1379, 1348, 1319, 1067, 1051, 1016, 982, 924, 845, 721, 635, 610. MS (ESI): *m/z* 199.3 $[M+H]^+$.



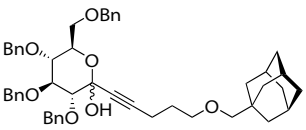
5-(Triethylsilyl)pent-4-ynyl trifluoromethanesulfonate (59). A dry solution of **58** (594 mg, 3 mmol) in DCM (30 mL) was cooled to –40 °C followed by addition of Et_3N (416 µL, 3 mmol). Next, Tf_2O (555 µL, 3.3 mmol) was added dropwise and the reaction mixture was stirred at –40 °C for 1 h. Cooling was ceased and the reaction mixture was concentrated at rt by means of a nitrogen flow. The residue was purified by silica gel column chromatography (isocratic 10% EtOAc in PE) and the product containing factions were concentrated under a nitrogen flow at rt to furnish **59** (885 mg, 2.68 mmol) in 89% yield as a colorless oil. R_F = 0.84 (EtOAc:PE; 3:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (t, *J* = 6.1, 2H), 2.44 (t, *J* = 6.7, 2H), 2.02 (m, 2H), 0.98 (t, *J* = 7.9, 9H), 0.59 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.6 (q, $J_{C\text{-}F}$ = 319.7, 1C), 104.5, 84.0, 75.6, 28.2, 15.8, 7.2, 4.3. IR ν_{max}(thin film)/ cm^{-1}: 1462, 1416, 1246, 1204, 1142, 1069, 1007, 926, 806, 721.



[5-(Adamantan-1-yl-methoxy)-pent-1-ynyl]-triethylsilane (60). Compound **59** (885 mg, 2.68 mmol) was dissolved in DCM (54 mL), to which adamantanemethanol (2.23 g, 13.4 mmol) and K_2CO_3 (1.83 g, 13.4 mmol) were successively added. The reaction mixture was refluxed for 3 days, after which the solids were removed via filtration and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0% » 10% EtOAc in toluene) to provide **60** (900 mg, 2.6 mmol) in 97% yield as a colorless oil. R_F = 0.84 (1:9; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.46 (t, *J* = 6.2, 2H, OCH_2-5 pentynyl), 2.96 (s, 2H, OCH_2-Ada), 2.33 (t, *J* = 7.3, 2H, CH_2-3 pentynyl), 1.95 (br s, 3H, 3×CH Ada), 1.83 – 1.60 (m, 8H, 3×CH_2 Ada, CH_2-4 pentynyl), 1.52 (br d, *J* = 3.0, 6H, 3×CH_2 Ada), 0.98 (t, *J* = 8.0, 9H, 3×CH_3 $SiEt_3$), 0.56 (m, 6H, 3×CH_2 $SiEt_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 108.1 (C_q-1 pentynyl), 82.0 (OCH_2-Ada), 81.4 (C_q-2 pentynyl), 69.8 (OCH_2-5 pentynyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.1 (C_q Ada), 29.0 (CH_2-4 pentynyl), 28.3 (3×CH Ada), 16.6 (CH_2-3 pentynyl), 7.4 (3×CH_3 $SiEt_3$), 4.5 (3×CH_2 $SiEt_3$). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 2176, 1458, 1420, 1366, 1234, 1150, 1111, 1018. HRMS: found *m/z* 347.2751 $[M+H]^+$, calcd for $[C_{22}H_{38}OSi+H]^+$ 347.2765.

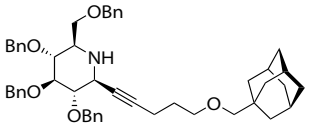


5-(Adamantan-1-yl-methoxy)-pent-1-yne (61). A dry solution of **60** (2.74 g, 7.92 mmol) in a mixture of THF (40 mL) and MeOH (40 mL) was charged with NaOMe (2.23 g, 41.2 mmol) and refluxed at 90 °C for 20 h. The reaction was quenched (water, 0.5 mL) and concentrated. The residue was dissolved in EtOAc (200 mL) and washed with water (2×200 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (2% » 10% acetone in PE) to provide **61** (1.70 g, 7.33 mmol) in 93% yield as a colorless oil. R_F = 0.80 (1:19; acetone:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.48 (t, *J* = 6.3, 2H, OCH_2-5 pentynyl), 2.96 (s, 2H, OCH_2-Ada), 2.28 (dt, *J* = 2.9, 7.3, 2H, CH_2-3 pentynyl), 1.95 – 1.92 (m, 4H, 3×CH Ada, CH-1 pentynyl), 1.83 – 1.60 (m, 8H, 3×CH_2 Ada, CH_2-4 pentynyl), 1.48 (br d, *J* = 3.0, 6H, 3×CH_2 Ada). ^{13}C NMR (50 MHz, $CDCl_3$) δ 84.0 (C_q-2 pentynyl), 81.8 (OCH_2-Ada), 69.5 (OCH_2-5 pentynyl), 68.1 (CH-1 pentynyl), 39.5 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 28.6 (CH_2-4 pentynyl), 28.2 (3×CH Ada), 15.6 (CH_2-3 pentynyl). IR ν_{max}(thin film)/ cm^{-1}: 3310, 2901, 2847, 2669, 1450, 1366, 1234, 1157, 1111, 9910, 725, 625. HRMS: found *m/z* 233.1897 $[M+H]^+$, calcd for $[C_{16}H_{24}O+H]^+$ 233.1900.

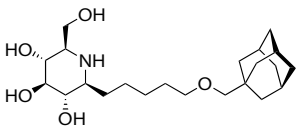


α/β-Mixture of 2,3,4,6-tetra-*O*-benzyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pent-1-ynyl)-D-glucose (62). A dry solution of **61** (536 mg, 2.31 mmol) in THF (12.5 mL) was cooled to –50 °C and BuLi (1.73 mL, 2.77 mmol, 1.6M in toluene) was added slowly to the solution. After stirring for 1 h at –50 °C, a dry solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[39] (2.49 g, 4.62 mmol) in THF (12.5 mL) was slowly added and the reaction was stirred at –50 °C for 2 h. The reaction mixture was quenched (sat aq NH_4Cl, 1 mL), warmed to rt and poured into sat aq NH_4Cl (100 mL). The aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 10% EtOAc in toluene) to provide **62** (1.364 g, 1.77 mmol) as an 1:1 anomeric mixture in 77% yield as a colorless oil. R_F = 0.68 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) α/β mixture

δ = 7.42 – 7.11 (m, 40H, H_{Ar} Bn α+β), 5.05 – 4.48 (m, 16H, 4×CH_2 Bn α+β), 4.03 (m, 1H, H-5 α or β), 3.92 (m, 1H, H-5 α or β), 3.90 (dd, *J* = 9.2, 9.2, 1H, H-3 α or β), 3.78 (dd, *J* = 9.2, 9.2, 1H, H-3 α or β), 3.74 – 3.62 (m, 7H, CH_2-6 α+β, H-4 α+β, H-2 α or β), 3.50 (d, $J_{H2\text{-}H3}$ = 9.5, 1H, H-2 α or β), 3.44 (t, *J* = 6.1, 2H, CH_2-5 pentynyl α or β), 3.39 (t, *J* = 6.0, 2H, CH_2-5 pentynyl α or β), 2.91 (s, 2H, OCH_2-Ada α or β), 2.89 (s, 2H, OCH_2-Ada α or β), 2.37 (t, *J* = 7.1, 2H, CH_2-3 pentynyl α or β), 3.31 (t, *J* = 7.3, 2H, CH_2-3 pentynyl α or β), 1.93 (br s, 6H, 3×CH Ada α+β), 1.80-1.72 (m, 4H, CH_2-4 pentynyl α+β), 1.70-1.60 (m, 12H, 3×CH_2 Ada α+β), 1.48 (br s, 12H, 3×CH_2 Ada α+β). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) α/β mixture δ = 138.6, 138.5, 138.1, 138.04, 138.02, 137.9 (8×C_q Bn α+β), 130.0, 128.2, 128.1, 128.0, 127.9, 127.85, 127.83, 127.74, 127. 71, 127.6, 127.5, 127.46, 127.40, 127.33 (CH_{Ar} Bn α+β), 95.5, 91.6 (2×C-1 α+β), 88.9, 84.7, 79.7, 76.2 (4×C_q pentynyl α+β), 84.3, 84.2 (2×C-2 α+β), 83.7, 82.4 (2×C-3 α+β), 81.9, 81.7 (2×OCH_2-Ada α+β), 77.7, 77.4 (2×C-4 α+β), 75.7, 75.6, 75.0, 74.8, 74.5, 73.3 (8×CH_2 Bn α+β), 73.6, 71.6 (2×C-5 α+β), 69.7, 69.6 (2×OCH_2-5 pentynyl α+β), 68.53, 68.49 (2×C-6 α+β), 39.6 (6×CH_2 Ada α+β), 37.1 (6×CH_2 Ada α+β), 34.0 (2×C_q Ada α+β), 28.5 (2×CH_2-4 pentynyl α+β) 28.2 (6×CH Ada α+β), 15.5, 15.4 (2×CH_2-3 pentynyl α+β). IR ν_{max}(thin film)/ cm^{-1}: 3348, 3032, 2901, 2847, 2373, 1728, 1605, 1497, 1450, 1358, 1265, 1211, 1072, 910, 810, 741, 694, 602, 571, 525. $[\alpha]^{20}_D$: 30.5 (*c* 18.5, $CHCl_3$). HRMS: found *m/z* 793.4057 $[M+Na]^+$, calcd for $[C_{50}H_{58}O_7+Na]^+$ 793.4075.

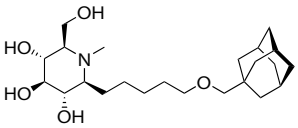


(1*S*)-2,3,4,6-Tetra-*O*-benzyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pent-1-ynyl]-1-deoxynojirimycin (63). A dry solution of **62** (549 mg, 0.71 mmol) in MeOH (5 mL) and DCM (1 mL) was cooled to 0 °C and $NaBH_4$ (134 mg, 3.57 mmol) was added. After stirring for 2 h at 0 °C, TLC analysis indicated full conversion to a lower running product. The reaction was quenched by addition of acetone (1 mL) and stirring for 15 min. The reaction mixture was concentrated, dissolved in little EtOAc, poured into sat aq NH_4Cl (100 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to provide the glucitol-derivative, which was used without further purification in the next reaction (ESI-MS found 795.6 $[M+Na]^+$; R_F diol = 0.45/ 0.35 in EtOAc:toluene; 1:3). The crude product was subjected to General procedure B and double reductive amination method B (R_F diketone = 0.80 in EtOAc:toluene; 1:3). However during the double reductive amination a mixture of MeOH/DCM (0.02M; 5/1) was used. The crude product was purified by silica gel column chromatography (0% » 25% EtOAc in toluene) to provide **63** (303 mg, 0.40 mmol) in 56% yield as a colorless oil. R_F = 0.55 (1:3; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$, COSY) δ 7.39 – 7.16 (m, 20H, H_{Ar} Bn), 5.03 (d, *J* = 10.5, 1H, C*H*H Bn), 4.91 (d, *J* = 10.9, 1H, C*H*H Bn), 4.83 (d, *J* = 10.9, 1H, C*H*H Bn), 4.82 (d, *J* = 10.5, 1H, CH*H* Bn), 4.80 (d, *J* = 10.9, 1H, CH*H* Bn), 4.48 (d, *J* = 10.9, 1H, CH*H* Bn), 4.47 (d, *J* = 11.8, 1H, C*H*H Bn), 4.43 (d, *J* = 11.8, 1H, CH*H* Bn), 3.68 (dd, $J_{H6a\text{-}H5}$ = 2.5, $J_{H6a\text{-}H6b}$ = 9.0, 1H, H-6a), 3.49 – 3.24 (m, 5H, H-1, H-2, H-3, H-6b), 3.41 (t, *J* = 6.1, 2H, OCH_2-5 pentynyl), 3.37 (dd, *J* = 9.3, 9.3, 1H, H-4), 2.90 (s, 2H, OCH_2-Ada), 2.76 (ddd, $J_{H5\text{-}H6a}$ = 2.5, *J* = 6.4, 9.7, 1H, H-5), 2.30 (t, *J* = 7.2, 2H, CH_2-3 pentynyl), 2.22 (br s, 1H, NH), 1.93 (br s, 3H, 3×CH Ada), 1.74 (m, 2H, CH_2-4 pentynyl), 1.71-1.61 (m, 6H, 3×CH_2 Ada), 1.49 (br d, *J* = 2.9, 6H, 3×CH_2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 138.7, 138.4, 138.2, 137.9 (4×C_q Bn), 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.67, 127.62, 127.5 (CH_{Ar}, Bn), 86.9 (C-3), 84.5 (C-2), 84.0 (C_q pentynyl), 81.8 (OCH_2-Ada), 79.9 (C-4), 78.9 (C_q pentynyl), 75.7, 75.4, 75.1, 73.4 (4×CH_2 Bn), 70.1 (C-6), 69.9 (OCH_2-5 pentynyl), 58.7 (C-5), 51.7 (C-1), 39.6 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 28.7 (CH_2-4 pentynyl), 28.2 (3×CH Ada), 15.6 (CH_2-3 pentynyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2901, 2847, 1497, 1450, 1358, 1265, 1211, 1072, 1018, 910, 741, 694. $[\alpha]^{20}_D$: 9.5 (*c* 5.3, $CHCl_3$). HRMS: found *m/z* 754.4421 $[M+H]^+$, calcd for $[C_{50}H_{59}NO_5+H]^+$ 754.4466.

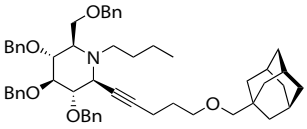


(1*S*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (17). Compound **63** (87 mg, 115 µmol) was subjected to Pd/C catalyzed hydrogenolysis according to General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 15% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **17** (39 mg, 98 µmol) as a colorless oil in 85% yield. R_F = 0.38 (1:2; MeOH:$CHCl_3$ + 0.5%

NH_4OH). ^1H NMR (300 MHz, MeOD, COSY) δ 3.91 (dd, $J_{H6a\text{-}H5}$ = 3.0, $J_{H6a\text{-}H6b}$ = 10.9, 1H, H-6a), 3.49 (dd, $J_{H6b\text{-}H5}$ = 7.8, $J_{H6b\text{-}H6a}$ = 10.9, 1H, H-6b), 3.38 (t, *J* = 6.4, 2H, OCH_2-5′ pentyl), 3.19 (dd, *J* = 9.0, 9.0, 1H, H-3), 3.10 (dd, *J* = 9.0, 9.0, 1H, H-4), 3.00 – 2.96 (m, 3H, H-2, OCH_2-Ada), 2.53 (m, 1H, H-5), 2.41 (m, 1H, H-1), 1.95 – 1.85 (m, 5H, 3×CH Ada, CH_2 pentyl), 1.76 – 1.66 (m, 6H, 3×CH_2 Ada), 1.58 – 1.50 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.45 – 1.25 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (75 MHz, MeOD, HSQC) δ 83.1 (OCH_2-Ada), 79.1 (C-3), 74.2 (C-2), 72.5 (OCH_2-5′ pentyl), 70.4 (C-4), 62.2 (C-5), 60.7 (C-1), 60.1 (C-6), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.7, 30.5 (2×CH_2 pentyl), 27.8 (3×CH Ada), 27.4, 26.7 (2×CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3310, 2901, 2847, 1450, 1366, 1312, 1258, 1150, 1096, 1018, 910, 826, 733, 671. $[\alpha]^{20}_D$: –12.5 (*c* 0.4, $CHCl_3$). HRMS: found *m/z* 398.2905 $[M+H]^+$, calcd for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.

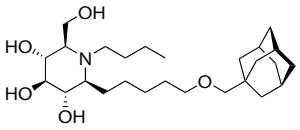


(1*S*)-*N*-Methyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (18). Argon was passed through a solution of compound **63** (70 mg, 93 µmol) and formaldehyde (1 mL; 37 wt % in water) in *n*-propanol (4 mL) for 5 min, after which a catalytic amount of Pd/C Degussa type (50 mg, 5 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 min. After stirring the reaction under atmospheric hydrogen pressure for 1 h, Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH. The filtrate was concentrated and the resulting residue was subjected to General procedure D. The crude product was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **18** (36 mg, 88 µmol) as a colorless oil in 94% yield. R_F = 0.50 (1:2; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^1H NMR (400 MHz, MeOD, COSY) δ 3.90 (dd, $J_{H6a\text{-}H6b}$ = 11.8, $J_{H6a\text{-}H5}$ = 3.0, 1H, H-6a), 3.82 (dd, $J_{H6b\text{-}H6a}$ = 11.8, $J_{H6b\text{-}H5}$ = 3.9, 1H, H-6b), 3.40 – 3.35 (m, 3H, H-3, OCH_2-5 pentyl), 3.22 (dd, *J* = 9.2, 9.2, 1H, H-2), 3.15 (dd, *J* = 9.1, 9.1, 1H, H-4), 2.96 (s, 2H, OCH_2-Ada), 2.29 (s, 3H, NCH_3), 2.08 – 2.03 (m, 2H, H-1, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.61 – 1.55 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.43 – 1.35 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.1 (OCH_2-Ada), 80.5 (C-3), 72.8 (C-2), 72.7 (OCH_2-5 pentyl), 70.9 (C-4), 69.8 (C-5), 67.9 (C-1), 60.4 (C-6), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 36.1 (NCH_3), 35.2 (C_q Ada), 30.7, 29.8 (2×CH_2 pentyl), 29.8 (3×CH Ada), 27.8, 25.4 (2×CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3348, 2901, 2847, 2793, 2677, 2499, 1664, 1450, 1366, 1234, 1103, 1011, 864, 810, 687, 617. $[\alpha]^{20}_D$: 2.3 (*c* 0.5, $CHCl_3$). HRMS: found *m/z* 412.3064 $[M+H]^+$, calcd for $[C_{23}H_{42}NO_5+H]^+$ 412.3058.



(1*S*)-2,3,4-Tri-*O*-benzyl-*N*-butyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pent-1-ynyl]-1-deoxynojirimycin (64). A dry solution of compound **63** (75 mg, 100 µmol) and butyraldehyde (100 µL, 1 mmol) in EtOH (0.75 mL) and AcOH (0.25 mL) was charged with $NaBH_3CN$ (19 mg, 0.3 mmol). The reaction mixture was stirred for 20 h and subsequently concentrated with coevaporation of toluene. The residue was dissolved EtOAc, poured into sat aq $NaHCO_3$ (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (8% » 20% EtOAc in PE) to provide **64** (65 mg, 80 µmol) as a colorless oil in 80% yield. R_F = 0.45 (1:4 EtOAc:PE). ^1H NMR (400 MHz, $CDCl_3$, COSY) δ 7.41 – 7.13 (m, 20H, H_{Ar} Bn), 5.00 (d, *J* = 10.5, 1H, C*H*H Bn), 4.90 – 4.78 (m, 4H, 2×CH Bn, CH_2 Bn), 4.54 – 4.44 (m, 3H, CH Bn, CH_2 Bn), 3.72 (dd, $J_{H6a\text{-}H5}$ = 2.4, $J_{H6a\text{-}H6b}$ = 10.4, 1H, H-6a), 3.62 (dd, *J* = 9.2, 9.2, 1H, H-4), 3.58 (dd, *J* = 9.3, 9.6, 1H, H-2), 3.55 (dd, $J_{H6b\text{-}H5}$ = 2.4, $J_{H6b\text{-}H6a}$ = 10.4, 1H, H-6b), 3.45 – 3.40 (m, 3H, H-3, OCH_2-5 pentynyl), 3.34 (m, 1H, NC*H*H butyl), 3.31 (dt, $J_{H1\text{-}H3'}$ = 2.0, $J_{H1\text{-}H2}$ = 9.6, 1H, H-1), 2.91 (s, 2H, OCH_2-Ada), 2.79 (m, 1H, NCH*H* butyl), 2.45 (m, 1H, H-5), 2.30 (dt, *J* = 2.0, 7.2, 2H, CH_2-3 pentynyl), 1.94 (br s, 3H, 3×CH Ada), 1.79 – 1.61 (m, 8H, 3×CH_2 Ada, CH_2-4 pentynyl), 1.49 (br s, 6H, 3×CH_2 Ada), 1.39 (m, 1H, C*H*H butyl), 1.26 – 1.17 (m, 3H, CH*H* butyl, CH_2 butyl), 0.85 (t, *J* = 7.2, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.6, 138.5, 137.7 (4×C_q Bn), 128.4, 128.3, 128.0, 127.8, 127.54, 127.50, 127.4 (CH_{Ar} Bn), 86.8 (C-3), 85.1 (C_q pentynyl), 82.8, 78.3 (C-2, C-4), 81.9 (OCH_2-

Ada), 77.7 (C_q pentynyl), 75.5, 75.4, 75.0, 73.4, 70.0 (4×CH_2 Bn, OCH_2-5 pentynyl), 65.9 (C-6), 61.9, 56.7 (C-1, C-5), 48.0 (NCH_2 butyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 28.3 (3×CH Ada), 28.8, 23.5, 20.4, 15.6 (4×CH_2 butyl/ pentynyl), 14.0 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3063, 3024, 2901, 2847, 1728, 1666, 1497, 1450, 1358, 1288, 1211, 1157, 1088, 1026, 903, 841, 741, 694. $[\alpha]^{20}_D$: 2.3 (*c* 1.3, $CHCl_3$). HRMS: found *m/z* 810.5037 $[M+H]^+$, calcd for $[C_{54}H_{67}NO_5+H]^+$ 810.5092.



(1*S*)-*N*-Butyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (19). General procedure D was applied to compound **64** (65 mg, 80 µmol) and the resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **19** (33 mg, 73 µmol) as a colorless oil in 91% yield. R_f = 0.60 (1:2; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^1H NMR (400 MHz, MeOD, COSY) δ 3.90 – 3.80 (m, 2H, CH_2-6), 3.40 – 3.25 (m, 3H, H-4, OCH_2-5 pentyl), 3.20 – 3.09 (m, 2H, H-2, H-3), 2.96 (s, 2H, OCH_2-Ada), 2.82 (m, 1H, NC*H*H butyl), 2.68 (m, 1H, NCH*H* butyl), 2.39 – 2.32 (m, 2H, H-1, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.55 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.50 – 1.30 (m, 4H, CH_2 butyl, CH_2 pentyl), 1.25 (m, 2H, CH_2 butyl), 0.93 (t, *J* = 7.1, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 81.0 (OCH_2-Ada), 80.5 (C-3), 72.9, 71.6 (C-2, C-4), 72.5 (OCH_2-5 pentyl), 65.8, 63.7 (C-1, C-5), 60.2 (C-6), 47.3 (NCH_2 butyl), 40.9 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.0 (C_q Ada), 30.7, 29.1, 27.9, 25.8, 24.5, 21.6 (6×CH_2 butyl/pentyl), 29.8 (3×CH Ada), 14.4 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3364, 2901, 2847, 2098, 1728, 1450, 1366, 1258, 1111, 1011, 926. $[\alpha]^{20}_D$: 1.2 (*c* 0.3, $CHCl_3$). HRMS: found *m/z* 454.3543 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

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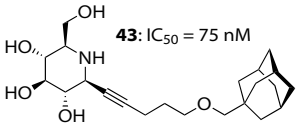
6 Lipophilic Aza-*C*-glycosides as Inhibitors of the Enzymes of Glucosylceramide Metabolism

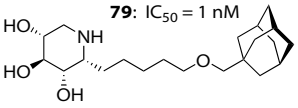
Abstract

The structure–activity relationship of lipophilic aza-*C*-glycosides as inhibitors of the three enzymes of glucosylceramide metabolism is described in this chapter. A library of β-aza-*C*-glycosides was synthesized with variations in *N*-alkylation and the linker length/type to the lipophilic moiety. A cross-metathesis reaction was used to prepare a second library of α-aza-*C*-glycosides with D-*gluco* and L-*ido* and D-*xylo* iminosugar cores and analogous linker variations. Evaluation of both libraries did not reveal a potent or selective inhibitor of glucosylceramide synthase. However, β-aza-*C*-glycoside **43** was found to be a selective inhibitor of β-glucosidase 2. The α-aza-*C*-glycosides – especially with a D-*xylo* core (*e.g.* **79**) – proved to be very potent and selective inhibitors of glucocerebrosidase.



43: IC_{50} = 75 nM

β-Glucosidase 2 inhibitor



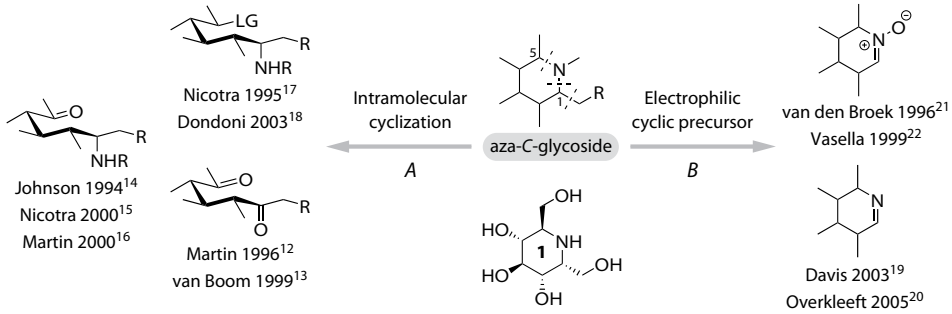
79: IC_{50} = 1 nM

Glucocerebrosidase inhibitor

Introduction

The first synthesis[1] of carbohydrate analogs with a nitrogen in the ring – so called iminosugars or azasugars – and their concurrent discovery as natural products in microorganisms[2,3] were reported during the 1960s. The continuously increasing amount of research on iminosugars since then can mainly be attributed to the subsequent discovery of their ability to inhibit glycoprocessing enzymes[4-6] combined with major advances in the field of glycobiology.[7] However, a recurring problem in the development of iminosugars as inhibitors of these enzymes is their lack of specificity. The countless complex carbohydrate structures and conjugates involved in human physiological processes are composed of a relatively limited selection of monosaccharide building blocks. Therefore, an iminosugar inhibitor that only mimics one monosaccharide subunit of the complex substrate of the target enzyme will often inhibit additional carbohydrate-processing enzymes that also create or cleave a glycosidic bond with this monosaccharide. A way to achieve selectivity for a specific enzyme is to add structural elements to the iminosugar that resemble the anomeric substituent/aglycon of the enzyme glycoside substrate or transition state. This should result in additional interactions with the aglycon binding site and as a consequence more selective binding. However, a true iminosugar mimic of the glycoside substrate would result in a labile *N*,*O*-acetal function, making it unsuitable as a potential drug or probe in biological research. Replacing the oxygen of the iminosugar's pseudo-anomeric centre for a methylene group results in a stable mimic of the target glycoside or transition state.

Figure 1. α-Homonojirimycin (**1**) and examples of strategies for the synthesis of aza-*C*-glycosides.



This class of iminosugars is called the aza-*C*-glycosides. The first piperidine based aza-*C*-glycoside to be discovered was α-homonojirimycin (**1**) that was synthesized in 1987[8] and later also discovered as a natural product[9] (Figure 1). Since then many synthetic strategies have been developed for the synthesis of aza-*C*-glycosides.[10,11] Most of these can be divided into two general categories depending on the disconnection(s) made in the retrosynthetic analysis. Disconnecting C1-N and C5-N results in approaches that use a final intramolecular cyclization to construct the aza-*C*-glycoside (Figure 1; *A*). A convenient method for cyclization that uses the ability of amines to form imines with

carbonyl compounds is the reductive amination. Both a double reductive amination of a C-1/C-5-diketone[12,13] or a single reductive amination of a C-1/C-5 amino-ketone penultimate[14-16] has proven to be a popular method for the preparation of aza-*C*-glycosides. Another method to achieve cyclization is to activate, with a suitable leaving group, the C-1 or C-5 position of an intermediate with an amine function on the opposing carbon center.[17,18] Alternatively, a disconnection made at C-1-CH_2R results in approaches that use a cyclic electrophilic precursor (Figure 1; *B*). For example, in this category organometal additions[19] and Ugi multicomponent reactions[20] have been used on cyclic imines to produce aza-*C*-glycosides. Carbohydrate derived cyclic nitrones have also been used. Aza-*C*-glycosides were constructed from these by 1,3-dipolar cycloadditions or nucleophilic additions.[21,22]

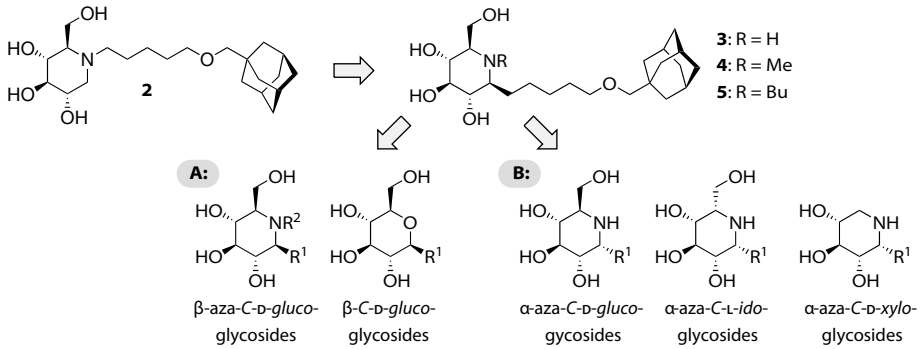
The overall goal of the research presented in this thesis was to develop lipophilic iminosugars as selective inhibitors of the enzymes involved in glucosylceramide metabolism. Glucosylceramide is a β-D-glucopyranoside of the lipid ceramide and belongs to the family of glycosphingolipids that are membrane components in eukaryotes and involved in many (patho)physiological processes.[23,24] The biosynthesis of glucosylceramide is realized by the membrane bound enzyme glucosylceramide synthase (GCS). Catabolism of glucosylceramide occurs in the lysosomes by glucocerebrosidase (GBA1). Additionally, the membrane bound β-glucosidase 2 (GBA2), located at or close to the cell surface is a second catabolic pathway for glucosylceramide with an as of yet unknown role.[25,26]

In this study the adamantan-1-yl-methoxy functionalized iminosugar **2**[27] was selected as the lead compound for further development of more selective inhibitors (Figure 2 on next page). Compound **2** was identified as a potent inhibitor of GCS (IC_{50} 200 nM), GBA1 (IC_{50} 200 nM) and GBA2 (IC_{50} 1 nM), but also inhibits several intestinal glycosidases (IC_{50} in the range of 0.4-35 μM). In chapter 5, derivatives of **2** were presented that varied in the position of the hydrophobic adamantan-1-yl-methoxy moiety on the 1-deoxynojirimycin ring and the functionalization of the endocyclic nitrogen. The main message from that library of compounds was that changing the position of the hydrophobic moiety in **2** abolished all GCS inhibitory activity except for β-aza-*C*-glucoside **3** (IC_{50} GCS: 9 μM).[28] Additionally, the *N*-butylated (**5**) derivative of **3**, but not its *N*-methylated (**4**) counterpart, also inhibited GCS (Figure 2). Expanding on these findings, the research described in this chapter further investigates the structure–activity relationship of this class of inhibitors by discussing the synthesis and evaluation of two libraries of adamantan-1-yl-methoxy functionalized aza-*C*-glycosides based on compound **3**.

The first library (**A**; Figure 2) consists of derivatives of **3** that retain the pseudo β-orientation (*S*-C-1) of the hydrophobic moiety, but vary in the length and the saturation of the pentyl spacer. The influence of the nitrogen atom on inhibition is also further investigated with *C*-glycoside derivatives (no nitrogen atom) and additional *N*-alkylated derivatives. For the second library (**B**; Figure 2) the C-1-stereochemistry was altered to

pseudo α (*R*-C1). For this library the iminosugar core was varied to also encompass L-*ido* and D-*xylo* substitution patterns besides the D-*gluco* pattern of **3**. This variation is based on the finding in Chapter 3 that the epimerization at the C5 position is a suitable entry for obtaining more selective inhibitors of GCS. Additionally, analogous spacer variations to library A were prepared for all three α-aza-*C*-glycoside cores. Both libraries were evaluated in an enzyme assay for inhibitory activity against GCS, GBA1, GBA2 and three intestinal glycosidases not associated with glucosylceramide metabolism.

Figure 2. Lead compound **2**, aza-*C*-glycosides **3**–**5** and the structural variations presented in this chapter. R^1 = adamantan-1-yl-methoxy–spacer moiety; R^2 = H or *N*-alkylation



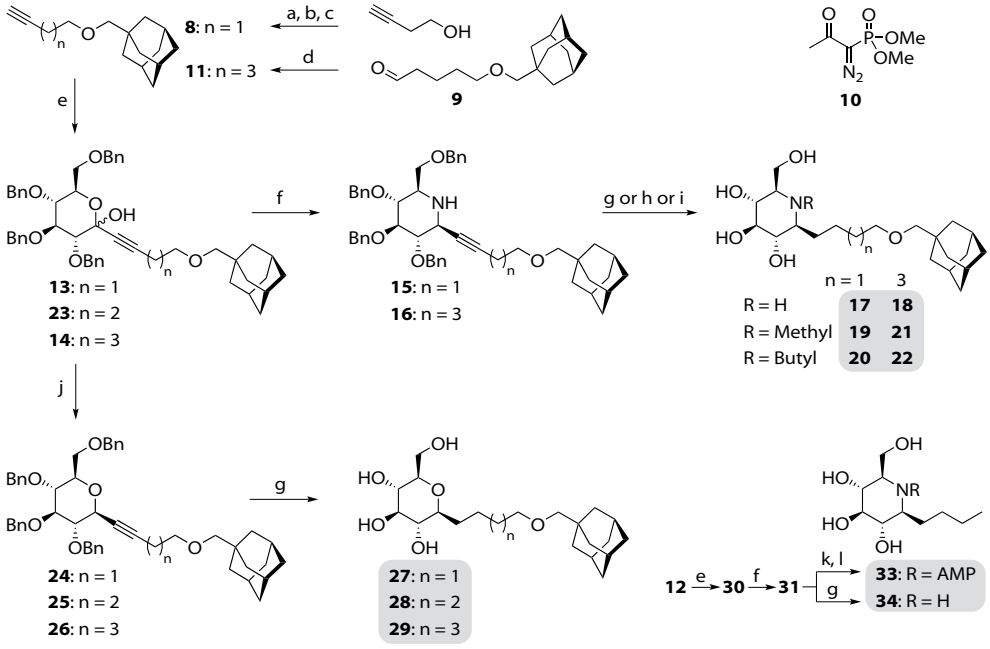
Results and Discussion

The entries of the first library of β-(aza)-*C*-glycosides with D-gluco stereochemistry could be synthesized either via the synthetic route as described for **3**–**4** in Chapter 5 or via synthetic intermediates from this route. Alkyne **8** was synthesized from but-3-yn-1-ol via the same protocol as described for pent-4-yn-1-ol on page 136 in Chapter 5 (Scheme 1). The synthesis of alkyne **11** was also attempted via this route but this proved low yielding. The intermediate triflate proved susceptible to side reactions[29] and only produced ~30% of the desired TES protected intermediate of **11** upon reaction with adamantane methanol. An alternative higher yielding route for the synthesis of **11** was found in treating aldehyde **9** (from Chapter 2) with the Bestmann–Ohira reagent (**10**)[30,31] in the presence of methanol and potassium carbonate to produce **11** in 87% yield. A phosphonate carbanion is formed *in situ* from **10** and undergoes a Horner–Wadsworth–Emmons-type reaction with **9**. After elimination of dimethylphosphate and extrusion of N_2, the resulting alkylidenecarbene undergoes a Fritsch–Buttenberg–Wiechell rearrangement (1,2-shift)[32] to produce the alkyne (**11**).

Alkynes **8** and **11** were deprotonated to the acetylenic anion and condensed with 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**12**)[33] (Scheme 1). The produced ketoses **13** and **14** were transformed into **15** and **16** by a tandem reduction/Swern oxidation/double reductive amination reaction sequence.[28] The double reductive amination solely yielded the β-aza-*C*-D-*gluco*-glycoside stereoisomer in both cases. This indicates

that the intramolecular cyclization probably occurs exclusively via axial hydride addition onto cyclic imines (C-1=N/C-5=N) that are in equilibrium with a bis-hemiaminal intermediate.[12,13,34] Compounds **15** and **16** were deprotected by Pd catalyzed hydrogenolysis to produce β-aza-*C*-glycosides **17** and **18**. Reductive amination of **15** and **16** with formaldehyde or butyraldehyde and hydrogenolysis of the crude intermediate produced the *N*-methylated (**19** and **21**) and *N*-butylated (**20** and **22**) derivatives, which together with **17** and **18** completed the butyl/ hexyl spacer length variations based on **3**-**5**. Reductive elimination of ketoses **13**, **14** and **23** (from Chapter 5) with borontrifluoride etherate/ triethylsilane and subsequent Pd/C catalyzed hydrogenolysis of the intermediates **24**, **25** and **26** produced the β-*C*-glycosides **27**, **28** and **29**.

Scheme 1. Synthesis of β-aza-*C*-glycoside spacer length variations and β-*C*-glycoside derivatives.

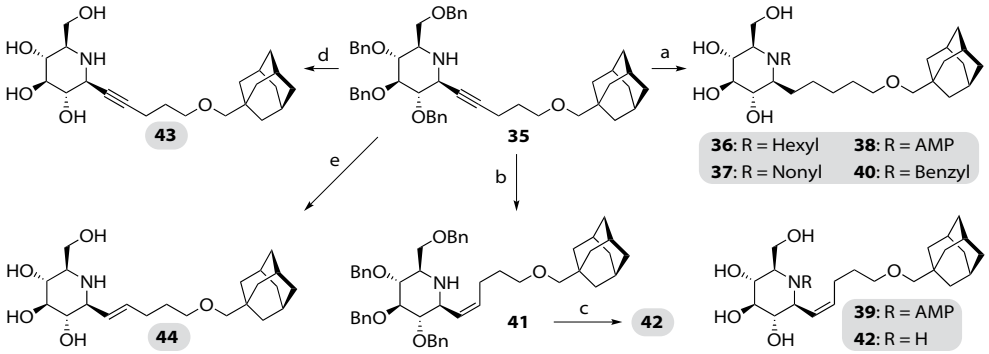


Reagents and conditions: [**a**] i: BuLi, THF, –68 °C, 1h; ii: TESCl, –68 °C to rt, 20h; iii: 2M HCl, 48h, **6**: 71%. [**b**] i. Tf_2O, Et_3N, DCM, –40 °C, 1h; ii: adamantanemethanol, K_2CO_3, DCM, reflux, 3 days, **7**: 84%. [**c**] 4 eq. NaOMe, THF/MeOH (2/1), 90 °C, 20h, **8**: 87%. [**d**] **10**, K_2CO_3, MeOH, 0 °C » rt, 16h, 87%. [**e**] i: BuLi, THF, –50 °C, 1h; ii: **12**, –50 °C, 2h, **13**: 60%; **14**: 86%; **30**: 72%. [**f**] i: $NaBH_4$, MeOH/DCM (5/1), 2h; ii: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; iii: Et_3N, –75 °C » rt, 0.5h; iv: $NaBH_3CN$, $HCOONH_4$, 3Å mol. sieves, MeOH/DCM (5/1), 0 °C » rt, 20h, **15**: 53%; **16**: 59%; **31**: 67% 3 steps. [**g**] Pd/C, H_2 atm, EtOH, HCl, 20h, **17**: 90%; **18**: 75%; **27**: 81%; **28**: 89%; **29**: 90%; **34**: 97%. [**h**] i: Pd/C (Degussa), H_2 atm, formaldehyde, *n*-propanol, 1h; ii: Pd/C, H_2 atm, EtOH, HCl, 20h, **19**: 89%; **21**: 69%. [**i**] i: butyraldehyde, $NaBH_3CN$, EtOH/AcOH (3/1), 20h; ii: Pd/C, H_2 4 bar, EtOH, HCl, 20h, **20**: 60%; **22**: 66%. [**j**] $BF_3 \cdot Et_2O$, Et_3SiH, CH_3CN, –30 °C, 1.5h, **24**: 89%; **25**: 79%; **26**: 60%. [**k**] **9**, $NaBH_3CN$, Na_2SO_4, CH_3CN/MeOH (5/1), 75 °C, 18h, **32**: 79%. [**l**] Pd/C, H_2 4 bar, EtOH, HCl, 20h, **33**: 85%.

Addition of butyllithium to lactone **12** and transformation of ketose **30** produced **31**. Reductive amination of **31** with aldehyde **9** and deprotection gave **33** that is an analogue of

5 with the C-1/*N*-substituents inverted. Straight deprotection of **31** produced additional library entry **34**.

Scheme 2. Synthesis of β-aza-*C*-glycoside derivatives of **3** and **5** varying in spacer saturation and *N*-alkylation.

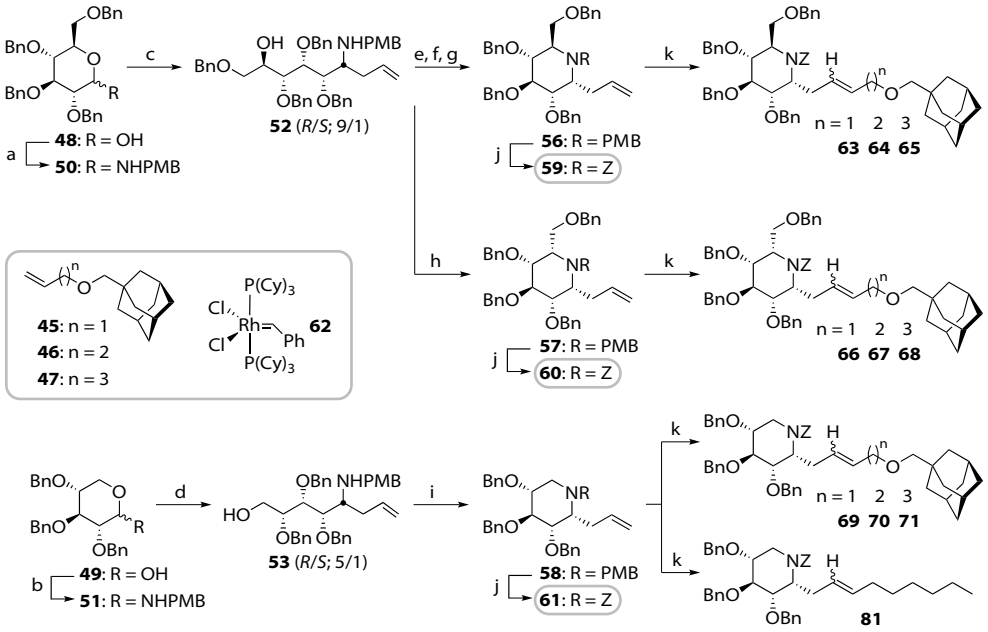


Reagents and conditions: [**a**] for **36**–**38** i: aldehyde, $NaBH_3CN$, EtOH/AcOH (3/1), 20h; ii: Pd/C, H_2 4 bar, EtOH, HCl, 20h, **36**: 71%; **37**: 63%; **38**: 79%; for **40**: BnBr, K_2CO_3, DMF, 85°C, 18h, 71%; for **39** i: **9**, $NaBH_3CN$, EtOH/AcOH (3/1), 20h; ii: Pd/C, H_2 atm, EtOH, HCl, 20h, 41%. [**b**] $Pd/CaCO_3$/Pb (Lindlar catalyst), H_2 atm, EtOAc, 18h, 74%. [**c**] Na, NH_3, –60 °C, 1h, 67%. [**d**] Na, NH_3, –60 °C, 0.5h, 24%. [**e**] Li, NH_3, –60 °C, 3h, 70%.

Manipulation of synthetic intermediate **35** from Chapter 5 provided the final two classes of derivatives for the first library (Scheme 2). Reductive amination of **35** with hexanal, nonanal or aldehyde **9** and subsequent deprotection gave **36**, **37** and **38** respectively. During the synthesis of **38**, palladium catalyzed hydrogenolysis of the alkyne function in the crude reductive amination product at atmospheric H_2 pressure proceeded sluggishly and gave a ~1:1 mixture of **38** and *Z*-alkene **39**. Alkylation of **3** with benzyl bromide under the agency of potassium carbonate at 90 °C in DMF produced the final *N*-alkylated derivative (**40**). Hydrogenolysis of **35** in the presence of Lindlar catalyst and subsequent Birch reduction of intermediate **41** produced *Z*-alkene (**42**). A Birch reduction of **35** with sodium for 30 minutes achieved complete debenzylation but only minor reduction of the alkyne function to yield alkyne derivative (**43**). A Birch reduction with lithium for 3 hours was able to satisfactorily reduce the alkyne function to give *E*-alkene derivative **44**.

For the preparation of the second library, the adamantan-1-yl-methoxy functionalized α-aza-*C*-glycosides, a cross-metathesis reaction approach was chosen.[35,36] In this way the three distinct spacer lengths can be made by using three appropriate adamantan-1-yl-methoxy functionalized terminal alkenes in combination with the same iminosugar cross-metathesis partner. Additionally, unsaturated spacer derivatives can be generated by a Birch reduction of the cross-metathesis products. Positioning of this alkene function at the same site as in library one entries **42** and **44** is not possible, since Compain and Martin have already shown that α-vinyl-aza-*C*-glycosides are not suitable for cross-metathesis.[35] Therefore D-*gluco*, L-*ido* and D-*xylo* α-allyl-aza-*C*-glycosides were selected as cross-metathesis partner (Scheme 3).

Scheme 3. Synthesis of protected α-aza-*C*-glycosides (cross-metathesis partners and catalyst are in boxes).



Reagents and conditions: [**a**] NH_2PMB, *p*-TsOH, Na_2SO_4, toluene, reflux, 18h, used crude. [**b**] NH_2PMB, CSA, Na_2SO_4, toluene, reflux, 2.5h, used crude. [**c**] AllylMgBr, Et_2O, 0 °C » rt, 16h, 93%. [**d**] AllylMgBr, THF, 0 °C » rt, 16h, 97%. [**e**] FmocCl, aq $NaHCO_3$, DCM, 16h, **54**: 91%. [**f**] Dess-Martin periodinane, DCM, 0 °C, 6h, **55**: 98%. [**g**] i: piperidine, DMF, 0 °C, 0.5h; ii: $NaCNBH_3$, AcOH, Na_2SO_4, MeOH, –35 °C » –20 °C, 16h, **56**: 81%. [**h**] MsCl, pyridine, 0 °C » rt, 4h; ii: 90 °C, 16h, 78%. [**i**] PPh_3, DEAD, DCM, 20h, 88%. [j] i: CAN, THF/H_2O (5/1), 0 °C, 3h; ii: ZCl, aq $NaHCO_3$, dioxane, 20h, **59**: 65%; **60**: 75%; **61**: 87%. [**k**] 25 mol% Grubbs' catalyst (**62**), DCM, 45 °C, 24h, 65–88%.

The adamantan-1-yl-methoxy functionalized alkenes **45** and **47** could be prepared by a Williamson etherification of adamantanemethanol with allylbromide and 5-bromopent-4-ene. Alkene **46** could be made by substitution of the triflate of 3-buten-1-ol with adamantanemethanol (Scheme 3). The synthesis of the α-allyl-aza-*C*-glycosides started with a Grignard reaction of allylmagnesiumbromide on the anomeric *p*-methoxybenzyl aminoglycosides **50** and **51**, which in turn were made from hemiacetals **48** and **49**. The Grignard reaction produced (*R*)-**52** and (*R*)-**53** as the major stereoisomer in both cases, which can be rationalized by taking into account an O-2/NPMB-chelated Felkin-Anh type intermediate. This stereochemistry was confirmed by a strong NOE between H-1–H-2 of both **52** and **53**.[37,38] Intermediate **52** could be transformed into D-*gluco* α-allyl-aza-*C*-glycoside **56** via an adapted procedure from Nicotra and co-workers (see Scheme 3).[15] Selective mesylation of the 5-OH in **52** and subsequent S_N2-like cyclization with a Walden inversion at C-5 produced L-*ido* **57**. Intermediate **53** could be transformed into the D-*xylo* α-aza-*C*-glycoside **58** by cyclization via an intramolecular Mitsunobu reaction.[39]

It is already known from literature that the cross-metathesis reaction is incompatible with endocyclic tertiary amines – probably by coordinating with the Grubbs' catalyst.[35] The *p*-methoxybenzylamines in **56**, **57** and **58** were therefore oxidatively cleaved with cerium(IV)ammonium nitrate and protected as a benzyloxy/Z carbamate (**59**, **60** and **61**) to make them suitable for cross-metathesis.

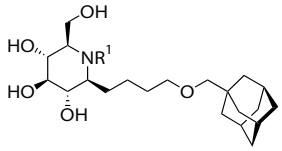
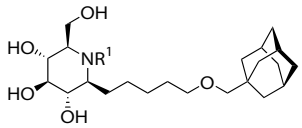
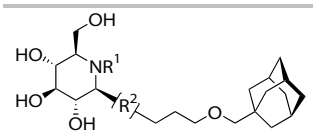
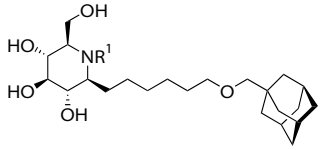
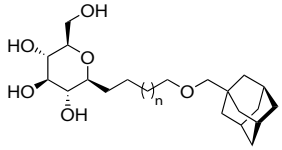
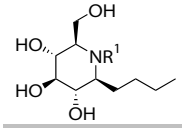
Cross-metathesis of α-allyl-aza-*C*-glycosides **59**, **60** and **61** with a threefold excess of the adamantan-1-yl-methoxy alkenes **45**, **46** and **47** under the agency of 25 mol% of Grubbs' generation 1 catalyst (**62**) gave the nine penultimates (**63**–**71**) as *E*/*Z* mixtures. Deprotection by Pd/C catalyzed hydrogenation at 4 bar gave library entries **72**–**80** (for structures see Table 2). As a reference compound in the enzyme assay the potent GBA1 inhibitor **82** (Table 2), reported by Compain and co-workers[40], was synthesized from **61** by cross-metathesis with non-1-ene and subsequent deprotection of **81** (Scheme 3). The final entries for the second library were made by a Birch reduction of protected cross-metathesis products **64**, **67**, **70** and **81** to provide double bond containing α-aza-*C*-glycosides **83**–**86** (Table 2). In the case of **86** this solely provided the *E*-isomer, but for **83**, **84** and **85** it gave an inseparable mixture of *E*/*Z*-isomers. These mixtures were tested as such in the enzyme assay.[41,42]

Biological evaluation

The inhibitory potency and selectivity of the two libraries of lipophilic aza-*C*-glycosides A: **17**–**22**; **27**–**29**; **33**–**34**; **36**–**40**; **42**–**44** and B: **72**–**80**; **82**–**86** were assessed by evaluating the compounds in assays for the three enzymes involved in glucosylceramide metabolism; glucosylceramide synthase (GCS), glucocerebrosidase (GBA1) and β-glucosidase 2 (GBA2). To further establish the selectivity profile of the library entries they were also tested in inhibition assays for the intestinal glycosidases sucrase, lactase and maltase. As an unwanted side-effect most 1-deoxynojirymycin based inhibitors of glucosylceramide metabolism also inhibit these glycosidases.

In Chapter 5, the hydrophobic moiety of lead compound **2** was translocated to produce β-aza-*C*-glycoside **3**. When comparing the structures of **2** and **3** this translocation lengthens the carbon chain connecting the endocyclic nitrogen and the adamantan-1-yl-methoxy group from five to six atoms. The influence of this change on the SAR could be assessed with derivatives **17** and **18**. The assay results for the first library show that neither shortening (**17**) nor lengthening (**18**) this carbon chain by one carbon atom improves inhibition of GCS, but instead abolishes it (Table 1). Evidently the carbon chain length of **3** is already optimal for GCS inhibition. Altering the saturation of the pentyl spacer of **3** into the *Z*-alkene (**42**), alkyne (**43**) or *E*-alkene (**44**) derivatives also prevented GCS inhibition. When compared to **3**, **42** is a more selective inhibitor of GBA1 and **43** and **44** of GBA2.

Table 1. Enzyme inhibition assay results for library A: β-(aza)-*C*-glycosides (apparent IC_{50} values in μM).[a,b]

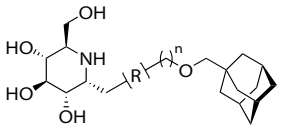
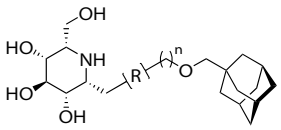
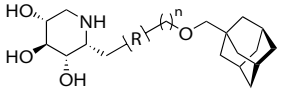
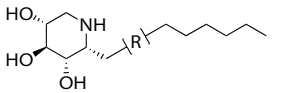
Compound	R^1 =	R^2 =	GCS *in vivo*	GBA1	GBA2	Sucrase	Lactase	Maltase
	**17:** H		> 10	5	0.2	260	180	500
	19: Methyl		> 10	50	0.3	1000	1000	> 1000
	20: Butyl		> 10	100	25	> 1000	> 1000	> 1000
	**3:** H		9	3	0.04	> 100	> 100	> 100
	4: Methyl		> 100	25	0.6	> 100	> 100	> 100
	5: Butyl		25	40	10	> 100	> 100	> 100
	36: Hexyl		> 10	10	1	1000	350	>1000
	37: Nonyl		> 10	35	1	180	450	500
	38: AMP		> 10	4	1	180	450	500
	40: Benzyl		> 10	12	> 1000	> 1000	1000	> 1000
	**42:** H	*Z*-C=C	> 10	0.4	4	180	35	500
	43: H	C≡C	> 10	20	0.075	100	180	1000
	44: H	*E*-C=C	> 10	3	0.150	150	75	1000
	39: AMP	*Z*-C=C	> 10	10	5	600	500	> 1000
	**18:** H		> 10	1	1	350	500	700
	21: Methyl		> 10	7	1	160	> 1000	1000
	22: Butyl		> 10	2	2	300	> 1000	> 1000
	**27:** n = 1		> 10	> 1000	> 1000	> 1000	> 1000	> 1000
	28: n = 2		> 10	> 1000	> 1000	> 1000	> 1000	> 1000
	29: n = 3		> 10	240	> 1000	> 1000	> 1000	> 1000
	**33:** AMP		15%[c]	130	40	> 1000	> 1000	> 1000
	34: H		> 10	350	100	200	550	> 1000

[a] AMP = 5-(adamantan-1-yl-methoxy)-pentyl; [b] Except for GCS, all assays are *in vitro*; [c] % inhibition at 10 μM.

The β-*C*-glycoside derivatives **27**, **28** and **29** did not inhibit any of the tested enzymes to a significant extent. When combined with the finding of Aerts *et al.* that derivatives of **3** with an endocyclic amide[27] are also inactive as inhibitors of glucosylceramide metabolism this strongly suggests that a basic nitrogen function is essential for inhibition. The effect discussed in Chapter 5 that the *N*-butylated (**5**) derivative of **3** inhibited GCS and the *N*-methylated (**4**) derivative did not, is not reproduced for the lengthened or shortened *N*-alkylated derivatives (**19**, **21** and **20**, **22**). Compound **19** is a relatively selective inhibitor of GBA2. Also the synthesized derivatives of **3** with alternate/lengthened *N*-alkyl moieties (**36**–**40**) all lost the ability to inhibit GCS and showed no improvement

of GBA1 or GBA2 inhibition. These findings indicate that the secondary endocyclic nitrogen of **3** plays an important part in the ability of **3** to inhibit GCS, GBA1 and GBA2. The only derivative from the first library that still very modestly inhibited GCS was **33** – the C-1/*N*-substituent inverted derivative of **5**. The related entry, **34**, did not significantly inhibit any of the enzymes in the assay. Compound **34** is a β-aza-*C*-glycoside derivative of the known clinically used GCS inhibitor *N*-butyl-1-deoxynojirimycin (GCS IC_{50} = 50 μM in this assay). This reconfirms the observation from Chapter 5 that relocating the hydrophobic moiety from the nitrogen to C-1 does not lead to more potent GCS inhibitors.

Table 2. Enzyme inhibition assay results for library B: α-aza-*C*-glycosides (apparent IC_{50} values in μM).[a]

Compound	R =	n =	GCS *in vivo*	GBA1	GBA2	Sucrase	Lactase	Maltase
	**72:** C–C	1	18%[b]	0.35	< 0.3	8	12	18
	73: C–C	2	18%[b]	0.07	< 0.3	8	7	20
	83: *E*/*Z*-C=C	2	11%[b]	0.25	0.020	2	18	3
	74: C–C	3	> 10	0.07	< 0.3	10	85	37
	**75:** C–C	1	> 10	2	8	> 1000	30	> 1000
	76: C–C	2	18%[b]	5.5	100	> 1000	3	> 1000
	84: *E*/*Z*-C=C	2	13%[b]	3	10	> 1000	18	> 1000
	77: C–C	3	12%[b]	6	100	> 1000	40	> 1000
	**78:** C–C	1	20%[b]	0.002	100	> 1000	3	> 1000
	79: C–C	2	14%[b]	0.001	10	> 1000	20	> 1000
	85: *E*/*Z*-C=C	2	> 10	0.001	20	> 1000	3	> 1000
	80: C–C	3	14%[b]	0.002	90	> 1000	15	> 1000
	**82:** C–C		18%[b]	0.001	250	> 1000	5	> 1000
	86: *E*-C=C		> 10	0.002	> 1000	> 1000	10	> 1000

[a] Except for GCS, all assays are *in vitro*; [b] % inhibition at 10 μM.

Almost all the entries of the second library of lipophilic α-aza-*C*-glycosides showed very modest inhibition of GCS with none being as potent as **3** (Table 2). These results corroborate an earlier study by Boucheron and co-workers that showed that *N*-alkylated α-aza-C-glycosides are poor inhibitors of GCS.[43] The three different iminosugar cores did however have a distinct effect on GBA2 inhibition. The D-*gluco* derivatives (**72**–**74**, **83**) in general were >25 fold more potent GBA2 inhibitors than the L-*ido* (**75**–**77**, **84**) or D-*xylo* (**78**–**80**, **82**, **85**, **86**) derivatives. For GBA1 inhibition the effect of the iminosugar core was even more pronounced. The D-*xylo* α-aza-*C*-glycosides (**78**–**80**, **82**, **85**, **86**) were all 1-2 nM inhibitors of GBA1 as opposed to the L-*ido* derivatives (**75**–**77**, **84**) that were 2-6 μM inhibitors of the same enzyme. D-*Xylo* analog **85** is an *E*/*Z* mixture and these

isomers should be tested separately to fully elucidate their relative contributions to GBA1 inhibition. In general the unsaturated pentyl spacer derivatives (**83**, **84** and **85**) did not show a significantly different inhibition profile for the tested enzymes compared to their saturated counterparts (**73**, **76** and **79**). However, introduction of an *E*-alkene into the known[40] potent GBA1 inhibitor **82** to give **86** does reduce inhibition of GCS and GBA2 to make it more selective.

Conclusion

In this chapter the syntheses of two libraries of lipophilic aza-*C*-glycosides are presented. The structures of the library entries are based on β-aza-*C*-glycosides **3** from chapter 5. The aim was to investigate the structure–activity relationship of this class of iminosugars as inhibitors of glucosylceramide metabolism.

The first library consisted of β-aza-*C*-glycosides and showed that for GCS inhibition an aliphatic pentyl spacer length between C-1 and the adamantan-1-yl-methoxy group combined with a secondary endocyclic nitrogen is optimal in this library. β-*C*-glycoside derivatives showed the importance of a basic endocyclic nitrogen for inhibition of glycosidases and glycosyltransferases in general. From this first library the alkyne containing **43** was found to be a potent and selective inhibitor of GBA2 and the *Z*-alkene containing **42** a selective inhibitor of GBA1.

The second library of α-aza-*C*-glycosides did not contain a potent inhibitor of GCS, which indicates that a pseudo β-orientation of the hydrophobic moiety is necessary for potent inhibition of GCS. The type of iminosugar core in the α-aza-*C*-glycosides proved to exert a pronounced influence on inhibition of GBA1 and GBA2. The D-*gluco* iminosugar core proved most suitable for GBA2 inhibition and the D-*xylo* core is optimal for GBA1 inhibition. All D-*xylo* analogs (**78**–**80**, **82**, **86**) were very potent and selective GBA1 inhibitors. Iminosugar **82** has already been reported by Compain, Martin and co-workers to hold potential as a pharmacological chaperone for improving the activity of Gaucher disease related GBA1 in N370S fibroblasts (section 1.3.4 of Chapter 1).[40] Therefore, it might prove interesting to also evaluate the here presented novel derivatives (**78**–**80**, **86**) to this end.

Experimental section

General methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at ambient temperatures unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere. Residual water was removed from starting compounds by repeated coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. Reaction grade acetonitrile, dimethylsulfoxide, isopropanol and methanol were stored on 3Å molecular sieves. Other reaction grade solvents were stored on 4Å molecular sieves. THF was distilled prior to use from $LiAlH_4$. Ethanol was purged of acetaldehyde contamination by distillation from zinc/KOH.

DCM was distilled prior to use from P_2O_5. R_F values were determined from TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by spraying with a solution of $(NH_4)_6Mo_7O_{24}\times4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times2H_2O$ (10 g/L) in 10% sulfuric acid or a solution of phosphomolybdic acid hydrate (7.5 wt% in ethanol) followed by charring at ~150 °C. Visualization of all deprotected iminosugar compounds during TLC analysis was accomplished by exposure to iodine vapour. Column chromatography was performed on silica gel (40–63 μm). Iminosugars (**43**, **72**–**80**, **82**, **86**–**86**) were purified with an automated HPLC system fitted with a semi-preperative C_{18} column (21 mm D × 150 mm L, 5 μm particle size, 25 mL/min). Isocratic or gradient elution was performed with eluent A: 0.1% aq TFA and eluent B: CH_3CN. Iminosugars samples were dissolved in a mixture of 0.1% aq TFA/*t*BuOH/CH_3CN (3/1/1, v/v/v, 2 mL) with optional MeOH for full solvation of the compound. The solution was filtered over a 5 μm filter and injected onto the column in 500 μL portions for preparative runs. Compound detection was carried out by a charged aerosol detector (Esa Corona, sensitivity setting: 100 pA). Appropriate fractions were collected, concentrated, coevaporated with water (2×) and lyophilized. ^{1}H and ^{13}C-APT NMR spectra were recorded on a Bruker DMX 600 (600/150 MHz), Bruker DMX 500 (500/125 MHz), or Bruker AV 400 (400/100 MHz) spectrometer in $CDCl_3$ or MeOD. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard (^{1}H NMR in $CDCl_3$) or the signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. All presented ^{13}C-APT spectra are proton decoupled. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150–2000) and dioctylpthalate (m/z = 391.28428) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Optical rotations were measured on a Propol automatic polarimeter (Sodium D-line, λ = 589 nm). ATR-IR spectra were recorded on a Shimadzu FTIR-8300 fitted with a single bounce Durasample IR diamond crystal ATR-element and are reported in cm^{-1}.

Enzyme Assays: The enzyme assays used for determining the inhibition of activity of glucosylceramide synthase (GCS), glucocerebrosidase (GBA1), β-glucosidase 2 (GBA2), sucrase, lactase and maltase are described in the experimental section of Chapter 3.

*General procedure A – Addition of acetylenic anion's of **8** and **11** to gluconolactone (**12**)*: A dry solution of the acetylene in THF (0.1M) was cooled to –50 °C and BuLi (1.2 eq, 1.6M in toluene) was added slowly to the solution. After stirring for 1 h at –50 °C, a dry solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[33] (2 eq) in THF (0.33M) was slowly added and the reaction was stirred at –50 °C for 2 h. The reaction mixture was quenched (sat aq NH_4Cl), warmed to rt and poured into sat aq NH_4Cl. The aqueous layer was extracted with Et_2O (3×) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography to provide the ketose product.

*General procedure B – Transformation of ketose **13**, **14** and **23** into β-C-glycosides by reductive elimination*: Triethylsilane (5 eq) and $BF_3{\cdot}Et_2O$ (6 eq) were successively added to a cooled (–30 °C) solution of the ketose in anhydrous acetonitrile (0.1M). After stirring 1.5 h at –30 °C, TLC analysis showed complete disappearance of the starting material. The reaction mixture was quenched by addition of aq Na_2CO_3 (6× reaction volume, 10 wt%) and subsequently extracted with Et_2O (3×). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography to provide the β-*C*-glycoside.

*General procedure C – Transformation of ketose **13** and **14** into β-aza-C-glycosides*:
Reduction of ketal: A dry solution of the ketose in MeOH/DCM (0.1M, 5/1, v/v) was cooled to 0 °C and $NaBH_4$ (5 eq) was added. After stirring for 2 h at 0 °C, TLC analysis indicated full conversion to a lower running product. The reaction was quenched by addition of acetone and additional stirring (15 min). The reaction mixture was concentrated, transferred into sat aq NH_4Cl and extracted with EtOAc (3×). The combined organic phases were dried ($MgSO_4$) and concentrated to provide the glucitol derivative, which was used without further purification in the Swern oxidation (R_F diol = ~0.4 in EtOAc:toluene; 1:3).
Swern oxidation of diol: A solution of oxalylchloride (4 eq) in DCM (1 M) was cooled to −78 °C. After dropwise addition of a solution of DMSO (5 eq) in DCM (2 M) over 10 minutes, the reaction mixture was stirred for 40 minutes while being kept below −70 °C. Next, a dry solution of the glucitol intermediate in DCM (0.5 M) was added dropwise to the reaction mixture over a 15 minute period, while keeping the reaction mixture below −70 °C. After stirring the reaction mixture for 2 h below −65 °C, Et_3N (12 eq) was added dropwise over a 10 minute period, while keeping the reaction mixture below −65 °C. After addition, the reaction mixture was allowed to warm to −5 °C over 2 h (R_F diketon = ~0.80 in EtOAc:toluene; 1:3).
Double reductive amination: The Swern reaction mixture was concentrated at a moderate temperature (~30 °C) with simultaneous coevaporation of toluene (3×). The residue was dissolved in a mixture of MeOH/DCM (0.02M, relative to starting compound, 5/1, v/v) and NH_4HCO_2 (20 eq) was added. The mixture was cooled to 0 °C and stirred until all NH_4HCO_2 had dissolved. Activated 3Å molsieves (10 g/mmol) were added and reaction mixture was stirred for 15 minutes, after which $NaBH_3CN$ (4 eq) was added. The reaction mixture was kept at 0 °C for one h after which the cooling source was removed and the reaction was stirred for an additional 20 h. After removal of the molsieves over a glass microfibre filter, the filtrate was concentrated, dissolved in EtOAc and washed with sat aq $NaHCO_3$. The aqueous phase was back-extracted with EtOAc (3×) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography to provide the β-aza-*C*-glycoside product (R_F = ~0.5 in EtOAc:toluene; 1:3).

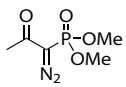
General method D – N-alkylation of β-aza-C-glycosides by reductive amination: A dry mixture of the tetra-benzylated iminosugar, the aldehyde (10 eq) and Na_2SO_4 (10 eq) in a mixture of EtOH/AcOH (0.1M, 3/1, v/v) was charged with $NaBH_3CN$ (4 eq). The reaction mixture was stirred for 20 h and subsequently concentrated with coevaporation of toluene. The residue was dissolved EtOAc, poured into sat aq $NaHCO_3$ and extracted with EtOAc (3×). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude *N*-alkylated iminosugar was used in the Pd/C catalyzed hydrogenolysis.

General method E – Oxidative cleavage of PMB group and reprotection as Z-carbamate: A solution of the PMB protected amine THF (0.5M) was slowly added to a cooled (0 °C) solution of ammonium cerium(IV)nitrate (4 eq) in H_2O/THF (0.05M, 1/5, v/v). The resulting suspension was stirred for 3 h at 0 °C, after which it was diluted with EtOAc (3× reaction volume) and washed with sat aq $NaHCO_3$ (3× reaction volume). The aqueous phase was back extracted with EtOAc (2×). The combined organic phases were concentrated. The residue was suspended in a mixture of dioxane/sat aq $NaHCO_3$ (0.1M, 2/1, v/v) after which benzyloxychloroformate (2 eq) was added. The reaction mixture was stirred for 20 h. The mixture was diluted with water and extracted with Et_2O (2×). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was dissolved in MeOH (0.2M) and cooled to 0 °C. Sodium borohydride (3 eq) was added and the mixture was stirred for 15 min and subsequently quenched by slow addition of acetone. The mixture was acidified to pH ~2 with 1M aq HCl, diluted with water (3× reaction volume) and extracted with Et_2O (3×). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography to afford the Z-carbamate protected iminosugar.

General procedure F – Cross-metathesis: The iminosugar cross-metathesis partner was coevaporated with DCE (3×). Next, the second alkene cross-metathesis partner (3 eq) was added and together they were dissolved in DCM (0.067M, relative to iminosugar). Alkenes **45**, **46** and **47** were not coevaporated because **46** and **47** are volatile. The solution was degassed under an argon flow by sonication for 10 min. Grubbs' first generation catalyst (**62**, 20 mol%) was added and the reaction mixture was refluxed at 45 °C for 24 h. The reaction mixture was concentrated and exposed to air at rt for 48 h. The residue was purified by silica gel column chromatography to afford the cross metathesis product. In case of difficult isolation of the product from residual iminosugar cross metathesis partner or catalyst breakdown products, the residue was purified once and then used impure in general procedure G or general procedure H (in Parr apparatus).

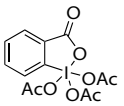
General procedure G – Birch reduction: A dry (100 mL) three-necked roundbottom flask was cooled to –60 °C and ammonia gas (via a CaO filled drying column) was passed through it until 20-30 mL ammonia has condensed. The ammonia gasflow was stopped and sodium (50–100 mg, rinsed beforehand with heptane) was added to the liquid ammonia. After stirring the dark blue mixture at –60 °C for 1 min, a solution of the benzylated iminosugar (50-200 mg) in *t*BuOH/ THF (0.5 mL/2 mL) was added. The reaction mixture was stirred for 1-2 h at –60 °C and additional sodium was added if the blue colour of the mixture disappeared. The reaction was quenched by slow addition of sat aq NH_4HCOOH (1 mL). The ammonia was evaporated and the resulting residue was coevaporated with dioxane. The solid residue was redissolved in MeOH and concentrated in the presence of celite. The celite-compound mixture was purified by silica gel column chromatography to afford the deprotected iminosugar.

General procedure H – Pd/C catalyzed hydrogenolysis:
Atmospheric H_2 pressure: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (4 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C (~50 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 minutes and the reaction was stirred for 20 h under atmospheric hydrogen pressure. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene. In the case of incomplete reduction hydrogenolysis was repeated after workup and coevaporation (3×) with 'acetaldehyde free' EtOH), at atmospheric pressure in the presence of Pd/C (~50 mg) and Pd black (~5 mg) or at higher H_2 pressure in a Parr-apparatus. *Hydrogenolysis in Parr-apparatus*: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (50 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C (50 mg, 10 wt % on act. carbon) was added. The reaction vessel was placed under vacuum and subsequently ventilated with hydrogen gas. This cycle was repeated one more time after which the vessel was placed under 4 bar of hydrogen gas and mechanically shaken for 20 h. Workup was the same as described before.

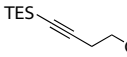


Dimethyl 1-diazo-2-oxo-propylphosphonate (10; Bestmann-Ohira reagent).[44,45] Trimethyl phosphite (12.41 g, 100 mmol) was added to a solution of chloroacetone (9.26 g, 100 mmol) and KI (16.60 g, 100 mmol) in acetone/ acetonitrile (55 mL, 6/ 5, v/ v). The reaction mixture was stirred for 18 h, after which it was filtered. The filtrate was concentrated and coevaporated with toluene (3×). The residue was purified by silica gel column chromatography (100% EtOAc) to provide dimethyl 2-oxopropylphosphonate (14.03 g, 84.5 mmol) in 84% yield as a colorless oil. R_F = 0.20 (100% EtOAc). ^{31}P-NMR (80.7 MHz, $CDCl_3$) δ 22.8. A solution of dimethyl 2-oxopropylphosphonate (2.49 g, 15 mmol) in toluene (15 mL) was added to a cooled (0 °C) suspension of NaH (60% in mineral oil, 630 mg, 15.7 mmol) in toluene/ THF (50 mL, 6/ 1, v/ v). The reaction mixture was stirred for 1 h at 0 °C, after which *p*-toluenesulfonylazide[46,47] (3.12 g, 15.7 mmol) was added. The mixture was stirred for 3 h at rt. Solids were removed by filtration and the filtrate was concentrated. The residue was purified

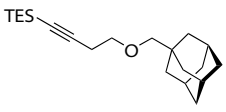
by silica gel column chromatography (100% EtOAc) to provide dimethyl-1-diazo-2-oxo-propylphosphonate (**10**, 2.11 g, 11 mmol) in 73% yield as a colorless oil. R_F = 0.25 (100% EtOAc). ^{31}P NMR (80.7 MHz, $CDCl_3$) δ 15.9. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3-3 propyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.2, 188.9 (C-1, C-2), 53.0, 52.9 (2×OCH_3), 26.4 (C-3).



1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane).[48,49] A solution of potassium bromate (101 g, 605 mmol) in aq 2M H_2SO_4 (927 mL) was heated to an internal temperature of 60 °C in a 2 L three-necked roundbottom flask fitted with a mechanical stirrer (glass shaft/ teflon stirring blade). Next, 2-iodobenzoic acid (100 g, 403 mmol) was added in 4 portions over a period of 40 minutes whilst passing a flow of nitrogen gas through the reaction mixture. The gas outlet was passed trough a trap filled with sat aq $Na_2S_2O_3$ (1 L) to neutralize evolved bromine gas. The reaction was stirred for 4 h at 65 °C (internal temperature) at which point most residual bromine had been evacuated via the nitrogen flow. NMR analysis of a sample of solids collected from the bottom of the reaction vessel indicated complete oxidation to 2-iodoxybenzoic acid (IBX). The reaction mixture was cooled to rt, stirring was halted and after the solids had settled to the bottom the residual floating solids on top were removed by decantation. The reaction mixture was filtered over a glass filter and the filter cake was successively washed with water (3×500 mL), EtOH (2×200 mL) and Et_2O (3×200 mL). The solids were collected and dried for 18 h under vacuum at rt to provide IBX (96 g, 343 mmol) in 85% yield as a an off-white solid. ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.15 (d, *J* = 7.8, 1H), 8.04 (d, *J* = 7.3, 1H), 8.00 (t, *J* = 7.8, 1H), 7.84 (t, *J* = 7.3, 1H), 2.5 (s, 1H). The dried IBX was suspended in acetic anhydride (400 mL) in the presence of *p*-TsOH (450 mg, 2.4 mmol) and heated at 80 °C (internal temperature) under argon for 4 h. The reaction mixture was cooled to rt and filtered under a nitrogen flow. The filter cake was washed with Et_2O (3×200 mL) under a nitrogen flow and dried for 4 h under vacuum at rt to provide Dess-Martin periodinane (125 g, 295 mmol) in 73% overall yield as a white solid. The Dess-Martin periodinane was stored at –20 °C in a darkened container. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 1.6, 7.3, 1H), 8.29 (dd, *J* = 1.1, 8.3, 1H), 8.07 (dt, *J* = 1.6, 8.3, 1H), 7.90 (dt, *J* = 1.1, 7.3, 1H), 2.33 (s, 3H, CH_3 OAc), 2.01 (s, 6H, 2×CH_3 OAc). *Warning: Dess-Martin periodinane and especially IBX are heat- and shock-sensitive (exotherms observed when heated above 130 °C) and should be handled with appropriate precautions.*

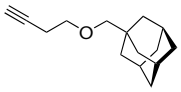


4-(Triethylsilyl)-but-3-yn-1-ol (6). A dry and cooled (–68 °C) solution of but-3-yn-1-ol (3.11 g, 44.3 mmol) in THF (50 mL) was charged with BuLi (60.9 mL, 97.5 mmol, 1.6M in toluene) and stirred at –68 °C for 1 h. Triethylsilylchloride (22.5 mL, 132.9 mmol) was added dropwise to the reaction and the mixture was stirred at –68 °C for 1 h, after which cooling was ceased and the solution was stirred for 18 h. 2M aq HCl (200 mL) was added and the reaction mixture was stirred for 48 h (R_F intermediate disilyl = 0.80 (1:2; EtOAc:PE)). The mixture was extracted with Et_2O (2×200 mL) and the combined organic layers were washed with water (2×200 mL). The organic phase was dried ($MgSO_4$), concentrated and the resulting residue was purified by silica gel column chromatography (0% » 30% EtOAc in PE) to provide product **6** (5.82 g, 31.5 mmol) in 71% yield as a colorless oil. R_F = 0.10 (1:9; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (t, *J* = 5.8, 2H, OCH_2-1 butynyl), 2.53 (t, *J* = 6.6, 2H, CH_2-2 butynyl), 1.82 (br s, 1H, OH), 0.99 (t, *J* = 8.0, 9H, 3×CH_3 $SiEt_3$), 0.58 (q, *J* = 8.0, 6H, 3×CH_2 $SiEt_3$). IR ν_{max}(thin film)/ cm^{-1}: 3323, 2953, 2876, 2174, 1458, 1414, 1236, 1018, 1004, 972, 889, 721. MS (ESI): found 185.2 $[M+H]^+$, calculated for $[C_{10}H_2OSi+H]^+$ 185.1

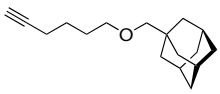


[4-(Adamantan-1-yl-methoxy)-but-1-ynyl]-triethylsilane (7). A dry solution of **6** (2.21 g, 12.0 mmol) in DCM (120 mL) was cooled to –40 °C followed by addition of Et_3N (1.66 mL, 12.0 mmol). Next, Tf_2O (2.42 mL, 14.4 mmol) was added dropwise and the reaction mixture was stirred at –40 °C for 1 h. Cooling was ceased and the reaction mixture was concentrated at rt by means of a nitrogen flow. The residue was purified by silica gel column

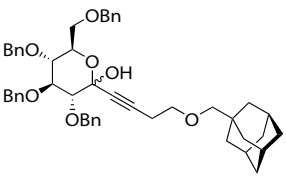
chromatography (isocratic 10% EtOAc in PE) and the product containing fractions were concentrated under a nitrogen flow at rt to provide the intermediate triflate. (R_F = 0.67 (EtOAc:PE; 1:9)). The triflate (~12 mmol) was dissolved in DCM (80 mL), to which adamantanemethanol (9.98 g, 60 mmol) and K_2CO_3 (8.17 g, 60 mmol) were successively added. The reaction mixture was refluxed (~55 °C) for 3 days, after which the solids were removed via filtration and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0% » 20% EtOAc in PE) to provide **7** (3.37 g, 10.1 mmol) in 84% yield as a colorless oil. R_F = 0.83 (1:9; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.52 (t, *J* = 7.1, 2H, OCH_2-4 butynyl), 3.02 (s, 2H, OCH_2-Ada), 2.49 (t, *J* = 7.1, 2H, CH_2-3 butynyl), 1.95 (s, 3H, 3×CH Ada), 1.79 – 1.57 (m, 6H, 3×CH_2 Ada), 1.53 (d, *J* = 2.7, 6H, 3×CH_2 Ada), 0.98 (t, *J* = 7.8, 9H, 3×CH_3 $SiEt_3$), 0.57 (q, *J* = 7.7, 6H, 3×CH_2 $SiEt_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 105.5 (C_q-2 butynyl), 82.6 (C_q-1 butynyl), 82.2 (OCH_2-Ada), 70.2 (OCH_2-4 butynyl), 39.9 (CH_2 Ada), 37.5 (CH_2 Ada), 34.3 (C_q Ada), 28.6 (CH Ada), 21.4 (CH_2-3 butynyl), 7.6 (CH_3 $SiEt_3$), 4.7 (CH_2 $SiEt_3$). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2874, 2849, 2175, 1456, 1236, 1157, 1111, 1003, 723. HRMS: found 333.2609 $[M+H]^+$, calculated for $[C_{21}H_{36}OSi+H]^+$ 333.2608.



4-(Adamantan-1-yl-methoxy)-but-1-yne (8). A dry solution of **7** (3.37 g, 10.1 mmol) in a mixture of THF (50 mL) and MeOH (25 mL) was charged with NaOMe (2.86 g, 52.95 mmol) and refluxed at 90 °C for 20 h. The reaction was quenched (water, 0.5 mL) and concentrated. The residue was dissolved in EtOAc (200 mL) and washed with water (2×200 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (2% » 10% acetone in PE) to provide **8** (1.92 g, 8.80 mmol) in 87% yield as a colorless oil. R_F = 0.70 (1:9; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.53 (t, *J* = 7.2, 2H, OCH_2-4 butynyl) 3.01 (s, 2H, OCH_2-Ada), 2.43 (dt, *J* = 2.7, 7.2, 2H, CH_2-3 butynyl), 1.97 (br s, 3H, 3×CH Ada), 1.94 (t, *J* = 2.6, 1H, CH-1 butynyl), 1.78 – 1.57 (m, 6H, 3×CH_2 Ada), 1.53 (d, *J* = 2.8, 6H, 3×CH_2 Ada). ^{13}C NMR (50 MHz, $CDCl_3$) δ 82.1, (OCH_2-Ada), 81.6 (C_q butynyl), 69.8 (OCH_2-4 butynyl), 69.2 (C_q butynyl), 39.8(CH_2 Ada), 37.3 (CH_2 Ada), 34.2 (C_q Ada), 28.4 (CH Ada), 19.8 (CH_2-3 butynyl). IR ν_{max}(thin film)/ cm^{-1}: 3312, 2899, 2847, 1450, 1362, 1157, 1103, 1070. MS (ESI): found 219.9 $[M+H]^+$, calculated for $[C_{15}H_{22}O+H]^+$ 219.2.

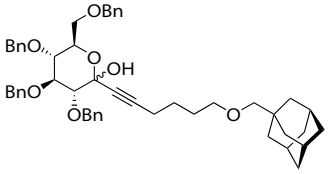


6-(Adamantan-1-yl-methoxy)-hex-1-yne (11). (1-Diazo-2-oxo-propyl)-di-*O*-methyl phosponate (**10**, 1.44 g, 7.5 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) were added to a cooled (0 °C) solution of 5-(adamantan-1-yl-methoxy)-1-pentanal (**9**, see Chapter 2 for synthesis, 1.25 g, 5.0 mmol) in methanol (25 mL). After 30 min the reaction mixture was allowed to warm to rt and stirred for an additional 16 h. The reaction mixture was transferred into sat aq NH_4Cl (20 mL) and extracted with Et_2O (4×50 mL). The combined organic phases were washed with sat aq NaCl (50 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel column chromatography (0% » 6% EtOAc in PE) to furnish **11** (1.07 g, 4.34 mmol) in 87% yield as a colorless oil. R_F = 0.6 (19:1; PE:acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.40 (t, *J* = 6.0, 2H, OCH_2-6 hex-1-yn), 2.95 (s, 2H, OCH_2-Ada), 2.28 – 2.17 (m, 2H, CH_2-3 hexynyl), 1.96 (br s, 3H, 3×CH Ada), 1.94 (t, *J* = 2.6, 1H, CH-1 hexynyl), 1.78 – 1.57 (m, 10H, 3×CH_2 Ada, 2×CH_2 hexynyl), 1.53 (d, *J* = 2.8, 6H, 3×CH_2 Ada). ^{13}C NMR (50 MHz, $CDCl_3$) δ 84.3 (C_q hexynyl), 82.0 (OCH_2-Ada), 70.9 (OCH_2-6 hexynyl), 68.6 (C_q hexynyl), 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 28.8 (CH_2-5 hexynyl), 28.5 (CH Ada), 25.5 (CH_2-4 hexynyl), 18.3 (CH_2-3 hexynyl). IR ν_{max}(thin film)/ cm^{-1}: 3311, 2899, 2847, 1452, 1360, 1157, 1113, 1056, 625. HRMS: found 247.2058 $[M+H]^+$, calculated for $[C_{17}H_{26}O+H]^+$ 247.2056.

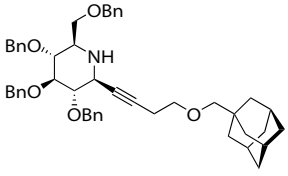


α/β-Mixture of 1-*C*-[4-(adamantan-1-yl-methoxy)-but-1-ynyl]-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl (13). Compound **8** (1.0 g, 4.58 mmol) was subjected to general procedure A to produce **13** (2.09 g, 2.76 mmol) in 60% yield after silica gel column purification (0% » 5% acetone in toluene). R_F = 0.46 (19:1; toluene:acetone). ^{1}H NMR (300 MHz, $CDCl_3$) α/β mixture δ 7.42 – 7.09 (m, 20H, H_{Ar} Bn), 5.07 – 4.43 (m, 8H, 4×CH_2 Bn), 4.06 – 3.56 (m, 6H, H-2,

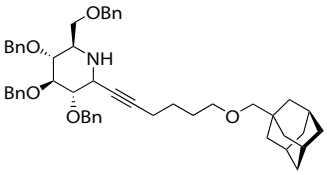
H-3, H-4, H-5, CH_2-6), 3.55 – 3.44 (m, 2H, OCH_2-4 butynyl), 3.01 – 2.90 (m, 2H, OCH_2-Ada), 2.56 – 2.43 (m, 2H, CH_2-3 butynyl), 1.91 (br s, 3H, 3×CH Ada), 1.74 – 1.54 (m, 6H, 3×CH_2 Ada), 1.48 (s, 6H, 3×CH_2 Ada). ^{13}C NMR (75 MHz, $CDCl_3$) α/β mixture δ 138.5, 138.4, 138.4, 138.3, 137.9, 137.9, 137.8 (C_q Bn α/β), 128.1, 128.0, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2 (CH_{Ar} Bn α/β), 95.3, 91.4, 86.2, 84.1, 84.0, 83.5, 82.9, 82.3, 81.9, 81.8 (OCH_2-Ada), 80.3, 78.0, 77.5, 77.3, 77.0, 76.8, 76.7, 76.4, 75.6, 75.5, 75.4, 74.9, 74.7, 74.4, 73.8, 73.2, 71.5, 69.2, 69.0 (OCH_2-4 butynyl), 68.3, 39.4 (CH_2 Ada), 36.9 (CH_2 Ada), 33.8 (C_q Ada), 28.0 (CH Ada), 19.8, 19.7 (CH_2-3 butynyl). IR ν_{max}(thin film)/ cm^{-1}: 3321, 3032, 2905, 2847, 1496, 1454, 1367, 1209, 1146, 1103, 1045, 1028, 1007, 986, 951, 910, 808, 754, 742. $[\alpha]^{20}_D$: 36.1 (*c* 4.6, $CHCl_3$). HRMS: found 774.4367 $[M+NH_4]^+$, calculated for $[C_{49}H_{56}O_7+NH_4]^+$ 774.4364.



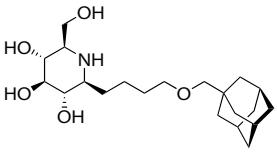
α/β-Mixture of 1-*C*-[6-(adamantan-1-yl-methoxy)-hex-1-ynyl]-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl (14). Compound **11** (493 mg, 2.0 mmol) was subjected to general procedure A to produce **14** (1.35 g, 1.72 mmol) in 86% yield after silica gel column purification (0% » 5% acetone in toluene). R_F = 0.50 (19:1; toluene:acetone). ^{1}H NMR (200 MHz, $CDCl_3$) α/β mixture δ 7.44 – 7.08 (m, 20H, H_{Ar} Bn), 5.07 – 4.45 (m, 8H, 4×CH_2 Bn), 3.96 – 3.25 (m, 8H, CH_2-6 hexenyl, H-2, H-3, H-4, H-5, CH_2-6), 2.92, 2.91 (s, 2H, OCH_2-Ada α/β), 2.36 – 2.21 (m, 2H, CH_2-3 hexenyl), 1.93 (br s, 3H, 3×CH Ada), 1.76 – 1.54 (m, 10H, 3×CH_2 Ada, 2×CH_2 hexenyl), 1.50 (d, *J* = 2.0, 6H, 3×CH_2 Ada). ^{13}C NMR (50 MHz, $CDCl_3$) α/β mixture δ 138.7, 138.7, 138.6, 138.1, 138.1, 138.0, 138.0 (C_q Bn α/β), 128.3, 128.2, 128.1, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3 (CH_{Ar} Bn α/β), 95.6, 91.6 (C-1 α/β), 89.1, 84.8(C_q hexenyl α/β), 84.4, 84.3, 83.7, 82.5, 81.8 (OCH_2-Ada), 79.9, 77.8, 77.4, 77.1, 76.4, 75.6, 75.6, 75.0, 74.8, 74.4, 73.8, 73.6, 73.4, 73.2, 73.2, 71.5, 70.8, 70.7, 68.5, 39.6 (CH_2 Ada), 37.1 (CH_2 Ada), 34.0 (C_q Ada), 28.8, 28.7 (CH_2 hexenyl α/β), 28.2 (CH Ada), 25.1, 24.9 (CH_2 hexenyl α/β), 18.5 (CH_2-3 hexenyl). IR ν_{max}(thin film)/ cm^{-1}: 3362, 3032, 2902, 2849, 1497, 1453, 1360, 1211, 1067, 1027, 910, 733, 695. $[\alpha]^{20}_D$: 33.4 (*c* 2.2, $CHCl_3$). HRMS: found 802.4681 $[M+NH_4]^+$, calculated for $[C_{51}H_{60}O_7+NH_4]^+$ 802.4677.



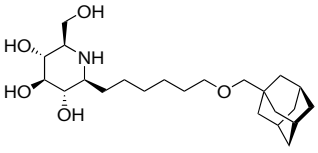
(1*S*)-1-*C*-[4-(Adamantan-1-yl-methoxy)-but-1-ynyl]-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (15). Compound **13** (371 mg, 0.49 mmol) was subjected to a tandem reduction/Swern oxidation/double reductive amination procedure (see general procedure C) to give **15** (191 mg, 0.26 mmol) as a colorless oil in 53% yield after silica gel column chromatography (0% » 20% EtOAc in toluene). R_F = 0.19 (9:1; toluene:EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.16 (m, 20H, H_{Ar} Bn), 5.02 (d, *J* = 10.5, 1H, C*H*H Bn), 4.91 (d, *J* = 10.8, 1H, C*H*H Bn), 4.83 (d, *J* = 11.0, 1H, C*H*H Bn), 4.81 (m, 2H, 2×CH*H* Bn), 4.49 – 4.42 (m, 3H, CH_2 Bn, CH*H* Bn), 3.68 (dd, *J* = 2.4, 9.0, 1H, H-6a), 3.54 – 3.48 (m, 4H, H-3, H-6b, OCH_2-4 butynyl), 3.44 – 3.43 (m, 2H, H-1, H-2), 3.37 (dd, *J* = 9.4, 9.4, 1H, H-4), 2.95 (s, 2H, OCH_2-Ada), 2.77 – 2.73 (m, 1H, H-5), 2.47 (t, *J* = 7.3, 2H, CH_2-3 butynyl), 1.93 (br. s, 3H, 3×CH Ada), 1.65 (dd, *J* = 12.0, 43.7, 6H, 3×CH_2 Ada), 1.49 (d, *J* = 2.4, 6H, 3×CH_2 Ada). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.9, 138.6, 138.4, 138.1 (4×C_q Bn), 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8 (CH_{Ar} Bn), 87.0 (C-3), 84.6 (C-2), 82.2 (OCH_2-Ada), 81.3 (C_q butynyl), 80.1 (C-4), 76.0, 75.7, 75.3, 73.6 (4×CH_2 Bn), 70.3 (C-6), 70.0 (CH_2-4 butynyl), 58.9 (C-5), 51.9 (C-1), 39.8 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 28.4 (CH Ada), 20.2 (CH_2-3 butynyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1454, 1360, 1151, 1096, 1070, 1028, 1007, 735, 696. $[\alpha]^{20}_D$: 6.8 (*c* 0.8, $CHCl_3$). HRMS: found 740.4309 $[M+H]^+$, calculated for $[C_{49}H_{57}NO_5+H]^+$ 740.4310.



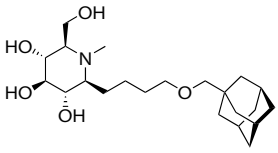
(1*S*)-1-*C*-[6-(Adamantan-1-yl-methoxy)-hex-1-ynyl]-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (16). Compound **14** (0.40 g, 0.51 mmol) was subjected to a tandem reduction/Swern oxidation/double reductive amination procedure (see general procedure C) to give **16** (234 mg, 0.30 mmol) as a colorless oil in 59% yield after silica gel column chromatography (0% » 20% EtOAc in toluene). R_F = 0.6 (9:1; toluene:acetone). ^{1}H NMR (400 MHz, C_6D_6) δ 7.23 – 7.05 (m, 20H, H_{Ar} Bn), 5.20 (d, *J* = 11.0, 1H, C*H*H Bn), 4.97 – 4.93 (m, 2H, CH*H* Bn, C*H*H Bn), 4.88 (d, *J* = 11.4, 1H, C*H*H Bn), 4.81 (d, *J* = 11.3, 1H, CH*H* Bn), 4.47 (d, *J* = 11.4, 1H, CH*H* Bn), 4.25 (d, *J* = 11.9, 1H, C*H*H Bn), 4.19 (d, *J* = 11.9, 1H, CH*H* Bn), 3.65 (dd, *J* = 2.4, 8.9, 1H, H-6a), 3.59 – 3.48 (m, 4H, H-1, H-2, H-3, H-6b), 3.45 (dd, *J* = 9.1, 9.1, 1H, H-4), 3.21 (t, *J* = 5.9, 2H, CH_2-6 hexenyl), 2.87 (s, 2H, OCH_2-Ada), 2.76 (ddd, *J* = 2.4, 6.2, 9.0, 1H, H-5), 2.08 (t, *J* = 6.5, 2H, CH_2-3 hexenyl), 1.94 (s, 3H, 3×CH Ada), 1.73 – 1.50 (m, 16H, 6×CH_2 Ada, 2×CH_2 hexenyl). ^{13}C NMR (100 MHz, C_6D_6) δ 140.2, 140.0, 139.8, 139.1 (4×C_q Bn), 129.0, 128.8, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9 (CH_{Ar} Bn), 87.9 (C-3), 85.6 (C-2), 84.2 (C_q hexenyl), 82.6 (OCH_2-Ada), 80.9 (C-4), 80.9 (C_q hexenyl), 76.0, 75.8, 75.4, 73.9 (4×CH_2 Bn), 71.4 (CH_2-6 hexenyl), 71.0 (C-6), 59.8 (C-5), 52.9 (C-1), 40.5 (CH_2 Ada), 38.0 (CH_2 Ada), 34.7 (C_q Ada), 29.7 (CH_2 hexenyl), 29.2 (CH Ada), 26.3(CH_2 hexenyl), 19.3 (C-3 hexenyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2901, 2848, 1497, 1452, 1359, 1209, 1071, 1027, 1007, 734, 696. $[\alpha]^{20}_D$: –6.2 (*c* 1.0, $CHCl_3$). HRMS: found 768.4623 $[M+H]^+$, calculated for $[C_{51}H_{61}NO_5+H]^+$ 768.4623.



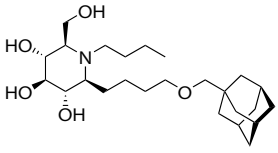
(1*S*)-1-*C*-[4-(Adamantan-1-yl-methoxy)-butyl]-1-deoxynojirimycin (17). Compound **15** (66 mg, 89 µmol) was subjected to hydrogenolysis at atmospheric H_2 (see general procedure H) to produce **17** (30 mg, 79 µmol) as a colorless oil in 90% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.22 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.92 (dd, *J* = 3.1, 10.8, 1H, H-6a), 3.50 (dd, *J* = 7.8, 10.8, 1H, H-6b), 3.41 (t, *J* = 6.2, 2H, OCH_2-4 butyl), 3.20 (dd, *J* = 8.9, 8.9, 1H, H-3), 3.11 (dd, *J* = 9.3, 9.3, 1H, H-4), 2.99 (dd, *J* = 9.2, 9.2, 1H, H-2), 2.97 (s, 2H, OCH_2-Ada), 2.56 (ddd, *J* = 3.1, 7.8, 9.9, 1H, H-5), 2.43 (dt, *J* = 2.8, 9.2, 1H, H-1), 1.94 (s, 3H, 3×CH Ada), 1.93 – 1.89 (m, 1H, C*H*H-1 butyl), 1.72 (dd, *J* = 11.9, 44.4, 6H, 3×CH_2 Ada), 1.65 – 1.52 (m, 3H, C*H*H-2 butyl, CH_2-3 butyl), 1.56 (d, *J* = 2.1, 6H, 3×CH_2 Ada), 1.45 – 1.28 (m, 2H, CH*H*-1 butyl, CH*H*-2 butyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 80.7 (C-3), 76.7 (C-2), 73.7 (C-4), 72.6 (CH_2-4 butyl), 63.7 (C-6), 62.6 (C-5), 60.9 (C-1), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.9 (CH_2-1 butyl), 31.1 (CH_2-3 butyl), 29.9 (CH Ada), 23.7 (CH_2-2 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3356, 2899, 2847, 1448, 1092, 999. $[\alpha]^{20}_D$: –3.3 (*c* 0.3, MeOH). HRMS: found 384.2746 $[M+H]^+$, calculated for $[C_{21}H_{37}NO_5+H]^+$ 384.2744.



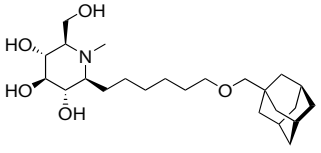
(1*S*)-1-*C*-[6-(Adamantan-1-yl-methoxy)-hexyl]-1-deoxynojirimycin (18). Compound **16** (75 mg, 98 µmol) was subjected to hydrogenolysis at atmospheric H_2 (see general procedure H) to produce **18** (30 mg, 73 µmol) as a colorless oil in 75% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.24 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.92 (dd, *J* = 3.0, 11.1, 1H, H-6a), 3.62 (dd, *J* = 6.8, 11.1, 1H, H-6b), 3.38 (t, *J* = 6.4, 2H, CH_2-6 hexyl), 3.28 – 3.20 (m, 2H, H-3, H-4), 3.12 – 3.06 (m, 1H, H-2), 2.96 (s, 2H, OCH_2-Ada), 2.71 – 2.64 (m, 1H, H-1), 2.61 – 2.54 (m, 1H, H-5), 1.94 (br s, 4H, 3×CH Ada, C*H*H-1 hexyl), 1.72 (dd, *J* = 12.1, 32.0, 6H, 3×CH_2 Ada), 1.59 – 1.51 (m, 8H, 3×CH_2 Ada, CH_2 hexyl), 1.39 (m, 7H, 3×CH_2 hexyl, CH*H*-1 hexyl).^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 80.2 (C-3), 75.9 (C-2), 72.8 (CH_2-6 hexyl), 72.6 (C-4), 62.5 (C-5), 62.5 (C-6), 60.9 (C-1), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.6 (CH_2-1 hexyl), 30.9 (CH_2 hexyl), 30.8 (CH_2-5 hexyl), 29.9 (CH Ada), 27.4 (CH_2 hexyl), 26.9 (CH_2 hexyl). IR ν_{max}(thin film)/ cm^{-1}: 3344, 2901, 2849, 1606, 1452, 1360, 1156, 1095, 753. $[\alpha]^{20}_D$: –6.5 (*c* 1.0, MeOH). HRMS: found 412.3056 $[M+H]^+$, calculated for $[C_{23}H_{41}NO_5+H]^+$ 412.3057.



(1*S*)-*N*-Methyl-1-*C*-[4-(adamantan-1-yl-methoxy)-butyl]-1-deoxy-nojirimycin (19). Argon was passed through a solution of compound **15** (62 mg, 84 µmol) and formaldehyde (1 mL; 37 wt % in water) in *n*-propanol (4 mL) for 5 min, after which a catalytic amount of Pd/C Degussa type (50 mg, 5 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 min. After stirring the reaction under atmospheric hydrogen pressure for 2 h, Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH (R_F intermediate = 0.73 (1:3; EtOAc:PE)). The filtrate was concentrated and the resulting residue was subjected to Pd/C catalyzed hydrogenolysis at atmospheric H_2 (see general procedure H). The crude product was purified by silica gel column chromatography (0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **19** (30 mg, 75 µmol) as a colorless oil in 89% yield. R_F = 0.35 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.92 (dd, *J* = 3.0, 11.8, 1H, H-6a), 3.83 (dd, *J* = 3.9, 11.9, 1H, H-6b), 3.40 (t, *J* = 6.3, 2H, CH_2-4 butyl), 3.39 (dd, *J* = 9.1, 10.0, 1H, H-4), 3.23 (dd, *J* = 9.4, 9.4, 1H, H-2), 3.17 (dd, *J* = 9.1, 9.4, 1H, H-3), 2.98 (s, 2H, OCH_2-Ada), 2.32 (s, 3H, NCH_3), 2.12 – 2.07 (m, 2H, H-1, H-5), 1.94 (s, 3H, 3×CH Ada), 1.82 – 1.66 (m, 8H, 3×CH_2 Ada, CH_2-1 butyl), 1.60 – 1.54 (m, 8H, 3×CH_2 Ada, CH_2-3 butyl), 1.51 – 1.43 (m, 2H, CH_2-2 butyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 80.6 (C-3), 72.9 (C-2), 72.7 (CH_2-4 butyl), 71.0 (C-4), 70.0 (C-5), 68.1 (C-1), 60.4 (C-6), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 36.3 (NCH_3), 35.3 (C_q Ada), 31.2 (CH_2-3 butyl), 29.9 (CH Ada), 29.7 (CH_2-1 butyl), 22.5 (CH_2-2 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3358, 2900, 2848, 1652, 1452, 1362, 1158, 1095, 1014. $[\alpha]^{20}_D$: 2.6 (*c* 0.3, MeOH). HRMS: found 398.2898 $[M+H]^+$, calculated for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.

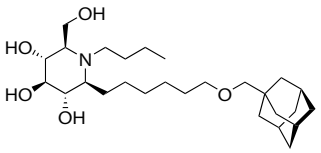


(1*S*)-*N*-Butyl-1-*C*-[4-(adamantan-1-yl-methoxy)-butyl]-1-deoxy-nojirimycin (20). Compound **15** (62 mg, 83 µmol) was *N*-butylated (see general procedure D) and the crude intermediate (R_F = 0.80 in EtOAc:PE; 1:3) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **20** (22 mg, 50 µmol) as a colorless oil in 60% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.45 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.87 (dd, *J* = 3.1, 11.8, 1H, H-6a), 3.84 (dd, *J* = 2.7, 11.8, 1H, H-6b), 3.41 (t, *J* = 6.1, 2H, CH_2-4 butyl), 3.34 (dd, *J* = 9.3, 9.3, 1H, H-4), 3.18 (dd, *J* = 9.3, 9.3, 1H, H-2), 3.11 (dd, *J* = 9.1, 9.1, 1H, H-3), 2.98 (s, 2H, OCH_2-Ada), 2.88 – 2.81 (m, 1H, NC*H*H butyl), 2.75 – 2.68 (m, 1H, NCH*H* butyl), 2.39 (dt, *J* = 3.6, 7.6, 1H, H-1), 2.33 (dt, *J* = 2.8, 9.7, 1H, H-5), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.6, 46.1, 8H, 3×CH_2 Ada, CH_2-1 butyl), 1.62 – 1.33 (m, 12H, 3×CH_2 Ada, 2×CH_2 butyl, CH_2 N-butyl), 1.30 – 1.24 (m, 2H, CH_2CH_3 N-butyl), 0.96 (t, *J* = 7.3, 3H, CH_3 N-butyl).^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 80.6 (C-3), 73.0 (C-2), 72.7 (CH_2-4 butyl), 71.6 (C-4), 65.8 (C-5), 63.7 (C-1), 60.0 (C-6), 47.3 (NCH_2 butyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 31.5 (CH_2-3 butyl), 29.9 (CH Ada), 29.0(CH_2-1 butyl), 25.4 (CH_2 N-butyl), 21.8 (CH_2-CH_3 N-butyl), 21.6 (CH_2-2 butyl), 14.6 (CH_3 N-butyl). IR ν_{max}(thin film)/ cm^{-1}: 3366, 2903, 2849, 1636, 1454, 1343, 1158, 1103. $[\alpha]^{20}_D$: –1.0 (*c* 0.1, MeOH). HRMS: found 440.3368 $[M+H]^+$, calculated for $[C_{25}H_{45}NO_5+H]^+$ 440.3370.

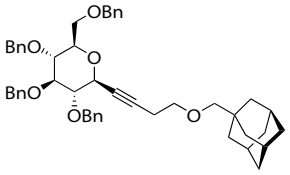


(1*S*)-*N*-Methyl-1-*C*-[6-(adamantan-1-yl-methoxy)-hexyl]-1-deoxy-nojirimycin (21). Argon was passed through a solution of compound **16** (76 mg, 99 µmol) and formaldehyde (1 mL; 37 wt % in water) in *n*-propanol (4 mL) for 5 min, after which a catalytic amount of Pd/C Degussa type (50 mg, 5 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 min. After stirring the reaction under atmospheric hydrogen pressure for 2 h, Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH (R_F intermediate = 0.75 (1:3; EtOAc:PE)). The filtrate was concentrated and the resulting residue was subjected to Pd/C catalyzed hydrogenolysis at atmospheric H_2 (see general procedure H). The crude product was purified by silica gel column

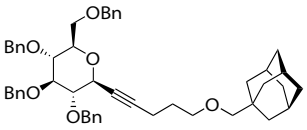
chromatography (0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **21** (29 mg, 68 µmol) as a colorless oil in 69% yield. R_F = 0.36 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 3.94 (s, 2H, CH_2-6), 3.48 (dd, *J* = 9.4, 9.4, 1H, H-4), 3.38 (t, *J* = 6.4, 2H, CH_2-6 hexyl), 3.34 – 3.25 (m, 2H, H-2, H-3), 2.97 (s, 2H, OCH_2-Ada), 2.56 (s, 3H, NCH_3), 2.50 – 2.42 (s, 2H, H-1, H-5), 1.95 (s, 3H, 3×CH Ada), 1.80 – 1.65 (m, 8H, 3×CH_2 Ada, CH_2 hexyl), 1.60 – 1.54 (m, 8H, 3×CH_2 Ada, CH_2-5 hexyl), 1.50 – 1.32 (m, 6H, 3×CH_2 hexyl). ^{13}C NMR (100 MHz, MeOD+$CDCl_3$) δ 81.1 (OCH_2-Ada), 77.7 (C-3), 70.8 (CH_2-6 hexyl), 70.5 (C-2), 67.9 (C-4), 67.8 (C-5), 66.3 (C-1), 57.0 (C-6), 38.9 (CH_2 Ada), 36.4 (CH_2 Ada), 34.3 (NCH_3), 33.2 (C_q Ada), 28.9 (CH_2 hexyl), 28.7 (CH_2 hexyl), 27.7 (CH Ada, CH_2 hexyl), 25.3 (CH_2 hexyl), 24.7 (CH_2 hexyl). IR ν_{max}(thin film)/ cm^{-1}: 3324, 2902, 2849, 1637, 1452, 1362, 1158, 1102, 1025, 753. $[\alpha]^{20}_D$: –1.6 (*c* 1.0, MeOH). HRMS: found 426.3212 $[M+H]^+$, calculated for $[C_{24}H_{43}NO_5+H]^+$ 426.3214.



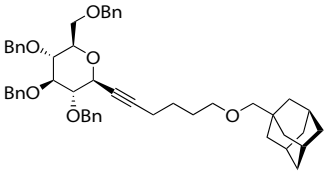
(1*S*)-*N*-Butyl-1-*C*-[6-(adamantan-1-yl-methoxy)-hexyl]-1-deoxy-nojirimycin (22). Compound **16** (77 mg, 100 µmol) was *N*-butylated (see general procedure D) and the crude intermediate (R_F = 0.77 in EtOAc:PE; 1:3) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **22** (31 mg, 66 µmol) as a colorless oil in 66% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.45 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.98 (d, *J* = 12.0, 1H, H-6a), 3.88 (d, *J* = 12.0, 1H, H-6b), 3.53 – 3.43 (m, 1H, H-4), 3.38 (t, *J* = 6.1, 2H, CH_2-5 hexyl), 3.34 – 3.29 (m, 1H, H-2), 3.28 – 3.20 (m, 1H, H-3), 3.16 – 3.09 (m, 1H, NC*H*H butyl), 3.01 – 2.93 (m, 3H, NCH*H* butyl, OCH_2-Ada), 2.80 – 2.68 (m, 2H. H-1, H-5), 1.94 (s, 3H, 3×CH Ada), 1.88 – 1.21 (m, 26H, 6×CH_2 Ada, 5×CH_2 hexyl, 2×CH_2 N-butyl), 0.98 (t, *J* = 7.2, 3H, CH_3 butyl).^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 79.5 (C-3), 72.7 (CH_2-6 hexyl), 72.6 (C-2), 70.1 (C-4), 66.7 (C-5), 65.1 (C-1), 58.4 (C-6), 48.5 (NCH_2 butyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 31.0 (CH_2), 30.8 (2×CH_2), 29.9 (CH Ada), 29.2 (CH_2), 27.4 (CH_2), 26.1 (CH_2), 21.4 (*C*H_2-CH_3 N-butyl), 14.3 (CH_3 N-butyl). IR ν_{max}(thin film)/ cm^{-1}: 3364, 2902, 2847, 1720 1453, 1366, 1258, 1011, 926. $[\alpha]^{20}_D$: –1.0 (*c* 0.2, MeOH). HRMS: found 468.3679 $[M+H]^+$, calculated for $[C_{27}H_{50}NO_5+H]^+$ 468.3684.



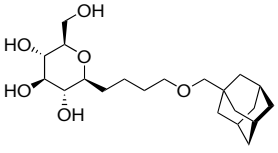
4-(Adamantan-1-yl-methoxy)-1-*C*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-but-1-yn (24). Compound **13** (100 mg, 132 µmol) was subjected to general procedure B to produce **24** (86 mg, 116 µmol) in 89% yield after silica gel column purification (0% » 5% acetone in toluene). R_F = 0.50 (9:1; toluene:EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.09 (m, 20H, H, H_{Ar} Bn), 5.02 (d, *J* = 10.5, 1H, C*H*H Bn), 4.91 (d, *J* = 10.9, 1H, C*H*H Bn), 4.83 – 4.77 (m, 3H, CH_2 Bn, CH*H* Bn), 4.60 (d, *J* = 12.2, 1H, C*H*H Bn), 4.54 – 4.49 (m, 2H, 2×CH*H* Bn), 4.03 (dt, *J* = 2.0, 9.0, 1H, H-1), 3.73 (dd, *J* = 1.6, 10.7, 1H, H-6a), 3.67 (dd, *J* = 4.4, 10.8, 1H, H-6b), 3.64 – 3.55 (m, 3H, H-2, H-3, H-4), 3.50 (t, *J* = 7.3, 2H, CH_2-4 butenyl), 3.42 (ddd, *J* = 1.8, 4.2, 9.1, 1H, H-5), 2.97 – 2.93 (m, 2H, OCH_2-Ada), 2.51 (dt, *J* = 1.8, 7.3, 2H, CH_2-3 butenyl), 1.92 (s, 3H, 3×CH Ada), 1.65 (dd, *J* = 11.9, 45.5, 6H, 3×CH_2 Ada), 1.49 (d, *J* = 2.4, 6H, 3×CH_2 Ada). ^{13}C NMR (151 MHz, CDCl3) δ 138.7, 138.3, 138.2, 138.2 (4×C_q Bn), 128.6, 128.6, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8 (CH_{Ar} Bn), 86.2 (C-3), 84.1 (C_q butynyl), 82.7 (C-2), 82.2 (OCH_2-Ada), 79.1 (C-5), 78.4 (C_q butynyl), 77.9 (C-4), 75.9, 75.6, 75.3, 73.7 (4×CH_2 Bn), 70.3 (C-1), 69.8 (CH_2-4 butynyl), 69.0 (C-6), 39.8 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 28.4 (CH Ada), 20.3 (CH_2-3 butynyl). IR ν_{max}(thin film)/ cm^{-1}: 3036, 2901, 2849, 1734, 1497, 1452, 1360, 1209, 1094, 1063, 1028, 1003, 733, 696. $[\alpha]^{20}_D$: –1.7 (*c* 0.6, $CHCl_3$). HRMS: found 758.4416 $[M+NH_4]^+$, calculated for $[C_{49}H_{56}O_6+NH_4]^+$ 758.4415.



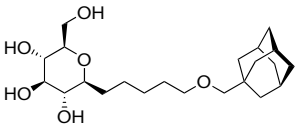
5-(Adamantan-1-yl-methoxy)-1-*C*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-pent-1-yn (25). Compound **23** (250 mg, 337 µmol) was subjected to general procedure B to produce **25** (201 mg, 266 µmol) in 79% yield after silica gel column purification (0% » 5% acetone in toluene). R_F = 0.55 (9:1; toluene:EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 – 7.08 (m, 20H, H_{Ar} Bn), 5.07 – 4.46 (m, 8H, 4×CH_2 Bn), 4.05 (d, *J* = 8.6, 1H, H-1), 3.78 – 3.53 (m, 6H, H-2, H-3, H-4, H-5, CH_2-6), 3.41 (t, *J* = 6.0, 2H, CH_2-5 pentenyl), 2.90 (s, 2H, OCH_2-Ada), 2.35 (dt, *J* = 1.6, 7.1, 2H, CH_2-3 pentenyl), 1.93 (s, 3H, 3×H Ada), 1.84 – 1.55 (m, 8H, 3×CH_2 Ada, CH_2-4 pentenyl), 1.49 (d, *J* = 2.7, 6H, 3×CH_2 Ada). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 138.3, 138.2, 138.1 (4×C_q Bn), 128.5, 128.4, 128.2, 128.2, 128.0, 128.0, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 86.7 (C_q pentynyl), 86.1 (C-3), 82.7 (C-2), 81.9 (OCH_2-Ada), 79.0 (C-5), 77.8 (C-4), 77.4 (C_q pentynyl), 75.8, 75.4, 75.1, 73.6 (4×CH_2 Bn), 70.3 (C-1), 69.9 (CH_2-5 pentynyl), 68.9 (C-6), 39.8 (CH_2 Ada), 37.3 (CH_2 Ada), 34.1 (C_q Ada), 28.7 (CH_2-4 pentynyl), 28.3 (CH Ada), 15.9 (CH_2-3 pentynyl). IR ν_{max}(thin film)/ cm^{-1}: 3033, 2901, 2848, 1724, 1452, 1361, 1269, 1090, 1065, 1026, 735, 696. $[\alpha]^{20}_D$: 3.5 (*c* 0.4, $CHCl_3$). HRMS: found 772.4572 $[M+NH_4]^+$, calculated for $[C_{50}H_{58}O_6+NH_4]^+$ 772.4572.



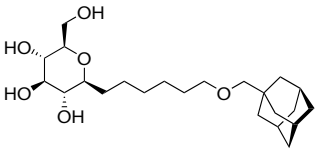
6-(Adamantan-1-yl-methoxy)-1-*C*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-hex-1-yn (26). Compound **14** (428 mg, 0.56 mmol) was subjected to general procedure B to produce **26** (257 mg, 0.33 mmol) in 60% yield after silica gel column purification (0% » 5% acetone in toluene). R_F = 0.65 (9:1; toluene:EtOAc). ^{1}H NMR (300 MHz, C_6D_6) δ 7.12 – 6.69 (m, 20H, H_{Ar} Bn), 4.77 (d, *J* = 11.0, 1H, CHH Bn), 4.62 – 4.41 (m, 4H, CH_2 Bn, CH*H* Bn, C*H*H Bn), 4.25 (d, *J* = 11.3, 1H, CH*H* Bn), 4.15 (d, *J* = 12.1, 1H, C*H*H Bn), 4.04 (d, *J* = 12.1, 1H, CH*H* Bn), 3.76 (dt, *J* = 1.8, 9.3, 1H, H-1), 3.42 (dd, *J* = 8.9, 9.6, 1H, H-4), 3.36 – 3.27 (m, 3H, H-2, CH_2-6), 3.22 (dd, *J* = 8.8, 8.9, 1H, H-3), 2.96 (dt, *J* = 2.7, 10.1, 1H, H-5), 2.86 (t, *J* = 5.8, 2H, CH_2-6 hexynyl), 2.52 (s, 2H, OCH_2-Ada), 1.78 (dt, *J* = 1.4, 6.5, 2H, CH_2-3 hexynyl), 1.60 (s, 3H, CH Ada), 1.38 – 1.18 (m, 16H, 6×CH_2 Ada, 2×CH_2 hexenyl). ^{13}C NMR (75 MHz, C_6D_6) δ 139.4, 139.1, 139.0, 138.8 (4×C_q Bn), 128.5, 128.4, 128.4, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 127.5 (CH_{Ar} Bn), 86.4 (C_q hexynyl), 86.3 (C-3), 83.2 (C-2), 82.0 (OCH_2-Ada), 79.3 (C-5), 78.6 (C_q pentynyl), 78.1 (C-4), 75.4, 75.2, 74.9, 73.5 (4×CH_2 Bn), 70.9 (CH_2-6 hexynyl), 70.6 (C-1), 69.3 (C-6), 40.0 (CH_2 Ada), 37.5 (CH_2 Ada), 34.2 (C_q Ada), 29.1(CH_2 hexynyl), 28.6 (CH Ada), 25.6 (CH_2 hexynyl), 18.8 (CH_2-3 hexynyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2901, 2848, 1497, 1453, 1360, 1294, 1210, 1155, 1091, 1064, 1027, 1005, 910, 734, 696. $[\alpha]^{20}_D$: 2.6 (*c* 1.0, $CHCl_3$). HRMS: found 786.4730 $[M+NH_4]^+$, calculated for $[C_{51}H_{60}O_6+NH_4]^+$ 786.4728.



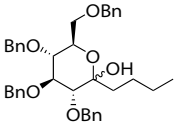
1-(Adamantan-1-yl-methoxy)-4-*C*-(β-D-glucopyranosyl)-butane (27). Compound **24** (86 mg, 116 µmol) was subjected to Pd/C catalyzed hydrogenolysis at atmospheric H_2 (see general procedure H). The resulting residue was purified by silica gel column chromatography (0% » 15% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **27** (36 mg, 94 µmol) as a colorless oil in 81% yield. R_F = 0.29 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.83 (dd, *J* = 2.3, 11.8, 1H, H-6a), 3.63 (dd, *J* = 5.7, 11.8, 1H, H-6b), 3.39 (t, *J* = 6.3, 2H, CH_2-4 butyl), 3.30 (dd, *J* = 8.8, 9.2, 1H, H-3), 3.25 (dd, *J* = 9.2, 9.4, 1H, H-4), 3.18 (ddd, *J* = 2.3, 5.6, 9.4, 1H, H-5), 3.15 – 3.09 (m, 1H, H-1), 3.04 (dd, *J* = 8.8, 9.3, 1H, H-2), 2.97 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.91 – 1.83 (m, 1H, C*H*H-1 butyl), 1.72 (dd, *J* = 11.8, 44.2, 6H, 3×CH_2 Ada), 1.66 – 1.52 (m, 9H, 3×CH_2 Ada, CH_2-3 butyl, C*H*H butyl), 1.48 – 1.39 (m, 2H, CH*H*-1 butyl, CH*H* butyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 81.7 (C-5), 81.0 (C-1), 80.0 (C-3), 75.6 (C-2), 72.9 (CH_2-6 hexyl), 72.2 (C-4), 63.3 (C-6), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.9 (CH_2-1 butyl), 30.9 (CH_2-3 butyl), 29.9 (CH Ada), 23.3 (CH_2 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3365, 2901, 2848, 1593, 1453, 1342, 1092, 1013. $[\alpha]^{20}_D$: –1.0 (*c* 0.2, MeOH). HRMS: found 385.2586 $[M+H]^+$, calculated for $[C_{21}H_{36}O_6+H]^+$ 385.2585.



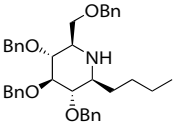
1-(Adamantan-1-yl-methoxy)-5-*C*-(β-D-glucopyranosyl)-pentane (28). Compound **25** (95 mg, 126 µmol) was subjected to Pd/C catalyzed hydrogenolysis at atmospheric H_2 (see general procedure H). The resulting residue was purified by silica gel column chromatography (0% » 15% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **28** (45 mg, 112 µmol) as a colorless oil in 89% yield. R_F = 0.32 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.83 (dd, *J* = 2.3, 11.8, 1H, H-6a), 3.63 (dd, *J* = 5.7, 11.9, 1H, H-6b), 3.38 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 3.31 – 3.28 (dd, *J* = 8.8, 9.1, 1H, H-3), 3.25 (dd, *J* = 9.1, 9.4, 1H, H-4), 3.17 (ddd, *J* = 2.3, 5.7, 9.4, 1H, H-5), 3.15 – 3.09 (m, 1H, H-1), 3.04 (dd, *J* = 8.8, 9.3, 1H, H-2), 2.97 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.90 – 1.82 (m, 1H, C*H*H-1 pentyl), 1.72 (dd, *J* = 11.7, 44.9, 6H, 3×CH_2 Ada), 1.65 – 1.51 (m, 9H, 3×CH_2 Ada, CH_2-4 pentyl, C*H*H pentyl), 1.45 – 1.31 (m, 4H, CH*H*-1 pentyl, CH_2 pentyl, CH*H* pentyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 81.7 (C-5), 81.0 (C-1), 80.0 (C-3), 75.6 (C-2), 72.8 (CH_2-5 pentyl), 72.1 (C-4), 63.3 (C-6), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 33.0 (CH_2-1 pentyl), 30.8 (CH_2-4 pentyl), 29.9 (CH Ada), 27.6 (CH_2 pentyl), 26.5 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3362, 2902, 2849, 1453, 1362, 1091, 1016. $[\alpha]^{20}_D$: –12.0 (*c* 0.2, MeOH). HRMS: found 399.2739 $[M+H]^+$, calculated for $[C_{22}H_{38}O_6+H]^+$ 399.2741.



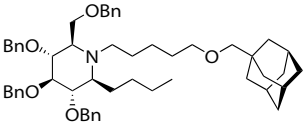
1-(Adamantan-1-yl-methoxy)-6-*C*-(β-D-glucopyranosyl)-hexane (29). Compound **26** (75 mg, 97 µmol) was subjected to Pd/C catalyzed hydrogenolysis at atmospheric H_2 (see general procedure H). The resulting residue was purified by silica gel column chromatography (0% » 15% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **29** (36 mg, 87 µmol) as a colorless oil in 90% yield. R_F = 0.33 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.83 (dd, *J* = 2.4, 11.9, 1H, H-6a), 3.63 (dd, *J* = 5.7, 11.9, 1H, H-6b), 3.37 (t, *J* = 6.5, 2H, CH_2-6 hexyl), 3.32 – 3.28 (dd, *J* = 8.7, 9.2, 1H, H-3), 3.25 (dd, *J* = 9.2, 9.4, 1H, H-4), 3.18 (ddd, *J* = 2.4, 5.7, 9.4, 1H, H-5), 3.14 – 3.09 (m, 1H, H-1), 3.04 (dd, *J* = 8.7, 9.4, 1H, H-2), 2.96 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.88 – 1.81 (m, 1H, C*H*H-1 hexyl), 1.72 (dd, *J* = 11.7, 44.9, 6H), 1.60 – 1.53 (m, 9H, 3×CH_2 Ada, CH_2-5 hexyl, C*H*H hexyl), 1.45 – 1.29 (m, 6H, CH*H*-1 hexyl, 2×CH_2 hexyl, CH*H* hexyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 81.7 (C-5), 81.0 (C-1), 80.0 (C-3), 75.6 (C-2), 72.9 (CH_2-6 hexyl), 72.2 (C-4), 63.3 (C-6), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 33.0 (CH_2-1 hexyl), 30.9 (CH_2 hexyl), 30.8 (CH_2-5 hexyl), 29.9 (CH Ada), 27.5 (CH_2 hexyl), 26.6 (CH_2 hexyl). IR ν_{max}(thin film)/ cm^{-1}: 3361, 2901, 2849, 1453, 1361, 1092, 1012. $[\alpha]^{20}_D$: –9.2 (*c* 1.0, MeOH). HRMS: found 413.2896 $[M+H]^+$, calculated for $[C_{23}H_{40}O_6+H]^+$ 413.2898.



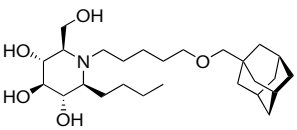
α/β-Mixture of 1-*C*-butyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl (30). A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (1.02 g, 1.9 mmol) in THF (3 mL) was added to a cooled (–50 °C) solution of BuLi (0.59 mL, 0.95 mmol, 1.6M in toluene) in THF (10 mL). The reaction mixture was stirred at –50 °C for 2 h. The reaction mixture was quenched (sat aq NH_4Cl), warmed to rt and poured into sat aq NH_4Cl (150 mL). The aqueous layer was extracted with Et_2O (3×150 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 20% EtOAc in PE) to give **30** (409 mg, 0.69 mmol) in 72% yield as a colorless oil. R_F = 0.45; (1:3; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 20H, H_{Ar} Bn), 4.96 – 4.41 (m, 9H, 2×CH_2 Bn, H-6a), 4.12 – 3.57 (m, 4H, H-3, H-4, H-5, H-6b), 3.43 (d, *J* = 9.2, 1H, H-2), 2.57 (s, 1H, OH-1), 1.70 – 1.50 (m, 2H, CH_2 butyl), 1.49 – 1.13 (m, 4H, 2×CH_2 butyl), 0.86 (t, *J* = 6.8, 3H, CH_3 butyl). NMR (50 MHz, $CDCl_3$) δ 138.9, 138.7, 138.5, 138.2 (4×C_q Bn), 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 127.9, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 98.6 (C_q-1), 84.1, 81.6, 76.6 (C-2, C-3, C-4), 75.8, 75.6, 75.1, 73.5 (2×CH_2 Bn), 71.8 (C-5), 69.0 (C-6), 38.6 (CH_2 butyl), 24.9 (CH_2 butyl), 23.0 (CH_2 butyl), 14.3 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2911, 2860, 1460, 1350, 1360, 1211, 1008, 736, 694. $[\alpha]^{20}_D$: 0.7 (*c* 2.9, $CHCl_3$). HRMS: found 596.3140 $[M+H]^+$, calculated for $[C_{38}H_{44}O_6+H]^+$ 596.3138.



(1*S*)-1-*C*-Butyl-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (31). Compound **30** (600 mg, 1.0 mmol) was subjected to a tandem reduction/Swern oxidation/double reductive amination procedure (see general procedure C) to give **31** (387 mg, 0.67 mmol) as a colorless oil in 67% yield after silica gel column chromatography (0% » 20% EtOAc in toluene). R_F diol = 0.33; R_F diketon = 0.77; R_F aza-*C*-glycoside = 0.56 (3:1; toluene:EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.16 (m, 20H, H_{Ar} Bn), 4.93 – 4.88 (m, 3H, C*H*H Bn, CH_2 Bn), 4.84 (d, *J* = 10.9, 1H, C*H*H Bn), 4.64 (d, *J* = 10.9, 1H, CH*H* Bn), 4.52 – 4.45 (m, 3H, CH*H* Bn, CH_2 Bn), 3.71 (dd, *J* = 2.4, 9.0, 1H, H-6a), 3.60 (dd, *J* = 9.1, 9.3, 1H, H-3), 3.45 (dd, *J* = 7.1, 9.0, 1H, H-6b), 3.35 (dd, *J* = 9.1, 9.4, 1H, H-4), 3.14 (dd, *J* = 9.1, 9.3, 1H, H-2), 2.78 (ddd, *J* = 2.4, 7.1, 9.4, 1H, H-5), 2.57 – 2.53 (m, 1H, H-1), 1.88 – 1.81 (m, 1H, C*H*H-2 butyl), 1.41 – 1.24 (m, 4H, CH_2-1 butyl, CH*H*-2 butyl, CH_2-3 butyl), 0.89 (t, *J* = 6.9, 3H, CH_3-4 butyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.9, 138.6, 138.4, 138.2 (4×C_q Bn), 128.6, 128.4, 128.2, 128.2, 128.0, 127.9, 127.9, 127.9, 127.7, 127.3 (CH_{Ar} Bn), 88.5 (C-3), 84.4(C-2), 80.9 (C-4), 75.8, 75.6, 75.2, 73.5 (4×CH_2 Bn), 70.7 (C-6), 59.2, 59.2 (C-1, C-5), 31.8 (CH_2-2 butyl), 28.2, 23.1 (CH_2-1 butyl, CH_2-3 butyl), 14.2 (CH_3-4 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2924, 2862, 1458, 1358, 1312, 1211, 1072, 1026, 1003, 741, 694. $[\alpha]^{20}_D$: 11.9 (*c* 2.2, $CHCl_3$). HRMS: found 580.3417 $[M+H]^+$, calculated for $[C_{38}H_{45}NO_4+H]^+$ 580.3421.

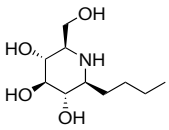


(1*S*)-*N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-*C*-butyl-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (32). A solution of **31** (210 mg, 360 µmol, see Chapter 5 for synthesis) and 5-(adamantan-1-yl-methoxy)-1-pentanal (**9**, 900 mg, 3.6 mmol, see Chapter 2 for synthesis) in acetonitrile/MeOH (1.8 mL, 5/ 1, v/ v) was acidified to pH 5-6 with AcOH (10 µL). Sodium sulfate (100 mg) and sodium cyanoborohydride (90 mg, 1.44 mmol) were added and the reaction mixture was heated at 75 °C for 18 h. The mixture was diluted with sat aq $NaHCO_3$ (20 mL) and extracted with Et_2O (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was subjected to Pd/C catalyzed hydrogenolysis at 4 bar H_2 (general procedure H). Purification by silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH) gave **32** (230 mg, 283 µmol) as a colorless oil in 79% yield. R_F = 0.75 (1:3; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 20H, H_{Ar} Bn), 4.95 – 4.79 (m, 4H, 2×CH_2 Bn), 4.67 – 4.39 (m, 4H, 2×CH_2 Bn), 4.01 – 3.26 (m, 8H, H-2, H-3, H-4, CH_2-6, CH_2-5 pentyl), 2.94 (m, 2H, OCH_2-Ada), 2.78 – 2.45 (m, 4H, NCH_2-1 pentyl, H-1, H-5), 1.95 (s, 3H, 3×CH Ada), 1.78 – 1.07 (m, 24H, 6×CH_2 Ada, 3×CH_2 butyl, 3×CH_2 pentyl), 0.89 (t, *J* = 6.9, 3H). NMR (50 MHz, $CDCl_3$) δ 139.1, 138.8, 138.2 (C_q Bn), 128.5, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 88.7 (C-3), 82.1 (OCH_2-Ada), 80.6(C2), 78.8 (C4), 75.3, 75.1, 73.5, 71.7 (4×CH_2 Bn), 67.7, 65.0 (C-6, CH_2-5 pentyl), 63.2, 62.5 (C1, C-5), 46.9 (NCH_2-1 pentyl), 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.3 (Cq Ada), 29.7, 29.6 (CH_2 pentyl/butyl), 28.5 (CH Ada), 27.2, 24.0, 23.5 (CH_2 pentyl/butyl), 14.5 (CH_3-4 butyl). IR ν_{max}(thin film)/ cm^{-1}: 2900, 2847, 1450, 1358, 1065, 941, 841, 733, 694. $[\alpha]^{20}_D$: –2.3 (*c* 1.2, $CHCl_3$). HRMS: found 814.5406 $[M+H]^+$, calculated for $[C_{54}H_{71}NO_5+H]^+$ 814.5405.

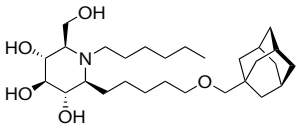


(1*S*)-*N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-*C*-butyl-1-deoxynojirimycin (33). Compound **32** (76 mg, 93 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **33** (36 mg, 79 µmol) as a colorless oil in 85% yield after purification (silica gel: 0% » 15% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.44 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.92 (dd, *J* = 2.7, 11.9, 1H, H-6a), 3.86 (dd, *J* = 2.5, 11.9, 1H, H-6b), 3.41 – 3.34 (m, 3H, H-4, CH_2-5 pentyl), 3.23 (dd, *J* = 9.4, 9.4, 1H, H-2), 3.16 (dd, *J* = 9.1, 9.1, 1H, H-3), 2.98 – 2.92 (m, 3H, OCH_2-Ada, NC*H*H-1 pentyl), 2.83 – 2.73 (m, 1H, NCH*H*-1 pentyl), 2.52 (d, *J* = 4.8, 1H, H-1), 2.47 (d, *J* = 8.1, 1H, H-5), 1.95 (s, 3H, 3×CH Ada), 1.84 – 1.66 (m, 7H, 3×CH_2 Ada, C*H*H-1 butyl), 1.62 – 1.53 (m, 9H, 3×CH_2 Ada, CH*H*-1 butyl, CH_2-4 pentyl), 1.45 – 1.29 (m, 8H, CH_2-2 butyl, CH_2-3 butyl, CH_2-2 pentyl, CH_2-3 pentyl), 0.95 (t, *J* = 7.2, 3H, CH_3-4 butyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 80.2 (C-3), 72.9 (C-2), 72.4 (CH_2-5 pentyl), 71.1 (C-4), 66.1 (C-5), 64.2 (C-1), 59.4 (C-6), 48.0 (NCH_2-1

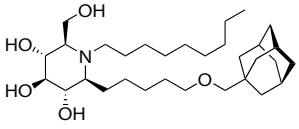
pentyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.6 (CH_2-4 pentyl), 29.9 (CH Ada), 28.9 (CH_2-1 butyl), 27.4 (CH_2-2 pentyl), 25.1, 24.5, 23.2 (3×CH_2 butyl, CH_2-3 pentyl), 14.6 (CH_3-4 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3348, 2901, 2847, 1450, 1366, 1234, 1096, 1003, 833. $[\alpha]^{20}_D$: –1.5 (*c* 0.2, MeOH). HRMS: found 454.3523 $[M+H]^+$, calculated for $[C_{26}H_{48}NO_5+H]^+$ 454.3527.



(1*S*)-1-*C*-Butyl-1-deoxynojirimycin (34). Compound **31** (60 mg, 104 µmol) was subjected to hydrogenolysis at atmospheric H_2 (see general procedure H) to furnish **34** (23 mg, 100 µmol) as a colorless oil in 97% yield after purification (silica gel: 10% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.12 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.00 – 3.86 (m, 2H, CH_2-6), 3.60 – 3.51 (m, 1H, H-4), 3.42 – 3.33 (m, 2H, H-2, H-3), 3.09 – 3.00 (m, 1H, H-5), 3.00 – 2.94 (m, 1H, H-1), 2.05 – 1.95 (m, 1H, C*H*H-1 butyl), 1.72 – 1.61 (m, 1H, CH*H*-1 butyl), 1.60 – 1.46 (m, 2H, CH_2-2 butyl), 1.46 – 1.33 (m, 2H, CH_2-3 butyl), 0.97 (t, *J* = 7.0, 3H, CH_3-4 butyl). ^{13}C NMR (100 MHz, MeOD) δ 78.7 (C-3), 73.6 (C-2), 69.4 (C-4), 62.3 (C-5), 60.9 (C-1), 59.0 (C-6), 31.1 (CH_2-1 butyl), 29.1 (CH_2-2 butyl), 24.0 (CH_2-3 butyl), 14.3 (CH_3-4 butyl).IR ν_{max}(thin film)/ cm^{-1}: 3331, 2959, 2932, 2870, 1636, 1436, 1380, 1098, 1014. $[\alpha]^{20}_D$: –6.1 (*c* 0.5, MeOH). HRMS: found 220.1545 $[M+H]^+$, calculated for $[C_{10}H_{21}NO_4+H]^+$ 220.1543.

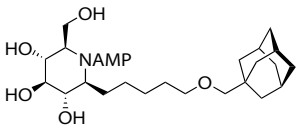


(1*S*)-*N*-Hexyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (36). Compound **35** (292 mg, 220 µmol) was *N*-alkylated (see general procedure D) and the crude intermediate was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **36** (75 mg, 156 µmol) as a colorless oil in 71% yield after purification (silica gel: 0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.49 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.88 (dd, *J* = 3.1, 11.8, 1H, H-6a), 3.84 (dd, *J* = 2.8, 11.7, 1H, H-6b), 3.39 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 3.34 (dd, *J* = 9.3, 9.6, 1H, H-4), 3.18 (dd, *J* = 9.0, 9.2, 1H, H-2), 3.11 (dd, *J* = 9.0, 9.3, 1H, H-3), 2.97 (s, 2H, OCH_2-Ada), 2.88 – 2.79 (m, 1H, NC*H*H hexyl), 2.73 – 2.64 (m, 1H, NCH*H* hexyl), 2.39 (dt, *J* = 3.5, 9.2, 1H, H-1), 2.33 (dt, *J* = 2.9, 9.6, 1H, H-5), 1.95 (s, 3H, 3×CH Ada), 1.83 – 1.67 (m, 7H, 3×CH_2 Ada, CH*H*-1 pentyl), 1.66 – 1.51 (m, 9H, 3×CH_2 Ada, CH*H*-1 pentyl, CH_2-4 pentyl), 1.41 – 1.18 (m, 14H, CH_2-2 pentyl, CH_2-3 pentyl, CH_2-4 pentyl, 4×CH_2 hexyl), 0.91 (t, *J* = 7.0, 3H, CH_3 hexyl). ^{13}C NMR (150 MHz, MeOD) δ 83.1 (OCH_2-Ada), 80.6 (C-3), 73.1 (C-2), 72.6 (CH_2-5 pentyl), 71.7 (C-4), 65.9 (C-5), 63.8 (C-1), 60.1 (C-1), 47.7 (NCH_2 hexyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 33.1 (CH_2 hexyl), 30.8 (CH_2-4 pentyl), 29.9 (CH Ada), 29.2 (CH_2-1 pentyl), 28.4, 28.0, 24.6, 24.0, 23.4 (2×CH_2 pentyl, 3×CH_2 hexyl), 14.6 (CH_3 hexyl). IR ν_{max}(thin film)/ cm^{-1}: 3366, 2903, 2849, 1592, 1454, 1358, 1157, 1098, 1012. $[\alpha]^{20}_D$: –2.3 (*c* 0.3, MeOH). HRMS: found 482.3835 $[M+H]^+$, calculated for $[C_{28}H_{51}NO_5+H]^+$ 482.3840.

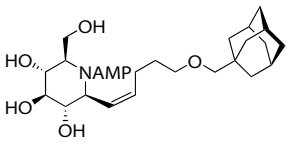


(1*S*)-*N*-Nonyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (37). Compound **35** (35 mg, 46 µmol) was *N*-alkylated (see general procedure D) and the crude intermediate was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **37** (15 mg, 29 µmol) as a colorless oil in 63% yield after purification (silica gel: 0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.53 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.88 (dd, *J* = 3.2, 11.8, 1H, H-6a), 3.84 (dd, *J* = 2.9, 11.8, 1H, H-6b), 3.39 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.35 (dd, *J* = 9.3, 9.3, 1H, H-4), 3.19 (dd, *J* = 9.3, 9.3, 1H, H-2), 3.13 (dd, *J* = 9.0, 9.0, 1H, H-3), 2.97 (s, 2H, OCH_2-Ada), 2.89 – 2.80 (m, 1H, NC*H*H nonyl), 2.74 – 2.66 (m, 1H, NCH*H* nonyl), 2.42 (dt, *J* = 3.6, 7.6, 1H, H-1), 2.37 (dt, *J* = 2.8, 9.7, 1H, H-5), 1.95 (s, 3H, 3×CH Ada), 1.83 – 1.66 (m, 7H, 3×CH_2 Ada, CH*H*-1 pentyl), 1.66 – 1.55 (m, 9H, 3×CH_2 Ada, CH*H*-1 pentyl, CH_2-4 pentyl), 1.49 – 1.36 (m, 6H, 2×CH_2 pentyl, NCH_2CH_2 nonyl), 1.36 – 1.18 (m, 12H, 6×CH_2 nonyl), 0.90 (t, *J* = 7.0, 3H, CH_3 nonyl).^{13}C NMR (150 MHz, MeOD) δ 83.2, 80.5 (C-3), 73.1(C-2), 72.6 (CH_2-5 pentyl), 71.6 (C-4), 66.0 (C-5), 64.0 (C-1), 60.1 (C-6), 47.8 (NCH_2

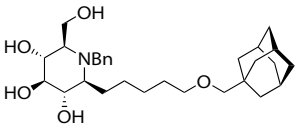
nonyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 33.2 (CH_2 nonyl), 30.9 (CH_2 nonyl), 30.8 (CH_2-4 pentyl), 30.7, 30.6 (2×CH_2 nonyl), 29.9 (CH Ada), 29.3 (CH_2-1 pentyl), 28.6, 28.0, 24.8, 23.9, 23.6 (2×CH_2 pentyl, 3×CH_2 nonyl), 14.6 (CH_3 nonyl). IR ν_{max}(thin film)/ cm^{-1}: 3395, 2903, 2850, 1622, 1456, 1361, 1259, 1110, 1037. $[\alpha]^{20}_D$: –3.0 (*c* 0.2, MeOH). HRMS: found 524.4304 $[M+H]^+$, calculated for $[C_{31}H_{58}NO_5+H]^+$ 524.4310.



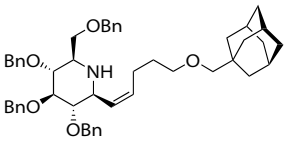
(1*S*)-*N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (38). A solution of **35** (271 mg, 0.36 mmol, see Chapter 5 for synthesis) and 5-(adamantan-1-yl-methoxy)-1-pentanal (**9**, 900 mg, 3.6 mmol, see Chapter 2 for synthesis) in acetonitrile/MeOH (1.8 mL, 5/ 1, v/ v) was acidified to pH 5-6 with AcOH (10 µL). Sodium sulfate (100 mg) and sodium cyanoborohydride (90 mg, 1.44 mmol) were added and the reaction mixture was heated at 75 °C for 18 h. The mixture was diluted with sat aq $NaHCO_3$ (20 mL) and extracted with Et_2O (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Half of the resulting crude residue was subjected to Pd/C catalyzed hydrogenolysis at 4 bar H_2 (see general procedure H). The resulting crude product was purified by silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **38** (90 mg, 142 µmol) as a colorless oil in 79% yield. R_F = 0.57 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.89 (dd, *J* = 2.9, 11.9, 1H, H-6a), 3.85 (dd, *J* = 2.5, 11.8, 1H, H-6b), 3.41 – 3.37 (m, 4H, 2×CH_2-5 pentyl), 3.35 (dd, *J* = 8.8, 10.2, 1H, H-4), 3.19 (t, *J* = 9.3, 1H, H-2), 3.12 (t, *J* = 9.0, 1H, H-3), 2.97 (s, 4H), 2.92 – 2.85 (m, 1H, NCH*H*-1 pentyl), 2.75 – 2.66 (m, 1H, NCH*H*-1 pentyl), 2.45 – 2.40 (m, 1H, H-1), 2.38 – 2.32 (m, 1H, H-5), 1.95 (s, 6H, 6×CH Ada), 1.87 – 1.66 (m, 14H, 6×CH_2 Ada, 2×CH*H*-1 pentyl), 1.66 – 1.53 (m, 18H, 6×CH_2 Ada, 2×CH*H*-1 pentyl, 2×CH_2-4 pentyl), 1.52 – 1.26 (m, 8H, 4×CH_2 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2, 83.1(2×OCH_2-Ada), 80.5 (C-3), 73.0 (C-2), 72.5, 72.4 (2×CH_2-5 pentyl), 71.4 (C-4), 65.9 (C-5), 63.7 (C-1), 59.8 (C-6), 47.8 (NCH_2-1 pentyl), 41.1, 41.0 (2×CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.8, 30.6 (2×CH_2-4 pentyl), 29.9 (CH Ada), 29.1(CH_2 pentyl), 28.1(CH_2 pentyl), 25.2 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3368, 2902, 2848, 1452, 1157, 1111. $[\alpha]^{20}_D$: 0.9 (*c* 0.2, MeOH). HRMS: found 632.4881 $[M+H]^+$, calculated for $[C_{38}H_{65}NO_6+H]^+$ 632.4885.



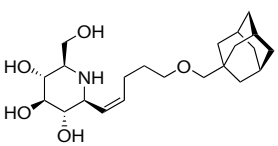
(1*S*)-*N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-*C*-[(*Z*)-5-(adamantan-1-yl-methoxy)-pent-1-enyl]-1-deoxynojirimycin (39). The other half of the crude product residue from the reductive amination towards **38** was subjected to Pd/C catalyzed hydrogenolysis at atmospheric H_2 pressure (see general procedure H). This resulted in a product mixture of **38** and **39**. Purification by silica gel column chromatography produced **38** (60 mg, 95 µmol) in 53% and *Z*-alkene **39** (47 mg, 74 µmol) in 41% yield. R_F = 0.43 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 5.72 (dt, *J* = 7.5, 11.0, 1H, =CH-2 pentenyl), 5.24 (dd, *J* = 9.9, 11.0, 1H, =CH-1 pentenyl), 3.93 (dd, *J* = 2.2, 11.9, 1H, H-6a), 3.82 (dd, *J* = 2.4, 11.9, 1H, H-6b), 3.47 – 3.34 (m, 6H, CH_2-5 pentyl, CH_2-5 pentenyl), 3.27 (t, *J* = 9.5, 1H), 3.21 (t, *J* = 9.2, 1H), 3.05 (t, *J* = 9.1, 1H), 2.99 – 2.94 (m, 5H, 2×OCH_2-Ada), 2.90 – 2.79 (m, 2H, NCH_2-1 pentyl), 2.34 (dt, *J* = 2.4, 9.2, 1H, H-5), 2.32 – 2.27 (m, 1H, C*H*H-3 pentenyl), 2.25 – 2.17 (m, 1H, CH*H*-3 pentenyl), 1.95 (s, 6H, 6×CH Ada), 1.73 (dd, *J* = 12.3, 46.5, 12H, 6×CH_2 Ada), 1.66 – 1.52 (m, 16H, 6×CH_2 Ada, CH_2-4 pentyl, CH_2-4 pentenyl), 1.48 – 1.17 (m, 4H, CH_2-2 pentyl, CH_2-3 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 135.6 (=CH-2 pentenyl), 130.1 (=CH-1 pentenyl), 83.1, 83.1 (2×OCH_2-Ada), 79.5 (C-3), 74.9 (C-2), 72.6, 72.3 (CH_2-5 pentenyl/ pentyl), 71.7 (C-4), 64.9 (C-5), 63.0 (C-1), 59.3 (C-6), 49.0 (NCH_2-1 pentyl), 41.1, 41.1(CH_2-Ada), 38.5 (CH_2-Ada), 35.3 C_q Ada), 31.0 (CH_2-4 pentyl), 30.8 (CH_2-4 pentenyl), 29.9 (CH Ada), 26.6 (CH_2-3 pentenyl, 25.3 (C-3), 22.0 (C-2). IR ν_{max}(thin film)/ cm^{-1}: 3362, 2901, 2848, 1452, 1157, 1109, 1011. $[\alpha]^{20}_D$: 23.7 (*c* 0.4, MeOH). HRMS: found 630.4725 $[M+H]^+$, calculated for $[C_{38}H_{63}NO_6+H]^+$ 630.4728.



(1*S*)-*N*-Benzyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (40). A suspension of (1*S*)-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (**3**, 40 mg, 101 µmol, see Chapter 5 for synthesis), benzylbromide (25 µL, 211 µmol) and K_2CO_3 (42 mg, 303 µmol) in DMF (0.5 mL) was heated at 85 C for 18 h. The reaction mixture was filtered over a glass microfibre filter and concentrated. The residue was purified by silica gel column chromatography (0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **40** (35 mg, 72 µmol) as a colorless oil in 71% yield. R_F = 0.67 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 7.43 (d, *J* = 7.4, 2H, *o*-CH_{Ar} Bn), 7.30 (t, *J* = 7.7, 2H, *m*-CH_{Ar} Bn), 7.20 (t, *J* = 7.4, 1H, *p*-CH_{Ar} Bn), 3.95 – 3.87 (m, 3H, H-6a, CH_2 Bn), 3.82 (dd, *J* = 4.5, 11.6, 1H, H-6b), 3.53 (dd, *J* = 9.1, 9.8, 1H, H-4), 3.35 (dd, *J* = 9.0, 9.7, 1H, H-2), 3.26 (t, *J* = 6.6, 2H,CH_2-5 pentyl), 3.24 (dd, *J* = 9.0, 9.1, 1H, H-3), 2.93 (s, 2H, OCH_2-Ada), 2.61 (ddd, *J* = 4.0, 4.5, 9.8, 1H, H-5), 2.56 (ddd, *J* = 3.5, 6.3, 9.7, 1H, H-1), 1.96 (s, 3H, 3×CH Ada), 1.80 – 1.67 (m, 7H, 3×CH_2 Ada, CH*H*-1 pentyl), 1.60 – 1.54 (m, 7H, 3×CH_2 Ada, CH*H*-1 penty), 1.45 – 1.28 (m, 4H, CH_2-2, CH_2-4 pentyl), 1.10 – 1.02 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (151 MHz, MeOD) δ 143.1 (C_q Bn), 129.3 (*m*-CH_{Ar} Bn), 129.0 (*o*-CH_{Ar} Bn), 127.6 (*p*-CH_{Ar} Bn), 83.1 (OCH_2-Ada), 80.8 (C-3), 73.1 (C-2), 72.8 (CH_2-5 pentyl), 72.1 (C-4), 68.2 (C-5), 67.1 (C-1), 62.4 (C-6), 52.4 (CH_2 Bn), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2-4 pentyl), 30.1 (CH_2-1 pentyl), 29.9 (CH Ada), 27.6 (CH_2-2 pentyl), 26.4 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3368, 2901, 2848, 1700, 1454, 1285, 1094, 729, 699. $[\alpha]^{20}_D$: –4.0 (*c* 0.5, MeOH). HRMS: found 488.3365 $[M+H]^+$, calculated for $[C_{29}H_{45}NO_5+H]^+$ 488.3370.

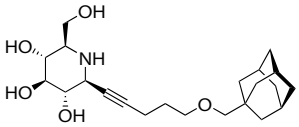


(1*S*)-1-*C*-[(*Z*)-5-(Adamantan-1-yl-methoxy)-pent-1-enyl]-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (41). A solution of **35** (151 mg, 0.2 mmol, see Chapter 5 for synthesis) in EtOAc (2 mL) was charged with Lindlar catalyst (25 mg). Argon was passed through the reaction mixture for 5 min and the mixture was subsequently exposed to atmospheric hydrogen pressure for 18 h. After 18 h the conversion was ~80% into a single lower running product. Longer or repeated exposure to hydrogen led to over reduction (R_F starting material = 0.57; R_F over reduced product = 0.49 (1:2; EtOAc:PE)). The reaction mixture was passed over a glass fibre filter and concentrated. The residue was purified by silica gel column chromatography (0% » 5% acetone in toluene) to furnish **41** (112 mg, 0.15 mmol) in 74% yield as a colorless oil (20% **35** recovered). R_F *E*-alkene = 0.52; (1:2; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.16 (m, 20H, H_{Ar} Bn), 5.62 (dt, *J* = 7.4, 10.8, 1H, =CH-2 pentenyl), 5.35 (dd, *J* = 9.2, 10.8, 1H, =CH-1 pentenyl), 4.91 (d, *J* = 10.8, 1H, C*H*H Bn), 4.84 (m, 2H, C*H*H Bn, CH*H* Bn), 4.73 (d, *J* = 10.7, 1H, C*H*H Bn), 4.69 (d, *J* = 10.7, 1H, CH*H* Bn), 4.50 (d, *J* = 11.0, 1H, CH*H* Bn), 4.46 (s, 2H, CH_2 Bn), 3.72 (dd, *J* = 2.6, 9.0, 1H, H-6a), 3.61 (dd, *J* = 9.0, 9.0, 1H, H-3), 3.50 (dd, *J* = 9.2, 9.2 1H, H-1), 3.38 (dd, *J* = 7.7, 8.9, 1H, H-6b), 3.34 – 3.31 (m, 3H, H-4, CH_2-5 pentenyl), 3.25 (dd, *J* = 9.2, 9.2 1H, H-2), 2.93 – 2.86 (m, 3H, H-5, OCH_2-Ada), 2.28 – 2.20 (m, 1H, C*H*H-3 pentenyl), 2.20 – 2.12 (m, 1H, CH*H*-3 pentenyl), 1.95 (s, 3H, 3×CH Ada), 1.77 (s, 1H, NH), 1.67 (dd, *J* = 11.7, 36.7, 6H, 3×CH_2 Ada), 1.62 – 1.54 (m, 2H, CH_2-4 pentenyl), 1.52 (d, *J* = 2.5, 6H, 3×CH_2 Ada).. ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.0, 138.7, 138.5, 138.1 (4×C_q Bn), 134.3 (=CH-2 pentenyl), 129.5 (=CH-1 pentenyl), 128.6, 128.6, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 87.9 (C-3), 84.6 (C-2), 82.0 (OCH_2-Ada), 80.6 (C-4), 75.9, 75.4, 75.2, 73.6 (4×CH_2 Bn), 70.9 (CH_2-5 pentenyl), 71.0 (C-6), 59.1 (C-5), 56.9 (C-1), 39.9 (CH_2 Ada), 37.5 (CH_2 Ada), 34.3 (C_q Ada), 29.7 (CH_2-4 pentenyl), 28.5 (CH Ada), 25.1 (CH_2-3 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2900, 2848, 1497, 1453, 1360, 1209, 1152, 1096, 1072, 1027, 734, 697. $[\alpha]^{20}_D$: 49.4 (*c* 1.0, $CHCl_3$). HRMS: found 756.4622 $[M+H]^+$, calculated for $[C_{50}H_{61}NO_5+H]^+$ 756.4623.

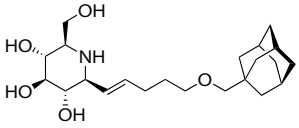


(1*S*)-1-*C*-[(*Z*)-5-(Adamantan-1-yl-methoxy)-pent-1-enyl]-1-deoxynojirimycin (42). Compound **41** (45 mg, 60 µmol) was subjected to a Birch reduction (see general procedure G) to produce **42** (16 mg, 40 µmol) as a colorless oil in 67% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.34 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600

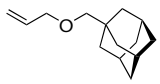
MHz, MeOD) δ 5.69 (dt, *J* = 7.6, 10.8, 1H, =CH-2 pentenyl), 5.32 (dd, *J* = 9.2, 10.8, 1H, =CH-1 pentenyl), 3.91 (dd, *J* = 3.1, 10.9, 1H, H-6a), 3.48 (dd, *J* = 7.9, 10.9, 1H, H-6b), 3.41 (t, *J* = 6.3, 2H, CH_2-5 pentenyl), 3.36 (dd, *J* = 9.2, 9.2 1H, H-1), 3.28 (dd, *J* = 8.9, 9.1, 1H, H-3), 3.14 (dd, *J* = 8.9, 9.6, 1H, H-4), 3.09 (d, *J* = 9.1, 9.2 1H, H-2), 3.01 – 2.96 (m, 2H, OCH_2-Ada), 2.64 (ddd, *J* = 3.1, 7.9, 9.6, 1H, H-5), 2.28 – 2.18 (m, 2H, CH_2-3 pentenyl), 1.95 (s, 3H, 3×CH Ada), 1.73 (dd, *J* = 11.5, 41.9, 6H, 3×CH_2 Ada), 1.67 – 1.59 (m, 2H, CH_2-4 pentenyl), 1.58 (d, *J* = 2.4, 6H, 3×CH_2 Ada). ^{13}C NMR (150 MHz, MeOD) δ 135.7 (=CH-2 pentenyl), 130.4 (=CH-1 pentenyl), 83.1 (OCH_2-Ada), 80.3 (C-3), 76.5 (C-2), 73.8 (C-4), 72.0 (CH_2-5 pentenyl), 63.8 (C-6), 62.5 (C-5), 58.5 (C-1), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.8 (CH_2-4 pentenyl), 29.9 (CH Ada), 25.9 (CH_2-3 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3319, 2900, 2848, 1661, 1448, 1344, 1096, 1005. [α]$^{20}_D$: 10.5 (*c* 0.3, MeOH). HRMS: found 396.2742 [M+H]$^+$, calculated for [$C_{22}H_{37}NO_5$+H]$^+$ 396.2744.



(1*S*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pent-1-ynyl]-1-deoxy-nojirimycin (43). Compound **35** (149 mg, 198 µmol, see Chapter 5 for synthesis) was subjected to a Birch reduction for 30 min (see general procedure G) to produce a ~4:1 mixture of **43** and **44** after silica gel column purification (0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH) from which **43** (19 mg, 48 µmol) could be obtained in 24% yield as a colorless oil after HPLC purification (1 min: isocratic 30% B » 11.5 min: 45% B » 12.5 min: 100% B, 20 min: isocratic 100% B; t_R **43** = 6.0 min; t_R **44** = 8.2 min). R_F = 0.37 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.92 – 3.87 (m, 2H, H-1, H-6a), 3.84 (dd, *J* = 4.9, 11.9, 1H, H-6b), 3.56 – 3.51 (m, 2H, H-2, H-4), 3.48 (t, *J* = 6.0, 2H, CH_2-5 pentynyl), 3.35 (dd, *J* = 9.1, 1H, H-3), 3.07 (ddd, *J* = 3.3, 4.9, 10.6, 1H, H-5), 2.98 (s, 2H, OCH_2-Ada), 2.39 (dt, *J* = 1.6, 7.2, 2H, CH_2-3 pentynyl), 1.94 (s, 3H, 3×CH Ada), 1.84 – 1.64 (m, 8H, 3×CH_2 Ada, CH_2-4 pentynyl), 1.56 (d, *J* = 2.4, 6H, 3×CH_2 Ada). ^{13}C NMR (150 MHz, MeOD) δ 90.2 (C_q pentynyl), 83.1 (OCH_2-Ada), 77.9 (C-3), 73.8 (C_q pentynyl), 73.3 (C-2), 70.9 (CH_2-5 pentynyl), 69.2 (C-4), 61.5 (C-5), 59.0 (C-6), 52.4 (C-1), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 29.6 (CH_2-4 pentynyl), 16.4 (CH_2-3 pentynyl). IR ν_{max}(thin film)/ cm^{-1}: 3366, 2902, 2849, 1444, 1201, 1141, 1114, 1078, 1024. [α]$^{20}_D$: –3.3 (*c* 0.2, MeOH). HRMS: found 394.2586 [M+H]$^+$, calculated for [$C_{22}H_{35}NO_5$+H]$^+$ 394.2588.

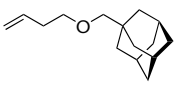


(1*S*)-1-*C*-[(*E*)-5-(adamantan-1-yl-methoxy)-pent-1-enyl]-1-deoxy-nojirimycin (44). Compound **35** (100 mg, 133 µmol, see Chapter 5 for synthesis) was subjected to a Birch reduction for 3 h with lithium instead of sodium (see general procedure G) to produce **44** (36 mg, 92 µmol) in 70% yield as a colorless oil after purification (0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH). R_F = 0.35 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 6.03 (dt, *J* = 6.9, 15.4, 1H, =CH-2 pentenyl), 5.47 (dd, *J* = 8.7, 15.4, 1H, =CH-1 pentenyl), 3.92 (dd, *J* = 3.9, 11.9, 1H, H-6a), 3.86 (dd, *J* = 2.9, 11.9, 1H, H-6b), 3.60 – 3.52 (m, 2H, H-1, H-4), 3.44 – 3.35 (m, 7H, H-2, H-3, CH_2-5 pentenyl), 3.08 (dt, *J* = 3.3, 10.7, 1H, H-5), 2.98 (s, 2H, OCH_2-Ada), 2.23 (dd, *J* = 6.7, 14.4, 2H, CH_2-3 pentenyl), 1.95 (s, 3H, 3×CH Ada), 1.83 – 1.65 (m, 8H, 3×CH_2 Ada, CH_2-4 pentenyl), 1.57 (d, *J* = 2.4, 6H, 3×CH_2 Ada). ^{13}C NMR (150 MHz, MeOD) δ 142.3 (=CH-2 pentenyl), 123.9 (=CH-1 pentenyl), 83.1(OCH_2-Ada), 78.3 (C-3), 72.5 (C-2), 71.7 (CH_2-5 pentenyl), 69.1 (C-4), 62.9 (C-1), 61.6 (C-5), 58.6 (C-6), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.4 (C-3), 29.9 (CH Ada), 29.8 (C-4). IR ν_{max}(thin film)/ cm^{-1}: 3366, 2904, 2850, 1440, 1203, 1140. [α]$^{20}_D$: –3.4 (*c* 0.1, MeOH). HRMS: found 396.2743 [M+H]$^+$, calculated for [$C_{22}H_{37}NO_5$+H]$^+$ 396.2744.

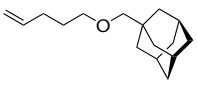


3-(Adamantane-1-yl-methoxy)-prop-2-ene (45). A stirred solution of admantane methanol (1.38 g, 8.3 mmol) in DMF (25 mL) was cooled to 0 °C and sodium hydride (60% in mineral oil, 0.5 g, 12.5 mmol) was added. After stirring for 1 h at 0 °C, allyl bromide (1.46 mL, 16.8 mmol) was added. The resulting mixture was allowed to warm to ambient temperature and stirred for an additional 16 h at ambient temperature. The reaction mixture was cooled to 0 °C and quenched by addition of water. The mixture was diluted with Et_2O (200 mL) and washed with water (3×200 mL). The organic phase

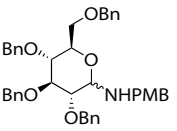
was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (0% » 5% EtOAc in PE) to produce **45** (1.359 g, 6.59 mmol) in 80% yield as a colorless liquid. R_F = 0.67 (100% toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 – 5.80 (m, 1H, =CH-2 propenyl), 5.25 (d, *J* = 17.3, 1H, =C*H*H-1 propenyl), 5.12 (d, *J* = 10.4, 1H, =CH*H*-1 propenyl), 3.92 (d, *J* = 5.0, 2H, CH_2-3 propenyl), 2.98 (s, 2H, OCH_2-Ada), 1.96 (s, 3H,), 1.68 (dd, *J* = 12.1, 26.0, 6H), 1.55 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5 (=CH-2 propenyl), 116.1(=CH_2-1 propenyl), 81.4 (OCH_2-Ada), 72.3 (CH_2-3 propenyl), 39.8 (CH_2 Ada), 37.4 (CH_2 Ada), 34.1 (C_q Ada), 28.4 (CH Ada). IR ν_{max}(thin film)/ cm^{-1}: 2902, 2849, 1733, 1453, 1378, 1258, 1158, 1090, 989, 919. MS (ESI): found 207.2 $[M+H]^+$, calculated for $[C_{14}H_{22}O+H]^+$ 207.2.



4-(Adamantane-1-yl-methoxy)-but-2-ene (46). A solution of 3-buten-1-ol (0.35 mL; 4.0 mmol) and Et_3N (0.55 mL, 4.0 mmol) in DCM (40 mL) was cooled to –40 °C and trifluoromethane sulfonic anhydride (0.73 mL, 4.4 mmol) was slowly added over 30 seconds. The mixture was allowed to warm to 0 °C over a 1 h period, after which TLC analysis indicated complete conversion to the volatile intermediate triflate (R_f-triflate = 0.80 (1:2; EtOAc:PE). The crude reaction mixture was poured into a stirred suspension of anhydrous K_2CO_3 (2.76 g, 10 mmol) and adamantanemethanol (3.32 g, 20 mmol) in DCM (80 mL). The resulting mixture was refluxed for 20 h at 50 °C. The suspension was cooled to ambient temperature and filtered. The solid residue was rinsed and the combined filtrate was concentrated. The concentrate was purified with silica gel column chromatography (2% » 5% EtOAc in PE) to afforded **46** (875 mg, 3.97 mmol) in 99% yield as a volatile colorless liquid. R_F = 0.85 (1:9; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 – 5.76 (m, 1H, =CH-2 butenyl), 5.06 (d, *J* = 17.2, 1H, =C*H*H-1 butenyl), 5.00 (d, *J* = 10.2, 1H, =CH*H*-1 butenyl), 3.42 (t, *J* = 6.8, 2H, CH_2-4 butenyl), 2.97 (s, 2H, OCH_2-Ada), 2.36 – 2.26 (m, 2H, CH_2-3 butenyl), 1.95 (s, 3H, 3×CH Ada), 1.68 (dd, *J* = 12.1, 26.2, 7H, 3×CH_2 Ada), 1.54 (s, 6H, 3×CH_2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (=CH-2 butenyl), 116.1 (=CH_2-1 butenyl), 82.0 (OCH_2-Ada), 71.0 (CH_2-4 butenyl), 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.3 (CH_2-3 butenyl), 34.2 (C_q Ada), 28.5 (CH Ada). IR ν_{max}(thin film)/ cm^{-1}: 2899, 2848, 1641, 1451, 1359, 1157, 1109, 992, 911. MS (ESI): found 221.4 $[M+H]^+$, calculated for $[C_{15}H_{24}O+H]^+$ 221.2.

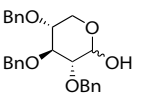


5-(Adamantane-1-yl-methoxy)-pent-2-ene (47). A stirred solution of admantane methanol (1.38 g, 8.3 mmol) in DMF (25 mL) was cooled to 0 °C and sodium hydride (60% in mineral oil, 0.5 g, 12.5 mmol) was added. After stirring for 1 h at 0 °C 5-bromo-pent-1-ene (2.5g, 16.8 mmol) was added. The resulting mixture was allowed to warm to ambient temperature and stirred for an additional 16 h at ambient temperature. The reaction mixture was cooled to 0 °C and quenched by addition of water. The mixture was diluted with Et_2O (200 mL) and washed with water (3×200 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (0% » 5% EtOAc in PE) to produce **47** (1.036 g, 4.42 mmol) in 53% yield as a volatile colorless liquid. R_F = 0.73 (100% toluene). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 6.6, 10.1, 16.9, 1H, =CH-2 pentenyl), 5.09 – 4.88 (m, 2H, =CH_2-1 pentenyl), 3.38 (t, *J* = 6.4, 2H, CH_2-5 pentenyl), 2.95 (s, 2H, OCH_2-Ada), 2.20 – 2.05 (m, 2H, CH_2-3 pentenyl), 1.95 (s, 3H, 3×CH Ada), 1.64 (m, 8H, CH_2-4 pentenyl, 3×CH_2 Ada), 1.53 (d, *J* = 2.8, 6H, 3×CH_2 Ada). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7 (=CH-2 pentenyl), 114.7 (=CH_2-1 pentenyl), 82.1 (OCH_2-Ada), 71.0 (CH_2-5 pentenyl), 40.0 (CH_2 Ada), 37.5 (CH_2 Ada), 34.3 (C_q Ada), 30.5, 29.1 (CH_2-3, CH_2-4 pentenyl), 28.5 (CH Ada). IR ν_{max}(thin film)/ cm^{-1}: 2899, 2848, 1641, 1451, 1361, 1157, 1111, 1050, 990, 910. MS (ESI): found 235.3 $[M+H]^+$, calculated for $[C_{16}H_{26}O+H]^+$ 235.2.

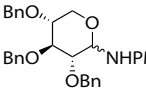


α/β-Mixture of *N*-4-methoxybenzyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylamine (50). A suspension of 2,3,4,6-tetra-*O*-benzyl-D-glucpyranose (**48**, 21.6 g, 40 mmol), *p*-methoxybenzylamine (15.7 mL, 200 mmol), *p*-toluenesulfonic acid (200 mg, 1 mmol) and Na_2SO_4 (17 g, 120 mmol) in toluene (400 mL) was refluxed for 18 h. The reaction mixture was cooled to rt, diluted with EtOAc (300 mL) and successively washed with aq 1M HCl (2×300 mL), sat aq $NaHCO_3$

(2×200 mL) and sat aq NaCl (200 mL). The organic phase was dried (Na_2SO_4) and concentrated to provide **50** as a white solid that was used crude in the subsequent reaction. A small sample of crude **50** was purified by silica gel column chromatography (0% » 10% EtOAc in PE) for characterization. R_F = 0.75 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.10 (m, 44H, H_{Ar}-α/β Bn/PMB), 6.83 (d, *J* = 7.7, 4H, H_{Ar}-α/β PMB), 5.06 – 4.43 (m, 17H, CH_2-α/β Bn, H-1α), 4.14 – 4.05 (m, 2H, C*H*H-6, C*H*H PMB), 4.03 (d, *J* = 8.8, 1H, H-1β), 3.94 – 3.54 (m, 20H, OMe-α/β PMB, CH_2-α/β PMB), 3.40 (d, *J* = 7.2, 1H), 3.30 (dd, *J* = 8.1, 8.8, 1H, H-2β), 2.21 (br s, 2H, NHPMB). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 158.7 (*p*-C_q-α/β PMB), 139.1, 138.9, 138.6, 138.6, 138.4, 138.3, 138.2 (C_q-α/β Bn), 132.5, 132.4 (C_q-α/β PMB), 129.6, 129.5, 128.6, 128.5, 128.5, 128.5, 128.4, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.7 (CH_{Ar}-α/β Bn/PMB), 113.9, 113.9 (CH_{Ar}-α/β PMB), 90.2 (C-1β), 84.1 (C-1α), 86.1, 82.7, 82.7, 80.4, 78.4, 78.3 (C-2, C-3, C-4 α/β), 75.8 (C-5β), 75.9, 75.7, 75.1, 75.1, 75.0, 73.7, 73.6, 73.0 (CH_2-α/β Bn), 69.0 (C-5α), 69.1, 68.9 (C-6α/β), 55.4, 55.3 (OMe-α/β PMB), 49.4, 49.3 (CH_2-α/β PMB). IR ν_{max}(thin film)/ cm^{-1}: 3318, 3030, 2864, 1611, 1514, 1454, 1354, 1244, 1121, 1058, 1028, 1011, 971, 748, 732, 693. $[\alpha]^{20}_D$: 25.7 (*c* 1.8, $CHCl_3$). HRMS: found 660.3317 $[M+H]^+$, calculated for $[C_{42}H_{45}NO_6+H]^+$ 660.3320.

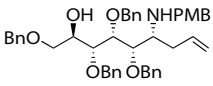


α/β-Mixture of 2,3,4-tri-*O*-benzyl-D-xylopyranose (49).[50] A dry and cooled (0 °C) solution of D-xylose (10 g, 66.6 mmol) in DMF (333 mL) was charged with sodium hydride (60% in mineral oil, 11.72 g, 293 mmol) and stirred for 1 h at 0 °C. Next, benzylbromide (34 mL, 286 mmol) was added to the suspension over a period of 5 min. The reaction mixture was stirred for 20 h and allowed to warm to rt. The reaction mixture was quenched with water and concentrated. The residue was dissolved in Et_2O (400 mL) and washed successively with water (300 mL) and sat aq NaCl (200 mL). The organic phase was dried (Na_2SO_4) and concentrated to provide a yellow oil that was used crude in the next reaction (R_F tetra-benzylated intermediate = 0.69 (EtOAc:PE; 1:3)). The crude intermediate was suspended in a mixture of AcOH (210 mL) and aq 1M HCl (93 mL) and refluxed at 105 °C for 4 h after which TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated and coevaporated with toluene (2×200 mL). The residue was transferred into aq sat $NaHCO_3$ (400 mL) and extracted with EtOAc (3×300 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The product was precipitated from PE>EtOAc to provide **49** (11.34 g, 27 mmol) as a white fluffy solid after drying at 50 °C for 20 h. The mother liquor was concentrated and purified by silica gel column chromatography (10% » 33% EtOAc in PE) to provide additional **49** (4.10 g, 9.76 mmol) and an overall yield of 55%. R_F = 0.20 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) major α-anomer δ 7.40 – 7.25 (m, 15H, H_{Ar} Bn), 5.08 (d, *J* = 2.1, 1H, H-1α), 4.90 – 4.82 (m, 2H, CH_2 Bn), 4.76 – 4.60 (m, 4H, 2×CH_2 Bn), 3.87 (dd, *J* = 9.1, 1H, H-3), 3.79 (dd, *J* = 10.6, 1H, H-5a), 3.65 (dd, *J* = 4.8, 11.8, 1H, H-5b), 3.59 – 3.50 (m, 1H, H-4), 3.47 (d, *J* = 8.9, 1H, H-2), 3.29 (s, 1H, OH-1). ^{13}C NMR (100 MHz, $CDCl_3$) 5/1 α/β-mixture δ 138.8, 138.4, 138.0 (C_q Bn), 128.7, 128.6, 128.5, 128.2, 127.9, 127.8 (CH_{Ar} Bn), 97.9 (C-1β), 91.6 (C-1α), 83.4 (C-3β), 82.6 (C-2β), 80.7 (C-3α), 79.6 (C-2α), 77.8 (C-4β), 77.7 (C-4α), 75.7 (CH_2 Bn α), 75.6 (CH_2 Bn β), 74.9 (CH_2 Bn β), 73.5 (CH_2 Bn α), 73.4 (CH_2 Bn β), 73.3 (CH_2 Bn α), 63.9 (C-5β), 60.4 (C-5α). IR ν_{max}(thin film)/ cm^{-1}: 3040, 2870, 1599, 1454, 1357, 1071, 1060, 747, 693. $[\alpha]^{20}_D$: +16.3 (*c* 0.6, $CHCl_3$). MS (ESI): found 421.3 $[M+H]^+$, calculated for $[C_{26}H_{28}O_5+H]^+$ 421.2

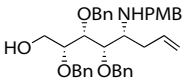


α/β-Mixture of *N*-4-methoxybenzyl-2,3,4-tri-*O*-benzyl-D-xylopyranosylamine (51). A suspension of **49** (2.1 g, 5 mmol), *p*-methoxybenzylamine (6.5 mL, 50 mmol), (±)-camphor-10-sulfonic acid (1.162 g, 5 mmol) and Na_2SO_4 (2.8 g , 20 mmol) in toluene (50 mL) was refluxed for 2.5 h, after which TLC analysis indicated complete consumption of **49**. The reaction mixture was cooled to rt, diluted with EtOAc (200 mL) and successively washed with aq 1M HCl (2×200 mL), sat aq $NaHCO_3$ (2×100 mL) and sat aq NaCl (100 mL). The organic phase was dried (Na_2SO_4) and concentrated to provide **51** as a white solid that was used crude in the subsequent reaction. A small sample of crude **51** was purified by silica gel column chromatography (10% » 25% EtOAc in PE) for characterization. R_F = 0.55 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.20 (m, 34H, H_{Ar}-α/β Bn/PMB), 6.90 – 6.80 (m, 4H, H_{Ar}-α/β PMB), 4.99 – 4.58 (m, 11H, CH_2-α/β

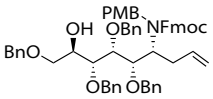
Bn), 4.50 – 4.44 (m, 2H, H-1α, CH*H*α Bn), 4.03 – 3.75 (m, 14H, H-1β, OMe-α/β PMB, CH_2-α/β PMB), 3.63 – 3.56 (m, 4H), 3.56 – 3.44 (m, 4H), 3.24 – 3.13 (m, 2H), 2.05 – 1.79 (m, 1H, NHPMB), 1.75 – 1.48 (m, 1H, NHPMB). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 158.8 (*p*-C_q-α/β PMB), 138.9, 138.7, 138.7, 138.5, 138.3 (C_q-α/β Bn), 132.5, 132.4 (C_q-α/β PMB), 129.6, 129.5, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8 (CH_{Ar}-α/β Bn/PMB), 114.0, 113.9 (CH_{Ar}-α/β PMB), 90.7 (C-1β), 84.2 (C-1α), 85.2, 82.3, 80.2, 79.3, 78.6, 77.7 (H-2, H-3, H-4 α/β), 75.9, 75.3, 75.2, 73.5, 73.2, 73.1 (CH_2-α/β Bn), 65.2 (C-5β), 60.3 (C-5α), 55.5, 55.5 (OMe-α/β PMB), 49.5 (CH_2-β PMB), 49.1 (CH_2-α PMB). IR ν_{max}(thin film)/ cm^{-1}: 3302, 3030, 2861, 1611, 1514, 1455, 1358, 1242, 1179, 1071, 1030, 933, 894, 814, 748, 693. $[\alpha]^{20}_D$: 0.8 (*c* 0.5, $CHCl_3$). MS (ESI): found 540.4 $[M+H]^+$, calculated for $[C_{34}H_{37}NO_5+H]^+$ 540.3.



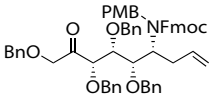
(1*R*/*S*)-1-Deoxy-1-(4-methoxybenzylamino)-1-*C*-(prop-2-enyl)-2,3,4,6-tetra-*O*-benzyl-D-glucitol (52). Allyl magnesiumbromide (1M in Et_2O, 350 mL, 350 mmol) was slowly added over a 30 min period to a dry and cooled (0 °C) solution of **50** (23.1 g, 35 mmol) in Et_2O (50 mL). The reaction mixture was stirred for an additional 16 h and allowed to warm to rt. The reaction was quenched with sat aq NH_4Cl, poured into Et_2O (200 mL), and washed with sat aq NH_4Cl (2×200 mL). The organic phase was dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (0% » 40% EtOAc in PE) to provide **52** (2.28 g, 32.5 mmol, inseparable 9:1 *R*/*S*-isomer mixture) in 93% yield as a colorless oil. R_F = 0.40 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.17 (m, 22H, H_{Ar} Bn, H_{Ar} PMB), 6.81 (d, *J* = 8.5, 2H, H_{Ar} PMB), 5.65 – 5.53 (m, 1H, =CH propenyl), 5.01 – 4.93 (m, 2H, =CH_2 propenyl), 4.85 (d, *J* = 11.4, 1H, C*H*H Bn), 4.78 (d, *J* = 11.3, 1H, C*H*H Bn), 4.69 (d, *J* = 11.3, 1H, CH*H* Bn), 4.60 – 4.49 (m, 5H, CH*H* Bn, C*H*H Bn, CH_2 Bn), 4.40 (d, *J* = 11.4, 1H, CH*H* Bn), 4.27 (dd, *J* = 2.8, 7.5, 1H, H-3), 4.09 – 4.04 (m, 1H, H-5), 3.87 – 3.78 (m, 2H, H-2, C*H*H PMB), 3.76 (s, 3H, OMe PMB), 3.66 – 3.51 (m, 2H, H-4, CH_2-6, CH*H* PMB), 2.62 (t, *J* = 5.1, 1H, H-1), 2.46 – 2.33 (m, 1H, C*H*H propenyl), 2.33 – 2.19 (m, 1H, CH*H* propenyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8 (*p*-Cq PMB), 139.1, 138.6, 138.3, 138.3 (C_q Bn/PMB), 136.3 (=CH propenyl), 129.8, 128.6, 128.5, 128.3, 128.0, 127.9, 127.9, 127.6 (CH_{Ar} Bn/PMB), 117.3 (=CH_2 propenyl), 113.9 (CH_{Ar} PMB), 80.3 (C-2), 79.6 (C-3), 77.9 (C-4), 74.7, 73.6, 73.0 (4×CH_2 Bn), 71.8 (C-6), 70.8 (C-5), 57.0 (C-1), 55.5 (OMe PMB), 50.5 (CH_2 PMB), 35.2 (CH_2 propenyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2863, 1610, 1513, 1454, 1245, 1067, 1028, 912, 825, 733, 696. $[\alpha]^{20}_D$: –0.4 (*c* 2.6, $CHCl_3$). HRMS: found 702.3786 $[M+H]^+$, calculated for $[C_{45}H_{51}NO_6+H]^+$ 702.3789.



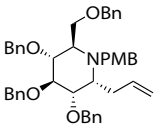
(1*R*/*S*)-1-Deoxy-1-(4-methoxybenzylamino)-1-*C*-(prop-2-enyl)-2,3,4-tri-*O*-benzyl-D-xylitol (53). Allyl magnesiumbromide (1M in Et_2O, 23 mL, 23 mmol) was slowly added over a 2 min period to a dry and cooled (0 °C) solution of **51** (2.14 g, 2.3 mmol) in THF (23 mL). The reaction mixture was stirred for an additional 5 min at 0 °C and then allowed to warm to rt. After stirring at rt for 1 h the reaction was quenched with sat aq NH_4Cl. The mixture was poured into additional sat aq NH_4Cl (100 mL) and extracted with EtOAc (3×100 mL). The combined organic phases were dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (10% » 50% EtOAc in PE) to provide **53** (1.31 g, 2.25 mmol, inseparable 5:1 *R*/*S*-isomer mixture) in 97% yield as a colorless oil. R_F = 0.11 (1:3; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 15H, H_{Ar} Bn), 7.16 (d, *J* = 8.6, 2H, H_{Ar} PMB), 6.79 (d, *J* = 8.7, 2H, H_{Ar} PMB), 5.71 – 5.51 (m, 1H, =CH propenyl), 5.01 – 4.91 (m, 2H, =CH_2 propenyl), 4.80 (d, *J* = 11.4, 1H, C*H*H Bn), 4.75 (d, *J* = 11.4, 1H, C*H*H Bn), 4.67 (d, *J* = 11.4, 1H, CH*H* Bn), 4.58 – 4.50 (m, 2H, C*H*H Bn, CH*H* Bn), 4.37 (d, *J* = 11.7, 1H, CH*H* Bn), 4.07 (dd, *J* = 4.1, 7.0, 1H, H-3), 3.81 – 3.60 (m, 7H, H-2, CH_2-5, C*H*H PMB, OMe PMB), 3.51 (d, *J* = 12.7, 1H, CH*H* PMB), 3.44 – 3.35 (m, 1H, H-4), 2.64 – 2.57 (m, 1H, H-1), 2.48 – 2.31 (m, 2H, CH_2 propenyl). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5 (*p*-C_q PMB), 138.7, 138.3, 138.2 (C_q Bn), 136.0 (=CH propenyl), 132.5 (C_q PMB), 129.6, 129.2, 128.2, 127.9, 127.8, 127.6, 127.5, 127.3 (CH_{Ar} Bn/PMB), 116.9 (=CH_2 propenyl), 113.5 (CH_{Ar} PMB), 79.9, 79.8, 78.5 (C-2, C-3, C-4), 74.5, 74.1, 71.9 (CH_2 Bn), 61.5 (C-5), 56.0 (C-1), 55.0 (OMe PMB), 50.2 (CH_2 PMB), 35.1 (CH_2 propenyl). IR ν_{max}(thin film)/ cm^{-1}: 2868, 1610, 1513, 1454, 1245, 1028, 913, 824, 733, 696. $[\alpha]^{20}_D$: –17.7 (*c* 3.3, $CHCl_3$). HRMS: found 582.3209 $[M+H]^+$, calculated for $[C_{37}H_{44}NO_5+H]^+$ 582.3214.



(1*R*)-1-Deoxy-1-(*N*-[(9H-fluoren-9-ylmethoxy)carbonyl]-4-methoxybenzylamido)-1-*C*-(prop-2-enyl)-2,3,4,6-tetra-*O*-benzyl-D-glucitol (54). Aqueous $NaHCO_3$ (10 wt%, 6.3 mL, 15 mmol) was added to a solution of **52** (2.1 g, 3.0 mmol) in DCM (9 mL) and 9-fluorenylmethyloxycarbonylchloride (0.93 g, 3.6 mmol). The mixture was stirred vigorously for 16 h. The mixture was diluted with EtOAc (100 mL) and washed with water (2 x 100 mL). The organic layer was dried ($MgSO_4$), concentrated and purified with silica gel column chromatography (0% » 20% - EtOAc in PE) to afford **54** (2.602 g, 2.75 mmol) in 91% yield as a white foam. R_F = 0.50 (1:2; EtOAc:PE). ^{1}H NMR (500 MHz, C_6D_6, 343K) δ 7.61 – 6.66 (m, 32H(m, 32H, CH_{Ar} Bn/PMB/Fmoc)), 5.56 – 5.29 (m, 1H, =CH propenyl), 4.97 – 3.64 (m, 21H, 6×CH_2 Bn/PMB/Fmoc, CH Fmoc, =CH propenyl, =CH_2, propenyl, H-1, H2, H-3, H-4, CH_2-6), 3.45 – 3.36 (m, 3H, OMe PMB), 2.71 – 2.12 (m, 2H, CH_2 propenyl). ^{13}C NMR (125 MHz, C_6D_6, 343K) δ 159.5, 145.6, 144.9, 142.1, 141.5, 139.7, 139.4, 139.0, 136.6, 135.9, 134.6, 134.1, 133.1, 130.5, 129.8, 129.6, 129.3, 129.1, 128.8, 128.7, 128.4, 128.2, 128.2, 128.0, 127.9, 127.8, 127.5, 127.3, 125.5, 125.4, 124.6, 120.4, 120.3, 117.3, 114.4, 114.2, 81.0, 79.7, 78.0, 76.0, 75.4, 74.6, 74.3, 74.2, 73.9, 72.3, 67.5, 65.6, 55.2, 51.1, 48.3, 35.4. $[\alpha]^{20}_D$: 14.5 (*c* 4.9, $CHCl_3$). IR ν_{max}(thin film)/ cm^{-1}: 3065, 3031, 2866, 1685, 1611, 1513, 1453, 1412, 1301, 1244, 1177, 1089, 1065, 1029, 916, 735, 696. HRMS: found 946.4292 $[M+Na]^+$, calculated for $[C_{45}H_{51}NO_6+Na]^+$ 946.4289.

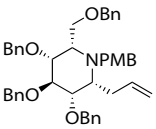


(1*R*)-1-Deoxy-1-(*N*-[(9H-fluoren-9-ylmethoxy)carbonyl]-4-methoxybenzylamido)-1-*C*-(prop-2-enyl)-2,3,4,6-tetra-*O*-benzyl-D-*arabino*-hex-5-ulose (55). Dess-Martin periodinane (0.73 g, 1.7 mmol) was added to a solution of **54** (1.0 g, 1.43 mmol) in DCM (17 mL). After the reaction mixture was stirred for 6 h, sat aq $Na_2S_2O_3$ (5 mL) and sat aq $NaHCO_3$ (5 mL) were added and vigorously mixed for 10 min. The mixture was diluted with EtOAc (50 mL) and washed with water (2×15 mL). The organic phase was dried ($MgSO_4$), concentrated and purified with silica gel column chromatography (0% » 20% EtOAc in PE) to afforded **55** (1.32 g, 1.4 mmol) in 98% yield as a white foam. R_F = 0.55 (1:2; EtOAc:PE). ^{1}H NMR (500 MHz, C_6D_6) δ 7.96 – 6.69 (m, 32H, CH_{Ar} Bn/PMB/Fmoc), 5.87 – 3.53 (m, 21H, 6×CH_2 Bn/PMB/Fmoc, CH Fmoc, =CH propenyl, =CH_2, propenyl, H-1, H2, H-3, H-4, CH_2-6), 3.43 (s, 3H, OMe PMB), 2.88 – 2.03 (m, 2H, CH_2 propenyl). ^{13}C NMR (125MHz, C_6D_6) δ 207.1, 159.6, 144.9, 142.2, 142.2, 139.3, 138.8, 138.4, 135.8, 129.5, 129.2, 129.1, 128.9, 128.9, 128.7, 128.6, 127.8, 127.7, 127.3, 125.6, 120.6, 118.0, 114.2, 114.1, 75.4, 73.6, 55.1, 48.1. IR ν_{max}(thin film)/ cm^{-1}: 2934, 1728, 1693, 1611, 1513, 1453, 1412, 1301, 1246, 1177, 1106, 1029, 917, 738, 698. HRMS: found 944.4140 $[M+Na]^+$, calculated for $[C_{60}H_{59}NO_8+Na]^+$ 944.4133.

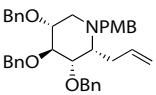


(1*R*)-*N*-(4-Methoxybenzylamino)-1-*C*-(prop-2-enyl)-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (56). Piperidine (75 µL, 0.76 mmol) was added to a cooled (0 °C) solution of **55** (0.5 g, 0.725 mmol) in DMF (5 mL). The resulting mixture was stirred for 30 min at 0 °C. The mixture was diluted with Et_2O (50 mL) and washed with water (2×50 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was dissolved in MeOH (15 mL) and the mixture was cooled to –35 °C. The mixture was acidified to pH 5 with AcOH followed by the successive addition of Na_2SO_4 (280 mg, 2 mmol) and $NaCNBH_3$ (160 mg, 2.53 mmol). The reaction mixture was stirred for 16 h at –20 °C under an argon atmosphere. The mixture was diluted with EtOAc (50 mL) and washed with sat aq $NaHCO_3$ (2×50 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by silica gel column chromatography (0% » 10% EtOAc in PE) to provide **56** (403 mg, 0.59 mmol) in 81% yield as a colorless oil. R_F = 0.30 (1:6.5; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.15 (m, 22H, H_{Ar} Bn/PMB), 6.80 (d, *J* = 8.7, 2H, H_{Ar} PMB), 5.76 – 5.67 (m, 1H,=CH propenyl), 5.02 – 4.92 (m, 3H, =CH_2 propenyl, C*H*H Bn), 4.90 (d, *J* = 10.7, 1H, C*H*H Bn), 4.80 (d, *J* = 10.9, 1H, CH*H* Bn), 4.58 (d, *J* = 10.7, 1H, CH*H* Bn), 4.51 – 4.46 (m, 2H, CH_2 Bn), 4.38 – 4.34 (m, 2H, CH_2 Bn), 3.95 (d, *J* = 13.9, 1H, C*H*H PMB), 3.84 (dd, *J* = 4.9, 10.4, 1H, H-6a), 3.81 – 3.69 (m, 8H, H-6b, H-4, H-3, H-2, CH*H* PMB, OMe PMB), 3.07 – 3.04 (m, 2H, H-1, H-5), 2.42 – 2.33 (m, 2H, CH_2 propenyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.5 (*p*-C_q PMB), 139.2, 138.8, 138.6,

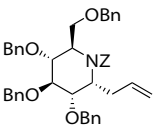
138.3 (4×C_q Bn), 137.9 (=CH propenyl), 132.7 (C_q PMB), 129.6 (=CH propenyl), 128.5, 128.5, 128.4, 128.1, 128.0, 128.0, 127.7, 127.6, 127.6, 127.6 (CH_{Ar} Bn/PMB), 115.4 (=CH_2 propenyl), 113.6 (CH_{Ar} PMB), 84.2, 79.3, 78.8 (C-2, C-3, C-4), 75.6, 75.3, 73.0, 72.2 (4×CH_2 Bn), 68.5 (C-6), 57.5, 56.6 (C-5, C-1), 55.3 (OMe PMB), 52.2 (CH_2 PMB), 29.1 (CH_2 propenyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2862, 1610, 1511, 1454, 1362, 1301, 1244, 1171, 1091, 1066, 1028, 908, 827, 733, 696. $[\alpha]^{20}_D$: 21.5 (*c* 3.7, $CHCl_3$). HRMS: found 684.3679 $[M+H]^+$, calculated for $[C_{45}H_{49}NO_5+H]^+$ 684.3684.



(1*R*)-*N*-(4-Methoxybenzylamino)-1-*C*-(prop-2-enyl)-2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (57). Methanesulfonyl chloride (0.56 mL, 7.2 mmol) was added to a cooled (0 °C) solution of **52** (4.21 g, 6.0 mmol) in pyridine (77 mL). The mixture was stirred for 4 h, warming to rt, and subsequently heated at 90 °C for 16 h (R_F mesylate = 0.73 (1:2; EtOAc:PE)). The reaction mixture was concentrated, redissolved in EtOAc (100 mL) and washed extensively with aq sat $CuSO_4$ (5 × 50 mL). The organic phase was dried ($MgSO_4$), concentrated and purified by silica gel column chromatography (0% » 10% EtOAc in PE) to provide **57** (3.21 g, 4.68 mmol) in 78% yield as a yellow oil. R_F = 0.70 (1:6.5; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 20H, H_{Ar} Bn), 7.16 (d, *J* = 8.6, 2H, H_{Ar} PMB), 6.81 (d, *J* = 8.7, 2H, H_{Ar} PMB), 5.91 – 5.82 (m, 1H, =CH propenyl), 5.00 – 4.90 (m, 2H, =CH_2 propenyl), 4.81 (d, *J* = 10.9, 1H, C*H*H Bn), 4.79 (d, *J* = 10.9, 1H, CH*H* Bn), 4.60 (d, *J* = 11.3, 1H, C*H*H Bn), 4.57 – 4.51 (m, 3H, CH*H* Bn, CH_2 Bn), 4.49 – 4.45 (m, 2H, CH_2 Bn), 4.03 (d, *J* = 14.5, 1H, C*H*H PMB), 3.98 (d, *J* = 14.5, 1H, CH*H* PMB), 3.83 – 3.67 (m, 7H, H-3, H-5, CH_2-6, OMe PMB), 3.60 (dd, *J* = 5.8, 8.2, 1H, H-2), 3.49 (dd, *J* = 5.6, 11.6, 1H, H-4), 3.20 – 3.16 (m, 1H, H-1), 2.51 – 2.43 (m, 1H, C*H*H propenyl), 2.37 – 2.29 (m, 1H, CH*H* propenyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (*p*-C_q PMB), 139.3 (C_q Bn), 138.9 (=CH propenyl), 138.8 (C_q Bn), 132.8 (C_q PMB), 129.8, 129.3, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6 (CH_{Ar} Bn/PMB), 115.6 (=CH_2 propenyl), 113.8 (CH_{Ar} PMB), 81.0 (C-2), 80.2 (C-3), 78.8 (C-5), 75.3, 73.4, 72.8, 72.7 (CH_2 Bn), 70.6 (C-6), 59.6 (C-1), 58.9 (C-4), 57.4 (CH_2 PMB), 55.4 (OMe PMB) 33.8 (CH_2 propenyl). IR ν_{max}(thin film)/ cm^{-1}: 3030, 2865, 1609, 1511, 1454, 1364, 1243, 1072, 1029, 908, 825, 733, 695. $[\alpha]^{20}_D$: 0.5 (*c* 3.8, $CHCl_3$). HRMS: found 684.3680 $[M+H]^+$, calculated for $[C_{45}H_{49}NO_5+H]^+$ 684.3684.

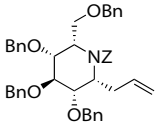


(1*R*)-*N*-(4-Methoxybenzylamino)-1,5-dideoxy-1,5-imino-1-*C*-(prop-2-enyl)-2,3,4-tri-*O*-benzyl-D-xylitol (58). Diethyl azodicarboxylate (1.8 mL, 3.92 mmol, 2.2M in toluene) was added over a 1 min period to a dry solution of **53** (1.14 g, 1.96 mmol) and PPh_3 (1.03 g, 3.92 mmol) in DCM (10 mL). The reaction mixture was stirred for 20 h and subsequently quenched by addition of water. The mixture was concentrated and purified by silica gel column chromatography (0% » 20% EtOAc in toluene) to produce **58** (976 mg, 1.73 mmol) in 88% yield as a colorless oil. R_F = 0.60 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.08 (m, 17H, H_{Ar} Bn/PMB), 6.78 (d, *J* = 8.7, 2H, H_{Ar} PMB), 5.92 – 5.79 (m, 1H, =CH propenyl), 5.14 – 4.37 (m, 8H, =CH_2 propenyl, 3×CH_2 Bn), 3.73 – 3.46 (m, 8H, H-2, H-3, H-4, OMe PMB, CH_2 PMB), 3.13 (dt, *J* = 4.9, 7.6, 1H, H-1), 2.78 (dd, *J* = 5.2, 12.3, 1H, H-5a), 2.53 (dd, *J* = 10.5, 11.9, 1H, H-5b), 2.49 – 2.32 (m, 2H, CH_2 propenyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (*p*-C_q PMB), 139.2, 138.6, 138.5 (3×C_q Bn), 138.2 (=CH propenyl), 131.0 (C_q PMB), 129.2, 128.1, 128.0, 127.7, 127.6, 127.5, 127.3, 127.2 (CH_{Ar} Bn/PMB), 115.3 (=CH_2 propenyl), 113.5 (CH_{Ar} PMB), 82.6, 80.3, 78.2 (C2, C-3, C-4), 75.2, 72.5, 72.2 (3×CH_2 Bn), 59.5 (C-2), 58.0 (CH_2 PMB), 54.8 (OMe PMB), 47.7 (C-5), 27.6 (CH_2 propenyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2904, 1610, 1512, 1455, 1364, 1244, 1069, 1029, 908, 822, 734, 696. $[\alpha]^{20}_D$: 27.1 (*c* 2.8, $CHCl_3$). HRMS: found 564.3103 $[M+H]^+$, calculated for $[C_{37}H_{41}NO_4+H]^+$ 544.3108.

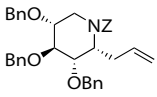


(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-(prop-2-enyl)-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (59). Compound **56** (2.07 g, 3.03 mmol) was subjected to general procedure E to provide **59** (1.38 g, 1.98 mmol) in 65% yield as a colorless oil after purification via silica gel column chromatography (0% » 5% EtOAc in toluene). R_F intermediate amine = 0.65 (2:1; EtOAc:PE). R_F **59** = 0.56 (1:4; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) major rotamer δ 7.44 – 7.16 (m, 25H, CH_{Ar} Bn/Z), 5.85 (s, 1H, =CH propenyl), 5.14 – 5.09 (m, 2H, CH_2 Z), 4.98 – 4.88 (m, 2H, =CH_2 propenyl), 4.68 – 4.33

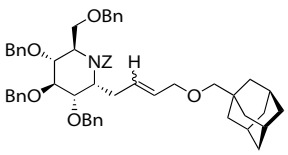
(m, 9H, H-1, 4×CH_2 Bn), 4.28 – 4.23 (m, 1H, H-5), 3.98 (dd, *J* = 2.0, 3.6, 1H, H-4), 3.88 (d, *J* = 8.3, 1H, H-3), 3.75 (dd, *J* = 5.5, 8.1, 1H, H-2), 3.66 (s, 1H, H-6a), 3.56 (s, 1H, H-6b), 2.65 – 2.59 (m, 1H, C*H*H propenyl), 2.59 – 2.52 (m, 1H, CH*H* propenyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0 (C=O Z), 138.4, 138.3, 138.3, 137.9 (C_q Bn), 136.7 (=CH propenyl), 136.5 (C_q Z), 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.5, 127.3 (CH_{Ar} Bn/Z), 116.1(=CH_2 propenyl), 81.5 (C-3), 80.6 (C-2), 77.0 (C-4), 73.0, 72.5, 72.3, 71.7 (4×CH_2 Bn), 69.9 (C-6), 67.3 (CH_2 Z), 54.6 (C-5), 52.8 (C-1), 34.1 (CH_2 propenyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2871, 1698, 1495, 1453, 1417, 1270, 1206, 1093, 1026, 995, 913, 734, 694. $[\alpha]^{20}_D$: 9.2 (*c* 4.6, $CHCl_3$). HRMS: found 698.3477 $[M+H]^+$, calculated for $[C_{45}H_{48}NO_6+H]^+$ 698.3476.



(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-(prop-2-enyl)-2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (60). Compound **57** (3.02 g, 4.41 mmol) was subjected to general procedure E to provide **60** (2.32 g, 3.31 mmol) in 75% yield as a colorless oil after purification via silica gel column chromatography (0% » 5% EtOAc in toluene). R_F intermediate amine = 0.60 (2:1; EtOAc:PE). R_F **57** = 0.53 (1:4; EtOAc:PE). ^{1}H NMR (500 MHz, C_6D_6, 343 K) major rotamer δ 7.38 – 6.96 (m, 25H), 6.17 – 5.93 (m, 1H, =CH propenyl), 5.25 – 4.80 (m, 7H, H-5, CH_2 Z, CH_2 Bn, =CH_2 propenyl), 4.66 – 4.28 (m, 7H, H-1, 3×CH_2 Bn), 3.95 – 3.89 (m, 2H, H-3, H-6a), 3.74 (dd, *J* = 6.1, 10.1, 1, H-6b), 3.54 (dd, *J* = 7.3, 9.3, 1H, H-4), 3.47 (dd, *J* = 6.7, 9.2, 1H, H-2), 2.82 – 2.71 (m, 1H, C*H*H propenyl), 2.54 – 2.40 (m, 1H, CH*H* propenyl). ^{13}C NMR (125 MHz, C_6D_6, 343 K) major rotamer δ 156.6 (C=O Z), 140.1, 139.2, 139.1, 137.6 (C_q Bn/Z), 137.4 (=CH propenyl), 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (CH_{Ar} Bn/Z), 116.5 (=CH_2 propenyl), 80.7 (C-2), 80.0 (C-4), 79.2 (C-3), 75.7, 73.7, 73.5, 73.4 (CH_2 Bn), 70.3(C-6), 68.1 (CH_2 Z), 54.4 (C-1), 53.8 (C-5), 34.7 (CH_2 propenyl). IR ν_{max}(thin film)/ cm^{-1}: 3065, 3031, 2868, 1696, 1496, 1453, 1416, 1364, 1308, 1210, 1092, 1026, 995, 911, 733, 695. $[\alpha]^{20}_D$: –9.9 (*c* 5.5, $CHCl_3$). HRMS: found 698.3476 $[M+H]^+$, calculated for $[C_{45}H_{48}NO_6+H]^+$ 698.3476.

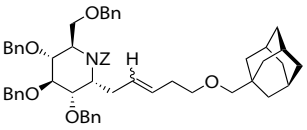


(1*R*)-*N*-Benzyloxycarbonyl-1,5-dideoxy-1,5-imino-1-*C*-(prop-2-enyl)-2,3,4-tri-*O*-benzyl-D-xylitol (61). Compound **58** (1.42 g, 2.52 mmol) was subjected to general procedure E to provide **61** (1.27 g, 2.20 mmol) in 87% yield as a colorless oil after purification via silica gel column chromatography (0% » 5% EtOAc in toluene). R_F intermediate amine = 0.11 (1:1; EtOAc:PE + 2% Et_3N). R_F **61** = 0.50 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers (a/b; ~1:1) δ 7.41 – 7.20 (m, 40H, $H_{Ar}{}^{a/b}$ Bn/Z), 5.78 – 5.65 (m, 1H, =CH^a propenyl), 5.62 – 5.50 (m, 1H, =CH^b propenyl), 5.16 – 4.90 (m, 8H, $CH_2{}^{a/b}$ Z, =$CH_2{}^{a/b}$ propenyl), 4.89 – 4.81 (m, 4H, $CH_2{}^{a/b}$ Bn), 4.77 – 4.72 (m, 1H, H-1^a), 4.72 – 4.59 (m, 8H, 2×$CH_2{}^{a/b}$ Bn), 4.45 – 4.39 (m, 2H, H-1^b, C*H*H-5^a), 4.17 (dd, *J* = 5.7, 13.7, 1H, CH*H*-5^a), 3.68 (dd, *J* = 8.6, 8.6, 2H, H-3$^{a/b}$), 3.60 – 3.37 (m, 4H, H-2$^{a/b}$, H-4$^{a/b}$), 2.80 – 2.70 (m, 2H, CH_2-5^b), 2.64 – 2.50 (dd, 2H, C*H*H$^{a/b}$ propenyl), 2.35 – 2.25 (dt, 2H, CH*H*$^{a/b}$ propenyl). ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers (a/b; ~1:1) δ 155.7, 155.6 (C=O$^{a/b}$ Z), 138.9, 138.2, 138.2 (3×$C_q{}^{a/b}$ Bn), 136.7, 136.6 ($C_q{}^{a/b}$ Z), 134.5, 134.4 (=CH$^{a/b}$ propenyl), 128.6, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7 ($CH_{Ar}{}^{a/b}$ Bn/Z), 117.6, 117.4 (=$CH_2{}^{a/b}$ propenyl), 82.2, 82.0 (C-3$^{a/b}$), 79.8 (C-2$^{a/b}$), 78.4, 78.3 (C-4$^{a/b}$), 75.8 ($CH_2{}^{a/b}$ Bn), 73.3 ($CH_2{}^a$ Bn), 73.2 ($CH_2{}^{a/b}$ Bn), 72.8 ($CH_2{}^b$ Bn), 67.6, 67.5 ($CH_2{}^{a/b}$ Z), 53.0, 52.3 (C-1$^{a/b}$), 41.1, 40.8 (C-5$^{a/b}$), 29.8, 29.7 ($CH_2{}^{a/b}$ propenyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2872, 1698, 1495, 1453, 1423, 1349, 1314, 1209, 1095, 1026, 991, 913, 734, 695. $[\alpha]^{20}_D$: –13.8 (*c* 3.4, $CHCl_3$). HRMS: found 578.2899 $[M+H]^+$, calculated for $[C_{37}H_{39}NO_5+H]^+$ 578.2801.

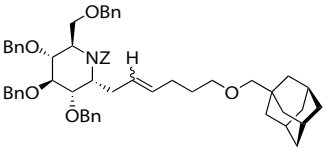


(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-[(*E*/*Z*)-4-(adamantan-1-yl-methoxy)-but-2-enyl]-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (63). Compound **59** (275 mg, 395 µmol) underwent a cross-metathesis reaction (see general procedure F) with alkene **45** to produce **63** (303 mg, 346 µmol) in 87% yield as a 3.3:1 mixture of *E*/*Z*-isomers after purification via silica gel column chromatography (0% » 10% EtOAc in PE). R_F = 0.51 (1:5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) *E*-isomer δ 7.45 –

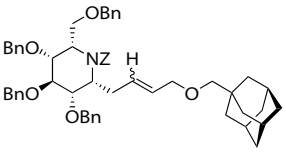
7.19 (m, 25H, H_{Ar} Bn/Z), 5.74 – 5.40 (m, 2H, =CH-2 butenyl, =CH-3 butenyl), 5.21 – 5.06 (m, 2H, CH_2 Z), 4.72 – 4.38 (m, 8H, 4×CH_2 Bn), 4.33 (s, 1H, H-1), 4.22 (s, 1H, H-5), 4.00 – 3.70 (m, 5H, H-2, H-3, H-4, CH_2-4 butenyl), 3.68 – 3.51 (m, 2H, CH_2-6), 2.89 (s, 2H, OCH_2-Ada), 2.66 – 2.47 (m, 2H, CH_2-1 butenyl), 1.93 (s, 3H, 3×CH Ada), 1.73 – 1.45 (m, 12H, 6×CH_2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$) *E*-isomer δ 156.0 (C=O Z), 138.5, 138.4, 138.4, 138.0 (4×C_q Bn), 136.7 (C_q Z), 131.4 (=CH-2 *E*-isomer butenyl), 130.3 (=CH-2 *Z*-isomer butenyl), 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 127.9, 127.8, 127.6, 127.4 (=CH-3 *E*/*Z* butenyl, CH_{Ar} Bn/Z), 81.6 (C-3), 81.2 (OCH_2-Ada), 80.8 (C-2), 77.2 (C-4), 73.1, 72.7, 72.4, 72.3, 71.8 (CH_2 Bn, CH_2-4 butenyl), 70.0 (C-6), 67.4 (CH_2 Z), 54.7 (C-5), 53.1 (C-1), 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 32.8 (CH_2-1 butenyl), 28.5 (CH Ada). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2900, 2848, 1698, 1453, 1403, 1302, 1209, 1069, 1026, 734, 695. $[\alpha]^{20}_D$: 6.5 (*c* 2.8, $CHCl_3$). HRMS: found 876.4840 $[M+H]^+$, calculated for $[C_{57}H_{65}NO_7+H]^+$ 876.4834.



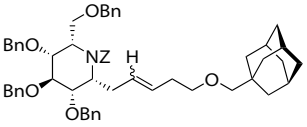
(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-[(*E*/*Z*)-5-(adamantan-1-yl-methoxy)-pent-2-enyl]-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (64). Compound **59** (275 mg, 395 µmol) underwent a cross-metathesis reaction (see general procedure F) with alkene **46** to produce **64** (289 mg, 325 µmol) in 82% yield as a 2.5:1 mixture of *E*/*Z*-isomers after purification via silica gel column chromatography (0% » 10% EtOAc in PE). R_F = 0.53 (1:5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) *E*-isomer δ 7.47 – 7.15 (m, 25H, H_{Ar} Bn/Z), 5.55 – 5.29 (m, 2H, =CH-2 pentenyl, =CH-3 pentenyl), 5.19 – 5.07 (m, 2H, CH_2 Z), 4.74 – 4.39 (m, 8H, 4×CH_2 Bn), 4.39 – 4.27 (m, 1H, H-1), 4.27 – 4.16 (m, 1H, H-5), 3.99 – 3.91 (m, 1H, H-4), 3.88 – 3.76 (m, 1H, H-3), 3.73 (dd, *J* = 5.5, 9.0, 1H, H-2), 3.71 – 3.50 (m, 2H, CH_2-6), 3.26 (t, *J* = 7.1, 2H, CH_2-5 pentenyl), 2.90 (s, 2H, OCH_2-Ada), 2.62 – 2.48 (m, 2H, CH_2-1 pentenyl), 2.29 – 2.09 (m, 2H, CH_2-4 pentenyl), 1.93 (s, 3H, 3×CH Ada), 1.77 – 1.45 (m, 12H, 6×CH_2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$) *E*-isomer δ 156.2 (C=O Z), 138.5 (C_q Bn), 129.8, 129.5, 129.0, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.8, 127.7, 127.5, 127.1 (=CH-2, =CH-3 *E*/*Z* pentenyl, CH_{Ar} Bn/Z), 82.1 (OCH_2-Ada), 81.8 (C-3), 80.8 (C-2), 77.3 (C-4), 73.1, 72.7, 72.4, 71.9, 71.7 (CH_2 Bn, CH_2-5 pentenyl), 70.1 (C-6), 67.4 (CH_2 Z), 54.7 (C-5), 53.0 (C-1), 39.9 (CH_2 Ada), 37.5 (CH_2 Ada), 34.3 (C_q Ada), 33.2 (CH_2-1 pentenyl), 28.5 (CH Ada), 28.0 (CH_2-4 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 2902, 2849, 1698, 1453, 1404, 1268, 1090, 1069, 1026, 734, 695. $[\alpha]^{20}_D$: 3.4 (*c* 1.1, $CHCl_3$). HRMS: found 890.4996 $[M+H]^+$, calculated for $[C_{58}H_{67}NO_7+H]^+$ 890.4990.



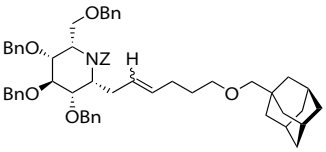
(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-[(*E*/*Z*)-6-(adamantan-1-yl-methoxy)-hex-2-enyl]-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (65). Compound **59** (275 mg, 395 µmol) underwent a cross-metathesis reaction (see general procedure F) with alkene **47** to produce **65** (305 mg, 338 µmol) in 85% yield as a 2:1 mixture of *E*/*Z*-isomers after purification via silica gel column chromatography (0% » 10% EtOAc in PE). R_F = 0.55 (1:5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) *E*-isomer δ 7.41 – 7.12 (m, 25H, H_{Ar} Bn/Z H), 5.52 – 5.27 (m, 2H, =CH-2 hexenyl, =CH-3 hexenyl), 5.16 – 5.06 (m, 2H, CH_2 Z), 4.68 – 4.38 (m, 8H, 4×CH_2 Bn), 4.38 – 4.28 (m, 1H, H-1), 4.24 – 4.14 (m, 1H, H-5), 3.98 – 3.91 (m, 1H, H-4), 3.90 – 3.83 (m, 1H, H-3), 3.77 – 3.69 (m, 1H, H-2), 3.69 – 3.50 (m, 2H, CH_2-6), 3.36 – 3.21 (m, 2H, CH_2-6 hexenyl), 2.97 – 2.87 (m, 2H, OCH_2-Ada), 2.61 – 2.39 (m, 2H, CH_2-1 hexenyl), 2.07 – 1.88 (m, 5H, CH_2-4 hexenyl, 3×CH Ada), 1.77 – 1.45 (m, 14H, CH_2-5 hexenyl, 6×CH_2 Ada).^{13}C NMR (100 MHz, $CDCl_3$) *E*-isomer δ 156.1 (C=O Z), 138.5, 138.5, 138.4, 138.1 (C_q Bn), 136.7 (C_q Z), 131.9 (=CH-3 *E* hexenyl), 130.5 (=CH-3 *Z* hexenyl), 128.7, 128.7, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 127.9, 127.9, 127.7, 127.6, 127.6, 127.4 (=CH-2 *E*/*Z* hexenyl, CH_{Ar} Bn/Z), 82.0 (OCH_2-Ada), 81.8 (C-3), 80.8 (C-2), 77.4 (C-4), 73.1, 72.8, 72.4, 72.0, 71.3 (CH_2 Bn, CH_2-6 hexenyl), 70.0 (C-6), 67.4 (CH_2 Z), 54.7 (C-5), 53.4 (C-1), 39.9 (CH_2 Ada), 37.5 (CH_2 Ada), 34.3 (C_q Ada), 32.8 (CH_2-1 hexenyl), 29.3 (CH_2-5 hexenyl), 28.5 (CH Ada), 23.9 (CH_2-4 hexenyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2901, 2848, 1698, 1453, 1403, 1361, 1267, 1210, 1089, 1070, 1026, 734, 695. $[\alpha]^{20}_D$: 4.8 (*c* 2.8, $CHCl_3$). HRMS: found 904.5152 $[M+H]^+$, calculated for $[C_{59}H_{69}NO_7+H]^+$ 904.5147.



(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-[(*E*/*Z*)-4-(adamantan-1-yl-methoxy)-but-2-enyl]-2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (66). Compound **60** (275 mg, 395 µmol) underwent a cross-metathesis reaction (see general procedure F) with alkene **45** to produce **66** (306 mg, 349 µmol) in 88% yield as a mixture of E/Z isomers in an unassignable ~2:1 ratio after purification via silica gel column chromatography (0% » 10% EtOAc in PE). R_F = 0.47 (1:5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) *E*/*Z*-isomers δ 7.45 – 7.19 (m, 25H, H_{Ar} Bn/Z H), 5.83 – 5.40 (m, 2H, =CH-2 butenyl, =CH-3 butenyl), 5.23 – 4.93 (m, 3H, H-5, CH_2 Z), 4.93 – 4.39 (m, 9H, H-1, 4×CH_2 Bn), 3.99 – 3.45 (m, 7H, H-2, H-3, H-4, CH_2-6, CH_2-4 butenyl), 2.98 – 2.84 (m, 2H, OCH_2-Ada), 2.75 – 2.52 (m, 2H, CH_2-4 butenyl), 2.42 – 2.24 (m, 2H, CH_2-1 butenyl), 2.06 – 1.84 (m, 3H, 3×CH Ada), 1.83 – 1.43 (m, 12H, 6×CH_2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$) *E*/*Z*-isomers δ 156.4 (C=O Z), 139.0, 138.4 (C_q Bn), 131.3, 131.1, 129.9, 129.3 (=CH *E*/*Z* butenyl), 128.6, 128.5, 128.5, 128.2, 128.1, 127.9, 127.7, 127.5 (=CH *E*/*Z* butenyl, CH_{Ar} Bn/Z), 81.3 (OCH_2-Ada), 80.2 (C-2), 79.6 (C-4), 78.7 (C-3), 75.9, 74.1, 73.6, 73.4, 73.1 (CH_2 Bn), 72.2 (CH_2-4 butenyl), 69.6 (C-6), 67.8 (CH_2 Z), 54.1, 53.5, 53.2, 52.7 (C-1, C-5), 40.0 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 33.0, 33.0 (CH_2-1 butenyl), 28.5 (CH Ada). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2900, 2848, 1698, 1453, 1403, 1360, 1302, 1209, 1069, 1026, 734, 695. $[\alpha]^{20}_D$: –6.0 (*c* 0.6, $CHCl_3$). HRMS: found 876.4840 $[M+H]^+$, calculated for $[C_{57}H_{65}NO_7+H]^+$ 876.4834.

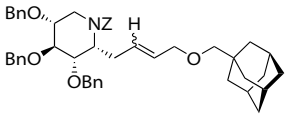


(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-[(*E*/*Z*)-5-(adamantan-1-yl-methoxy)-pent-2-enyl]-2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (67). Compound **60** (275 mg, 395 µmol) underwent a cross-metathesis reaction (see general procedure F) with alkene **46** to produce **67** (260 mg, 292 µmol) in 74% yield as a mixture of E/Z isomers in an unassignable ~2:1 ratio after purification via silica gel column chromatography (0% » 10% EtOAc in PE). R_F = 0.50 (1:5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) *E*/*Z*-isomers δ 7.48 – 7.14 (m, 25H, H_{Ar} Bn/Z H H), 5.87 – 5.23 (m, 2H, =CH-2 pentenyl, =CH-3 pentenyl), 5.23 – 4.92 (m, 3H, H-5, CH_2 Z), 4.92 – 4.36 (m, 9H, H-1, 4×CH_2 B), 3.97 – 3.44 (m, 5H, H-2, H-3, H-4, CH_2-6), 3.40 – 3.17 (m, 2H, CH_2-5 pentenyl), 2.99 – 2.86 (m, 2H, OCH_2-Ada), 2.77 – 2.47 (m, 1H, C*H*H-1 pentenyl), 2.40 – 2.09 (m, 3H, CH*H*-1 pentenyl, CH_2-4 pentenyl), 2.09 – 1.87 (m, 3H, 3×CH Ada), 1.81 – 1.43 (m, 12H, 6×CH_2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$) *E*/*Z*-isomers δ 156.4 (C=O Z), 138.9, 138.5, 138.2, 138.1 (C_q Bn), 136.6 (C_q Z), 131.2, 130.9 (=CH *E*/*Z* pentenyl), 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.7, 127.6, 127.3 (CH_{Ar} Bn/Z), 126.9, 126.7, 125.6 (=CH *E*/*Z* pentenyl), 81.9 (OCH_2-Ada), 80.1, 79.5, 79.4, 79.2, 78.9, 78.8, 78.7, 78.6 (C-2, C-3, C-4), 75.8, 75.7, 73.9, 73.4, 73.1, 72.9, 72.5, 72.2, 72.0, 71.9, 71.4 (CH_2 Bn, CH_2-5 pentenyl), 69.1 (C-6), 67.7 (CH_2 Z), 54.6, 53.9, 53.6, 53.2, 52.5 (C-1, C-5), 39.8, 39.6, 39.1 (CH_2 Ada), 37.3, 37.2, 37.2 (CH_2 Ada), 34.5, 34.1, 33.7 (C_q Ada), 32.7 (CH_2-1 pentenyl), 28.4, 28.2, 28.1 (CH Ada, CH_2-4 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 2902, 2849, 1698, 1453, 1416, 1271, 1093, 1026, 734, 695. $[\alpha]^{20}_D$: –7.8 (*c* 1.0, $CHCl_3$). HRMS: found 890.4996 $[M+H]^+$, calculated for $[C_{58}H_{67}NO_7+H]^+$ 890.4990.

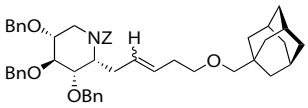


(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-[(*E*/*Z*)-6-(adamantan-1-yl-methoxy)-hex-2-enyl]-2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (68). Compound **60** (275 mg, 395 µmol) underwent a cross-metathesis reaction (see general procedure F) with alkene **47** to produce **68** (312 mg, 345 µmol) in 87% yield as a mixture of E/Z isomers in an unassignable ~2:1 ratio after purification via silica gel column chromatography (0% » 10% EtOAc in PE). R_F = 0.52 (1:5; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) *E*/*Z*-isomers δ 7.45 – 7.14 (m, 25H, H_{Ar} Bn/Z H), 5.58 – 5.24 (m, 2H, =CH-2 hexenyl, =CH-3 hexenyl), 5.23 – 4.98 (m, 3H, H-5, CH_2 Z), 4.94 – 4.37 (m, 9H, H-1, 4×CH_2 Bn), 3.95 – 3.45 (m, 5H, H-2, H-3, H-4, CH_2-6), 3.38 – 3.26 (m, 2H, CH_2-6 hexenyl), 2.93 (s, 2H, OCH_2-Ada), 2.79 – 2.51 (m, 1H, C*H*H-1 hexenyl), 2.32 – 2.18 (m, 1H, CH*H*-1 hexenyl), 2.09 – 1.80 (m, 5H, CH_2-4 hexenyl, 3×CH Ada), 1.77 – 1.40 (m, 16H, CH_2-5 hexenyl, 6×CH_2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$) *E*/*Z*-isomers δ 156.5 (C=O Z), 139.0, 138.5, 138.4, 138.3, 137.9 (C_q Bn), 136.8, 136.6 (C_q

Z), 132.4, 132.3, 130.9 (=CH *E*/*Z* hexenyl), 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 127.4 (=CH *E*/*Z* hexenyl, CH_{Ar} Bn/Z), 127.1, 127.0 (=CH *E*/*Z* hexenyl), 82.0 (OCH_2-Ada), 80.3, 80.2 (C-2), 79.5 (C-4), 78.7, 78.7 (C-3), 75.9, 75.8, 73.6, 73.4, 73.3, 73.1 (CH_2 Bn), 71.3, 71.2, 71.1 (CH_2-6 hexenyl), 69.9, 69.7 (C-6), 67.8, 67.7 (CH_2 Z), 55.5, 54.3, 53.8, 53.4, 53.2, 52.7 (C-1, C-5), 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.3 (C_q Ada), 33.2, 32.8 (CH_2-1 hexenyl), 29.6, 29.3 (CH_2 hexenyl), 28.5 (CH Ada), 27.6, 27.2 (CH_2 hexenyl), 24.3, 24.2 (CH_2 hexenyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2901, 2848, 1698, 1453, 1416, 1364, 1273, 1094, 1026, 734, 695. $[\alpha]^{20}_D$: −10.5 (*c* 2.0, $CHCl_3$). HRMS: found 904.5153 $[M+H]^+$, calculated for $[C_{59}H_{69}NO_7+H]^+$ 904.5147.

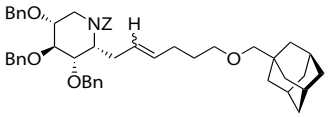


(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-[(*E*/*Z*)-4-(adamantan-1-yl-methoxy)-but-2-enyl]-1,5-dideoxy-1,5-imino-2,3,4-tri-*O*-benzyl-D-xylitol (69). Compound **61** (200 mg, 346 µmol) underwent a cross-metathesis reaction (see general procedure F) with alkene **45** to produce **69** (170 mg, 225 µmol) in 65% yield as a 5:1 mixture of *E*/*Z*-isomers after purification via silica gel column chromatography (0% » 10% EtOAc in PE). R_F = 0.51 (1:4; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) *E*-isomer rotamers (a/b; ~1:1) δ 7.39 – 7.21 (m, 40H, $H_{Ar}^{a/b}$ Bn/Z), 5.61 – 5.51 (m, 3H, =CH-3$^{a/b}$ butenyl, =CH-2^a butenyl), 5.49 – 5.39 (m, 1H, =CH-2^b butenyl), 5.16 – 5.02 (m, 4H, $CH_2^{a/b}$ Z), 4.91 – 4.81 (m, 4H, $CH_2^{a/b}$ Bn), δ 4.75 – 4.57 (m, 9H, 2×$CH_2^{a/b}$ Bn, H-1^a), 4.48 – 4.38 (m, 2H, H-1^b, C*H*H-5^a), 4.16 (dd, *J* = 5.7, 13.6, 1H, CH*H*-5^a), 4.00 – 3.71 (m, 4H, CH_2-4$^{a/b}$ butenyl), 3.68 (dd, *J* = 9.2, 9.4, 2H, H-3$^{a/b}$), 3.56 (dd, *J* = 5.9, 9.4, 1H, H-2^a), 3.53 – 3.35 (m, 3H, H-2^b, H-4$^{a/b}$), 2.98 – 2.85 (m, 4H, OCH_2-Ada$^{a/b}$), 2.79 – 2.69 (m, 2H, CH_2-5^b), 2.63 – 2.51 (m, 2H, C*H*H-1$^{a/b}$ butenyl), 2.36 – 2.26 (m, 2H, CH*H*-1$^{a/b}$ butenyl), 1.94 (s, 6H, 6×CH Ada$^{a/b}$) 1.67 (dd, *J* = 11.7, 30.7, 12H, 6×CH_2 Ada$^{a/b}$), 1.51 (s, 12H, 6×CH_2 Ada$^{a/b}$). ^{13}C NMR (125 MHz, $CDCl_3$) *E*-isomer rotamers (a/b; ~1:1) δ 155.5, 155.5 (C=O$^{a/b}$ Z), 138.9, 138.3, 138.2, 138.1, 138.0 (3×$C_q^{a/b}$ Bn), 136.7, 136.6 ($C_q^{a/b}$ Z), 130.3, 130.1 (=CH-3$^{a/b}$ butenyl), 128.9 (=CH-2^a butenyl), 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.2, 128.2, 128.0, 128.0, 127.9, 127.9 (=CH-2^b butenyl, $CH_{Ar}^{a/b}$ Bn/Z), 82.1, 82.0 (C-3$^{a/b}$), 81.1, 81.0 (OCH_2-Ada$^{a/b}$), 79.7 (C-2$^{a/b}$), 78.3, 78.2 (C-4$^{a/b}$), 75.8, 75.8, 73.3, 73.2, 72.8 ($CH_2^{a/b}$ Bn), 71.8, 71.7 (CH_2-4$^{a/b}$ butenyl), 67.5, 67.5 ($CH_2^{a/b}$ Z), 53.1, 52.3 (C-1$^{a/b}$), 41.1, 40.8 (C-5$^{a/b}$), 39.8 ($CH_2^{a/b}$ Ada), 37.3 $CH_2^{a/b}$ Ada), 34.1, 34.1 ($C_q^{a/b}$ Ada), 28.4 (CH $^{a/b}$ Ada), 28.3, 28.2 (CH-1$^{a/b}$ butenyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2848, 1700, 1452, 1423, 1352, 1314, 1238, 1199, 1158, 1097, 970, 734, 696. $[\alpha]^{20}_D$: −7.8 (*c* 1.6, $CHCl_3$). HRMS: found 778.4076 $[M+Na]^+$, calculated for $[C_{49}H_{57}NO_6+Na]^+$ 778.4078.

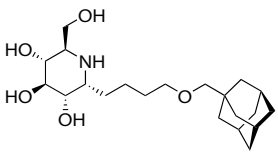


(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-[(*E*/*Z*)-5-(adamantan-1-yl-methoxy)-pent-2-enyl]-1,5-dideoxy-1,5-imino-2,3,4-tri-*O*-benzyl-D-xylitol (70). Compound **61** (200 mg, 346 µmol) underwent a cross-metathesis reaction (see general procedure F) with alkene **46** to produce **70** (190 mg, 247 µmol) in 71% yield as a 2:1 mixture of *E*/*Z*-isomers after purification via silica gel column chromatography (0% » 10% EtOAc in PE). R_F = 0.53 (1:4; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) *E*/*Z*-isomers (Z-rotamers a/b; ~1:1) δ 7.38 – 7.21 (m, 40H, $H_{Ar}^{a/b}$ Bn/Z), 5.53 – 5.42 (m, 2H, =CH-3$^{a/b}$ pentenyl), 5.42 – 5.34 (m, 1H, =CH-2^a pentenyl), 5.28 – 5.20 (m, 1H, =CH-2^b pentenyl), 5.17 – 4.99 (m, 4H, $CH_2^{a/b}$ Z), 4.91 – 4.80 (m, 4H, $CH_2^{a/b}$ Bn), 4.76 – 4.60 (m, 9H, 2×$CH_2^{a/b}$ Bn, H-1^a), 4.45 – 4.36 (m, 2H, H-1^b, C*H*H-5^a), 4.22 – 4.13 (m, 1H, CH*H*-5^a), 3.73 – 3.64 (m, 2H, H-3$^{a/b}$), 3.56 (dd, *J* = 5.9, 9.4, 1H, H-2^a), 3.53 – 3.25 (m, 7H, H-2^b, H-4$^{a/b}$, CH_2-5$^{a/b}$ pentenyl), 2.98 – 2.88 (m, 4H, OCH_2-Ada$^{a/b}$), 2.77 – 2.70 (m, 2H, CH_2-5^b), 2.59 – 2.10 (m, 8H, CH_2-1$^{a/b}$, CH_2-4$^{a/b}$ pentenyl), 1.95 (s, 6H, 6×CH Ada$^{a/b}$), 1.67 (dd, *J* = 11.7, 29.8, 12H, 6×CH_2 Ada$^{a/b}$), 1.56 – 1.50 (m, 12H, 6×CH_2 Ada$^{a/b}$). ^{13}C NMR (125 MHz, $CDCl_3$) *E*/*Z*-isomers (Z-rotamers a/b; ~1:1) δ 155.6, 155.6, 155.5, 155.5 (C=O$^{a/b}$ *E*/*Z* Z), 138.9, 138.3, 138.2, 138.2, 138.2, 138.2 (3×$C_q^{a/b}$ *E*/*Z* Bn), 136.7, 136.7, 136.6, 136.6 ($C_q^{a/b}$ *E*/*Z* Z) 130.1, 129.8 (=CH-3$^{a/b}$ *E* pentenyl), 128.8, 128.7, 128.6, 128.6, 128.6, 128.5, 128.4, 128.2, 128.2, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7 (=CH-3$^{a/b}$ *Z* pentenyl, $CH_{Ar}^{a/b}$ *E*/*Z* Bn/Z), 127.4, 127.3 (=CH-2$^{a/b}$ *E* pentenyl), 126.8, 126.7 (=CH-2$^{a/b}$ *Z* pentenyl), 82.3, 82.2, 82.1, 82.1 (C-3$^{a/b}$ *E*/*Z*), 82.1, 82.0, 82.0, 82.0 (OCH_2-Ada$^{a/b}$ *E*/*Z*), 79.9, 79.9, 79.8, 79.8 (C-2$^{a/b}$ *E*/*Z*), 78.4, 78.3, 78.3 (C-4$^{a/b}$ *E*/*Z*), 75.9, 75.9, 75.8, 75.8, 73.3, 73.3, 73.2,

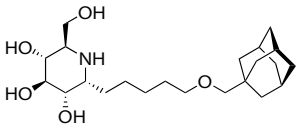
73.2, 73.1, 72.9, 72.7 (CH_2[a/b] *E/Z* Bn), 71.6, 71.4, 71.2, 71.1 (CH_2-5[a/b] *E/Z* pentenyl), 67.6, 67.5, 67.5, 67.4 (CH_2[a/b] *E/Z* Z), 53.5, 53.2, 53.0, 52.9 (C-1[a/b] *E/Z*), 41.1, 41.1, 40.9, 40.8 (C-5[a/b] *E/Z*), 39.9 (CH_2[a/b] *E/Z* Ada), 37.4 (CH_2[a/b] *E/Z* Ada), 34.2 (C_q[a/b] *E/Z* Ada), 33.1, 33.0 (CH_2-4[a/b] *E/Z* pentenyl), 28.6, 28.5, 28.2 (CH_2-1[a/b] *E/Z* pentenyl), 28.4 (CH[a/b] Ada), 23.2 (CH_2-1[a/b] *E/Z* pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2848, 1700, 1453, 1423, 1360, 1314, 1237, 1198, 1158, 1098, 970, 734, 696.$[\alpha]^{20}_D$: –11.6 (*c* 1.7, $CHCl_3$).HRMS: found 770.4416 $[M+H]^+$, calculated for $[C_{50}H_{59}NO_6+H]^+$ 770.4415.



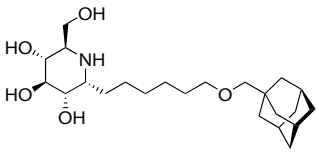
(1*R*)-*N*-Benzyloxycarbonyl-1-*C*-[(*E/Z*)-6-(adamantan-1-yl-methoxy)-hex-2-enyl]-1,5-dideoxy-1,5-imino-2,3,4-tri-*O*-benzyl-D-xylitol (71). Compound **61** (200 mg, 346 µmol) underwent a cross-metathesis reaction (see general procedure F) with alkene **47** to produce **71** (222 mg, 280 µmol) in 82% yield as a 3:1 mixture of *E/Z*-isomers after purification via silica gel column chromatography (0% » 10% EtOAc in PE). R_F = 0.55 (1:4; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) *E/Z*-isomers (Z-rotamers a/b; ~1:1) δ 7.39 – 7.19 (m, 40H, H_{Ar}[a/b] Bn/Z), 5.52 – 5.39 (m, 2H, =CH-3[a/b] hexenyl), 5.37 – 5.29 (m, 1H, =CH-2[a] hexenyl), 5.25 – 5.18 (m, 1H, =CH-2[b] hexenyl), 5.15 – 5.01 (m, 4H, CH_2[a/b] Z), 4.90 – 4.80 (m, 4H, CH_2[a/b] Bn), 4.73 – 4.59 (m, 9H, 2×CH_2[a/b] Bn, H-1[a]), 4.45 – 4.36 (m, 2H, H-1[b], C*H*H-5[a]), 4.20 – 4.13 (m, 1H, CH*H*-5[a]), 3.71 – 3.65 (m, 2H, H-3[a/b]), 3.59 – 3.53 (m, 1H, H-2[a]), 3.53 – 3.43 (m, 2H, H-2[b], H-4[a]), 3.43 – 3.37 (m, 1H, H-4[b]), 3.36 – 3.29 (m, 4H, CH_2-6[a/b] hexenyl), 2.97 – 2.92 (m, 4H, OCH_2-Ada[a/b]), 2.79 – 2.70 (m, 2H, CH_2-5[b]), 2.57 – 1.93 (m, 14H, CH_2-1[a/b], CH_2-4[a/b] hexenyl, 6×CH Ada[a/b]), 1.74 – 1.48 (m, 28H, CH_2-5[a/b] hexenyl, 12×CH_2 Ada[a/b]).^{13}C NMR (125 MHz, $CDCl_3$) *E/Z*-isomers (Z-rotamers a/b; ~1:1) δ 155.7, 155.6, 155.5, 155.5 (C=O[a/b] *E/Z* Z), 139.0, 138.9, 138.3, 138.2, 138.2, 138.2, 138.2 (3×C_q[a/b] *E/Z* Bn), 136.7, 136.7, 136.6, 136.6 (C_q[a/b] *E/Z* Z), 133.3, 133.0 (=CH-3[a/b] *E* hexenyl), 132.1, 131.9 (=CH-3[a/b] *Z* hexenyl), 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.6 (H_{Ar}[a/b] *E/Z* Bn/Z), 125.9, 125.7(=CH-2[a/b] *E* hexenyl), 125.6, 125.4 (=CH-2[a/b] *Z* hexenyl), 82.4, 82.2, 82.2 (C-3[a/b] *E/Z*), 82.1, 82.0, 82.0 (OCH_2-Ada[a/b] *E/Z*), 79.9, 79.8 (C-2[a/b] *E/Z*), 78.4, 78.3, 78.2 (C-4[a/b] *E/Z*), 75.9, 75.8, 75.8, 75.8, 73.3, 73.3, 73.2, 73.1, 72.9, 72.7 (CH_2[a/b] *E/Z* Bn), 71.0, 71.0, 70.8 (CH_2-6[a/b] *E/Z* hexenyl), 67.5, 67.5, 67.5, 67.4 (CH_2[a/b] *E/Z* Z), 53.6, 53.3, 53.0, 52.4 (C-1[a/b] *E/Z*), 41.1, 41.1, 40.9, 40.8 (C-5[a/b] *E/Z*), 39.9 (CH_2[a/b] *E/Z* Ada), 37.4, 37.4 (CH_2[a/b] *E/Z* Ada), 34.2 (C_q[a/b] *E/Z* Ada), 29.6, 29.5, 29.5, 29.3, 29.2, 28.9, 28.5, 28.5(CH_2[a/b] *E/Z* hexenyl), 28.4, 28.4 (CH[a/b] Ada), 24.2, 24.2, 23.0, 22.9 (CH_2[a/b] *E/Z* hexenyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2848, 1700, 1452, 1423, 1360, 1314, 1239, 1206, 1157, 1098, 969, 734, 696. $[\alpha]^{20}_D$: –10.4 (*c* 2.0, $CHCl_3$). HRMS: found 784.4572 $[M+H]^+$, calculated for $[C_{51}H_{61}NO_6+H]^+$ 784.4572.



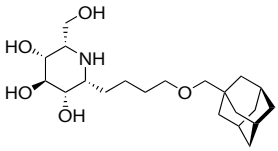
(1*R*)-1-*C*-[4-(Adamantan-1-yl-methoxy)-butyl]-1-deoxynojirimycin (72). Compound **63** (155 mg, 177 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **72** (38 mg, 99 µmol) as a colorless oil in 56% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of minor a 5-10% impurity (1 min: isocratic 25% B » 11.5 min: 45% B » 12.5 min: 100% B, 15 min: isocratic 100% B; t_R = 8.3` min). R_F = 0.32 (1:3; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (500 MHz, MeOD) δ 3.90 – 3.80 (m, 2H, CH_2-6), 3.73 (dd, *J* = 4.1, 7.1, 1H, H-2), 3.64 (dd, *J* = 7.0, 7.1, 1H, H-3), 3.49 (dd, *J* = 7.0, 7.0, 1H, H-4), 3.41 (t, *J* = 6.2, 2H, CH_2-4 butyl), 3.38 – 3.32 (m, 1H, H-1), 3.22 – 3.14 (m, 1H, H-5), 2.97 (s, 2H, OCH_2-Ada), 1.94 (s, 3H, 3×CH Ada), 1.91 – 1.85 (m, 1H, C*H*H-1 butyl), 1.71 (dd, *J* = 12.1, 39.6, 7H, 3×CH_2 Ada), 1.65 – 1.58 (m, 3H, CH*H*-1 butyl, CH_2-3 butyl), 1.58 – 1.54 (m, 7H, 3×CH_2 Ada), 1.54 – 1.44 (m, 2H, CH_2-2 butyl). ^{13}C NMR (100 MHz, MeOD) δ 83.3 (OCH_2-Ada), 74.1 (C-3), 72.4 (CH_2-4 butyl), 72.0 (C-2), 71.5 (C-4), 60.7 (C-6), 58.3 (C-5), 56.2 (C-1), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2-3 butyl), 29.9 (CH Ada), 26.8 (CH_2-1 butyl), 24.1 (CH_2-2 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3326, 2902, 2848, 1594, 1452, 1362, 1157, 1094. $[\alpha]^{20}_D$: 10.9 (*c* 0.2, MeOH). HRMS: found 384.2746 $[M+H]^+$, calculated for $[C_{21}H_{37}NO_5+H]^+$ 384.2744.



(1*R*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (73). Compound **64** (148 mg, 155 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **73** (54 mg, 136 µmol) as a colorless oil in 82% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 10% B » 12 min: 100% B » 12 min: 100% B, 15 min: isocratic 100% B; t_R = 7.2 min). R_F = 0.33 (1:3; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 4.00 (dd, *J* = 7.1, 12.0, 1H, H-6a), 3.83 (dd, *J* = 3.8, 12.0, 1H, H-6b), 3.78 (dd, *J* = 3.6, 6.5, 1H, H-2), 3.72 (t, *J* = 6.5, 6.6, 1H, H-3), 3.63 (t, *J* = 6.6, 6.6, 1H, H-4), 3.47 (dt, *J* = 3.6, 6.9, 1H, H-1), 3.40 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.36 – 3.32 (m, 1H, H-5), 2.97 (s, 2H, OCH_2-Ada), 1.98 – 1.91 (m, 4H, C*H*H-1 pentyl, 3×CH Ada), 1.72 (dd, *J* = 11.9, 48.4, 6H, 3×CH_2 Ada), 1.66 – 1.57 (m, 3H, CH*H*-1 pentyl, CH_2-4 pentyl,), 1.56 (d, *J* = 2.5, 6H, 3×CH_2 Ada), 1.52 – 1.41 (m, 4H, CH_2-2, CH_2-3 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 81.7 (OCH_2-Ada), 71.2 (C-3), 71.0 (CH_2-5 pentyl), 68.8 (C-2), 68.0 (C-4), 58.0 (C-5), 57.0 (C-6), 53.5 (C-1), 48.0 (C-6), 39.4 (CH_2 Ada), 36.9 (CH_2 Ada), 33.8 (C_q Ada), 29.0 (CH_2-4 pentyl), 28.4 (CH Ada), 26.0, 25.8, 25.5 (3×CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2901, 2849, 1454, 1363, 1087. $[\alpha]^{20}_D$: 7.6 (*c* 0.6, MeOH). HRMS: found 398.2898 $[M+H]^+$, calculated for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.

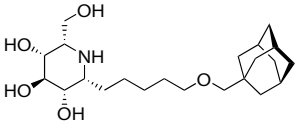


(1*R*)-1-*C*-[6-(Adamantan-1-yl-methoxy)-hexyl]-1-deoxynojirimycin (74). Compound **65** (158 mg, 175 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **74** (58 mg, 141 µmol) as a colorless oil in 81% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 10% B » 12 min: 100% B » 12 min: 100% B, 15 min: isocratic 100% B; t_R = 7.8 min). R_F = 0.35 (1:3; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 4.00 (dd, *J* = 7.1, 12.0, 1H, H-6a), 3.83 (dd, *J* = 3.8, 12.0, 1H, H-6b), 3.78 (dd, *J* = 3.6, 6.6, 1H, H-2), 3.71 (dd, *J* = 6.6, 6.7, 1H, H-3), 3.62 (dd, *J* = 6.7, 6.7, 1H, H-4), 3.46 (dt, *J* = 3.6, 6.9, 1H, H-1), 3.38 (t, *J* = 6.4, 2H, CH_2-6 hexyl), 3.34 – 3.32 (m, 1H, H-5), 2.97 (s, 2H, OCH_2-Ada), 1.98 – 1.90 (m, 4H, CH*H*-1 hexyl, 3×CH Ada), 1.72 (dd, *J* = 11.8, 48.2, 6H, 3×CH_2 Ada), 1.65 – 1.60 (m, 1H, CH*H*-1 hexyl), 1.59 – 1.54 (m, 8H, CH_2-5 hexyl, 3×CH_2 Ada), 1.50 – 1.44 (m, 2H, CH_2-2 hexyl), 1.44 – 1.39 (m, 4H, 2×CH_2 hexyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 72.8 (C-3), 72.7 (CH_2-6 hexyl), 70.4 (C-2), 69.5 (C-4), 59.5 (C-5), 58.6 (C-6), 55.3 (C-1), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2-5 hexyl), 30.5 (CH_2 hexyl), 29.9 (CH Ada), 27.6 (CH_2-1 hexyl), 27.3 (CH_2 hexyl), 27.2 (CH_2-2 hexyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2901, 2848, 1593, 1452, 1361, 1096, 1046. $[\alpha]^{20}_D$: 9.2 (*c* 0.7, MeOH). HRMS: found 412.3055 $[M+H]^+$, calculated for $[C_{23}H_{41}NO_5+H]^+$ 412.3057.

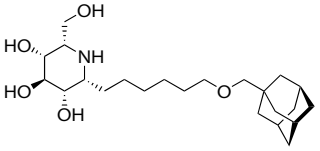


(1*R*)-1-*C*-[4-(Adamantan-1-yl-methoxy)-butyl]-L-*ido*-1-deoxynojirimycin (75). Compound **66** (141 mg, 161 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **75** (33 mg, 86 µmol) as a colorless oil in 53% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 25% B » 11.5 min: 45% B » 12.5 min: 100% B, 15 min: isocratic 100% B; t_R = 9.0 min). R_F = 0.49 (1:3; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 4.02 (dd, *J* = 3.5, 3.5, 1H, H-3), 3.93 – 3.90 (m, 1H, H-4), 3.90 – 3.88 (m, 1H, H-2), 3.87 – 3.81 (m, 2H, CH_2-6), 3.54 – 3.50 (m, 1H, H-5), 3.44 – 3.39 (m, 3H, H-1, CH_2-4 butyl), 2.98 (s, 2H, OCH_2-Ada), 2.00 – 1.92 (m, 4H, C*H*H-1 butyl, 3×CH Ada), 1.79 – 1.66 (m, 7H, CH*H*-1 butyl, 3×CH_2 Ada), 1.66 – 1.58 (m, 2H, CH_2-3 butyl), 1.58 – 1.50 (m, 7H, 3×CH_2 Ada, C*H*H-2 butyl), 1.46 – 1.38 (m, 1H, CH*H*-2 butyl). ^{13}C NMR (150 MHz, MeOD) δ 83.3 (OCH_2-Ada), 72.3 (CH_2-4 butyl), 69.2 (C-4), 69.0 (C-2), 68.2 (C-3), 60.6 (C-6), 58.8 (C-5), 56.9 (C-5), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.6 (CH_2-3 butyl), 29.9 (CH Ada),

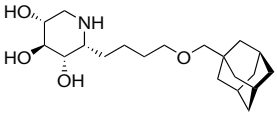
28.9 (CH_2-1 butyl), 22.9 (CH_2-2 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2902, 2848, 1451, 1068, 996. $[\alpha]^{20}_D$: –14.0 (*c* 0.2, MeOH). HRMS: found 384.2747 $[M+H]^+$, calculated for $[C_{21}H_{37}NO_5+H]^+$ 384.2744.



(1*R*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pentyl]-L-*ido*-1-deoxy-nojirimycin (76). Compound **67** (139 mg, 156 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **76** (46 mg, 116 µmol) as a colorless oil in 73% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 10% B » 12 min: 100% B » 12 min: 100% B, 15 min: isocratic 100% B; t_R = 7.4 min). R_F = 0.50 (1:3; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 4.02 (t, *J* = 3.5, 1H, H-3), 3.93 – 3.91 (m, 1H, H-4), 3.91 – 3.88 (m, 1H, H-2), 3.86 – 3.80 (m, 2H, CH_2-6), 3.54 – 3.50 (m, 1H, H-5), 3.43 – 3.38 (m, 3H, H-1, CH_2-5 pentyl), 2.97 (s, 2H, OCH_2-Ada), 2.00 – 1.91 (m, 4H, C*H*H-1 pentyl, 3×CH Ada), 1.79 – 1.65 (m, 7H, CH*H*-1 pentyl, 3×CH_2 Ada), 1.64 – 1.57 (m, 2H, CH_2-4 pentyl), 1.56 (d, *J* = 2.2, 6H, 3×CH_2 Ada), 1.53 – 1.41 (m, 3H, C*H*H-2 pentyl, CH_2-3 pentyl), 1.41 – 1.33 (m, 1H, CH*H*-2 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 72.5 (CH_2-5 pentyl), 69.2 (C-4), 69.0 (C-2), 68.2 (C-3), 60.6 (C-6), 58.8 (C-5), 56.9 (C-1), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.6 (CH_2-4 pentyl), 29.9 (CH Ada), 29.0 (CH_2-1 pentyl), 27.3 (CH_2-3 pentyl), 25.9 (CH_2-2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3331, 2902, 2849, 1590, 1451, 1259, 1068, 998. $[\alpha]^{20}_D$: –14.3 (*c* 0.3, MeOH). HRMS: found 398.2897 $[M+H]^+$, calculated for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.

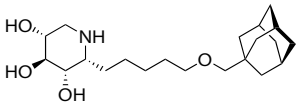


(1*R*)-1-*C*-[6-(Adamantan-1-yl-methoxy)-hexyl]-L-*ido*-1-deoxy-nojirimycin (77). Compound **68** (154 mg, 170 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **77** (51 mg, 124 µmol) as a colorless oil in 73% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 10% B » 12 min: 100% B » 12 min: 100% B, 15 min: isocratic 100% B; t_R = 7.8 min). R_F = 0.53 (1:3; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 4.02 (dd, *J* = 3.5, 1H, H-3), 3.92 – 3.90 (m, 1H, H-4), 3.90 – 3.87 (m, 1H, H-2), 3.86 – 3.80 (m, 2H, CH_2-6), 3.53 – 3.49 (m, 1H, H-5), 3.43 – 3.37 (m, 3H, H-1, CH_2-6 hexyl), 2.97 (s, 2H, OCH_2-Ada), 1.99 – 1.91 (m, 4H, C*H*H-1 hexyl, 3×CH Ada), 1.79 – 1.65 (m, 7H, CH*H*-1 hexyl, 3×CH_2 Ada), 1.60 – 1.54 (m, 8H, CH_2-5 hexyl, 3×CH_2 Ada), 1.51 – 1.31 (m, 6H, 3×CH_2 hexyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 72.7 (CH_2-6 hexyl), 69.2 (C-4), 69.0 (C-2), 68.2 (C-3), 60.6 (C-6), 58.8 (C-5), 57.0 (C-1), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2-5 hexyl), 30.5 (CH_2 hexyl), 29.9 (CH Ada), 29.0 (CH_2-1 hexyl), 27.3 (CH_2 hexyl), 26.1 (CH_2 hexyl). IR ν_{max}(thin film)/ cm^{-1}: 3327, 2901, 2848, 1590, 1451, 1203, 1111, 1068, 999. $[\alpha]^{20}_D$: –11.0 (*c* 0.3, MeOH). HRMS: found 412.3055 $[M+H]^+$, calculated for $[C_{23}H_{41}NO_5+H]^+$ 412.3057.

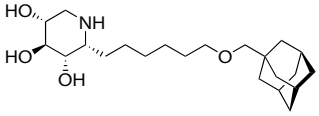


(1*R*)-1-*C*-[4-(Adamantan-1-yl-methoxy)-butyl]-1,5-dideoxy-1,5-imino-D-xylitol (78). Compound **69** (111 mg, 147 µmol) was subjected to hydrogenolysis at at 4 bar H_2 (see general procedure H) to furnish **78** (41 mg, 116 µmol) as a colorless oil in 79% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 25% B » 11.5 min: 45% B » 12.5 min: 100% B, 15 min: isocratic 100% B; t_R = 9.2 min). R_F = 0.30 (1:4; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.96 (dd, *J* = 3.3, 1H, H-3), 3.92 – 3.89 (m, 1H, H-4), 3.86 – 3.83 (m, 1H, H-2), 3.44 – 3.38 (m, 4H, H-1, C*H*H-5, CH_2-4 butyl), 3.19 (d, *J* = 13.1, 1H, CH*H*-5), 2.98 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.91 – 1.84 (m, 1H, C*H*H-1 butyl), 1.72 (dd, *J* = 11.6, 49.2, 6H, 3×CH_2 Ada), 1.66 – 1.59 (m, 3H, CH*H*-1 butyl, CH_2-3 butyl), 1.56 (d, *J* = 2.3, 6H, 3×CH_2 Ada), 1.55 – 1.49 (m, 1H, C*H*H-2 butyl), 1.49 – 1.42 (m, 1H, CH*H*-2 butyl). ^{13}C NMR (150 MHz, MeOD) δ 83.3 (OCH_2-Ada), 72.2 (CH_2-4 butyl), 69.6 (C-2), 68.3 (C-4), 68.0 (C-3),

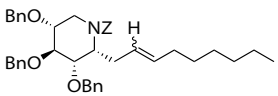
56.5 (C-1), 47.5 (C-5), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.6 (CH_2-3 butyl), 29.9 (CH Ada), 29.6 (CH_2-1 butyl), 22.9 (CH_2-2 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3368, 2903, 2849, 1451, 1203, 1139, 1060. $[\alpha]^{20}_D$: –13.4 (*c* 0.2, MeOH). HRMS: found 354.2639 $[M+H]^+$, calculated for $[C_{20}H_{35}NO_4+H]^+$ 354.2639.



(1*R*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1,5-dideoxy-1,5-imino-D-xylitol (79). Compound **70** (140 mg, 182 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **79** (62 mg, 169 µmol) as a colorless oil in 93% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 30% B » 11.5 min: 50% B » 12.5 min: 100% B, 15 min: isocratic 100% B; t_R = 6.5 min). R_F = 0.31 (1:4; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.96 (dd, *J* = 3.2, 1H, H-3), 3.92 – 3.89 (m, 1H, H-4), 3.86 – 3.83 (m, 1H, H-2), 3.43 – 3.37 (m, 4H, H-1, C*H*H-5, CH_2-5 pentyl), 3.19 (d, *J* = 13.1, 1H, CH*H*-5), 2.97 (s, 2H, OCH_2-Ada), 1.94 (s, 3H, 3×CH Ada), 1.90 – 1.83 (m, 1H, C*H*H-1 pentyl), 1.72 (dd, *J* = 11.9, 49.3, 6H, 3×CH_2 Ada), 1.66 – 1.57 (m, 3H, CH*H*-1 pentyl, CH_2-4 pentyl), 1.56 (d, *J* = 2.3, 6H, 3×CH_2 Ada), 1.52 – 1.38 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 72.5 (CH_2-5 pentyl), 69.6 (C-2), 68.4 (C-4), 68.0 (C-3), 56.4 (C-1), 47.4 (C-5), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.5 (CH_2-4 pentyl), 29.9 (CH Ada, 29.8 (CH_2-1 pentyl), 27.3 (CH_2 pentyl), 25.8 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3367, 2903, 2849, 1450, 1202, 1139, 1060. $[\alpha]^{20}_D$: –15.8 (*c* 0.3, MeOH). HRMS: found 368.2796 $[M+H]^+$, calculated for $[C_{21}H_{37}NO_4+H]^+$ 368.2795.

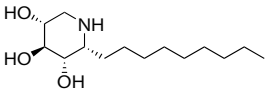


(1*R*)-1-*C*-[6-(Adamantan-1-yl-methoxy)-hexyl]-1,5-dideoxy-1,5-imino-D-xylitol (80). Compound **71** (173 mg, 221 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **80** (75 mg, 197 µmol) as a colorless oil in 89% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 10% B » 12 min: 100% B » 12 min: 100% B, 15 min: isocratic 100% B; t_R = 7.9 min). R_F = 0.33 (1:4; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.96 (dd, *J* = 3.3, 1H, H-3), 3.92 – 3.90 (m, 1H, H-4), 3.85 – 3.83 (m, 1H, H-2), 3.43 – 3.36 (m, 4H, H-1, C*H*H-5, CH_2-6 hexyl), 3.19 (d, *J* = 13.1, 1H, CH*H*-5), 2.97 (s, 2H, OCH_2-Ada), 1.94 (s, 3H, 3×CH Ada), 1.89 – 1.82 (m, 1H, C*H*H-1 hexyl), 1.79 – 1.61 (m, 7H, CH*H*-1 hexyl, 3×CH_2 Ada), 1.61 – 1.53 (m, 8H, CH_2-5 hexyl, 3×CH_2 Ada), 1.50 – 1.43 (m, 1H, C*H*H-2 hexyl), 1.43 – 1.37 (m, 5H, CH*H*-2 hexyl, 2×CH_2 hexyl). ^{13}C NMR (150 MHz, MeOD) δ 83.2 (OCH_2-Ada), 72.7 (CH_2-6 hexyl), 69.6 (C-2), 68.3 (C-4), 68.0 (C-3), 56.4 (C-1), 47.4 (C-5), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2-5 hexyl), 30.4 (CH_2 hexyl), 29.9 (CH Ada), 29.7 (CH_2-1 hexyl), 27.3 (CH_2 hexyl), 26.0 (CH_2 hexyl). IR ν_{max}(thin film)/ cm^{-1}: 3370, 2902, 2849, 1449, 1202, 1139, 1061. $[\alpha]^{20}_D$: –13.7 (*c* 0.6, MeOH). HRMS: found 382.2954 $[M+H]^+$, calculated for $[C_{22}H_{39}NO_4+H]^+$ 382.2952.

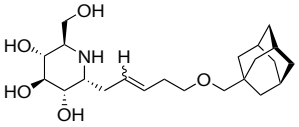


(1*R*)-*N*-Benzyloxycarbonyl-1,5-dideoxy-1,5-imino-1-*C*-[(*E*/*Z*)-non-2-enyl]-2,3,4-tri-*O*-benzyl-D-xylitol (81). Compound **61** (200 mg, 346 µmol) underwent a cross-metathesis reaction (see general procedure F) with non-1-ene to produce **81** (197 mg, 297 µmol) in 86% yield as a 5:1 mixture of *E*/*Z*-isomers after purification (0% » 10% EtOAc in PE). R_F = 0.61 (1:4; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) *E*-isomer rotamers (a/b; ~1:1) δ 7.41 – 7.03 (m, 40H, H_{Ar} $^{a/b}$ Bn/Z), 5.39 – 5.30 (m, 2H, =CH-3$^{a/b}$ nonenyl), 5.24 – 5.17 (m, 1H, =CH-2^a nonenyl), 5.13 – 5.06 (m, 1H, =CH-2^b nonenyl), 5.06 – 4.93 (m, 4H, CH_2 $^{a/b}$ Z), 4.82 – 4.72 (m, 4H, CH_2 $^{a/b}$ Bn), 4.65 – 4.50 (m, 9H, 2×CH_2 $^{a/b}$ Bn, H-1^a), 4.35 – 4.27 (m, 2H, H-1^b, C*H*H-5^a), 4.07 (dd, *J* = 5.7, 13.7, 1H, CH*H*-5^a), 3.63 – 3.55 (m, 2H, H-3$^{a/b}$), 3.47 (dd, *J* = 5.9, 9.5, 1H, H-2^a), 3.44 – 3.36 (m, 2H, H-2^b, H-4^a), 3.32 (ddd, *J* = 5.9, 8.8, 11.2, 1H, H-4^b), 2.68 – 2.62 (m, 2H, CH_2-5^b), 2.50 – 2.34 (m, 2H, C*H*H-1$^{a/b}$ nonenyl), 2.19 – 2.09 (m, 2H, CH*H*-1$^{a/b}$ nonenyl), 1.87 – 1.74 (m, 4H, CH_2-4$^{a/b}$ nonenyl), 1.29 – 1.11 (m, 16H, 4×$CH_2$$^{a/b}$ nonenyl), 0.83 – 0.75 (m, 6H, CH_3-9$^{a/b}$ nonenyl). ^{13}C NMR (125 MHz, $CDCl_3$)

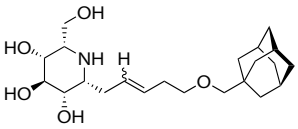
E-isomer rotamers (a/b; ~1:1) δ 155.8, 155.6 (C=O$^{a/b}$ Z), 139.0, 138.4, 138.3, 138.3, 138.2 (3×$C_q^{a/b}$ Bn), 136.8, 136.7 ($C_q^{a/b}$ Z), 134.0, 133.7 (=CH-3$^{a/b}$ nonenyl), 128.7, 128.6, 128.6, 128.6, 128.5, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.7 ($CH_{Ar}^{a/b}$ Bn/Z), 125.5, 125.3 (=CH-2$^{a/b}$ nonenyl), 82.3, 82.1 (C-3$^{a/b}$), 80.0 (C-2$^{a/b}$), 78.5, 78.4 (C-4$^{a/b}$), 75.9, 75.9, 73.4, 73.3, 73.2, 72.8 ($CH_2^{a/b}$ Bn), 67.5, 67.5 ($CH_2^{a/b}$ Z), 53.3, 52.5 (C-1$^{a/b}$), 41.1, 40.8 (C-5$^{a/b}$), 32.8, 32.7 (CH_2-4$^{a/b}$ nonenyl), 31.9 ($CH_2^{a/b}$ nonenyl), 29.6, 29.5 ($CH_2^{a/b}$ nonenyl), 29.1, 29.0 ($CH_2^{a/b}$ nonenyl), 28.6, 28.5 (CH_2-1$^{a/b}$ nonenyl), 22.8 ($CH_2^{a/b}$ nonenyl), 14.3 (CH_3-9 nonenyl). IR ν_{max}(thin film)/ cm^{-1}: 2926, 2855, 1700, 1454, 1423, 1359, 1313, 1203, 1096, 968, 734, 696. $[\alpha]^{20}_D$: –11.9 (*c* 1.7, $CHCl_3$). HRMS: found 662.3839 $[M+H]^+$, calculated for $[C_{43}H_{51}NO_5+H]^+$ 662.3840.



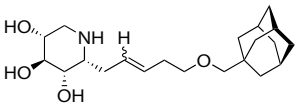
(1*R*)-1,5-Dideoxy-1,5-imino-1-*C*-nonyl-D-xylitol (82). Compound **81** (305 mg, 461 µmol) was subjected to hydrogenolysis at 4 bar H_2 (see general procedure H) to furnish **82** (113 mg, 438 µmol) as a colorless oil in 95% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 10% B » 12 min: 100% B » 12 min: 100% B, 15 min: isocratic 100% B; t_R = 6.7 min). R_F = 0.25 (1:4; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.97 – 3.96 (m, 1H, H-3), 3.93 – 3.89 (m, 1H, H-4), 3.85 – 3.82 (m, 1H, H-2), 3.41 (dd, *J* = 1.7, 13.1, 1H, H-5a), 3.37 (d, *J* = 7.4, 1H, H-1), 3.19 (d, *J* = 13.1, 1H, H-5b), 1.88 – 1.81 (m, 1H, C*H*H-1 nonyl), 1.63 (ddd, *J* = 5.0, 10.5, 18.5, 1H, C*H*H-1 nonyl), 1.48 – 1.41 (m, 1H, CH*H*-2), 1.41 – 1.25 (m, 13H, C*H*H-2 nonyl, 6×CH_2 nonyl), 0.90 (t, *J* = 7.0, 3H, CH_3-9 nonyl). ^{13}C NMR (150 MHz, MeOD) δ 69.6 (C-2), 68.3 (C-4), 68.0 (C-3), 56.5 (C-1), 47.4 (C-6), 33.2, 30.7, 30.6, 30.5, 30.4 (5×CH_2 nonyl), 29.8 (CH_2-1 nonyl), 26.0 (CH_2-1 nonyl), 23.9 (CH_2 nonyl), 14.6 (CH_3-9 nonyl). IR ν_{max}(thin film)/ cm^{-1}: 3367, 2927, 2857, 1438, 1200, 1139, 1061. $[\alpha]^{20}_D$: –19.6 (*c* 0.4, MeOH). HRMS: found 260.2222 $[M+H]^+$, calculated for $[C_{14}H_{29}NO_3+H]^+$ 260.2220.



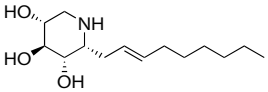
(1*R*)-1-*C*-[(*E*/*Z*)-5-(Adamantan-1-yl-methoxy)-pent-2-enyl]-1-deoxy-nojirimycin (83). Compound **64** (105 mg, 118 µmol) was subjected to a Birch reduction (see general procedure G) to furnish **83** (34 mg, 85 µmol) as a colorless oil in 72% yield as a 3/1 mixture of *E*/*Z* isomers after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 30% B » 12 min: 100% B » 12 min: 100% B, 15 min: isocratic 100% B; t_R = 4.5 min). R_F = 0.30 (1:4; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) *E*/*Z* isomers (integrals for *E*-isomer) δ 5.74 (dt, *J* = 6.8, 15.4, 1H, =CH-3 *E* pentenyl) 5.73 – 5.71 (m, =CH-3 *E* pentenyl), 5.52 – 5.44 (m, 1H, =CH-2 *E*/*Z* pentenyl), 4.02 (dd, *J* = 7.3, 11.9, H-6a *Z*), 3.97 (dd, *J* = 7.4, 11.9, 1H, H-6a-*E*), 3.84 – 3.78 (m, 2H, H-6b *E*/*Z*, H-2 *E*/*Z*), 3.76 (t, *J* = 6.0, H-3 *Z*), 3.73 (t, *J* = 6.5, 1H, H-3 *E*), 3.65 (t, *J* = 6.1, H-4 *Z*), 3.62 (t, *J* = 6.6, 1H, H-4 *E*), 3.54 – 3.48 (m, 1H, H-1 *E*/*Z*), 3.44 (t, *J* = 6.6, 2H, CH_2-5 *E*/*Z* pentenyl), 3.38 – 3.33 (m, 1H, H-5 *E*/*Z*), 3.00 (s, OCH_2-Ada *Z*), 2.99 (s, 2H, OCH_2-Ada *E*), 2.77 – 2.71 (m, C*H*H-1 *Z* pentenyl), 2.70 – 2.64 (m, 1H, *CH*H-1 *E* pentenyl), 2.51 – 2.45 (m, CH*H*-1 *Z* pentenyl), 2.43 – 2.36 (m, 1H, CH*H*-1 *E* pentenyl), 2.34 – 2.28 (m, 2H, CH_2-4 *E*/*Z* pentenyl), 1.95 (s, 3H, 3×CH Ada *E*/*Z*), 1.72 (dd, *J* = 11.9, 47.7, 6H, 3×CH_2 Ada *E*/*Z*), 1.56 (d, *J* = 2.4, 6H, 3×CH_2 Ada *E*/*Z*). ^{13}C NMR (150 MHz, MeOD) *E*/*Z* isomers δ 134.3 (=CH-3 *E* pentenyl), 132.6 (=CH-3 *Z* pentenyl), 126.4 (=CH-2 *E* pentenyl), 125.4 (=CH-2 *Z* pentenyl), 83.3 (OCH_2-Ada *Z*), 83.2 (OCH_2-Ada *E*), 72.7 (C-3 *E*), 72.5 (C-3 *Z*), 72.3 (CH_2-5 pentenyl *Z*), 72.1 (CH_2-5 pentenyl *E*), 70.1 (C-2 *E*), 70.1 (C-2 *Z*), 69.6 (C-4 *E*), 69.4 (C-4 *Z*), 59.5 (C-5 *E*/*Z*), 58.6 (C-6 *E*), 58.5 (C-6 *Z*), 54.7 (C-1 *E*/*Z*), 41.0 (CH_2 Ada), 38.4 (CH_2 Ada), 35.3 (C_q Ada *E*/*Z*), 34.1 (CH_2-4 pentenyl *E*), 30.7 (CH_2-1 pentenyl *E*), 29.9 (CH Ada), 29.2 (CH_2-4 pentenyl *Z*), 25.8(CH_2-1 pentenyl *Z*). IR ν_{max}(thin film)/ cm^{-1}: 3351, 2903, 2849, 1443, 1203, 1139, 1050. $[\alpha]^{20}_D$: 5.5 (*c* 0.3, MeOH). HRMS: found 396.2741 $[M+H]^+$, calculated for $[C_{22}H_{37}NO_5+H]^+$ 396.2744.



(1*R*)-1-*C*-[(*E*/*Z*)-5-(Adamantan-1-yl-methoxy)-pent-2-enyl]-L-*ido*-1-deoxynojirimycin (84). Compound **67** (95 mg, 107 µmol) was subjected to a Birch reduction (see general procedure G) to furnish **84** (30 mg, 75 µmol) as a colorless oil in 70% yield as a 1.3:2 mixture of *E*/*Z*-isomers after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (30% B » 11 min: 100% B, 15 min: isocratic 100% B; t_R = 3.8 min). R_F = 0.41/0.45 (1:4; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) *E*/*Z* isomers (integrals for *Z*-isomer) δ 5.72 (dt, *J* = 6.7, 15.4, =CH-3 *E* pentenyl), 5.67 (dt, *J* = 7.3, 10.9, 1H, =CH-3 *Z* pentenyl), 5.52 – 5.39 (m, 1H, =CH-2 *E*/*Z* pentenyl), 4.01 (dd, *J* = 3.3, 1H, H-3 *E*/*Z*), 3.93 – 3.89 (m, 1H, H-4 *E*/*Z*), 3.89 – 3.81 (m, 5H, H-2 *E*/*Z*, CH_2-6 *E*/*Z*), 3.55 – 3.50 (m, 1H, H-5 *E*/*Z*), 3.47 – 3.39 (m, 5H, H-1 *E*/*Z*, CH_2-5 *E*/*Z* pentenyl), 3.00 (s, 2H, OCH_2-Ada *Z*), 2.99 (s, OCH_2-Ada *E*), 2.80 – 2.74 (m, 1H, C*H*H-1 *Z* pentenyl), 2.64 – 2.58 (m, C*H*H-1 *E* pentenyl), 2.50 – 2.43 (m, 1H, CH*H*-1 *Z* pentenyl, CH*H*-1 *E* pentenyl), 2.43 – 2.37 (m, 2H, CH_2-4 *Z* pentenyl), 2.31 – 2.28 (m, CH_2-4 *E* pentenyl), 1.94 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.9, 47.0, 6H, 3×CH_2 Ada), 1.56 (d, *J* = 1.8, 6H, 3×CH_2 Ada). ^{13}C NMR (150 MHz, MeOD) δ 134.0 (=CH-3 *E* pentenyl), 132.5 (=CH-3 *Z* pentenyl), 126.0 (=CH-2 *E* pentenyl), 124.9 (=CH-2 *Z* pentenyl), 83.3 (OCH_2-Ada *Z*), 83.2 (OCH_2-Ada *E*), 72.3 (CH_2-5 *E* pentenyl), 72.2 (CH_2-5 *Z* pentenyl), 69.3 (C-4 *E*), 69.2 (C-4 *Z*), 69.1(C-2 *Z*), 69.0 (C-2 *E*), 68.2 (C-3 *E*/*Z*), 60.7 (C-6 *Z*), 60.6 (C-6 *E*), 58.9 (C-5 *Z*), 58.8 (C-5 *E*), 56.8 (C-1 *E*), 56.7 (C-1 *Z*), 41.0 (CH_2 Ada *E*), 40.9 (CH_2 Ada *Z*), 38.5 (CH_2 Ada *E*), 38.4 (CH_2 Ada *Z*), 35.3 (C_q Ada *Z*), 35.2 (C_q Ada *E*), 34.1 (CH_2-4 *E* pentenyl), 32.5 (CH_2-1 *E* pentenyl), 29.9 (CH Ada *E*), 29.8 (CH Ada *Z*), 29.2 (CH_2-4 *Z* pentenyl), 27.3 (CH_2-1 *Z* pentenyl). 432 IR ν_{max}(thin film)/ cm^{-1}: 3365, 2903, 2849, 1444, 1203, 1140, 1075, 1011. $[\alpha]^{20}_D$: –10.1 (*c* 0.3, MeOH). HRMS: found 396.2741 $[M+H]^+$, calculated for $[C_{22}H_{37}NO_5+H]^+$ 396.2744.



(1*R*)-1-*C*-[(*E*/*Z*)-5-(Adamantan-1-yl-methoxy)-pent-2-enyl]-1,5-dideoxy-1,5-imino-D-xylitol (85). Compound **70** (110 mg, 143 µmol) was subjected to a Birch reduction (see general procedure G) to furnish **85** (34 mg, 93 µmol) as a colorless oil in 65% yield as a 1.2:1 mixture of *E*/*Z*-isomers after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for removal of a minor 5-10% impurity (1 min: isocratic 10% B » 12 min: 100% B » 12 min: 100% B, 15 min: isocratic 100% B; t_R = 7.3 min). R_F = 0.39/0.45 (1:4; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) *E*/*Z* isomers (integrals for *E*-isomer) δ 5.75 – 5.67 (m, 2H, =CH-3 *E*/*Z* pentenyl), 5.52 – 5.42 (m, 2H, =CH-2 *E*/*Z* pentenyl), 3.96 (dd, *J* = 3.6, 2H, H-3), 3.93 – 3.90 (m, 2H, H-4), 3.84 – 3.82 (m, 1H, H-2 *E*), 3.82 – 3.80 (m, H-2 *Z*), 3.46 – 3.37 (m, 4H, H-1 *E*/*Z*, C*H*H-5 *E*/*Z*, CH_2-5 pentenyl *E*/*Z*), 3.23 – 3.21 (m, 1H, CH*H*-5 *E*), 3.21 – 3.19 (m, CH*H*-5 *Z*), 3.00 (s, OCH_2-Ada *Z*), 2.99 (s, 2H, OCH_2-Ada *E*), 2.67 – 2.61 (m, C*H*H-1 *Z* pentenyl), 2.56 – 2.49 (m, 1H, C*H*H-1 *E* pentenyl), 2.49 – 2.43 (m, CH*H*-1 *Z* pentenyl), 2.43 – 2.35 (m, 1H, CH*H*-1 *E* pentenyl, CH_2-4 *Z* pentenyl), 2.35 – 2.28 (m, 2H, CH_2-4 *E* pentenyl), 1.94 (s, 3H, 3×CH Ada *E*/*Z*), 1.72 (dd, *J* = 11.8, 47.5, 6H, 3×CH_2 Ada *E*/*Z*), 1.56 (d, *J* = 2.6, 6H, 3×CH_2 Ada *E*/*Z*). ^{13}C NMR (150 MHz, MeOD) *E*/*Z* isomers δ 134.2 (=CH-3 *E*/*Z* pentenyl), 132.8 (=CH-3 *Z* pentenyl), 125.9 (=CH-2 *E* pentenyl), 124.9 (=CH-2 *Z* pentenyl), 83.3 (OCH_2-Ada *Z*), 83.2 (OCH_2-Ada *E*), 72.2 (CH_2-5 *E* pentenyl), 72.1 (CH_2-5 *Z* pentenyl), 69.7 (C-2 *E*), 69.7 (C-2 *Z*), 68.4 (C-4 *E*), 68.3 (C-4 *Z*), 68.0 (C-3 *E*/*Z*), 56.4 (C-1 *Z*), 56.4 (C-1 *E*), 47.5 (C-5 *E*/*Z*), 40.9 (CH_2 Ada *E*/*Z*), 38.4 (CH_2 Ada *E*/*Z*), 35.3 (C_q Ada *Z*), 35.2 (C_q Ada *E*), 34.1 (CH_2-4 *E* pentenyl), 33.3 (CH_2-1 *E* pentenyl), 29.9 (CH Ada *E*/*Z*), 29.2 (CH_2-4 *Z* pentenyl), 28.0 (CH_2-1 *Z* pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3367, 2902, 2849, 1444, 1200, 1137, 1064, 1012, 940. $[\alpha]^{20}_D$: –12.0 (*c* 0.5, MeOH). HRMS: found 366.2639 $[M+H]^+$, calculated for $[C_{21}H_{35}NO_4+H]^+$ 366.2639.



(1*R*)-1,5-Dideoxy-1,5-imino-1-*C*-[(*E*)-non-2-enyl]-D-xylitol (86). Compound **81** (110 mg, 166 µmol) was subjected to a Birch reduction (see general procedure G) to furnish **86** (30 mg, 115 µmol) as a colorless oil in 69% yield after purification (silica gel: 0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH). Additional HPLC purification was required for

removal of a minor 5-10% impurity (1 min: isocratic 20% B » 11.5 min: 40% B » 12.5 min: 100% B, 20 min: isocratic 100% B; t_R = 7.6 min)**.** R_F = 0.32 (1:4; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 5.69 (dt, *J* = 6.8, 15.2, 1H, =CH-2 nonenyl), 5.40 (dt, *J* = 7.2, 15.2, 1H, =CH-3 nonenyl), 3.97 – 3.93 (m, 1H, H-3), 3.93 – 3.89 (m, 1H, H-4), 3.84 – 3.80 (m, 1H, H-1), 3.42 – 3.36 (m, 2H, H-1, H-5a), 3.20 (d, *J* = 13.2, 1H, H-5b), 2.55 – 2.48 (m, 1H, C*H*H-1 nonenyl), 2.38 (dt, *J* = 6.8, 13.7, 1H, CH*H*-1 nonenyl), 2.09 – 2.02 (m, 2H, CH_2-4 nonenyl), 1.43 – 1.36 (m, 2H, CH_2-5 nonenyl), 1.36 – 1.26 (m, 6H, 3×CH_2 nonenyl), 0.90 (t, *J* = 7.0, 3H, CH_3-9 nonenyl). ^{13}C NMR (150 MHz, MeOD) δ 137.7 (=CH-3 nonenyl), 124.0 (=CH-2 nonenyl), 69.7 (C-2), 68.4 (C-4), 68.0 (C-3), 56.4 (C-1), 47.5 (C-6), 33.8 (CH_2-4 nonenyl), 33.2 (CH_2-1 nonenyl), 33.0 (CH_2 nonenyl), 30.4 (CH_2-5 nonenyl), 30.1 (CH_2 nonenyl), 23.8 (CH_2 nonenyl), 14.6 (CH_3-9 nonenyl). IR ν_{max}(thin film)/ cm^{-1}: 3366, 2928, 2857, 1436, 1199, 1139, 1062, 1007, 971. $[\alpha]^{20}_D$: –13.2 (*c* 0.4, MeOH). HRMS: found 258.2065 $[M+H]^+$, calculated for $[C_{14}H_{27}NO_3+H]^+$ 258.2064.

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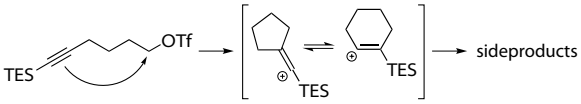

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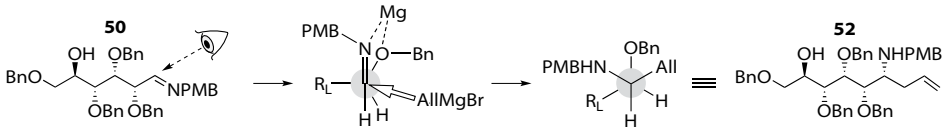

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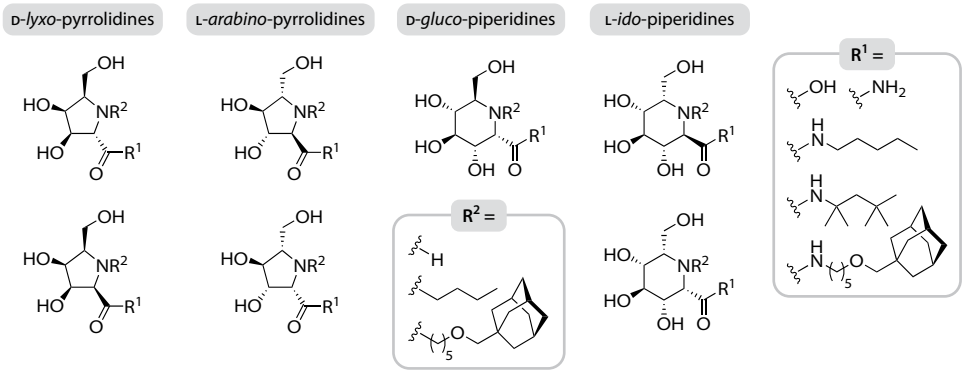
7 Combinatorial Synthesis of Lipophilic Iminosugars

via a Tandem Staudinger/aza-Wittig/ Ugi Three-component Reaction

Abstract

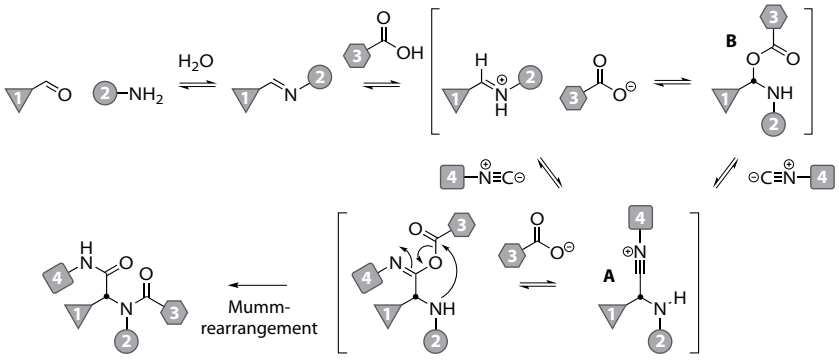
This chapter reports the use of the tandem Staudinger/aza-Wittig/Ugi three-component reaction to synthesize four libraries of lipophilic iminosugars in a combinatorial fashion. Four azido-aldehyde derivatives of D-lyxose, L-arabinose, D-glucose and L-idose were exposed to trimethylphosphine to provide the intermediate cyclic imines that were subsequently exposed to pent-4-enoic acid and four different isocyanides to provide 16 library precursors. Deprotection of the pent-4-enamide moiety and subsequent deprotection or *N*-alkylation and deprotection provided the final 73 library entries. Evaluation of the four libraries in an enzyme assay for inhibition of glucocerebrosidase, β-glucosidase 2 and glucosylceramide synthase produced several hits in the μM range.



Introduction

Multicomponent reactions (MCRs) are frequently used as a powerful method to generate large families of structurally related molecules.[1-6] MCRs are generally defined as processes in which three or more starting materials react in one-pot to form a product that incorporates essentially all of the atoms of the reactants.[6] Among MCRs, the Ugi reaction is one of the most explored to date and is widely used in organic and medicinal chemistry research because of its versatility in the creation of densely functionalized α-acylamino amides.[7]

Figure 1. Overview of the Ugi four-component reaction mechanism.

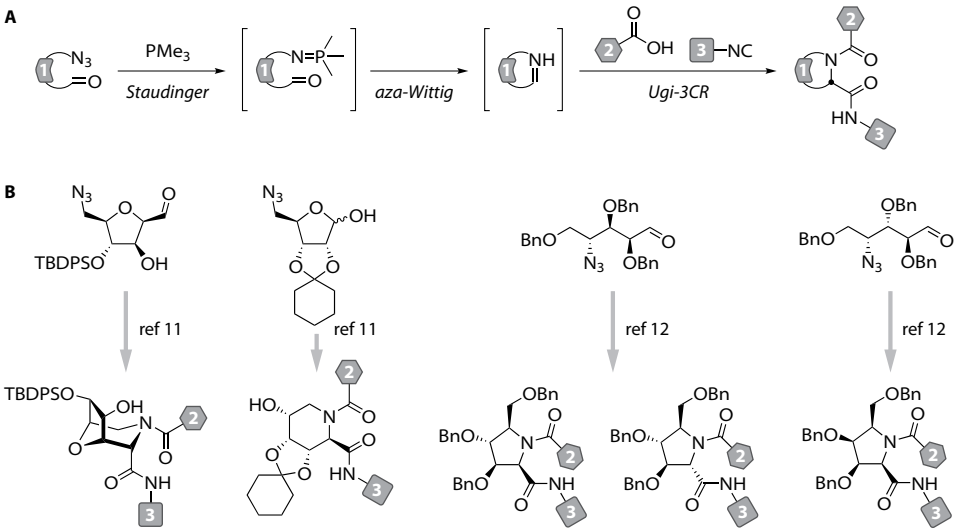


In the classic Ugi four-component reaction (Ugi-4CR), reported in 1959,[8] an aldehyde, an amine, a carboxylic acid and an isocyanide, all of which may possess a variety of different functionalities, are combined to form α-acylamino amides.[9,10] The first step in this process is the condensation of the aldehyde and amine entities to an intermediate imine (Figure 1). The imine is protonated by the carboxylic acid after which two pathways are possible. In the first pathway, the isocyanide attacks the α-carbon atom of the activated imine to form an intermediate nitrilium ion species (**A**). The second proposed pathway involves attack of the carboxylate on the protonated imine to generate an intermediate acyloxy intermediate (**B**).[5,9] The isocyanide can displace the acyl moiety in an S_N2 attack that generates nitrilium ion **A**. Intermediate **A** is attacked by the carboxylate and the subsequent product undergoes a Mumm-rearrangement to yield the Ugi product. The imine can also be preformed and subsequently mixed with a carboxylic acid and isocyanide. This variant is called the Ugi three-component reaction (Ugi-3CR).

Timmer *et al.* recently reported a variation of the Ugi-3CR, which was termed the tandem Staudinger/aza-Wittig/Ugi-3C reaction (SAWU-3CR).[11] In this process an azido-aldehyde is reacted with a trialkylphosphine (Staudinger reaction) to give an intermediate phosphazene that undergoes an intramolecular aza-Wittig reaction with the aldehyde moiety to provide a cyclic imine. Addition at this stage of a carboxylic acid and an isocyanide provides an α-acylamino amide product in an Ugi-3CR sequence of events (Figure 2A). The versatility of the SAWU-3CR has since been demonstrated by

its application on a variety of carbohydrate derived azido-aldehydes to produce small libraries of bridged morpholine derivatives, pipecolic acid derivatives and pyrrolidine iminosugars (Figure 2B).[11-13]

Figure 2. Overview of the tandem SAWU-3CR sequence of events (**A**) and its reported applications (**B**).

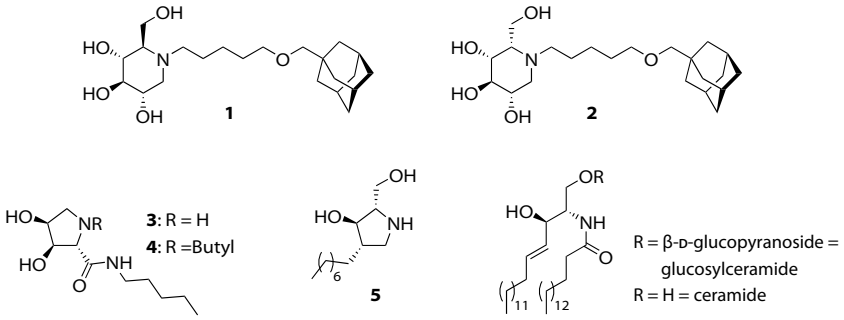


The overall goal of the research presented in this thesis is the development of selective and potent inhibitors of the enzymes involved in the metabolism of glucosylceramide (Figure 3). These targeted enzymes are glucosylceramide synthase (GCS), glucocerebrosidase (GBA1) and β-glucosidase 2 (GBA2). The structure of the developed compounds is based on lead compound **1** (Figure 3) that has been identified as a potent inhibitor of all three enzymes and its L-*ido* derivative **2** – a more selective inhibitor of GCS than **1**.

The chapters leading up to here have mostly discussed the development of new lipophilic iminosugars based on **1** and **2** via traditional linear multistep syntheses that often require separate routes for each target. In an alternative approach the preparation and use of the appropriate azido-aldehydes in the SAWU-3CR with a selection of carboxylic acids and isocyanides would in a combinatorial fashion generate a wide variety of lipophilic iminosugars in a few steps. Davis and co-workers have already applied this approach and developed a large library of lipophilic pyrrolidines via the Ugi-3CR and evaluated them as inhibitors of GCS among others.[14] In that study the cyclic imine was generated by elimination of a precursor *N*-chloropyrrolidine. However, none of the Ugi-3CR products were active against GCS. This can be explained by the fact that all studies on GCS inhibitors up to now have shown that GCS inhibitors require a basic nitrogen function. Indeed Davis and co-workers were able to identify two GCS inhibitors from the library, **3** and **4**, upon reduction or cleavage of the amide function on the endocylic nitrogen (Figure 3). In general, inhibitors of glucosylceramide metabolism based on pyrrolidine iminosugars have not been extensively investigated yet. A recent study by

Baltas and co-workers identified another distinct pyrrolidine iminosugar inhibitor of GCS. They modelled their target compounds on the structure of ceramide and found that compound **5** was a potent inhibitor of GCS (Figure 3).[15]

Figure 3. Structures of piperidine and pyrrolidine GCS inhibitors; structures of glucosylceramide and ceramide.



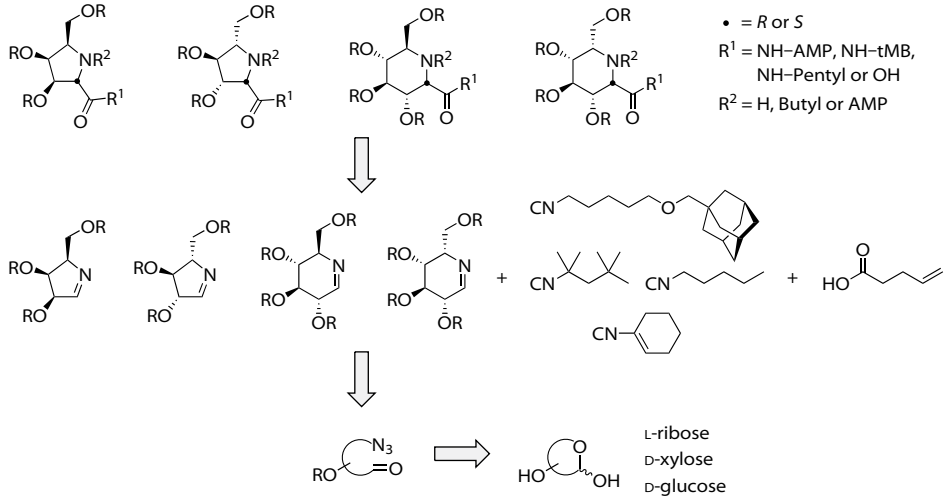
The research described in this chapter addresses the topics discussed above. It will discuss the use of the SAWU-3CR in a combinatorial approach towards the development of pyrrolidine and piperidine based lipophilic iminosugars. Simultaneously this will also further explore the scope of the SAWU-3CR and advance the structure–activity relationship knowledge on pyrrolidine-based inhibitors of GCS, GBA1 and GBA2.

The SAWU-3CR was applied on a previously studied[12,13] azido-aldehyde, synthesized from L-ribose, to create a library of lipophilic pyrrolidines with D-*lyxo* stereochemistry that among others generated derivatives of the above discussed compounds **3** and **4** of Davis and co-workers. A second azido-aldehyde, synthesized from D-xylose, was incorporated in the SAWU-3CR and generated a library of pyrrolidines with L-*arabino* stereochemistry – similar to the substitution pattern of **5**.

Finally, D-glucose was used as a starting material to prepare two azido-aldehydes that produced two libraries of lipophilic iminosugars. One based on lead compound **1** with D-*gluco* stereochemistry and another with L-*ido* stereochemistry based on **2**. For the isocyanides that were used in conjunction with the four azido-aldehyes, 5-(adamantane-1yl-methoxy)-pentyl- (AMP), 1,1,3,3-tetramethylbutyl- (tMB), pentyl- and cyclohexenyl-isocyanide were selected. The first isocyanide was selected for structural mimicry of **1** and **2**. The second and third were chosen as a way of introducing either a bulky or linear alternate hydrophobic moiety. The fourth isocyanide produces a cyclohexenamidoacyl function in the Ugi-3CR product that is known to be able to isomerize and hydrolyze when exposed to aqueous acidic conditions to generate a carboxylic acid.

The choice of suitable carboxylic acids for incorporation in the SAWU-3CR was restricted. Previous inhibition studies with amide derivatives of **1** and the earlier discussed results as obtained by Davis and co-workers have shown that amides of the iminosugar endocyclic nitrogen do not produce inhibitors of GCS, GBA1 or GBA1. Post-Ugi reduction of this amide results in low yields and difficultly separable mixtures of starting compound, the reduced amide and the free secondary amide.[16]

Figure 4. Retro-synthetic analysis of the four libraries of lipophilic iminosugars.



Therefore it was decided to incorporate pent-4-enoic acid in all the here presented SAWU-3C reactions. This produces the pent-4-enamide of the endocyclic nitrogen that can be cleaved to the secondary amine under mild conditions. The secondary nitrogen was then functionalized via reductive amination with butyraldehyde or 5-(adamantane-1yl-methoxy)-pentanal. All the prepared library entries were evaluated in an *in vitro* enzyme assay for inhibition of GBA1 and a selection of entries were also evaluated as inhibitors of GBA2 (*in vitro*) and GCS (*in vivo*).

Results and Discussion

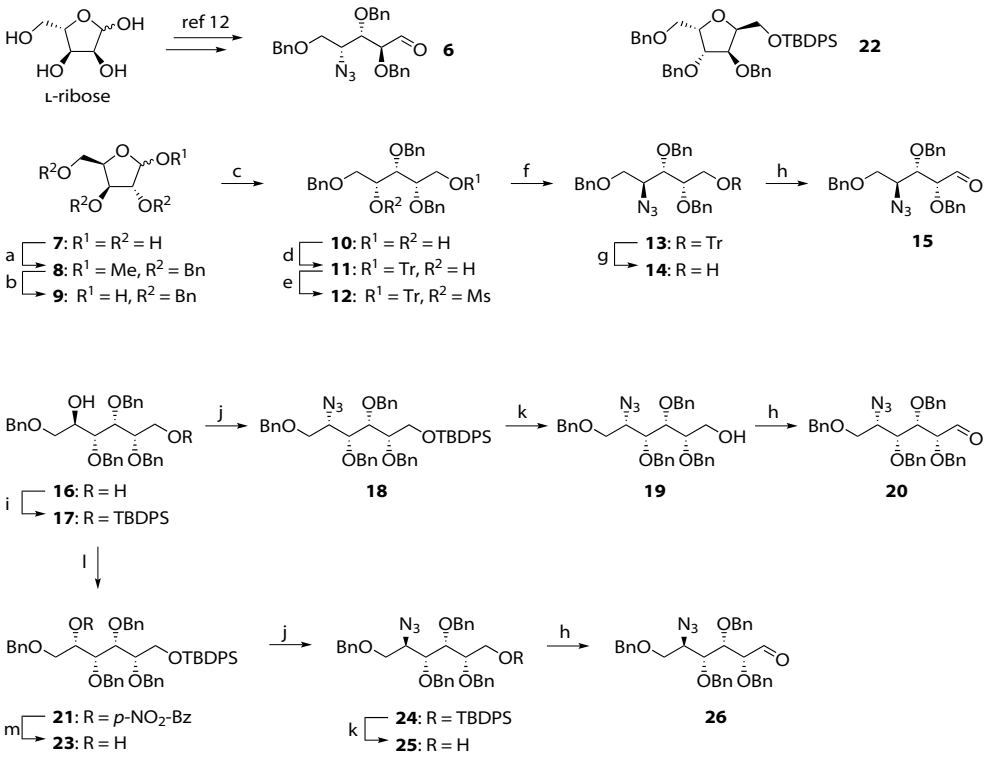
Synthesis of the Azido-aldehydes and Isocyanides.

Azido-aldehyde **6** was synthesized from L-ribose as previously reported.[12] Azido-alcohol **14** was synthesized starting from D-xylose in seven steps and 40% overall yield via the same route as reported for **6** (Scheme 1 on the next page). Dess-Martin periodinane mediated oxidation of **14** provided the azido-aldehyde **15**. The synthesis of azido-aldehydes **20** and **26** started from the common building block **17** that was prepared by silylation of the previously described glucitol derivate **16**. Azido-aldehyde **20** was prepared from **17** by introduction of an azide function at C-5 with inversion (**18**) via a Mitsunobu reaction with diphenylphosphoryl azide (DPPA) und subsequent desilylation to **19** and oxidation to **20**.

The synthesis of azido-aldehyde **26** with D-*gluco*-stereochemistry required a double inversion of the C-5 position. Inversion of the C-5 position with a Mitsunobu reaction with *p*-nitrobenzoic acid produced **21**, but was accompanied by the formation of byproduct **22** in 40–50%. Intramolecular cyclization of D-glucitol derivatives by nucleophilic attack of a C-2 benzylether upon activation of C-5 as a sulfon-ester has been

described in literature.[17] It has also been reported for a PPh_3-mediated C-5 iodination reaction.[18,19] Using different acids (AcOH, trichloroacetic acid and benzoic acid) in the Mitsunobu reaction and variation of other reaction conditions did not diminish the formation of byproduct **22**. Product **21** and **22** were difficult to separate and therefore the crude concentrated Mitsunobu reaction mixture was exposed to alkaline ester hydrolysis conditions that produced **23** in 38% yield over two steps, which could now be easily separated from **22**. Intermediate **23** could now be transformed into azido-aldehyde **26** by successive C-5 azide insertion (**24**), desilylation at C-1 (**25**) and oxidation.

Scheme 1. Synthesis of azido-aldehyes **6**, **15**, **20** and **26**.

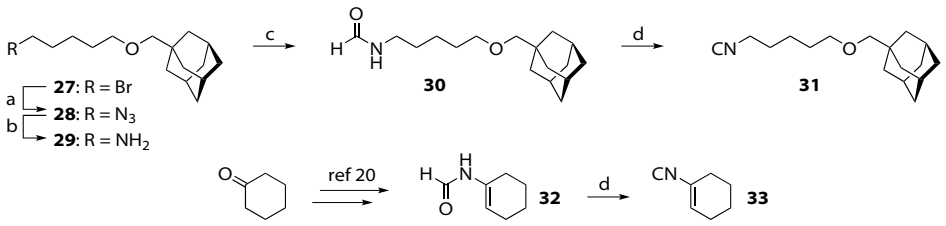


Reagents and conditions: [**a**] i: HCl, MeOH, rt, 20h; ii: BnBr, NaH, TBAI, DMF, 0 °C » rt, 48h, 93% 2 steps. [**b**] aq HCl, dioxane, reflux, 5h, 70%. [**c**] $NaBH_4$, MeOH, 0 °C, 3h, 87%. [**d**] TrCl, pyridine, 40 °C, 20h, 94%. [**e**] MsCl, Et_3N, DCM, 85%. [**f**] NaN_3, 15-crown-5, DMF, 90 °C, 48h, 88%. [**g**] $BF_3{\cdot}OEt_2$, MeOH, toluene, 3h, 98%. [**h**] Dess-Martin periodinane, DCM, 0 °C » rt, 1.5h, **15**: 76%, **20**: 89%, **26**: 96%. [**i**] TBDPSCl, imidazole, DMF, 20h, 99%. [**j**] DPPA, DIAD, PPh_3, THF, 0 °C » rt, 20h, **18**: 66%, **24**: 63%. [**k**] TBAF, THF, 20h, **19**: 71%, **25**: 74%. [**l**] *p*-NO_2-benzoic acid, DIAD, PPh_3, 0 °C » rt, 20h, used crude. [m] LiOH, H_2O/THF/EtOH, 2h, 38%, **22**: 46% from previous reaction.

Of the four isocyanides that were needed for the preparation of the libraries, 1,1,3,3-tetramethylbutylisocyanide and pentylisocyanide are commercially available. The synthesis of isocyanide **31** started with substitution of the bromide in the previously reported **27** with sodium azide to provide **28** (Scheme 2). Staudinger reduction of the azide to amine

29 and subsequent treatment with acetic formic anhydride produced formamide **30**. Phosphorylchloride mediated dehydration of **30** produced isocyanide **31** that showed two indicative triplets in ^{13}C-NMR due to ^{14}N–^{13}C coupling. Known isocyanide **33** could be prepared by dehydration of formamide **32**, which in turn was prepared via a known procedure from cyclohexanone.[20,21]

Scheme 2. Synthesis of isocyanides **31** and **33**.



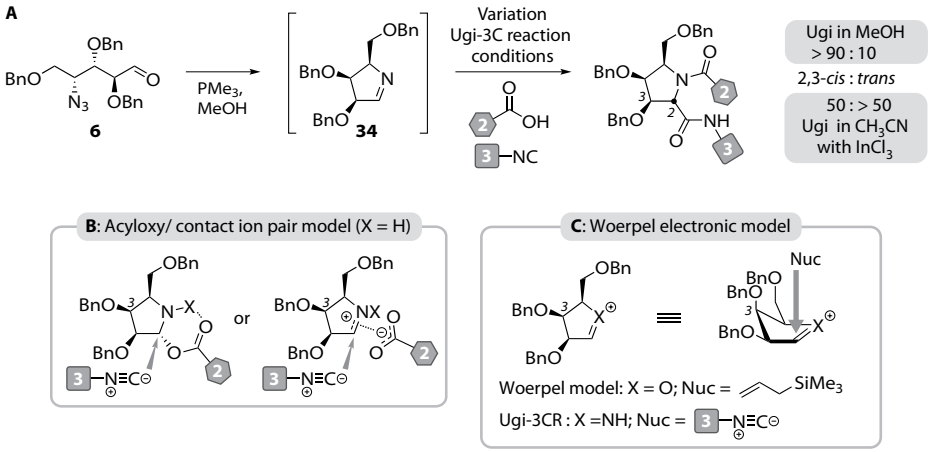
Reagents and conditions: [**a**] NaN_3, DMSO, rt, 20h, 95%. [**b**] PMe_3, H_2O, THF, 0 °C, 3h, 84%. [**c**] acetic formic anhydride, DCM, 0 °C » rt, 20h, 82%. [**d**] $POCl_3$, Et_3N, DCM, 30 °C, 1h, **31**: 81%, **33**: 65%.

Evaluation of Azido-aldehydes 6, 15, 20 and 26 in the SAWU-3C Reaction.

With the azido-aldehydes **6**, **15**, **20**, **26** and isocyanides **31**, **33** in hand attention was focused on the SAWU-3CR. Application of the SAWU-3CR on azido-aldehyde **6** has already been investigated extensively.[12,13] An initial study revealed that it almost exclusively (> 90%) produces pyrrolidines with a counter-intuitive 2,3-*cis* relationship during the final Ugi-3CR step with the intermediate cyclic imine,[14,22-25] regardless of the used carboxylic acid or isocyanide component (see Figure 5A on the next page).[12] There are numerous examples in the literature about the effect of Lewis acids on the reaction rate, yields and diastereoselectivity of the Ugi-reaction.[26-32] Consequently, a second study reported the effect of Lewis acids in the Ugi-3CR with cyclic imine **34**. This study established that carrying out the Ugi-3CR part of the SAWU-3CR process with **34** in acetonitrile in the presence of a stoichiometric amount of indium(III)chloride was able to promote the formation of the 2,3-*trans* product.[13] The hereby obtained ratios were dependant on the used carboxylic acid and isocyanide and varied from 1:1–1:9 (2,3-*cis*:*trans*) in yields ranging from 20–72% (Figure 5A).

A possible explanation for the diastereoselective formation of 2,3-*cis* pyrrolidines in the Ugi-3C reaction with **34** in the absence of Lewis acids may be found in the involvement of the previously mentioned acyloxy intermediate in the course of the reaction (Figure 5B). This intermediate was already postulated by Ugi in 1967 and its involvement in the Ugi reaction has subsequently been proposed by others.[5,9,23,33] Attack of the carboxylate from the less hindered side and subsequent inversion after S_N2 attack of the isocyanide on this acyloxy intermediate would lead to the 2,3-*cis* pyrrolidine. The carboxylate may also form a non-covalent contact ion pair with the protonated cylic imine and thereby shield the less hindered face of the imine from isocyanide attack.

Figure 5. The effect of Lewis acids on the stereochemistry in the Ugi-3CR with cyclic imine **34** (**A**). Two possible models (**B**/**C**) for the observed 2,3-*cis* diastereoselectivity of the Ugi-3CR in the absence of Lewis acids.



Another plausible explanation for the 2,3-*cis* pyrrolidine formation in the absence of Lewis acids involves the influence of electronic effects on the conformation of the activated cyclic imine. Woerpel and co-workers proposed a model for nucleophilic additions to five-membered ring oxocarbenium ion electrophiles (Figure 5C; X = O) that may also be applied to protonated cyclic imines (X = NH).[34,35] In this model, a pseudoaxial position of the benzyloxy substituent at C-3 of the protonated cyclic imine ion produces the lowest energy conformer that is preferentially attacked by the isocyanide from the concave side of the envelope conformation – giving the 2,3-*cis* pyrrolidine.

At present there is no conclusive evidence to discount or confirm either of the above discussed models. However, if the acyloxy intermediate is incorporated in the electronic Woerpel model, in the absence of Lewis acids, it would predict 1,3-*cis* attack of the carboxylate resulting in 2,3-*trans* pyrrolidines – making the two models mutually exclusive. An explanation for the role of the Lewis acid in promoting 2,3-*trans* pyrrolidine formation is challenging because of the multitude of instances where Lewis acids could have an effect in the complex interplay of equilibria between intermediates in the Ugi-3CR (Figure 1). A Lewis acid can coordinate to the endocylic nitrogen of the imine and activate it (X = LA in Figure 5B and X = N–LA in 5C).[36] In the acyloxy model the Lewis acid activated imine might favor direct attack of the isocyanide from the less hindered side. In the electronic model coordination and activation of cyclic imine by a Lewis acid via the nitrogen might disturb the electronic effects of the C-3 position. Additionally, coordination of the Lewis acid with the benzyloxy ether substituents might disfavour an axial orientation of C-3 or shield the *cis*-face of activated imine.

The three novel azido-aldehydes (**15**, **20** and **26**) were also subjected to the SAWU-3CR process. Treatment of **15**, **20** and **26** with trimethylphosphine and subsequent concentration of the reaction mixture produced the intermediate cyclic imines. The

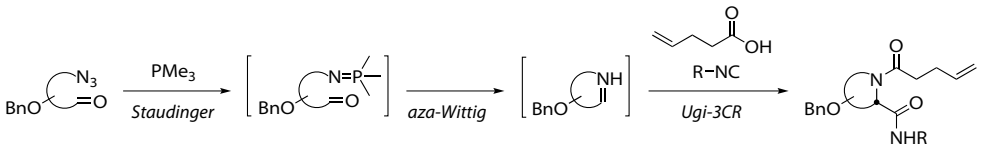
cyclic imines derived from **15** and **26** proved more stable than the cyclic imine from **20**, which already showed minor degradation during concentration. The cyclic imines were exposed to pent-4-enoic acid and pentylisocyanide at 0 °C in either methanol or in the presence of $InCl_3$ in acetonitrile. The cyclic imine from **15** produced a ~1:2 mixture of diastereoisomers in methanol, and the ratio changed to ~1:1 in the $InCl_3$ mediated Ugi-3CR. This result conforms to the Woerpel electronic model (Figure 5C), because epimerization of the C-3 benzyloxy in this cyclic imine disfavors its axial orientation and subsequent preferential isocyanide attack from one side. Azido-aldehyde **26** produced a single product in the SAWU-3CR. Addition of a Lewis acid only resulted in multiple minor byproducts and an overall lowered yield. None of the byproducts could be identified as the other diastereoisomer. Azido-aldehyde **20** produced a ~1:1.6 mixture of diastereoisomers in methanol. Addition of a Lewis acid resulted in a similar ratio and lowered yields. The stereochemistry of the introduced chiral centers at C-2 of these products could not be elucidated at this stage due to rotamers of the pent-4-enamide during NMR-analysis.

First Step in Library Synthesis: The SAWU-3C Reactions.

Synthesis of the four libraries started with sixteen SAWU-3C reactions of azido-aldehydes **6**, **15**, **20** and **26** with the four isocyanides and pent-4-enoic acid. The Ugi-3CR part of the four SAWU-3C reactions with **6** was also carried out in the presence of $InCl_3$ in acetonitrile to generate the 2,3-*trans* D-*lyxo*-pyrrolidines. Due to the lack of influence on stereochemistry by the Lewis acid in the SAWU-3CR with **15**, **20** and **26** the synthesis of the three libraries from them was solely carried out in the absence of $InCl_3$. The results of the SAWU-3C reactions are summarized in Table 1 on the next page.

Notably, from this point on in the chapter each library intermediate and final entry is identified by a three part code (*e.g.* **F1-V**): the type of iminosugar core and stereochemistry at C-2 is denoted by the letters **A**–**G**; the subsequent number relates to the state of the endocyclic nitrogen (pent-4-enamide, free or *N*-alkylated) and iminosugar hydroxyls (protected or deprotected); the final roman numeral (**I**–**VI**) specifies the moiety appended at C-1 (the coding system is explained with structures in Figure 7 on page 223).

Table 1. Yields and 2,3-*cis* : 2,3-*trans* ratios for products of SAWU-3CR with azido-aldehydes **6**, **15**, **20** and **26**.



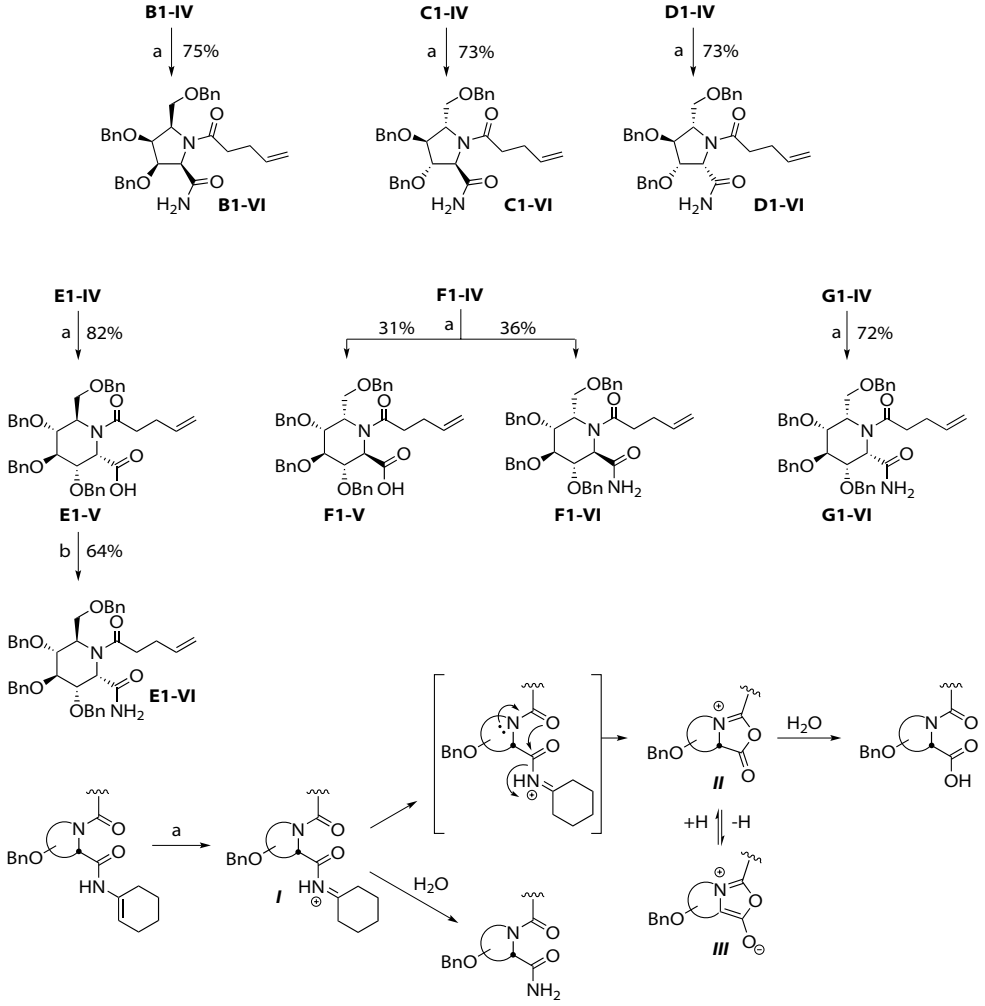
	D-*lyxo*-pyrrolidines			L-*arabino*-pyrrolidines			D-*gluco*-piperidines	L-*ido*-piperidines		
	2,3-*trans* **A1**	:	2,3-*cis* **B1**	2,3- *trans* **C1**	:	2,3-*cis* **D1**	2,3-*cis* **E1**	2,3-*trans* **F1**	:	2,3-*cis* **G1**
R = **I**	47% (+$InCl_3$) 1.7	:	1	41% 1	:	1.9	73%	55% 1	:	1.25
	62% 1	:	20							
R = **II**	63% (+$InCl_3$) 5.3	:	1	54% 1	:	1.1	81%	61% 1	:	0.94
	72% 1	:	15							
R = **III**	34% (+$InCl_3$) 5.4	:	1	43% 1	:	2.1	77%	57% 1	:	1.6
	94% 1	:	21							
R = **IV**	23% (+$InCl_3$) 1	:	4.2	45% 1	:	2.4	80%	41% 1	:	1.5
	54% 1	:	11							

Second Step: Isomerization & Hydrolysis of Cyclohexenylamide Library Intermediates.

The next step in the library synthesis involved the isomerization and hydrolysis of the cyclohexenyl containing SAWU-3CR products. The reaction of **6** with cyclohexenylisocyanide in the presence of $InCl_3$ produced very low yields and only minor amounts of the 2,3-*trans* pyrrolidine **A1-IV**. Therefore **A1-IV** was not incorporated in this step of the library synthesis. First the pyrrolidine SAWU-3CR products were exposed to aqueous hydrochloric acid in THF (Scheme 3). Instead of resulting in the C-1 carboxylic acid all three reactions produced the primary amide (**B1-VI**, **C1-VI** and **D1-VI**) in good yields. The first step in the reaction is the protonation and isomerization of the double bond to produce an acyliminium ion ***I*** (bottom of Scheme 3).[21] To obtain the carboxylic acid, intermediate ***I*** needs to cyclize into intermediate ***II*** with expulsion of cyclohexanimine. For the pyrrolidines this would result in two fused strained five-

membered rings. Therefore intermediate ***I*** is instead hydrolyzed by water to produce the primary amide.

Scheme 3. The isomerization and hydrolysis of cyclohexene containing SAWU-3CR products.



Reagents and conditions: [**a**] aq HCl, THF, 20h. [**b**] i: ClC(O)OEt, Et_3N, THF, 0 °C; ii: addition 25% aq NH_3, 0 °C, 1h.

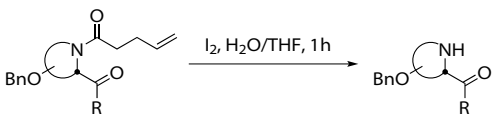
Treatment of D-*gluco* **E1-IV** did result in carboxylic acid **E1-V**. Armstrong and co-workers have proposed that the mechanism for cyclohexenyl cleavage to the carboxylic acid also involves Münchnone intermediate ***III*** that is formed upon proton abstraction of cyclized intermediate ***II***.[21] A Münchnone is a 1,3-dipole and Armstrong and co-workers indeed observed cycloaddition products upon exposing the reaction mixtures to 1,3-dipolarophiles.[21] This could also lead to racemization of the new chiral center created during the Ugi-reaction. However, product **E1-V** was not racemized and the C-2

chiral center was also not epimerized. Carboxylic acid **E1-V** was also transformed into its primary amide **E1-VI** (Scheme 3). Treatment of the two L-*ido* SAWU-3CR products resulted in the formation of a mixture of the carboxylic acid **F1-V** and primary amide **F1-VI** from **F1-IV** and the sole formation of primary amide **G1-VI** from **G1-IV**.

Third Step: Removal of the Pent-4-enamide and Assignment of C-2 Stereochemistry.

The penultimate step in the library synthesis consisted of the removal of the pent-4-enamides in the SAWU-3CR products and the products from the cyclohexenyl cleavage. This was carried out by exposing them to molecular iodine in THF in the presence of water.[37] All reactions successfully produced the free secondary amines of which the yields are summarized in Table 2. Several depent-4-enoylation reactions produced the secondary amine in a low to moderate yield. Upon investigation of the major byproduct observed in these reactions it turned out to be the hydrolyzed product of the iodonium ion intermediate (*e.g.* for **E1-V** to **E2-V**: 37% yield of the byproduct; found HRMS: 794.2189 = $C_{40}H_{44}INO_8$).

Table 2. Yields (%) for deprotection of pent-4-enamides.



	Product	A2	B2	C2	D2	E2	F2	G2
	I = NH–AMP	75	97	55	62	99	50	65
	II = NH–tMB	69	92	95	75	90	40	55
R =	**III** = NH–Pentyl	80	77	95	83	95	59	77
	V = OH	-	-	-	-	35	63	-
	VI = NH_2	-	52	26	55	79	66	72

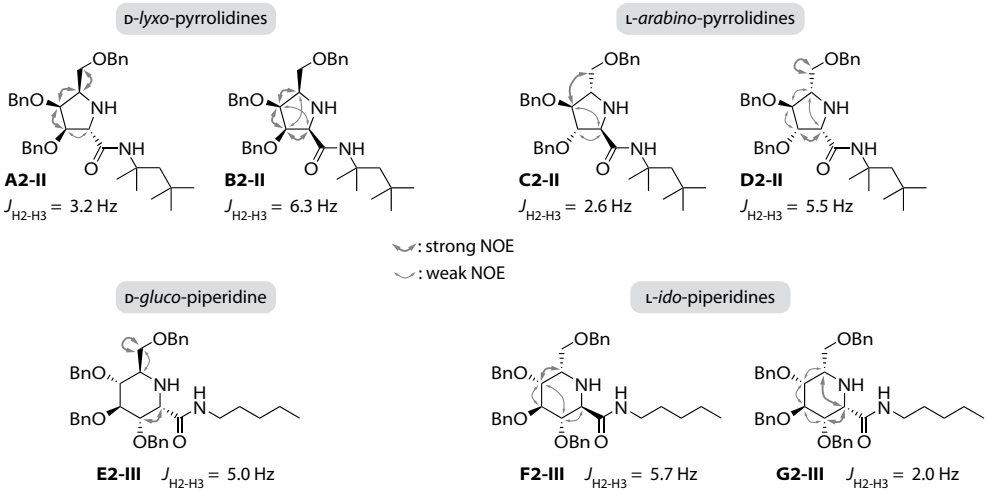
AMP = 5-(adamantan-1yl-methoxy)-pentyl; tMB = 1,1,3,3-tetramethylbutyl.

Elucidation of the stereochemistry of the newly formed chiral center at C-2 by NMR-analysis was now possible due to the removal of the pent-4-enamide and its associated rotamers. Determination of the coupling constants for the pyrrolidine and piperidine ring protons in combination with NOESY spectra resulted in the C-2 stereochemistry assignments as summarized in Figure 6.

Final Step: Alkylation of Endocyclic Nitrogen and Deprotection.

The final step in the library synthesis consisted of either straight deprotection of the benzyl ethers of the compounds listed in Table 2 or prior *N*-alkylation of the free secondary amine. The deprotection reactions were carried out via two methods. All penultimate library entries that did not contain an adamantane-1yl-methoxy ether function were

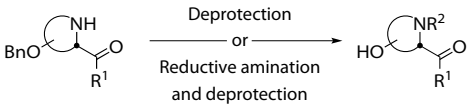
Figure 6. Overview of the assignment of C-2 stereochemistry based on ^{1}H- and NOESY-NMR analysis.



treated with boron trichloride in dichloromethane at 0 °C to deprotect the benzyl ethers. The adamantane-1yl-methoxy ether is labile under these conditions so all library entries containing this moiety were exposed to a palladium catalyzed hydrogenation at atmospheric or 4 bar hydrogen pressure to effect benzyl ether deprotection. The results for these straight deprotections are listed in Table 3 (on the next page) under the **A3** to **G3** entries.

As mentioned, the secondary amines of the library intermediates listed in Table 2 were also subjected to a reductive amination with either butyraldehyde or 5-(adamantane-1yl-methoxy)-pentanal. The *N*-alkylated intermediates were isolated via extraction and employed crude in the deprotection reaction via one of the two methods described above. The reductive amination worked for all entries except the 2,3-*cis*-L-*ido*-piperidines (**G2-I** to **G2-VI**). These did not produce any or only trace amounts of *N*-alkylated intermediates. For these library entries the reductive amination was repeated, but now with the deproteced free secondary amines of **G3-I**, **G3-II** and **G3-III**. This time the reductive amination with butyraldehyde proceeded in all instances. The reductive amination with 5-(adamantane-1yl-methoxy)-pentanal only resulted in *N*-alkylated products in combination with **G3-II** and **G3-III**. The yields for all the deprotection reactions, reductive aminations and final compositions of the libraries are summarized in Table 3.

Table 3. Yields (%) for reductive amination and/or deprotection of lipophilic iminosugars.



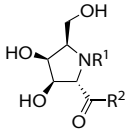
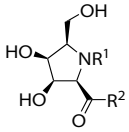
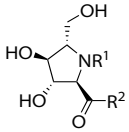
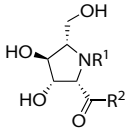
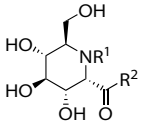
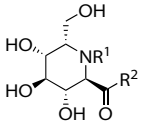
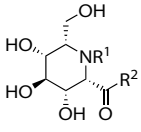
Product		R1 = **I** = NH–AMP	**II** = NH–tMB	**III** = NH–Pentyl	**V** = OH	**VI** = NH_2
2,3-*trans*-D-*lyxo*-pyrrolidines	**A3** R^2 = H	82	93	89	-	-
	A4 R^2 = Butyl	67	85	44	-	-
	A5 R^2 = AMP	72	72	73	-	-
2,3-*cis*-D-*lyxo*-pyrrolidines	**B3** R^2 = H	37	53	66	-	-
	B4 R^2 = Butyl	48	87	86	-	78
	B5 R^2 = AMP	59	74	69	-	57
2,3-*trans*-L-*arabino*-pyrrolidines	**C3** R^2 = H	85	58	51	-	-
	C4 R^2 = Butyl	75	53	31	-	-
	C5 R^2 = AMP	65	42	22	-	92
2,3-*cis*-D-*arabino*-pyrrolidines	**D3** R^2 = H	55	78	78	-	-
	D4 R^2 = Butyl	74	55	49	-	92
	D5 R^2 = AMP	79	86	52	-	97
2,3-*cis*-D-*gluco*-piperidines	**E3** R^2 = H	36	67	77	-	-
	E4 R^1 = Butyl	92	82	71	69	30
	E5 R^2 = AMP	60	54	71	-	39
2,3-*trans*-L-*ido*-piperidines	**F3** R^2 = H	41	88	92	-	-
	F4 R^2 = Butyl	83	59	64	95	88
	F5 R^2 = AMP	79	69	51	80	-
2,3-*cis*-L-*ido*-piperidines	**G3** R^2 = H	71	81	79	-	-
	G4 R^2 = Butyl	41	49	33	-	-
	G5 R^2 = AMP	-	21	24	-	-

Deprotections: Method A = BCl_3, DCM, 0 °C, 20h or Method B = Pd/C, H_2 (atm/4 bar), HCl, EtOH, 20h; *Reductive aminations*: Method A = Butyraldehyde or 5-(adamantan-1yl-methoxy)-pentanal, $NaCNBH_3$, Na_2SO_4, AcOH/EtOH (1/20) or Method B: **G3**-**I**/**II**/**III**, aldehyde, $NaCNBH_3$, AcOH/MeOH (1/100); AMP = 5-(adamantan-1yl-methoxy)-pentyl; tMB = 1,1,3,3-tetramethylbutyl.

Biological evaluation

All the 73 entries in the four libraries were evaluated in an *in vitro* enzyme assay for inhibition of glucocerebrosidase (GBA1). GBA1 degrades glucosylceramide in the lysosomes and constitutes the primary catabolic pathway. Inhibitors of GBA1 are currently being scrutinized in many studies as potential pharmacoligical chaperones for improving the lysosomal activity of GBA1 in Gaucher disease. In Gaucher disease the gene encoding GBA1 is mutated and produces a deficient enzyme (see sections 1.3.4 and 1.3.3 in Chapter 1). The results of the inhibition assay of GBA1 are summarized in Table 4.

Table 4. Enzyme inhibition assay results for GBA1 and GBA2 (right *italic* value): apparent IC_{50} values in μM.

Compound[a]		**I**: R^2 = NH–AMP	**II**: R^2 = NH–tMB	**III**: R^2 = NH–Pentyl	**V**: R^2 = OH	**VI**: R^2 = NH_2
	**A3**: R^1 = H	3.75; *55*	400	350; > *1000*	-	-
	A4: R^1 = Bu	20	150	650; > *1000*	-	-
	A5: R^1 = AMP	15	50	50	-	-
	**B3**: R^1 = H	80; *30*	> 1000	> 1000	-	-
	B4: R^1 = Bu	200	> 1000	> 1000	-	> 1000
	B5: R^1 = AMP	100	800	140	-	140; *90*
	**C3**: R^1 = H	45; *30*	> 1000	> 1000	-	-
	C4: R^1 = Bu	50	100	1000	-	-
	C5: R^1 = AMP	25	100	40	-	140; *100*
	**D3**: R^1 = H	3.5; *125*	100	450	-	-
	D4: R^1 = Bu	40	500	> 1000	-	> 1000
	D5: R^1 = AMP	20	300	500	-	350; *1000*
	**E3**: R^1 = H	*7*; *2.25*	400	> 1000	-	-
	E4: R^1 = Bu	45	1000	> 1000	> 1000	-
	E5: R^1 = AMP	30	40	100	5; *0.1*	200; *7*
	**F3**: R^1 = H	30; *40*	> 1000	> 1000	-	-
	F4: R^1 = Bu	40	> 1000	> 1000	> 1000	> 1000
	F5: R^1 = AMP	50	250	70	-	80; *4*
	**G3**: R^1 = H	150; *85*	> 1000	> 1000	-	-
	G4: R^1 = Bu	20	> 1000	> 1000	-	-
	G5: R^1 = AMP	-	250	130	-	-

[a]Bu = butyl; tMB = 1,1-3,3-tetramethylbutyl; AMP = 5-(adamantan-1-yl-methoxy)-pentyl.

A general trend observed in the assay results for GBA1 inhibition is that iminosugars functionalized with a single 5-(adamantan-1-yl-methoxy)-pentyl (AMP) moiety on either the endocyclic nitrogen or the C-1 amide produce the most potent GBA1 inhibitors. The iminosugars with a pentyl or 1,1,3,3-tetramethylbutyl (tMB) moiety on the C-1 amide only yield sub 100 μM inhibitors when the endocylic nitrogen is functionalized with a AMP as a second hydrophobic moiety. Pyrrolidines **A3-I** and **D3-I** represent the most potent GBA1 inhibitors with an IC_{50} of 3.75 and 3.5 μM. D-*Gluco* library entries **E3-I** and **E5-V** are the other two potent entries with an IC_{50} for GBA1 of 7 and 5 μM. From

all four libraries, lipophilic iminosugars **E5-V** and **E5-VI** most closely resemble lead compound **1**. Interestingly, they show a 40-fold difference in their IC_{50} for GBA1 and the main difference between them is that the carboxylic acid in **E5-V** probably forms an intramolecular salt with the tertiary nitrogen atom.

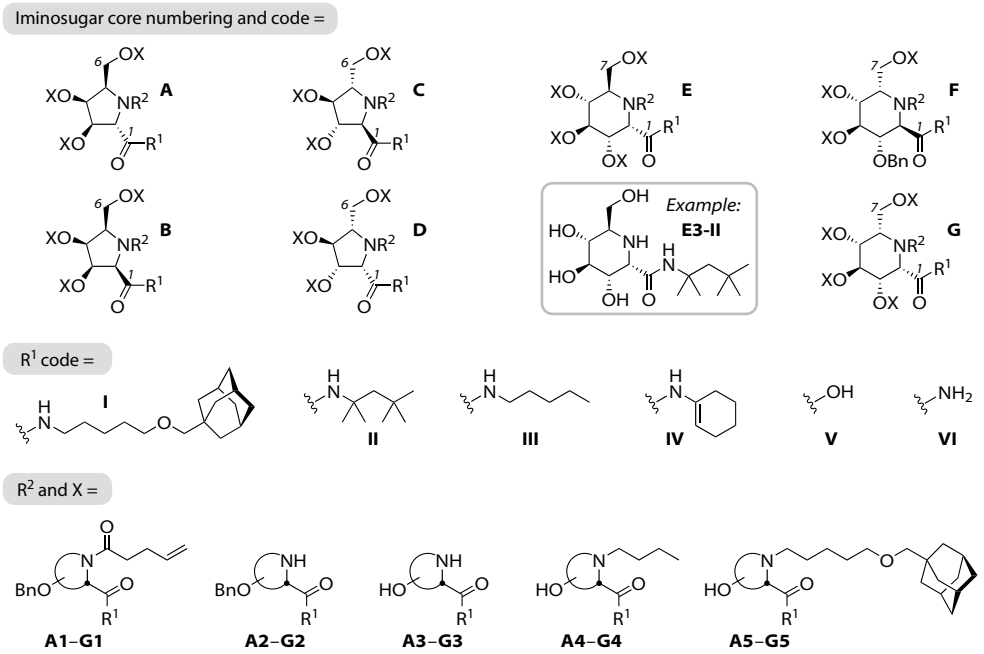
A selection of 15 entries from the four libraries was also evaluated for inhibition of GBA2 (*in vitro*) and GCS (*in vivo*). The selection consisted of all library entries containing a single AMP moiety. Additionally, **A3-III** and **A4-III** were evaluated because they constitute C-5 hydroxymethyl analogues of known GCS inhibitors **3** and **4** (see Figure 3). In the GBA2 assay the selected pyrroldine entries proved poor GBA2 inhibitors. From the selection of piperidines, **E3-I**, **E5-V**, **E5-VI** and **F5-V** inhibited GBA2 with **E5-V** being the most potent with an IC_{50} of 0.1 μM (right *italic* values in Table 4). With the exeption of **E5-V** none of the selected entries significantly inhibited GCS at 20 μM. Entry **E5-V** inhibited GCS activity with an IC_{50} of 20 μM.

Conclusion

This chapter describes the use of the tandem SAWU-3CR to synthesize four libraries of lipophilic iminosugars. Azido-aldehydes **6**, **15**, **20**, **26** were prepared from carbohydrates and subjected to a Staudinger reaction. The resulting cyclic imines were exposed to pent-4-enoic acid and a panel of four isocyanides (**31**, **33**, pentyl- and 1,1,3,3-tetramethylbutyl-isocyanide) that reacted together in an Ugi-3CR to produce 16 library precursors. The use of pent-4-enoic acid together with cyclohexenylisocyanide (**33**) in the Ugi-3CR introduced two post SAWU-3CR cleavable groups. This allowed for the production of lipophilic iminosugars with two or a single hydrophobic tail. Straight deprotection of penultimates or prior *N*-alkylation created two libraries of lipophilic D-*lyxo* and L-*arabino* pyrrolidines; and two libraries of lipophilic D-*gluco* and L-*ido* piperdines with a total of 73 entries. All compounds were evaluated for inhibition of GBA1, which identified pyrrolidines **A3-I**, **D3-I** and piperdines **E3-I**, **E5-V** as low μM inhibitors of GBA1. A selection of entries was also evaluated for inhibition of GBA2 and GCS. Entry **E5-V** proved to be the most potent GBA2 and GCS inhibitor in this selection.

Experimental section

Figure 7. Compound coding system for library intermediates and final entries used throughout this chapter.



General methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at ambient temperatures unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere. Residual water was removed from starting compounds by repeated coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. Reaction grade acetonitrile, *n*-propanol and methanol were stored on 3Å molecular sieves. Other reaction grade solvents were stored on 4Å molecular sieves. Methanol used in the SAWU-3C-reaction was distilled from magnesium (5 g/L)/molecular iodine (0.5 g/L) and stored on activated 3Å molecular sieves under argon. Ethanol was purged of acetaldehyde contamination by distillation from zinc/KOH. DCM was distilled prior to use from P_2O_5. R_F values were determined from TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by spraying with a solution of $(NH_4)_6Mo_7O_{24}\times 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times 2H_2O$ (10 g/L) in 10% sulfuric acid or a solution of phosphomolybdic acid hydrate (7.5 wt% in ethanol) followed by charring at ~150 °C. Visualization of all deprotected iminosugar compounds during TLC analysis was accomplished by exposure to iodine vapour. Column chromatography was performed on silica gel (40–63 µm). ^{1}H and ^{13}C-APT NMR spectra were recorded on a Bruker DMX 600 (600/150 MHz), Bruker DMX 500 (500/125 MHz), or Bruker AV 400 (400/100 MHz) spectrometer in $CDCl_3$ or MeOD. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard (^{1}H NMR in $CDCl_3$) or the signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. All presented ^{13}C-APT spectra are proton decoupled. High resolution mass spectra were recorded by direct injection (2 µL of a 2 µM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150–2000) and dioctylpthalate (m/z = 391.28428) as a "lock mass". The high resolution

mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Optical rotations were measured on a Propol automatic polarimeter (Sodium D-line, λ = 589 nm). ATR-IR spectra were recorded on a Shimadzu FTIR-8300 fitted with a single bounce Durasample IR diamond crystal ATR-element and are reported in cm^{-1}.

Enzyme Assays: The enzyme assays used for determining the inhibition of activity of glucosylceramide synthase (GCS), glucocerebrosidase (GBA1) are described in the experimental section of Chapter 3. All compounds were strored (−20 °C) and tested as their hydrochloric acid salt .

*General Procedure A – Dess-Martin periodinane mediated oxidation of azido-alcohols **15**, **20** and **26***: Dess-Martin periodinane (1.5 eq; synthesis described in Chapter 6) was added to a dry and cooled (0 °C) solution of the azido- alcohol (1 eq) in DCM (0.2M). The reaction mixture was stirred for 30 min at 0 °C and a further hour at rt. The reaction mixture was quenched by the addition of sat aq $NaHCO_3$ (5 mL/mmol) and 1M aq $Na_2S_2O_3$ (5 mL/mmol). The resulting two-phase mixture was rapidly stirred/mixed for 15 min. The mixture was diluted with additional DCM and washed successively with sat $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (5% » 25% EtOAc in PE) to provide the aldehyde that should preferably be used immediately but can be stored for 20 h at −20 °C under argon.

*General procedure B – The tandem Staudinger/ aza-Wittig/ Ugi three-component reaction of azido-aldehydes **6**, **15**, **20** and **26***: The synthesis of azido-aldehyde **6** is described in reference 12. Trimethylphosphine (2 eq, 1M in toluene) was added to a dry and cooled (0 °C) solution of the appropriate azido-aldehyde (1 eq) in anhydrous MeOH (0.2M). The reaction mixture was stirred for 3 hours at 0 °C until TLC analysis indicated complete consumption of the azido-aldehyde and the appearance of the intermediate phosphazene (R_F = 0 in 1:2; EtOAc:toluene). The reaction mixture was concentrated and coevaporated with toluene (3×), concomitant TLC analysis showed complete disappearance of the baseline phosphazene intermediate and emergence of the cyclic imine (R_F of imine from **6** = 0.34 (1:4; EtOAc:toluene); imine from **15** = 0.38 (1:1; EtOAc:PE), imine from **20** = 0.15 (1:4; EtOAc:toluene), imine from **26** = 0.33 (1:3; EtOAc:toluene)). The crude cyclic imine was dissolved in anhydrous MeOH (0.3M) or CH_3CN (0.3M for reactions with $InCl_3$), divided in the appropriate amount of portions and cooled to 0 °C. Where appropriate, $InCl_3$ (1.1 eq) was added to the CH_3CN solutions of cyclic imine. Next, the appropriate carboxylic acid (1.1 eq) and isocyanide (1.3 eq) were successively added and the reaction mixture was stirred for 20 hours at 0–5 °C. Saturated aq $NaHCO_3$ was added to the mixture and it was allowed to warm to room temperature whilst stirring. Ethyl acetate was added to the mixture and the organic phase was washed with aq. sat. $NaHCO_3$. The organic phase was dried (Na_2SO_4), concentrated and the product was isolated by silica gel column chromatography (5% » 50% EtOAc in toluene) to afford the SAWU-3CR product as a light yellow oil.

General procedure C – Acid mediated isomerization and hydrolysis of 1-cyclohexene-amides: The 1-cyclohexene-amide containing iminosugar was dissolved in THF (0.05M) containing 1.6% aq HCl (from 36% aq HCl). The reaction mixture was stirred 20 h during which it turned brown. Sodium carbonate was added to quench the reation mixture and subsequently removed by filtration. The filtrate was concentrated and the resulting residue was purified by silica gel column chromatography (0% » 100% EtOAc in toluene; 5% AcOH was added to the eluent if the hydrolysis produced a carboxylic acid) to provide the product as a colorless oil.

General procedure D – Iodine mediated deprotection of pent-4-enamides: Molecular iodine (3 eq) was added to a solution of the pent-4-enamide (1 eq) in THF/H_2O (0.05M; 3/1, v/v). The reaction mixture was stirred for 30–60 min until TLC analysis indicated complete conversion into a lower running product. Aqueous 1M $Na_2S_2O_3$ was added and the mixture was vigorously stirred for 30 min. The suspension was poured into a mixture of 1M aq

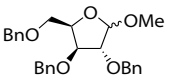
$Na_2S_2O_3$/sat aq NaCl (1/1, v/v) and extracted with EtOAc (3×). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (1: 25% EtOAc in toluene until (*R/S*)-γ-iodomethyl-gamma-butyrolactone has eluted; 2: 25% » 100% EtOAc in toluene; 3: optional isocratic 10% MeOH in EtOA + 2% NH_4OH for low running products) to yield the deprotected secondary amine as a colorless oil. R_F (*R/S*)-γ-Iodomethyl-gamma-butyrolactone = 0.70 (2:1; EtOAc:toluene).

General method E – N-alkylation of benzyl protected iminosugars by reductive amination: Sodium sulphate (10 eq) was added to a dry solution of the iminosugar (1 eq) and either butyraldehyde (5 eq) or 5-(adamantane-1-yl-methoxy)-1-pentanal **(**3 eq; synthesis described in Chapter 2**)** in a mixture of 'acetaldehyde free' EtOH and AcOH (0.05M, 20/1, v/v). Subsequently, $NaBH_3CN$ (4 eq) was added to the mixture. The reaction mixture was stirred for 20 h and subsequently Et_20 (2-fold reaction volume) and sat aq $NaHCO_3$ (2-fold reaction volume) were added and vigorously mixed with the reaction mixture. The organic phase was isolated and the aqueous phase was extracted with Et_2O (2×). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude *N*-alkylated compound was used in the ensuing benzyl-ether deprotection reaction.

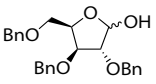
General procedure F – Deprotection of benzyl-ethers: All 5-(adamantane-1-yl-methoxy)-1-pentyl moiety containing iminosugars were deprotected by Pd/C catalyzed hydrogenation. *Hydrogenolysis at atmospheric H_2 pressure*: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (4 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C (~50 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 minutes and the reaction was stirred for 20 h under atmospheric hydrogen pressure. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene. In the case of incomplete reduction hydrogenolysis was repeated after workup and coevaporation (3×) with 'acetaldehyde free' EtOH), at atmospheric pressure in the presence of Pd/C (~50 mg) and Pd black (~5 mg) or at higher H_2 pressure in a Parr-apparatus. *Hydrogenolysis in Parr-apparatus*: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (50 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C (50 mg, 10 wt % on act. carbon) was added. The reaction vessel was placed under vacuum and subsequently ventilated with hydrogen gas. This cycle was repeated one more time after which the vessel was placed under 4 bar of hydrogen gas and mechanically shaken for 20 h. Work-up was the same as described before. The obtained residue was purified by silica gel column chromatography (5% » 20% MeOH in DCM + 2% NH_4OH) to yield the deprotected iminosugar as a colorless oil.

All iminosugars that do not contain a 5-(adamantane-1-yl-methoxy)-1-pentyl moiety were deprotected by a BCl_3 mediated debenzylatyion. *Boron trichloride mediated debenzylation*: Boron trichloride (10 eq, 1M in DCM) was added to a cooled (0 °C) solution of the benzylated iminosugar (1 eq) in DCM (0.05M). The reaction mixture was stirred for 20 hours at 0–5 °C after which MeOH (0.5 mL) was carefully added. The reaction mixture was concentrated and coevaporated with toluene (3×). The obtained residue was purified by silica gel column chromatography (5% » 20% MeOH in DCM + 2% NH_4OH) to yield the deprotected iminosugar as a colorless oil.

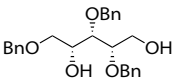
General method G – N-alkylation of deprotected iminsugars by reductive amination: Sodium cyanoborohydride (5 eq) was added to a dry solution of the iminosugar (1 eq) and either butyraldehyde (5 eq) or 5-(adamantane-1-yl-methoxy)-1-pentanal **(**3 eq; synthesis described in Chapter 2**)** in a mixture of anhydrous MeOH and AcOH (0.05M, 100/1, v/v). The reaction mixture was stirred for 20 h and subsequently 4M HCl (0.5 mL; in dioxane/H_2O) was added. The mixture was stirred for 3h and subsequently concentrated and coevaporated with toluene (3×). The obtained residue was purified by silica gel column chromatography (5% » 20% MeOH in DCM + 2% NH_4OH) to yield the deprotected iminosugar as a colorless oil.



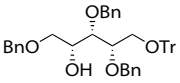
Mixture of 2,3,5-tri-*O*-benzyl-1-*O*-methyl-α/β-D-xylofuranoside (8). A dry solution of HCl (prepared by careful addition of 2 mL AcCl) in MeOH (100 mL) was added to a dry solution of D-xylose (**7**: 20.07 g, 133.7 mmol) in MeOH (340 mL). The reaction mixture was stirred for 20 h at rt. The reaction was quenched by adjusting the pH of the reaction mixture to ~7 by addition of 3M aq NaOH. The mixture was concentrated and coevaporated with toluene (4×100 mL). The crude residue was dissolved in DMF (500 mL) and cooled to 0°C. Subsequently, NaH (30.04 g, 751 mmol; 60% in mineral oil), tetrabutylammonium iodide (32.312 g, 88 mmol) and benzyl bromide (52 mL, 437 mmol) were added. After stirring the reaction mixture for 48 h at rt, methanol (10 mL) was added and the mixture was concentrated. The residue was dissolved in ethyl acetate (100 mL) and washed successively with H_2O (4×50 mL) and sat aq NaCl (50 mL). The organic layer was dried ($MgSO_4$) concentrated. The resulting residue was purified by silica gel column chromatography (5% » 20% EtOAc in toluene) to provide **8** (53.9 g, 124.1 mmol) in 93% yield as a colourless oil. R_F β-anomer = 0.58; α-anomer = 0.42 (5:1 EtOAc:PE). ^{1}H NMR ($CDCl_3$, 200 MHz) δ β-anomer: 7.28 – 7.26 (m, 15H, H_{Ar} Bn), 4.91 (d, 1H, *J* = 1.8, H-1), 4.56 – 4.40 (m, 7H), 4.04 (dd, 1H, *J* = 2.5, 2.6), 3.97 (m, 1H), 3.77 – 3.71 (m, 2H), 3.37 (s, 3H, OMe); α-anomer: 7.29 – 7.25 (m, 15H, H_{Ar} Bn), 4.80 (d, 1H, *J* = 4.0, H-1), 4.67 – 4.46 (m, 6H, 3×CH_2 Bn), 4.43 – 4.26 (m, 2H, H-3, H-4), 4.03 – 4.01 (m, 1H, H-2), 3.74 – 3.53 (m, 2H, CH_2-5), 3.39 (s, 3H, OMe). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ β-anomer: 139.1, 138.6, 138.1 (3×C_q Bn), 129.0, 128.6, 128.4, 127.7, 127.5 (CH_{Ar} Bn), 108.1 (C-1), 87.0, 82.0, 80.0 (C-2, C-3, C-4), 73.3, 72.1, 71.8 (3×CH_2 Bn), 69.9 (C-5), 55.9 (OMe); α-anomer: 138.4, 138.2, 137.9 (3×C_q Bn), 127.9, 127.5, 127.4 (CH_{Ar} Bn), 100.5 (C-1), 84.0, 81.5, 76.0 (C-2, C-3, C-4), 73.2, 72.3 (3×CH_2 Bn), 69.3 (C-5), 54.9 (OMe).



Mixture of 2,3,5-tri-*O*-benzyl-α/β-D-xylose (9). The comined α/β-anomers of **8** (25.11 g, 57.8 mmol) in dioxane (200 mL) and 4M aq HCl (200 mL) were refluxed for 5 h until TLC analysis indicated complete conversion of the starting material. The reaction mixture was cooled to rt, diluted with Et_2O (200 mL) and washed successively with sat aq $NaHCO_3$ (100 mL), H_2O (3×50 mL) and sat aq NaCl (50 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 20% EtOAc in toluene) to provide **9** (16.9 g, 40.2 mmol) in 70% yield as a colourless oil. R_F = 0.38 (1:1; EtOAc:toluene). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.34 – 7.17 (m, 15H, H_{Ar} Bn), 5.46 (d, 1H, *J* = 4.4, H-1α), 5.23 (s, 1H, H-1β), 4.65 – 4.46 (m, 6H, 3×CH_2 Bn), 4.42 – 4.33 (m, 1H), 4.10 – 3.90 (m, 2H), 3.79 – 3.60 (m, 2H), 2.34 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.3, 136.8, 136.6, 136.1 (3×C_q Bn α/β), 128.2, 127.6, 127.3, 127.1, 127.0, 126.9, 126.5, 126.0 (CH_{Ar} Bn α/β), 100.8 (C-1 β), 95.1 (C-1 α), 85.8, 80.6, 80.4, 80.2, 78.9, 72.7, 72.5, 71.9, 71.6, 71.4, 71.9, 67.9, 67.6, 64.0.

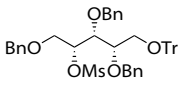


2,3,5-Tri-*O*-benzyl-D-xylitol (10). Sodium borohydride (10.78 g, 285 mmol) was added to a cooled solution (0 °C) of **9** (20 g, 48.0 mmol) in MeOH (240 mL). The reaction mixture was stirred for 3 h at rt after which the pH was adjusted to 5 by addition of acetic acid. The mixture was concentrated, dissolved in Et_2O (500 mL), and washed successively with water (200 mL), 1M aq. HCl (300 mL), 10% aq. $NaHCO_3$ (300 mL), and sat aq NaCl (200 mL). The organic phase was dried ($MgSO_4$), concentrated, and the residue was purified by silica gel column chromatography (20% » 60% EtOAc in PE) to give **10** (17.6 g, 41.6 mmol) in 87% yield as a colorless oil. R_F = 0.45 (1:1; EtOAc:PE). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26 – 7.19 (m, 15H, H_{Ar} Bn), 4.94 – 4.37 (m, 6H, 3×CH_2 Bn), 4.15 – 4.01 (m, 1H), 3.77 – 3.70 (m, 4H), 3.63 – 3.36 (m, 2H), 2.94 (br s, 2H, OH-1, OH-4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.9, 137.8, 137.7 (3×C_q Bn), 128.1, 127.6, 127.5, 127.4 (CH_{Ar} Bn), 78.7, 77.3 (C-2, C-3), 73.9, 72.9, 72.0 (3×CH_2 Bn), 70.9 (C-5), 68.4 (C-4), 60.2 (C-1).

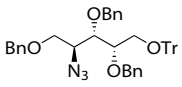


2,3,5-Tri-*O*-benzyl-1-*O*-trityl-D-xylitol (11). Triphenylmethyl chloride (14.1 g, 50.6 mmol) was added to a solution of **10** (17.6 g, 40.5 mmol) in pyridine (210 mL). The reaction mixture was stirred 20 h at 40 °C. Excess triphenylmethyl chloride was quenched by addition of H_2O

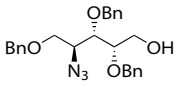
(5 mL) and the mixture was concentrated. The residue was redissolved in Et_2O (100 mL) and washed successively with 0.1M aq HCl (2×100 mL), sat aq $NaHCO_3$ (100 mL) and sat aq NaCl (50 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 20% EtOAc in toluene) to give **11** (25.3 g, 38.1 mmol) in 94% yield as a colourless oil. R_F = 0.45 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 6H, H_{Ar} Tr), 7.35 – 7.13 (m, 24H, H_{Ar} Bn/Tr), 4.73 – 4.65 (m, 2H, 2×C*H*H Bn), 4.55 – 4.48 (m, 2H, 2×CH*H* Bn), 4.42 (s, 2H, CH_2 Bn), 3.91 (dd, *J* = 3.1, 5.6, 1H, H-3), 3.85 – 3.79 (m, 2H, H-2, H-4), 3.44 (dd, *J* = 4.2, 10.2, 1H, H-1a), 3.38 (d, *J* = 6.0, 2H, CH_2-5), 3.32 (dd, *J* = 5.0, 10.2, 1H, H-1b), 2.45 (d, *J* = 6.3, 1H, OH-4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1 (C_q-Ph Tr), 138.5, 138.4, 138.3 (3×C_q Bn), 128.9, 128.5, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.8, 127.2 (CH_{Ar} Bn/Tr), 87.0 (C_q Tr), 79.6 (C-2), 78.3 (C-3), 75.0, 73.3, 73.0 (3×CH_2 Bn), 71.2 (C-5), 70.0 (C-4), 63.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2956, 1726, 1491, 1452, 1285, 1069, 747, 700. $[\alpha]^{20}_D$: −3.3 (*c* 2.2, $CHCl_3$). HRMS: found 687.3080 $[M+Na]^+$, calculated for $[C_{45}H_{44}O_5+Na]^+$ 687.3080.



2,3,5-Tri-*O*-benzyl-4-methanesulfonyl-1-*O*-trityl-D-xylitol (12). Methanesulfonyl-chloride (6.7 mL, 86 mmol) was added to a dry solution of **11** (14.4 g, 21.7 mmol) and Et_3N (10.9 mL, 78.0 mmol) in DCM (110 mL). The reaction mixture and stirred for 20 hours, after which it was quenched by addition of H_2O (5 mL). The reaction mixture was washed successively with 0.1M aq HCl (50 mL), sat aq $NaHCO_3$ (50 mL) and sat aq NaCl (50 mL). The organic phase was dried ($MgSO_4$), concentrated and the residue was purified by silica gel column chromatography (5% » 25% EtOAc in PE) to produce **12** (13.7 g, 18.5 mmol) in 85% yield as a colorless oil. R_F = 0.60 (1:9; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 6H, H_{Ar} Tr), 7.34 – 7.08 (m, 26H, H_{Ar} Bn/Tr), 4.79 (ddd, *J* = 2.8, 5.3, 6.9, 1H, H-4), 4.62 – 4.55 (m, 2H, 2×C*H*H Bn), 4.52 (d, *J* = 11.2, 1H, CH*H* Bn), 4.47 (d, *J* = 11.9, 1H, C*H*H Bn), 4.32 – 4.27 (m, 2H, 2×CH*H* Bn), 4.11 (dd, *J* = 3.4, 6.8, 1H, H-3), 3.73 (ddd, *J* = 3.5, 5.1, 6.1, 1H, H-2), 3.62 (dd, *J* = 2.8, 11.5, 1H, H-6a), 3.47 (dd, *J* = 5.1, 9.8, 1H, H-1a), 3.39 (dd, *J* = 5.3, 11.5, 1H, H-6b), 3.35 (dd, *J* = 6.2, 9.8, 1H, H-1b), 2.81 (s, 3H, CH_3 Ms). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9 (C_q-Ph Tr), 137.9, 137.8, 137.7 (3×C_q Bn), 128.8, 128.7, 128.6, 128.5, 128.5, 128.5, 128.1, 128.0, 127.3 (CH_{Ar} Bn/Tr), 87.3 (C_q Tr), 82.1 (C-4), 77.3 (C-3), 76.9 (C-2), 75.3, 73.4, 72.6 (3×CH_2 Bn), 69.3 (C-5), 62.1 (C-1), 38.3 (CH_3 Ms). IR ν_{max}(thin film)/ cm^{-1}: 3032, 1492, 1452, 1358, 1213, 1175, 1073, 918, 748, 701. $[\alpha]^{20}_D$: 23.5 (*c* 1.6, $CHCl_3$). HRMS: found 765.2860 $[M+Na]^+$, calculated for $[C_{46}H_{46}O_7S+Na]^+$ 765.2862.

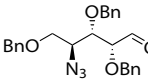


4-Azido-2,3,5-tri-*O*-benzyl-4-deoxy-1-*O*-trityl-L-arabinitol (13). Sodium azide (7.80 g, 120 mmol) and 15-crown-5 (0.25 mL, 1.25 mmol) were added to a dry solution of **12** (9.21, 12.4 mmol) in DMF (60 mL). The resulting suspension was stirred at 90 °C for 48h. The reaction mixture was concentrated. The residue was dissolved in Et_2O (100 mL) and washed successively with water (100 mL) and sat aq NaCl (100 mL). The organic layer was dried ($MgSO_4$), concentrated and the resulting residue was purified by silica gel column chromatography (5% » 20% EtOAc in PE) to produce **13** (7.5g, 10.9 mmol) in 88% yield as a colorless oil. R_F = 0.80 (1:9; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 6H, H_{Ar} Tr), 7.33 – 7.02 (m, 24H, H_{Ar} Bn/Tr), 4.63 (d, *J* = 11.6, 1H, C*H*H Bn), 4.49 (d, *J* = 11.6, 1H, CH*H* Bn), 4.46 – 4.38 (m, 4H, 2×CH_2 Bn), 3.86 (dd, *J* = 3.3, 7.4, 1H, H-3), 3.82 – 3.78 (m, 1H, H-2), 3.77 – 3.71 (m, 2H, H-4, H-5a), 3.63 (dd, *J* = 6.5, 10.2, 1H, H-5b), 3.45 (dd, *J* = 5.3, 9.8, 1H, H-1a), 3.30 (dd, *J* = 6.5, 9.8, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1 (C1-Ph Tr), 138.5, 138.1, 138.1 (3×C_q Bn), 128.9, 128.7, 128.6, 128.5, 128.2, 128.0, 128.0, 127.8, 127.4 (CH_{Ar} Bn/Tr), 87.4 (C_q Tr), 78.3 (C-3), 78.2 (C-2), 75.0, 73.5, 73.4 (3×CH_2 Bn), 70.0 (C-5), 62.9 (C-1), 61.3 (C-4). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2870, 2096, 1492, 1452, 1073, 747, 699. $[\alpha]^{20}_D$: 11.2 (*c* 1.2, $CHCl_3$). HRMS: found 712.3147 $[M+Na]^+$, calculated for $[C_{45}H_{43}N_3O_4+Na]^+$ 712.3151.

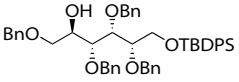


4-Azido-2,3,5-tri-*O*-benzyl-4-deoxy-L-arabinitol (14). Boron trifluoride diethyletherate (4.8 mL, 38.0 mmol) was added to a solution of **13** (7.3 g, 10.5 mmol) in a mixture of toluene/ MeOH (265 mL, 16/1, v/v). The reaction mixture was stirred for 3 h, after which the reaction

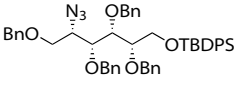
was successively washed with sat aq $NaHCO_3$ (100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was dissolved in EtOAc, cooled to 0 °C and the triphenylmethoxymethane that precipitated was removed by filtration. Subsequent concentration and purification of the residue by silica gel column chromatography (5% » 50% EtOAc in toluene) afforded **14** (4.6 g, 10.3 mmol) in 98% yield as a colorless oil. R_F = 0.15 (1:19; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.15 (m, 15H, H_{Ar} Bn), 4.62 – 4.51 (m, 4H, 2×CH_2 Bn), 4.49 (s, 2H, CH_2 Bn), 3.82 – 3.61 (m, 7H, CH_2-1, H-2, H-3, H-4, CH_2-5), 2.27 (s, 1H, OH-1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.7, 137.7 (3×C_q Bn), 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 126.9 (CH_{Ar} Bn), 79.1, 78.0 (C-2, C-3), 74.4, 73.4, 73.1 (3×CH_2 Bn), 69.6 (C-5), 61.3 (C-4), 61.3 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3465, 3033, 2868, 2096, 1496, 1454, 1267, 1211, 1093, 1027, 735, 698. $[\alpha]^{20}_D$: 18.5 (*c* 7.0, $CHCl_3$). HRMS: found 470.2046 $[M+Na]^+$, calculated for $[C_{26}H_{29}N_3O_4+Na]^+$ 470.2056.



4-Azido-2,3,5,-tri-*O*-benzyl-4-deoxy-L-arabinose (15). Azido-alcohol **14** (2.00 g, 4.47 mmol) was subjected to a Dess-Martin mediated oxidation (General Procedure A) to produce **15** (1.51 g, 3.39 mmol) in 76% yield as a colourless oil. R_F = 0.60 (1:9; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.1, 1H, C(O)H-1), 7.37 – 7.14 (m, 15H, H_{Ar} Bn), 4.75 (d, *J* = 11.7, 1H, C*H*H Bn), 4.60 (d, *J* = 11.7, 1H, CH*H* Bn), 4.53 (s, 2H, CH_2 Bn), 4.44 (s, 2H, CH_2 Bn), 4.03 (dd, *J* = 1.2, 3.0, 1H, H-2), 3.96 (dd, *J* = 3.0, 8.1, 1H, H-3), 3.85 (dt, *J* = 2.7, 5.7, 1H, H-4), 3.81 (dd, *J* = 2.7, 9.9, 1H, H-5a), 3.70 (dd, *J* = 5.6, 9.9, 1H, H-5b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2 (C(O)H-1), 137.7, 137.1, 136.9 (3×C_q Bn), 128.8, 128.7, 128.7, 128.6, 128.6, 128.3, 128.3, 128.1, 128.0 (CH_{Ar} Bn), 83.4 (C-2), 78.0 (C-3), 74.5, 73.9, 73.6 (3×CH_2 Bn), 69.3 (C-5), 60.9 (C-4). IR ν_{max}(thin film)/ cm^{-1}: 2867, 2097, 1728, 1496, 1454, 1315, 1266, 1210, 1093, 1026, 912, 734, 695. $[\alpha]^{20}_D$: 12.6 (*c* 1.8, $CHCl_3$). HRMS: found 468.1891 $[M+Na]^+$, calculated for $[C_{26}H_{27}N_3O_4+Na]^+$ 468.1899.

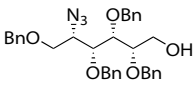


2,3,4,6-Tetra-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-D-glucitol (17). *tert*-Butyldiphenylsilylchloride (21 mL, 80.7 mmol) was added over a 2 min period to a dry solution of 2,3,4,6-tetra-*O*-benzyl-D-glucitol (**16**: 39.0 g, 71.9 mmol; synthesis described in Chapter 2) and imidazole (10.8 g, 158.6 mmol) in DMF (75 mL). The reaction mixture was stirred for 20 hours and subsequently concentrated. The residue was purified by silica gel column chromatography (20% » 25% EtOAc in PE) to provide **17** (55.7 g, 71.4 mmol) as a colourless oil in 99% yield. R_F = 0.85 (1:1; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 4H, H_{Ar} TBDPS), 7.42 – 7.07 (m, 26H, H_{Ar} TBDPS/Bn), 4.64 (s, 2H, CH_2 Bn), 4.63 (d, *J* = 11.6, 1H, C*H*H Bn), 4.54 – 4.45 (m, 5H, CH*H* Bn, 2×CH_2 Bn), 3.97 (dd, *J* = 4.5, 1H, H-3), 3.96 – 3.92 (m, 1H, H-5), 3.88 (dd, *J* = 4.9, 10.6, 1H, H-1a), 3.83 (dd, *J* = 4.9, 9.9, 1H, H-2), 3.78 (dd, *J* = 3.9, 6.5, 1H, H-4), 3.76 (dd, *J* = 4.9, 10.1, 1H, H-1b), 3.60 (dd, *J* = 2.5, 8.9, 1H, H-6b), 3.58 (dd, *J* = 4.2, 8.9, 1H, H-6b), 2.91 (d, *J* = 4.8, 1H, OH-5), 1.04 (s, 9H, *t*-butyl-Si). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.4, 138.3, 138.3 (4×C_q Bn), 135.8 (CH_{Ar} TBDPS), 133.5 (C_q Si-Ph), 129.9, 129.9, 128.6, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7(CH_{Ar} Bn/TBDPS), 79.8 (C-2), 78.1 (C-3), 77.6 (C-4), 74.4, 73.6, 73.5, 73.2 (4×CH_2 Bn), 71.4 (C-6), 71.2 (C-5), 63.3 (C-1), 27.1 (CH_3 *t*-butyl), 19.4 (C_q *t*-butyl). IR ν_{max}(thin film)/ cm^{-1}: 3030, 2929, 2862, 1490, 1454, 1358, 1208, 1080, 1027, 823, 735, 698. $[\alpha]^{20}_D$: 16.2 (*c* 2.1, $CHCl_3$). HRMS: found 803.3739 $[M+Na]^+$; calculated for $[C_{50}H_{56}O_6Si+Na]^+$ 803.3744.

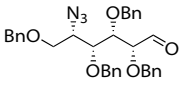


5-Azido-2,3,4,6-tetra-*O*-benzyl-*tert*-1-*O*-butyldiphenylsilyl-L-iditol (18). Diisopropyl azodicarboxylate (2.52 mL, 12.8 mmol) and diphenylphosphoryl azide (2.76 mL, 12.8 mmol) were successively added over 2 min periods to a dry and cooled (0 °C) solution of **17** (5.00 g, 6.4 mmol) and triphenylphosphine (3.36 g, 12.8 mmol) in THF (48 mL). The reaction mixture was stirred for 20 h and allowed to warm to rt. The mixture was concentrated and the resulting residue was purified by silica gel column chromatography (0% » 10% EtOAc in PE) to afford **18** (3.70 g, 4.2 mmol) in 66% yield as a colourless oil. R_F = 0.60 (1:6; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 6.7, 19.6, 4H, H_{Ar} TBDPS),

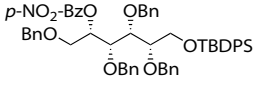
7.43 – 7.13 (m, 26H, H_{Ar} TBDPS/Bn), 4.78 – 4.71 (m, 2H, C*H*H Bn, C*H*H Bn), 4.64 (d, *J* = 11.3, 1H, CH*H* Bn), 4.59 (d, *J* = 12.0, 1H, C*H*H Bn), 4.52 (d, *J* = 11.5, 1H, CH*H* Bn), 4.39 – 4.32 (m, 2H, CH_2 Bn), 4.29 (d, *J* = 12.0, 1H, CH*H* Bn), 4.04 (dd, *J* = 2.7, 7.6, 1H, H-3), 3.93 (dd, *J* = 6.3, 10.5, 1H, H-1a), 3.87 (dd, *J* = 5.6, 10.5, 1H, H-1b), 3.82 (dd, *J* = 3.0, 7.7, 1H, H-4), 3.61 – 3.56 (m, 1H, H-2), 3.53 (dd, *J* = 8.1, 9.2, 1H, H-6a), 3.34 (dd, *J* = 4.8, 9.5, 1H, H-6b), 3.30 – 3.23 (m, 1H, H-5), 1.08 (s, 9H, *t*-butyl-Si). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.8, 138.6, 138.4 (4×C_q Bn), 136.3, 136.2 (CH_{Ar} TBDPS), 133.9 (C_q Si-Ph), 130.5, 130.4, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2 (CH_{Ar} Bn/TBDPS), 79.6, 79.0, 78.6 (C-2, C-2, C-4), 75.8, 75.5, 73.8, 73.0 (4×CH_2 Bn), 70.4 (C-6), 63.0 (C-1), 61.9 (C-5), 27.5 (CH_3 *t*-butyl), 19.8 (C_q *t*-butyl). IR ν_{max}(thin film)/ cm^{-1}: 3030, 2928, 2857, 2955, 2097, 1494, 1454, 1428, 1358, 1208, 1080, 1027, 734, 699. $[\alpha]^{20}_D$: 21.3 (*c* 8.2, $CHCl_3$). HRMS: found 828.3807 $[M+Na]^+$; calculated for $[C_{50}H_{55}N_3O_5Si+Na]^+$ 828.3809.



5-Azido-2,3,4,6-tetra-*O*-benzyl-L-iditol (19). Tetrabutylammoniumflouride (12 mL, 12 mmol; 1M in THF) was added to a dry solution of **18** (7.25 g, 9.0 mmol) in THF (150 mL) and the resulting reaction mixture was stirred for 20 h. The mixture was concentrated, redissolved in Et_2O (100 mL) and washed with sat aq NaCl (100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (9% » 25% EtOAc in PE) to produce **19** (3.62 g, 6.38 mmol) in 71% yield as a colourless oil. R_F = 0.20 (1:4; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.17 (m, 20H, H_{Ar} Bn), 4.75 (d, *J* = 11.5, 1H, C*H*H Bn), 4.67 (d, *J* = 11.1, 1H, C*H*H Bn), 4.65 – 4.60 (m, 2H, C*H*H Bn, CH*H* Bn), 4.55 – 4.52 (m, 2H, C*H*H Bn, C*H*H Bn), 4.38 (d, *J* = 11.8, 1H, C*H*H Bn), 4.35 (d, *J* = 11.8, 1H, CH*H* Bn), 3.91 (dd, *J* = 4.0, 7.3, 1H, H-3), 3.87 (dd, *J* = 2.8, 7.4, 1H, H-4), 3.78 (dd, *J* = 5.0, 11.5, 1H, H-1a), 3.71 (dd, *J* = 5.0, 11.6, 1H, H-1b), 3.60 (dd, *J* = 4.9, 9.2, 1H, H-2), 3.59 – 3.52 (m, 2H, H-5, H-6a), 3.46 (dd, *J* = 4.5, 8.9, 1H, H-6b), 3.24 – 2.79 (m, 1H, OH-1).^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8, 137.7, 137.5 (4×C_q Bn), 128.2, 128.1, 128.1, 128.1, 127.9, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 127.3 (CH_{Ar} Bn), 78.9 (C-3), 78.1 (C-2), 78.0 (C-4), 74.6, 74.5, 72.9, 72.1 (4×CH_2 Bn), 69.3(C-6), 61.0 (C-1), 60.8 (C-5). IR ν_{max}(thin film)/ cm^{-1}: 3469, 3032, 2866, 2097, 1496, 1454, 1353, 1263, 1210, 1061, 1027, 734, 698. $[\alpha]^{20}_D$: 17.8 (*c* 13.2, $CHCl_3$). HRMS: found 590.2620 $[M+Na]^+$; calculated for $[C_{34}H_{37}N_3O_5+Na]^+$ 590.2631.

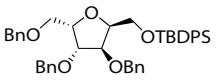


5-Azido-2,3,4,6-tetra-*O*-benzyl-L-idose (20). Azido-alcohol **19** (2.22 g, 3.9 mmol) was subjected to a Dess-Martin mediated oxidation (General Procedure A) to produce **20** (1.97 g, 3.5 mmol) in 89% yield as a colourless oil. R_F = 0.55 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H, H-1), 7.36 – 7.21 (m, 18H, H_{Ar} Bn), 7.21 – 7.13 (m, 2H, H_{Ar} Bn), 4.81 (d, *J* = 11.9, 1H, C*H*H Bn), 4.63 (d, *J* = 11.1, 1H, C*H*H Bn), 4.56 – 4.50 (m, 3H, CH*H* Bn, CH_2 Bn), 4.47 (d, *J* = 11.9, 1H, CH*H* Bn), 4.41 (d, *J* = 12.2, 1H, C*H*H Bn), 4.38 (d, *J* = 12.2, 1H, CH*H* Bn), 3.96 (dd, *J* = 4.8, 4.8, 1H, H-3), 3.92 (d, *J* = 4.6, 1H, H-2), 3.86 (dd, *J* = 5.0, 5.0, 1H, H-4), 3.58 – 3.51 (m, 1H, H-5), 3.51 – 3.43 (m, 2H, CH_2-6).^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8 (CH-1), 137.8, 137.6, 137.2, 137.0 (4×C_q Bn), 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 127.9, 127.9, 127.8 (CH_{Ar} Bn), 80.9 (C-2), 79.3 (C-3), 77.4 (C-4), 74.5, 74.1, 73.3, 73.2 (4×CH_2 Bn), 69.5 (C-6), 61.6 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2864, 2097, 1729, 1496, 1454, 1352,1264, 1210, 1092, 1027, 734, 697. $[\alpha]^{20}_D$: 23.7 (*c* 10.7, $CHCl_3$). HRMS: found 588.2468 $[M+Na]^+$; calculated for $[C_{34}H_{35}N_3O_5+Na]^+$ 588.2474.

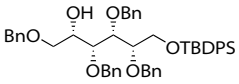


2,3,4,6-Tetra-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-*O*-*para*-nitrobenzoyl-L-iditol (21). Diisopropyl azodicarboxylate (7.54 mL, 38.4 mmol) was added over a 2 min period to a dry and cooled (0 °C) solution of **17** (15.02 g, 19.2 mmol), *p*-nitrobenzoic acid (6.42 g, 38.4 mmol) and triphenylphosphine (10.07 g, 38.4 mmol) in THF (77 mL). The reaction mixture was stirred for 20h and allowed to warm to rt. The reaction mixture was diluted with EtOAc (200 mL) and successively washed with sat aq $NaHCO_3$ (3×100 mL) and sat aq NaCl (100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was used crude in the next reaction. A portion of the residue was purified for characterization by silica gel column chromatography (2% » 5% EtOAc in PE) to provide **21** as

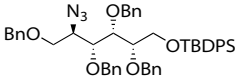
a colourless oil. R_F = 0.60 (1:6; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 6H, H_{Ar} TBDPS/*p*-NO_2Bz), 7.45 – 7.07 (m, 28H, H_{Ar} Bn/TBDPS/*p*-NO_2Bz), 5.49 (dd, *J* = 5.3, 9.5, 1H, H-5), 4.84 – 4.27 (m, 8H, 4×CH_2 Bn), 4.19 – 3.48 (m, 7H, CH_2-1, H-2, H-3, H-4, CH_2-6), 0.90 (s, 9H, *t*-butyl-Si). ESI-MS: found 930.4 $[M+H]^+$; calculated for $[C_{57}H_{59}NO_9Si+H]^+$ 930.4.



2,5-Anhydro-1-*O*-*tert*-butyldiphenylsilyl-3,4,6-tri-*O*-benzyl-L-iditol (22). Side product **22** could be separated from **23** by silica gel column chromatography (5% » 15% EtOAc in PE) to provide **22** (5.94 g, 8.83 mmol) as a colourless oil in 46% yield. R_F = 0.65 (1:6; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4H, H_{Ar} TBDPS), 7.42 – 7.16 (m, 21H, H_{Ar} TBDPS/Bn), 4.59 (d, *J* = 12.0, 1H, C*H*H Bn), 4.56 – 4.44 (m, 5H, CH*H* Bn, 2×CH_2 Bn), 4.37 – 4.30 (m, 2H, H-2, H-5), 4.09 (dd, *J* = 1.5, 4.0, 1H, H-3), 4.04 (dd, *J* = 1.4, 4.0, 1H, H-4), 3.98 (dd, *J* = 7.9, 9.9, 1H, H-1a), 3.87 (dd, *J* = 5.2, 10.0, 1H, H-1b), 3.71 (dd, *J* = 5.8, 9.9, 1H, H-6a), 3.66 (dd, *J* = 6.5, 9.8, 1H, H-6b), 1.06 (s, 9H, *t*-butyl-Si). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.2, 138.1 (3×C_q Bn), 135.7, 135.7 (CH_{Ar} TBDPS), 133.7, 133.5 (2×C_q Si-Ph), 129.7, 129.7, 128.5, 128.5, 128.4, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6 (CH_{Ar} Bn/TBDPS), 81.9 (C-4), 81.3 (C-3), 80.5 (C-2), 79.2 (C-5), 73.5, 72.6, 72.4 (3×CH_2 Bn), 68.8 (C-6), 61.7 (C-1), 27.0 (CH_3 *t*-butyl), 19.3(C_q *t*-butyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2931, 2858, 1494, 1454, 1428, 1358, 1208, 1080, 1027, 823, 735, 699, 611, 504. $[\alpha]^{20}_D$: 9.4 (*c* 10.6, $CHCl_3$). HRMS: found 695.3161 $[M+Na]^+$; calculated for $[C_{43}H_{48}O_5Si+Na]^+$ 695.3169.

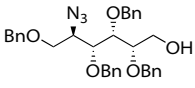


2,3,4,6-Tetra-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-L-iditol (23). The crude **21**- and **22**-containing residue from the previous reaction was dissolved in a mixture of H_2O/EtOH/THF (100 mL, 1/2/2, v/v/v). Lithiumhydroxide (2.85 g, 119 mmol) was added to the solution and the resulting yellow coloured reaction mixture was stirred for 2h, after which TLC analysis showed complete consumption of the starting material. The pH of reaction mixture was adjusted to pH ~7 with 1M aq HCl. The mixture was concentrated to ~¼ of its initial volume, diluted with Et_2O (100 mL) and washed successively with sat aq $NaHCO_3$ (3×100 mL) and sat aq NaCl (100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (5% » 15% EtOAc in PE) to provide **23** (5.68 g, 7.28 mmol) in 38% yield over the two steps as a colourless oil. R_F = 0.35 (1:6; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 – 7.63 (m, 4H, H_{Ar} TBDPS), 7.47 – 7.16 (m, 26H, H_{Ar} TBDPS/Bn), 4.77 – 4.70 (m, 2H, C*H*H Bn, C*H*H Bn), 4.67 – 4.58 (m, 2H, C*H*H Bn, CH*H* Bn), 4.49 (d, *J* = 11.2, 1H, CH*H* Bn), 4.43 (d, *J* = 11.9, 1H, C*H*H Bn), 4.41 (d, *J* = 8.9, 1H, CH*H* Bn), 4.38 (d, *J* = 11.9, 1H, CH*H* Bn), 4.02 (dd, *J* = 3.1, 7.7, 1H, H-3), 3.87 (dd, *J* = 4.5, 9.1, 1H, H-1a), 3.85 (dd, *J* = 4.5, 9.1, 1H, H-1b), 3.80 (dd, *J* = 2.3, 7.7, 1H, H-4), 3.75 – 3.69 (m, 2H, H-2, H-5), 3.42 (dd, *J* = 6.8, 9.2, 1H, H-6a), 3.26 (dd, *J* = 5.7, 9.2, 1H, H-6b), 2.51 (d, *J* = 6.5, 1H, OH-5), 1.04 (s, 9H, *t*-butyl-Si). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 138.5, 138.4, 138.3 (4×C_q Bn), 135.9, 135.8 (CH_{Ar} TBDPS), 133.5 (C_q Si-Ph), 130.0, 129.9, 128.6, 128.5, 128.4, 128.0, 127.9, 127.9, 127.9, 127.8 (CH_{Ar} Bn/TBDPS), 79.0 (C-3), 78.9 (C-2), 78.7 (C-4), 75.1, 75.0, 73.4, 73.1 (4×CH_2 Bn), 71.6 (C-6), 69.9 (C-5), 63.2 (C-1), 27.1 (CH_3 *t*-butyl), 19.3 (C_q *t*-butyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2929, 2861, 1495, 1454, 1358, 1208, 1080, 1027, 823, 734, 699. $[\alpha]^{20}_D$: 13.0 (*c* 0.3, $CHCl_3$). HRMS: found 803.3736 $[M+Na]^+$; calculated for $[C_{50}H_{56}O_6Si+Na]^+$ 803.3744.

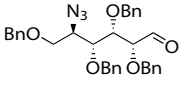


5-Azido-2,3,4,6-tetra-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-D-glucitol (24). Diiso-propyl azodicarboxylate (2.87 mL, 14.6 mmol) and diphenylphosphoryl azide (3.15 mL, 14.6 mmol) were successively added over 2 min periods to a dry and cooled (0 °C) solution of **23** (5.68, 7.3 mmol) and triphenylphosphine (3.83 g, 14.6 mmol) in THF (55 mL). The reaction mixture was stirred for 20 h and allowed to warm to rt. The mixture was concentrated and the resulting residue was purified by silica gel column chromatography (0% » 10% EtOAc in PE) to afford **24** (3.70 g, 4.60 mmol) in 63% yield as a colourless oil. R_F = 0.6 (1:6; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 4H, H_{Ar}

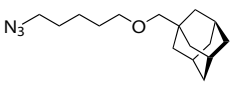
TBDPS), 7.42 – 7.11 (m, 26H, H_{Ar} TBDPS/Bn), 4.69 – 4.64 (m, 3H, C*H*H Bn, CH_2 Bn), 4.58 (d, *J* = 11.2, 1H, C*H*H Bn), 4.54 (d, *J* = 11.2, 1H, CH*H* Bn), 4.48 – 4.43 (m, 3H, CH*H* Bn, CH_2 Bn), 3.93 – 3.61 (m, 8H, CH_2-1, H-2, H-3, H-4, H-5, CH_2-6), 1.06 (s, 9H, *t*-butyl-Si). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 138.2, 138.0 (4×C_q Bn), 135.8 (CH_{Ar} TBDPS), 133.4 (C_q Si-Ph), 129.9, 129.9, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7 (CH_{Ar} Bn/TBDPS), 79.5, 78.9, 78.7 (C-2, C-2, C-4), 75.1, 74.5, 73.4, 72.9 (4×CH_2 Bn), 69.8 (C-6), 63.1 (C-1), 61.9 (C-5), 27.0 (CH_3 *t*-butyl), 19.3 (C_q *t*-butyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2926, 2864, 2097, 1495, 1454, 1354, 1209, 1076, 1027, 734, 699. $[\alpha]^{20}_D$: −4.1 (*c* 0.7, $CHCl_3$).HRMS: found 828.3805 $[M+Na]^+$; calculated for $[C_{50}H_{55}N_3O_5Si+Na]^+$ 828.3809.



5-Azido-2,3,4,6-tetra-*O*-benzyl-D-glucitol (25). Tetrabutylammoniumflouride (4.2 mL, 4.2 mmol; 1M in THF) was added to a dry solution of **24** (2.26 g, 2.8 mmol) in THF (47 mL) and the resulting reaction mixture was stirred for 20 h. The mixture was concentrated, redissolved in Et_2O (100 mL) and washed with sat aq NaCl (100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (9% » 25% EtOAc in PE) to produce **25** (1.17 g, 2.07 mmol) in 74% yield as a colourless oil. R_F = 0.20 (1:4; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.15 (m, 20H, H_{Ar} Bn), 4.70 (d, *J* = 11.2, 1H, C*H*H Bn), 4.68 – 4.61 (m, 3H, CH*H* Bn, C*H*H Bn), 4.58 (d, *J* = 11.8, 1H, CH*H* Bn), 4.47 (s, 2H, CH_2 Bn), 3.86 – 3.83 (m, 1H, H-4), 3.82 – 3.78 (m, 3H, H-1a, H-3, H-5), 3.76 – 3.66 (m, 3H, H-1b, H-2, H-6a), 3.59 (dd, *J* = 4.9, 11.7, 1H, H-6b), 3.09 – 2.72 (m, 1H, OH-1). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.0, 138.0, 137.8, 137.6 (4×C_q Bn), 128.3, 128.3, 128.2, 128.2, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{Ar} Bn), 79.1 (C-4), 78.8 (C-3), 78.3 (C-2), 74.8, 74.0, 73.1, 72.6 (4×CH_2 Bn), 69.4 (C-6), 61.4 (C-5), 61.3 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3031,2865, 2095, 1495, 1454, 1353, 1353, 1264, 1209, 1094, 1027, 734, 697. $[\alpha]^{20}_D$: −3.1 (*c* 11.5, $CHCl_3$). HRMS: found 590.2621 $[M+Na]^+$; calculated for $[C_{34}H_{37}N_3O_5+Na]^+$ 590.2631.

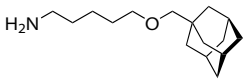


5-Azido-2,3,4,6-tetra-*O*-benzyl-D-glucose (26). Azido-alcohol **25** (1.80 g, 3.2 mmol) was subjected to a Dess-Martin mediated oxidation (General Procedure A) to produce **26** (1.71 g, 3.0 mmol) in 96% yield as a colourless oil. R_F = 0.60 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H, H-1), 7.40 – 7.20 (m, 18H, H_{Ar} Bn), 7.20 – 7.14 (m, 2H, H_{Ar} Bn), 4.85 (d, *J* = 12.0, 1H, C*H*H Bn), 4.64 (d, *J* = 11.5, 1H, C*H*H Bn), 4.59 (d, *J* = 11.5, 1H, CH*H* Bn), 4.56 – 4.47 (m, 4H, CH_2 Bn, CH*H* Bn, C*H*H Bn), 4.37 (d, *J* = 10.9, 1H, CH*H* Bn), 4.02 (dd, *J* = 2.9, 5.8, 1H, H-3), 3.89 (d, *J* = 5.9, 1H, H-2), 3.86 – 3.78 (m, 2H, H-4, H-6a), 3.75 – 3.67 (m, 2H, H-5, H-6b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2 (CH-1), 137.7, 137.5, 137.4, 137.3 (4×C_q Bn), 128.8, 128.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.0, 128.0, 127.9 (CH_{Ar} Bn), 80.0 (C-2), 79.9 (C-3), 76.7 (C-4), 74.3, 74.0, 73.6, 73.3 (4×CH_2 Bn), 69.5 (C-6), 60.8 (C-5). IR ν_{max}(thin film)/ cm^{-1}: 3064, 3032, 2865, 2096, 1727, 1496, 1454, 1328, 1265, 1211, 1072, 1027, 734, 697. $[\alpha]^{20}_D$: 3.8 (*c* 10.2, $CHCl_3$). HRMS: found 588.2466 $[M+Na]^+$; calculated for $[C_{34}H_{35}N_3O_5+Na]^+$ 588.2474.

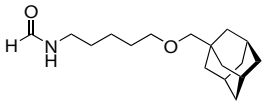


5-(Adamantan-1-yl-methoxy)-pentan-1-azide (28). Sodium azide (1.56 g, 240 mmol) was added to a dry solution of 5-(adamantan-1-yl-methoxy)-1-bromo-pentane **(27**: 6.0 g, 191 mmol; synthesis described in Chapter 5) in DMSO (20 mL). The reaction mixture was stirred for 20h. The mixture was diluted with Et_2O (500 mL) and washed successively with H_2O (2×500 mL) and sat aq NaCl (200 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (10% » 70% toluene in PE) to give **28** (5.14 g, 185 mmol mol) in 95% yield as a colourless oil. R_F **27** = 0.60 (4% EtOAc in PE); **28** = 0.70 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.27 (t, *J* = 7.0, 2H, CH_2-1 pentyl), 2.95 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.77 – 1.54 (m, 12H, 3×CH_2 Ada, CH_2-2, CH_2-4 pentyl), 1.53 (d, *J* = 2.7, 6H, 3×CH_2 Ada), 1.49 – 1.39 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.2 (OCH_2-Ada), 71.4 (CH_2-5 pentyl), 51.6 (CH_2-1 pentyl), 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.3 (C_q Ada), 29.3 (CH_2-4 pentyl), 28.9 (CH_2-2 pentyl), 28.5 (CH Ada), 23.7 (CH_2-3 pentyl).

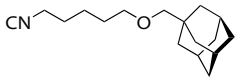
IR ν_{max}(thin film)/ cm^{-1}: 2902, 2848, 2093, 1727, 1453, 1358, 1259, 1158, 1112. HRMS: found 278.2228 $[M+H]^+$; calculated for $[C_{16}H_{27}N_3O+H]^+$ 278.2227.



5-(Adamantan-1-yl-methoxy)-pentan-1-amine (29). Trimethylphosphine (33 mL, 33 mmol, 1M solution in THF) was added over a 2 min period to a cooled (0 °C) solution of **28** (4.57 g, 16.5 mmol) in THF (83 mL) and H_2O (7 mL). The reaction mixture stirred for 3 h at 0 °C after which it was concentrated and coevaporated three times with toluene. The residue was purified by silica gel column chromatography (10% » 70% MeOH in EtOAc + 5% NH_4OH). Purified **29** contained some dissolved silica gel that could be removed by redissolving **29** in DCM and passing it over a glassfibre filter to provide **29** (3.48 g, 13.86 mmol) after concentration in 84% yield as a colourless oil. R_F = 0.10 (25% MeOH in EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.38 (t, *J* = 6.4, 1H, CH_2-5 pentyl), 2.95 (s, 2H, OCH_2-Ada), 2.70 (t, *J* = 6.7, 1H, CH_2-1 pentyl), 1.94 (s, 3H, 3×CH Ada), 1.73 – 1.44 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 81.8 (OCH_2-Ada), 71.3 (CH_2-5 pentyl), 41.9 (CH_2-1 pentyl), 39.6 (CH_2 Ada), 37.2 (CH_2 Ada), 34.0 (C_q Ada), 29.4, 29.3 (2×CH_2 pentyl), 28.2 (CH Ada), 23.4 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3358, 2899, 2847, 1575, 1453, 1297, 1156, 1111, 945, 860, 745. HRMS: found 252.2321 $[M+H]^+$; calculated for $[C_{16}H_{29}NO+H]^+$ 252.2322.

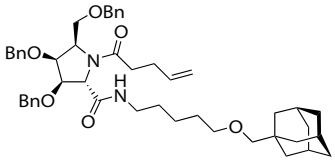


***N*-[5-(Adamantan-1-yl-methoxy)-pentan]formamide (30).** Acetic formic anhydride was prepared by heating a mixture of acetic anhydride (1.51 mL, 16.0 mmol) and formic acid (0.66 mL, 17.6 mmol) at 55 °C for 2 h. The prepared acetic formic anhydride (16.0 mmol) was cooled to 0 °C and added to a cooled (0 °C) solution of **29** (2.01 g, 8.0 mmol) in DCM (22 mL). The reaction mixture was stirred at rt for 20 h, after which it was concentrated. The residue was purified by silica gel column chromatography (30% » 90% EtOAc in PE) to afford **30** (1.84 g, 6.6 mmol) in 82% yield as a colourless oil. R_F = 0.39 (EtOAc); $KMnO_4$ staining. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H, HC(O)N), 5.56 – 5.41 (m, 1H, C(O)NH), 3.38 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.32 (dd, *J* = 6.7, 13.4, 1H, C*H*H-1 pentyl), 3.25 (dd, *J* = 7.0, 13.0, 1H, CH*H*-1 pentyl), 2.95 (s, 2H, OCH_2-Ada), 1.96 (s, 3H, 3×CH Ada), 1.68 (dd, *J* = 12.0, 34.5, 6H, 3×CH_2 Ada), 1.62 – 1.53 (m, 4H, CH_2-2, CH_2-4 pentyl), 1.52 (d, *J* = 2.3, 6H, 3×CH_2 Ada), 1.45 – 1.32 (m, 2H, CH_2-3pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.5 (C=O), 81.9 (OCH_2-Ada), 71.3 (CH_2-5 pentyl), 39.7 (CH_2 Ada), 38.1 (CH_2-1 pentyl), 37.2 (CH_2 Ada), 34.0 (C_q Ada), 29.1, 29.1 (2×CH_2 pentyl), 28.2 (CH Ada), 23.5 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3288, 2899, 2847, 1666, 1540, 1452, 1382, 1232, 1157, 110, 753. HRMS: found 280.2272 $[M+H]^+$; calculated for $[C_{17}H_{29}NO_2+H]^+$ 280.2271.

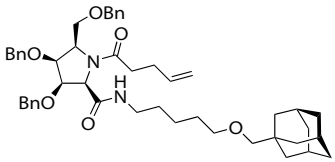


***N*-[5-(Adamantan-1-yl-methoxy)-pentan]isocyanide (31).** Phosphorylchloride (0.51 mL, 5.49 mmol) was added dropwise to a dry and cooled (–30 °C) solution of **30** (1.02 g, 3.66 mmol) and Et_3N (2.54 mL, 18.3 mmol) in DCM (19 mL). The reaction mixture was stirred for 1 h at –30 °C, after which TLC analysis indicated complete consumption of **30**. The dark brown reaction mixture was quenched by addition of sat aq $NaHCO_3$ (5 mL).The reaction mixture was diluted with Et_2O (100 mL) and washed successively with sat aq $NaHCO_3$ (2×100 mL) and brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (20% » 100% DCM in hexane) to afford **31** (773 mg, 2.96 mmol) in 81% yield as a colourless oil. Isocyanide **31** was preferably used immediately but was stable when stored at –20 °C under argon. R_F = 0.90 (EtOAc); 0.40 (1:9; EtOAc:PE); $KMnO_4$ staining. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 – 3.34 (m, 4H, CH_2-1 pentyl, CH_2-5 pentyl), 2.95 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.76 – 1.45 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (t, J_{CN} = 5.5, NC), 81.9 (OCH_2-Ada), 71.0 (CH_2-5 pentyl), 41.5(t, $J_{N\text{-}C1}$ = 6.4, CH_2-1), 39.7 (CH_2 Ada), 37.2 (CH_2 Ada), 34.0 (C_q Ada), 28.9, 28.6, 28.3 (CH Ada), 23.2 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2900, 2847, 2146, 1453, 1358, 1157, 1102,, 2929, 1652, 1460, 1058.

***N*-(1-Cyclohexene)isocyanide (33).** Phorphorylchloride (1.15 mL, 12.35 mmol) was added dropwise to a dry and cooled (−30 °C) solution of known[20,21] *N*-(1-cyclohexene)formamide (**32**: 1.03 g, 8.23 mmol) and Et_3N (5.70 mL, 41.1 mmol) in DCM (41 mL). The reaction mixture was stirred for 1 h at −30 °C, after which TLC analysis indicated complete consumption of **32**. The dark brown reaction mixture was quenched by addition of sat aq $NaHCO_3$ (5 mL).The reaction mixture was diluted with Et_2O (100 mL) and washed successively with sat aq $NaHCO_3$ (2×100 mL) and brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (20% » 100% DCM in hexane) to afford **33** (574 mg, 5.35 mmol) in 65% yield as a colourless oil. Isocyanide **3** was preferably used immediately, but was stable when stored at −20 °C under argon. R_F **33** = 0.85 (1:1; EtOAc:PE); **32** = 0.40 (1:1; EtOAc:PE); $KMnO_4$ staining. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 – 5.88 (m, 1H, =CH-2), 2.26 – 2.19 (m, 2H, CH_2 3 or 6), 2.15 – 2.07 (m, 2H, CH_2 3 or 6), 1.73 – 1.65 (m, 2H, CH_2 4 or 5), 1.61 – 1.52 (m, 2H, CH_2 4 or 5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (t, J_{CN} = 5.7, NC), 129.1 (=CH-2), 124.9 (t, J_{CN} = 11.7, N-C1), 28.6, 24.3 (t, J = 1.6), 21.9, 21.0.

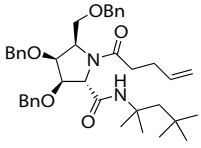


5-(Adamantan-1yl-methoxy)-pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-D-*talo*-hexonamide (A1-I). Subjecting azido-aldehyde **6** (750 μmol) to the tandem SAWU-3CR (General procedure B in the presence of $InCl_3$ in CH_3CN) produced a separable 1.7:1 mixture of **A1-I** (170 mg, 223 μmol) and **B1-I** (100 mg, 131 μmol) in a combined yield of 47%. R_F = 0.49 (2:3; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) 10:1 mixture of rotamers; major rotamer: δ 7.36 – 7.23 (m, 15H, H_{Ar} Bn), 6.63 (t, J = 5.6, 1H, C(O)NH), 5.76 (ddt, J = 6.5, 10.2, 16.8, 1H, =CH pentenyl), 5.00 – 4.91 (m, 2H, =CH_2 pentenyl), 4.67 (d, J = 12.0, 1H, C*H*H Bn), 4.61 (d, J = 11.6, 1H, C*H*H Bn), 4.59 – 4.55 (m, 2H, 2×CH*H* Bn), 4.48 (d, J = 11.9, 1H, C*H*H Bn), 4.46 (dd, J = 4.3, 7.8, 1H, H-4), 4.42 (d, J = 11.9, 1H, CH*H* Bn), 4.39 (s, 1H, H-2), 4.38 – 4.35 (m, 1H, H-5), 4.13 (dd, J = 3.5, 10.6, 1H, H-6a), 4.06 (d, J = 4.3, 1H, H-3), 3.70 (dd, J = 6.1, 10.6, 1H, H-6b), 3.35 (t, J = 6.6, 2H, CH_2-5 pentyl), 3.20 (dt, J = 7.1, 13.5, 1H, NC*H*H-1 pentyl), 3.07 (dt, J = 7.1, 12.7, 1H, NCH*H*-1 pentyl), 2.94 (s, 2H, OCH_2-Ada), 2.75 (ddd, J = 6.3, 8.8, 15.4, 1H, NC*H*H pentenyl), 2.53 (ddd, J = 6.4, 8.9, 15.6, 1H, NCH*H* pentenyl), 2.40 – 2.25 (m, 2H, CH_2 pentenyl), 1.95 (s, 3H, 3×CH Ada), 1.67 (dd, J = 12.1, 36.2, 6H, 3×CH_2 Ada), 1.59 – 1.49 (m, 8H, 3×CH_2 Ada, CH_2-4 pentyl), 1.49 – 1.42 (m, 2H, CH_2-2 pentyl), 1.36 – 1.29 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer: δ 174.3 (NC=O pentenyl), 169.6 (NHC(O)-1), 138.2, 137.9, 137.9 (3×C_q Bn), 137.6 (=CH pentenyl), 128.6, 128.5, 128.0, 128.0, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 115.2 (=CH_2 pentenyl), 82.1 (OCH_2-Ada), 78.9 (C-4), 78.4 (C-3), 73.5, 72.7 (3×CH_2 Bn), 71.7 (C-6), 71.6 (CH_2-5 pentyl), 65.4 (C-2), 59.3 (C-5), 39.9 (CH_2 Ada), 39.8 (NCH_2-1 pentyl), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 33.8 (NCH_2 pentenyl), 29.4, 29.3, 29.3 (CH_2 pentenyl, CH_2-2, CH_2-4 pentyl), 28.4 (CH Ada), 23.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3308, 2901, 2848, 1651, 1622, 1545, 1452, 1360, 1146, 1097, 1054, 1027, 911, 734, 696. $[\alpha]^{20}_D$: 25.5 (*c* 2.4, $CHCl_3$). HRMS: found 763.4684 $[M+H]^+$, calculated for $[C_{48}H_{62}O_6N_2+H]^+$ 763.4681.

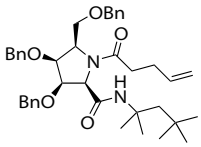


5-(Adamantan-1yl-methoxy)-pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-D-*galacto*-hexonamide (B1-I). Subjecting azido-aldehyde **6** (200 μmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1:20 mixture of **A1-I** (4 mg, 5 μmol) and **B1-I** (91 mg, 119 μmol) in a combined yield of 62%. R_F = 0.15 (2:3; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) 2:1 mixture of rotamers; major rotamer: δ 7.41 – 7.12 (m, 15H, H_{Ar} Bn), 6.22 (t, J = 5.7, 1H, C(O)NH), 5.84 – 5.72 (m, 1H, =CH pentenyl), 5.06 – 4.89 (m, 2H), 4.85 – 4.66 (m, 2H, =CH_2 pentenyl), 4.85 – 4.66 (m, 2H), 4.64 (d, J = 6.0, 1H, H-2), 4.60 – 4.46 (m, 3H), 4.44 – 4.40 (m, 1H, H-4), 4.39 – 4.33 (m, 1H, H-5), 4.14 (t, J = 10.1, 1H, H-6a), 3.88 (dd, J = 5.0, 6.7, 1H, H-3), 3.82 (dd, J = 3.3, 10.1, 1H, H-6b), 3.29 – 3.20 (m, 2H, CH_2-5 pentyl), 3.18 – 2.97 (m, 1H, NCH_2-1 pentyl), 2.90 (s, 2H, OCH_2-Ada), 2.87 – 2.72 (m, 2H, NCH_2 pentenyl),

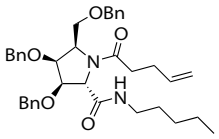
2.45 – 2.27 (m, 2H, CH_2 pentenyl), 1.95 (s, 3H, 3×CH Ada), 1.67 (dd, *J* = 12.7, 38.4, 6H, 3×CH_2 Ada), 1.59 – 0.97 (m, 12H, 3×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer: δ 173.7 (NC=O pentenyl), 167.7 (NHC(O)-1), 138.3, 137.7, 137.4 (3×C_q Bn), 137.2 (=CH pentenyl), 128.6 – 127.5 (CH_{Ar} Bn), 115.2 (=CH_2 pentenyl), 81.8 (OCH_2-Ada), 78.8 (C-3), 76.7 (C-4), 74.8, 73.5, 72.4 (3×CH_2 Bn), 71.3(CH_2-5 pentyl), 69.3 (C-6), 64.3 (C-2), 58.5 (C-5), 39.7 (CH_2 Ada), 39.4 (NCH_2-1 pentyl), 37.3 (CH_2 Ada), 34.0 (C_q Ada), 33.4 (NCH_2 pentenyl), 29.3, 29.2, 28.9 (CH_2 pentenyl, CH_2-2, CH_2-4 pentyl), 28.3 (CH Ada), 23.4 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3316, 2901, 2848, 1653, 1532, 1453, 1407, 1359, 1212, 1097, 911, 733, 696. $[\alpha]^{20}_D$: 6.3 (*c* 9.0, $CHCl_3$). HRMS: found 763.4683 $[M+H]^+$, calculated for $[C_{48}H_{62}O_6N_2+H]^+$ 763.4681.



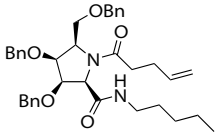
1,1,3,3-Tetramethylbutyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-D-*talo*-hexonamide (A1-II). Subjecting azido-aldehyde **6** (600 µmol) to the tandem SAWU-3CR (General procedure B in the presence of $InCl_3$ in CH_3CN) produced a separable 5.3:1 mixture of **A1-II** (204 mg, 318 µmol) and **B1-II** (38 mg, 60 µmol) in a combined yield of 63%. R_F = 0.72 (2:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) 6:1 mixture of rotamers; major rotamer: δ 7.33 – 7.22 (m, 15H, H_{Ar}), 6.28 (s, 1H, C(O)NH), 5.81 – 5.74 (m, 1H, =CH pentenyl), 4.97 (ddd, *J* = 1.2, 16.8, 37.2, 2H, =CH_2 pentenyl), 4.65 (d, *J* = 12.0, 1H, C*H*H Bn), 4.63 (d, *J* = 12.0, 1H, C*H*H Bn), 5.58 (d, *J* = 12.0, 1H, CH*H* Bn), 4.55 (d, *J* = 12.0, 1H, CH*H* Bn), 4.47 (d, *J* = 12.0, 1H, C*H*H Bn), 4.44 (dd, *J* = 4.2, 7.8 Hz, 1H, H-4), 4.41 (d, *J* = 12.0, 1H, CH*H* Bn), 4.34 – 4.32 (m, 2H, H-2, H-5), 4.16 (dd, *J* = 3.6, 10.8, 1H, H-6a), 4.08 (d, *J* = 4.2, 1H, H-3), 3.69 (dd, *J* = 5.4, 10.8, 1H, H-6b), 2.76 – 2.71 (m, 1H, NC*H*H pentenyl), 2.56 – 2.51 (m, 1H, NCH*H* pentenyl), 2.41 – 2.31 (m, 2H, CH_2 pentenyl), 1.71 (d, *J* = 15.0, 1H, C*H*H-2 tMB), 1.60 (d, *J* = 15.0, 1H, CH*H*-2 tMB), 1.32 (d, *J* = 14.4, 6H, 2×CH_3 tMB), 0.95 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer: δ 174.1 (NC=O pentenyl), 168.1 (NHC(O)-1), 137.8, 137.7, 137.6 (3×C_q Bn), 137.3 (=CH pentenyl), 128.4, 128.3, 128.2, 128.0, 127.6, 127.5, 127.4 (CH_{Ar} Bn), 114.9 (=CH_2 pentenyl), 78.7 (C-4), 77.9 (C-3), 73.2, 72.4 (3×CH_2 Bn), 71.5 (C-6), 65.8 (C-2), 59.1 (C-5), 55.2 (NHC_q-1 tMB), 51.4 (CH_2-2 tMB), 33.6 (NCH_2 pentenyl), 31.4 (C_q-3 tMB), 31.3 (CH_3-4, 2×CH_3 tMB), 29.0 (CH_2 pentenyl), 28.8, 28.6 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3329, 2950, 1679, 1624, 1544, 1422, 1096, 733, 696. $[\alpha]^{20}_D$: 22.3 (*c* 6.1, $CHCl_3$). HRMS: found 641.3949 $[M+H]^+$, calculated for $[C_{40}H_{52}O_5N_2+H]^+$ 641.3949.



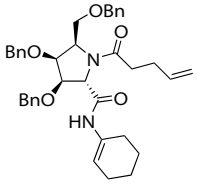
1,1,3,3-Tetramethylbutyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-D-*galacto*-hexonamide (B1-II). Subjecting azido-aldehyde **6** (500 µmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1:15 mixture of **A1-II** (15 mg, 23 µmol) and **B1-II** (216 mg, 338 µmol) in a combined yield of 72%. R_F = 0.24 (2:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) 2:1 mixture of rotamers; major rotamer: δ 7.32 – 7.25 (m, 15H, H_{Ar} Bn), 6.02 (s, 1H, C(O)NH), 5.85 – 5.73 (m, 1H, =CH pentenyl), 5.06 – 4.91 (m, 2H, =CH_2 pentenyl), 4.75 (d, *J* = 11.5, 1H, C*H*H Bn), 4.69 (d, *J* = 11.6, 1H, CH*H* Bn), 4.58 (d, *J* = 11.6, 1H, C*H*H Bn), 4.53 – 4.47 (m, 3H, H-2, C*H*H Bn, CH*H* Bn), 4.44 – 4.36 (m, 2H, H-4, CH*H* Bn), 4.34 – 4.27 (m, 1H, H-5), 4.11 (dd, *J* = 10.2, 1H, H-6a), 3.87 (d, *J* = 9.9, 1H, H-6b), 3.83 (dd. *J* = 4.8, 1H, H-3), 2.89 – 2.84 (m, 1H, NC*H*H pentenyl), 2.46 – 2.31 (m, 3H, NCH*H* pentenyl, CH_2 pentenyl), 1.61 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.46 (d, *J* = 15.2, 1H, CH*H*-2 tMB), 1.00 (d, *J* = 5.6, 6H, 2×CH_3 tMB), 0.87 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer: δ 173.8 (NC=O pentenyl), 166.3 (NHC(O)-1), 138.0, 137.5 (2×C_q Bn), 137.1 (=CH pentenyl), 137.0 (C_q Bn), 128.3 – 127.1 (CH_{Ar} Bn), 114.9 (=CH_2 pentenyl), 78.7 (C-4), 76.6 (C-3), 74.6, 73.3, 72.0 (3×CH_2 Bn), 69.8 (C-6), 64.7 (C-2), 59.0 (C-5), 55.6 (NHC_q-1 tMB), 53.3 (CH_2-2 tMB), 33.3 (CH_2 pentenyl), 31.4 (C_q-3 tMB), 31.3, 31.2 (2×CH_3-2 tMB), 31.1 (3×CH_3 tMB), 28.6 (CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3323, 2951, 1666, 1521, 1400, 1098, 734, 697. $[\alpha]^{20}_D$: 11.4 (*c* 9.0, $CHCl_3$). HRMS: found 641.3949 $[M+H]^+$, calculated for $[C_{40}H_{52}O_5N_2+H]^+$ 641.3949.



Pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-D-*talo*-hexonamide (A1-III). Subjecting azido-aldehyde **6** (750 µmol) to the tandem SAWU-3CR (General procedure B in the presence of $InCl_3$ in CH_3CN) produced a separable 5.4:1 mixture of **A1-III** (128 mg, 215 µmol) and **B1-III** (24 mg, 40 µmol) in a combined yield of 34%. R_F = 0.72 (2:3; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) 5.5:1 mixture of rotamers; major rotamer: δ 7.35 – 7.24 (m, 15H, H_{Ar} Bn), 6.76 (t, *J* = 5.6, 1H, C(O)NH), 5.76 (ddt, *J* = 6.5, 10.2, 16.8, 1H, =CH pentenyl), 4.99 – 4.89 (m, 2H, =CH_2 pentenyl), 4.67 – 4.52 (m, 4H, 2×CH_2 Bn), 4.50 – 4.45 (m, 2H, H-4, C*H*H Bn), 4.43 (s, *J* = 12.2, CH*H* Bn), 4.42 (s, 1H, H2), 4.40 – 4.36 (m, 1H, H-5), 4.13 (dd, *J* = 3.5, 10.6, 1H, H-6a), 4.04 (d, *J* = 4.3, 1H, H-3), 3.70 (dd, *J* = 6.2, 10.6, 1H, H-6b), 3.20 (dt, *J* = 7.1, 13.5, 1H, NC*H*H-1 pentyl), 3.04 (dt, *J* = 7.2, 12.7, 1H, NCH*H*-1 pentyl), 2.75 (ddd, *J* = 6.2, 8.9, 15.5, 1H, NC*H*H pentenyl), 2.54 (ddd, *J* = 6.3, 9.0, 15.6, 1H, NCH*H* pentenyl), 2.44 – 2.26 (m, 2H, CH_2 pentenyl), 1.46 – 1.39 (m, 2H, CH_2-2 pentyl), 1.33 – 1.21 (m, 4H, CH_2-3, CH_2-4 pentyl), 0.88 (t, *J* = 7.2, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer: δ 174.3 (NC=O pentenyl), 169.6 (NHC(O)-1), 138.2, 137.9, 137.8 (3×C_q Bn), 137.6 (=CH pentenyl), 129.0, 128.6, 128.6, 128.5, 128.4, 128.3, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 115.2 (=CH_2 pentenyl), 78.8 (C-4), 78.4 (C-3), 73.4, 72.6, 72.5 (3×CH_2 Bn), 71.7 (C-6), 65.4 (C-2), 59.2 (C-5), 39.7 (NCH_2-1 pentyl), 33.8 (NCH_2 pentenyl), 29.3 (CH_2 pentenyl), 29.2, 29.1, 22.5 (3×CH_2 pentyl), 14.2. IR ν_{max}(thin film)/ cm^{-1}: 3312, 2956, 2929, 2869, 1652, 1622, 1557, 1453, 1434, 1361, 1143, 1097, 1027, 1000, 911, 734, 697. $[\alpha]^{20}_D$: 26.6 (*c* 2.5, $CHCl_3$). HRMS: found 599.3478 $[M+H]^+$, calculated for $[C_{37}H_{46}O_5N_2+H]^+$ 599.3479.

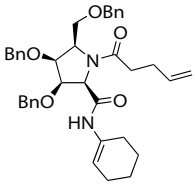


Pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-D-*galacto*-hexonamide (B1-III). Subjecting azido-aldehyde **6** (194 µmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1:21 mixture of **A1-III** (5 mg, 8 µmol) and **B1-III** (104 mg, 174 µmol) in a combined yield of 94%. R_F = 0.40 (2:1; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) 2:1 mixture of rotamers; major rotamer: δ 7.38 – 7.20 (m, 15H, H_{Ar} Bn), 6.19 (t, *J* = 5.5, 1H, C(O)NH), 5.84 – 5.74 (m, 1H, =CH pentenyl), 5.07 – 4.91 (m, 2H, =CH_2 pentenyl), 4.86 – 4.46 (m, 7H, H-2, 3×CH_2 Bn), 4.44 – 4.41 (m, 1H, H-4), 4.39 – 3.34 (m, 1H, H-5), 4.14 (dd, *J* = 10.2, 1H, H-6a), 3.88 (dd, *J* = 5.0, 6.7, 1H, H-3), 3.83 (dd, *J* = 3.6, 10.3, 1H, H-6b), 3.19 – 2.97 (m, 2H, NCH_2-1 pentyl), 2.97 – 2.69 (m, 2H, NCH_2 pentenyl), 2.46 – 2.29 (m, 2H, CH_2 pentenyl), 1.35 – 0.94 (m, 6H, 3×CH_2 pentyl), 0.80 – 0.73 (m, 6H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer: δ 173.8 (NC=O pentenyl), 167.7 (NHC(O)-1), 138.4, 137.8, 137.5 (3×C_q Bn), 137.2 (=CH pentenyl), 128.7 – 127.5 (CH_{Ar} Bn), 115.2 (=CH_2 pentenyl), 78.8 (C-4), 76.8 (C-3), 74.9, 73.6, 72.4 (3×CH_2 Bn), 69.4 (C-6), 64.4 (C-2), 58.6 (C-5), 39.4 (NCH_2-1 pentyl), 33.5 (NCH_2 pentenyl), 29.0, 22.3, 14.1 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3320, 2939, 2868, 1652, 1532, 1454, 1406, 1212, 1142, 1096, 1025, 911, 734, 696. $[\alpha]^{20}_D$: 8.9 (*c* 4.2, $CHCl_3$). HRMS: found 599.3478 $[M+H]^+$, calculated for $[C_{37}H_{46}O_5N_2+H]^+$ 599.3479.

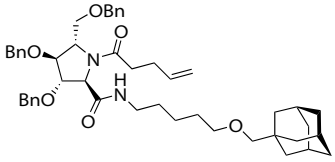


1-Cyclohexenyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-D-*talo*-hexonamide (A1-IV). Subjecting azido-aldehyde **6** (750 µmol) to the tandem SAWU-3CR (General procedure B in the presence of $InCl_3$ in CH_3CN) produced a separable 1:4.2 mixture of **A1-IV** (20 mg, 33 µmol) and **B1-IV** (84 mg, 139 µmol) in a combined yield of 23%. R_F = 0.72 (2:3; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) 8.7:1 mixture of rotamers; major rotamer: δ 7.74 (s, 1H, C(O)NH), 7.47 – 6.94 (m, 15H, H_{Ar} Bn), 6.11 – 6.03 (m, 1H, =CH-2 cyclohexenyl), 5.84 – 5.68 (m, 1H, =CH pentenyl), 5.04 – 4.88 (m, 2H, =CH_2 pentenyl), 4.73 – 4.40 (m, 10H, 3×CH_2 Bn, H-2, H-4), 4.37 – 4.32 (m, 1H, H-5), 4.23 – 4.09 (m, 2H, H-3, H-6a), 3.68 (dd, *J* = 5.9, 10.6, 1H, H-6b), 2.77 – 2.70 (m, 1H, NC*H*H pentenyl), 2.58 – 2.50 (m, 1H, NCH*H* pentenyl), 2.41 – 2.27 (m, 2H, CH_2 pentenyl), 2.12 – 1.93 (m, 4H, CH_2-2, CH_2-3 cyclohexenyl), 1.77 – 1.45 (m, 4H, CH_2-2, CH_2-3 cyclohexenyl). ^{13}C NMR (151 MHz, CDCl3) major rotamer: δ 174.6 (NC=O pentenyl), 167.8 (NHC(O)-1), 138.2, 138.0, 137.9 (3×C_q Bn), 137.5 (=CH pentenyl), 132.8 (C_q-1 cyclohexenyl), 128.6, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 115.3 (=CH_2 pentenyl),

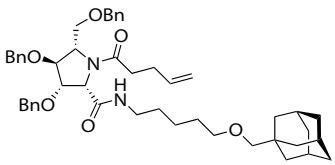
112.9 (=CH-2 cyclohexenyl), 79.0 (C-4), 78.3 (C-3), 73.5, 72.8, 72.7 (3×CH_2 Bn), 71.8 (C-6), 65.9 (C-2), 59.4 (C-5), 33.9 (NCH_2 pentenyl), 29.3 (CH_2 pentenyl), 28.0 (CH_2-3 cyclohexenyl), 24.2 (CH_2-4 cyclohexenyl), 22.6, 22.1 (2×CH_2 cyclohexenyl). IR ν_{max}(thin film)/ cm^{-1}: 3310, 2929, 2860, 1683, 1622, 1558, 1453, 1362, 1210, 1096, 1027, 914, 35, 698. $[\alpha]^{20}_D$: 3.2 (*c* 0.5, $CHCl_3$). HRMS: found 609.3323 $[M+H]^+$, calculated for $[C_{38}H_{44}O_5N_2+H]^+$ 609.3323.



1-Cyclohexenyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-D-*galacto*-hexonamide (B1-IV). Subjecting azido-aldehyde **6** (750 µmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1:11 mixture of **A1-IV** (21 mg, 34 µmol) and **B1-IV** (228 mg, 371 µmol) in a combined yield of 54%. R_F = 0.40 (2:1; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) 2:1 mixture of rotamers; major rotamer: δ 8.23 (s, 1H, C(O)NH), 7.56 – 7.17 (m, 15H, H_{Ar} Bn), 6.01 (s, 1H, =CH-2 cyclohexenyl), 5.90 – 5.72 (m, 1H, =CH pentenyl), 5.14 – 4.94 (m, 2H, =CH_2 pentenyl), 4.89 – 4.52 (m, 7H, 3×CH_2 Bn, H-2), 4.49 – 4.46 (m, 1H, H-4), 4.45 – 4.39 (m, 1H, H-5), 4.22 – 4.14 (m, 1H, H-6a), 4.00 – 3.89 (m, 1H, H-3), 3.89 – 3.84 (m, 1H, H-6b), 2.99 – 2.81 (m, 1H, NC*H*H pentenyl), 2.51 – 2.34 (m, 3H, NCH_H, CH_2 pentenyl), 2.14 – 1.43 (m, 8H, 4×CH_2 cyclohexenyl). ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer: δ 173.9 (NC=O pentenyl), 165.9 (NHC(O)-1), 138.3, 137.8, 137.4 (3×C_q Bn), 137.3 (=CH pentenyl), 132.2 (C_q-1 cyclohexenyl), 128.6 –127.5 (CH_{Ar} Bn), 115.2 (=CH_2 pentenyl), 113.3 (CH-2 cyclohexenyl), 78.8 (C-3), 76.9 (C-4), 74.8, 73.7, 72.4 (3×CH_2 Bn), 69.4 (C-6), 64.9 (C-2), 58.7 (C-5), 33.4 (NCH_2 pentenyl), 28.9 (CH_2 pentenyl), 27.8, 24.0, 22.5, 22.0 (4×CH_2 cyclohexenyl). IR ν_{max}(thin film)/ cm^{-1}: 3314, 3032, 2930, 2860, 1653, 1529, 1453, 1407, 1359, 1305, 1214, 1142, 1100, 1056, 913, 735, 697. $[\alpha]^{20}_D$: 17.2 (*c* 5.0, $CHCl_3$). HRMS: found 609.3323 $[M+H]^+$, calculated for $[C_{38}H_{44}O_5N_2+H]^+$ 609.3323.

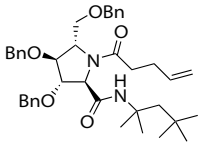


5-(Adamantan-1yl-methoxy)-pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*gulo*-hexonamide (C1-I). Subjecting azido-aldehyde **15** (1.04 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1:1.9 mixture of **C1-I** (114 mg, 0.15 mmol) and **D1-I** (213 mg, 0.28 mmol) in a combined yield of 41%. R_F = 0.63 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) 2:1 mixture of rotamers; major rotamer δ 7.37 – 7.20 (m, 15H, H_{Ar} Bn), 6.17 (t, *J* = 5.8, 1H, C(O)NH), 5.84 – 5.71 (m, 1H, =CH pentenyl), 5.10 – 4.92 (m, 2H, =CH_2 pentenyl), 4.70 – 4.41 (m, 7H, 3×CH_2 Bn, H-5), 4.38 (s, 1H, H-2), 4.22 (s, 1H, H-3), 4.18 (s, 1H, H-4), 3.98 (dd, *J* = 4.4, 8.8, 1H), 3.49 (dd, *J* = 8.8, 10.5, 1H, H-6b), 3.27 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 3.17 – 2.92 (m, 2H, NCH_2-1 pentyl), 2.91 (s, 2H, OCH_2-Ada), 2.47 – 2.19 (m, 4H, 2×CH_2 pentenyl), 1.95 (s, 3H, 3×CH Ada), 1.68 (dd, *J* = 12.0, 27.2, 6H, 3×CH_2 Ada), 1.51 (d, *J* = 2.6, 6H, 3×CH_2 Ada), 1.48 – 1.35 (m, 2H, CH_2-2 pentyl), 1.35 – 1.04 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 173.0 (NC=O pentenyl), 169.9 (NHC(O)-1), 138.5, 137.1 (3×C_q Bn), 137.0 (=CH pentenyl), 128.8 – 127.8 (CH_{Ar} Bn), 115.8 (=CH_2 pentenyl), 85.9 (C-4), 82.1 (OCH_2-Ada), 80.9 (C-3), 73.3, 71.9 (2×CH_2 Bn), 71.5 (CH_2-5 pentyl), 71.4 (CH_2 Bn), 69.1 (C-2), 66.8 (C-6), 64.1 (C-5), 39.9 (CH_2 Ada), 39.8 (NCH_2-1 pentyl), 37.5 (CH_2 Ada), 34.3 (C_q Ada), 34.1 (CH_2 pentenyl), 29.3, 29.1, 29.0 (CH_2 pentenyl, 2×CH_2 pentyl), 28.5 (CH Ada), 23.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3338, 2901, 2848, 1654, 1648, 1454, 1407, 1206, 1096, 734, 698. $[\alpha]^{20}_D$: 12.8 (*c* 2.2, $CHCl_3$). HRMS: found 763.4683 $[M+H]^+$, calculated for $[C_{48}H_{62}O_6N_2+H]^+$ 763.4681.

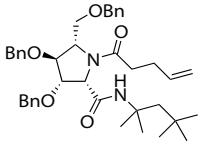


5-(Adamantan-1yl-methoxy)-pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*ido*-hexonamide (D1-I). R_F = 0.50 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) 6:1 mixture of rotamers; major rotamer δ 7.65 (t, *J* = 5.9, 1H, C(O)NH), 7.45 – 7.19 (m, 15H, H_{Ar} Bn), 5.87 – 5.71 (m, 1H, =CH pentenyl), 5.09 – 4.92 (m, 2H, =CH_2 pentenyl), 4.78 (d, *J* = 11.8, 1H, C*H*H Bn), 4.67 – 4.36 (m, 6H, H-2, H-6a, CH*H* Bn, C*H*H Bn, CH_2 Bn), 4.26 – 4.20 (m, 3H, CH*H* Bn, H-3, H-4),

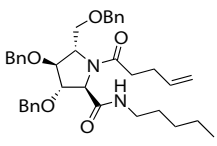
3.84 – 3.79 (m, 1H, H-5), 3.48 (dd, *J* = 1.3, 9.6, 1H, H-6b), 3.26 (t, *J* = 6.6, 2H, CH_2-5 pentyl), 2.92 (s, 2H, OCH_2-Ada), 2.68 – 2.56 (m, 2H, NCH_2-1 pentyl), 2.41 – 2.31 (m, 4H, 2×CH_2 pentenyl), 1.96 (s, 3H, 3×CH Ada), 1.68 (dd, *J* = 11.8, 27.1, 6H, 3×CH_2 Ada), 1.53 (d, *J* = 2.6, 6H, 3×CH_2 Ada), 1.46 – 1.33 (m, 2H, CH_2-2 pentyl), 1.13 – 1.01 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 173.3 (NC=O pentenyl), 168.8 (NHC(O)-1), 138.2, 137.7, 137.0 (3×C_q Bn), 137.1 (=CH pentenyl), 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9 (CH_{Ar} Bn), 115.7 (=CH_2 pentenyl), 82.1 (OCH_2-Ada), 82.1, 79.0 (C-3, C-4), 73.8, 73.4, 73.0 (3×CH_2 Bn), 71.7 (CH_2-5 pentyl), 66.6 (C-6), 63.4 (C-2), 60.2 (C-5), 40.0 (CH_2 Ada), 39.2 (NCH_2-1 pentyl), 37.5 (CH_2 Ada), 34.3 (C_q Ada), 33.5 (CH_2 pentenyl), 29.8, 29.5, 29.3, 28.8 (CH_2 pentenyl, 2×CH_2 pentyl), 28.5 (CH Ada), 23.6 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3322, 2902, 2848, 1664, 1560, 1454, 1406, 1095, 1028, 737, 698. $[\alpha]^{20}_D$: 16.8 (*c* 4.0, $CHCl_3$).HRMS: found 763.4684 $[M+H]^+$, calculated for $[C_{48}H_{62}O_6N_2+H]^+$ 763.4681.



1,1,3,3-Tetramethylbutyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*gulo*-hexonamide (C1-II). Subjecting azido-aldehyde **15** (1.59 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1:1.1 mixture of **C1-II** (269 mg, 0.42 mmol) and **D1-II** (282 mg, 0.44 mmol) in a combined yield of 54%. R_F = 0.75 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) 4:1 mixture of rotamers; major rotamer δ 7.40 – 7.18 (m, 15H, H_{Ar} Bn), 6.13 (s, 1H, C(O)NH), 5.88 – 5.73 (m, 1H, =CH pentenyl), 5.08 – 4.93 (m, 2H, =CH_2 pentenyl), 4.70 – 4.39 (m, 7H, H-5, 3×CH_2 Bn), 4.24 (s, 1H, H-2), 4.21 (s, 1H, H-3), 4.16 (s, 1H, H-4), 3.99 (dd, *J* = 4.3, 8.8, 1H, H-6a), 3.45 (dd, *J* = 8.8, 10.9, 1H, H-6b), 2.43 – 2.24 (m, 4H, 2×CH_2 pentenyl), 1.48 – 1.32 (m, 2H, CH_2-2 tMB), 1.23 (s, 3H, CH_3 tMB), 1.18 (s, 3H, CH_3 tMB), 0.85 (s, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 172.9 (NC=O pentenyl), 168.7 (NHC(O)-1), 138.5, 137.2, 136.9 (3×C_q Bn), 137.1 (=CH pentenyl), 128.7, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.8 (CH_{Ar} Bn), 115.8 (=CH_2 pentenyl), 85.9 (C-4), 81.3 (C-3), 73.3, 71.8 (3×CH_2 Bn), 70.0 (C-2), 66.7 (C-6), 64.0 (C-5), 55.8 (NHC_q-1 tMB), 53.4 (CH_2-2 tMB), 34.2 (NCH_2 pentenyl), 31.6 (CH_3-4, 2×CH_3 tMB, C_q-3 tMB), 28.9 (CH_2 pentenyl), 28.3, 27.3 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 2952, 1654, 1560, 1458, 1096, 736, 698, 668. $[\alpha]^{20}_D$: 11.2 (*c* 2.0, $CHCl_3$). HRMS: found 641.3949 $[M+H]^+$, calculated for $[C_{40}H_{52}O_5N_2+H]^+$ 641.3949.

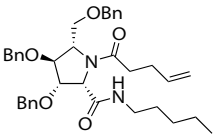


1,1,3,3-Tetramethylbutyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*ido*-hexonamide (D1-II). R_F = 0.65 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) 5:1 mixture of rotamers; major rotamer δ 7.41 – 7.14 (m, 15H, H_{Ar} Bn), 6.99 (s, 1H, C(O)NH), 5.83 (ddd, *J* = 6.3, 12.3, 16.8, 1H, =CH pentenyl), 5.09 – 4.90 (m, 2H, =CH_2 pentenyl, C*H*H Bn), 4.65 (d, *J* = 11.7, 1H, C*H*H Bn), 4.59 – 4.41 (m, 5H, H-2, CH_2 Bn, 2×CH*H* Bn), 4.26 – 4.20 (m, 2H, H-3, H-4), 4.17 (dd, *J* = 4.3, 9.7, 1H, H-6a), 3.95 – 3.89 (m, 1H, H-5), 3.50 (dd, *J* = 2.3, 9.7, 1H, H-6b), 2.45 – 2.29 (m, 4H, 2×CH_2 pentenyl), 1.92 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.59 (d, *J* = 14.5, 1H, CH*H*-2 tMB), 1.32 (d, *J* = 9.6, 6H, 2×CH_3 tMB), 0.93 (s, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 173.8 (NC=O pentenyl), 167.9 (NHC(O)-1), 138.0, 137.7, 137.6 (3×C_q Bn), 137.1 (=CH pentenyl), 128.7, 128.5, 128.2, 128.2, 128.0, 127.8 (CH_{Ar} Bn), 115.7 (=CH_2 pentenyl), 82.7, 79.3 (C-3, C-4), 73.4, 73.0, 72.8 (3×CH_2 Bn), 66.1 (C-6), 64.5 (C-2), 60.7 (C-5), 55.7 (NHC_q-1 tMB), 51.5 (CH_2-2 tMB), 33.7 (NCH_2 pentenyl), 31.7 (CH_3-4, 2×CH_3 tMB), 31.6 (C_q-3 tMB), 29.4, 28.8 (2×CH_3 tMB), 28.8 (CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 2952, 2361, 2343, 1668, 1540, 1455, 1398, 1365, 1206, 1096, 1028, 736, 698, 668. $[\alpha]^{20}_D$: 12.1 (*c* 2.1, $CHCl_3$). HRMS: found 641.3949 $[M+H]^+$, calculated for $[C_{40}H_{52}O_5N_2+H]^+$ 641.3949.

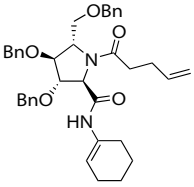


Pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*gulo*-hexonamide (C1-III). Subjecting azido-aldehyde **15** (3.39 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1:2.1 mixture of **C1-III** (285 mg, 0.48 mmol) and **D1-III** (585 mg, 0.98 mmol) in a combined yield of 43%. R_F = 0.65 (1:1; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) 3.5:1 mixture of rotamers; major rotamer δ 7.39

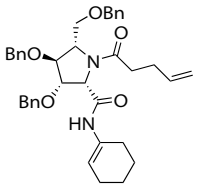
– 7.20 (m, 15H, H_{Ar} Bn), 6.16 (t, *J* = 5.6, 1H, C(O)NH), 5.83 – 5.72 (m, 1H, =CH pentenyl), 5.07 – 4.93 (m, 2H, $=CH_2$ pentenyl), 4.68 – 4.39 (m, 7H, H-5, 3×CH_2 Bn), 4.38 (s, 1H, H-2), 4.22 (s, 1H, H-3), 4.18 (s, 1H, H-4), 3.98 (dd, *J* = 4.4, 8.8, 1H, H-6a), 3.49 (dd, *J* = 9.7, 1H, H-6b), 3.13 – 3.05 (m, 1H, NC*H*H-1 pentyl), 2.97 – 2.86 (m, 1H, NCH*H*-1 pentyl), 2.48 – 2.24 (m, 4H, 2×CH_2 pentenyl), 1.28 – 1.06 (m, 6H, 3×CH_2 pentyl), 0.81 (t, *J* = 7.2, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer δ 173.0 (NC=O pentenyl), 169.9 (NHC(O)-1), 138.5, 137.7, 137.1 (3×C_q Bn), 137.0 (=CH pentenyl), 128.7, 128.7, 128.6, 128.3, 128.2, 127.9, 127.9, 127.8 (CH_{Ar} Bn), 115.8 ($=CH_2$ pentenyl), 85.9 (C-4), 80.9 (C-3), 73.3, 71.9, 71.5 (3×CH_2 Bn), 69.1 (C-2), 66.8 (C-6), 64.1 (C-2), 39.8 (NCH_2-1 pentyl), 34.1 (NCH_2 pentenyl), 29.2, 28.9, 22.4 (CH_2 pentyl/pentenyl), 14.1 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3325, 2930, 1652, 1540, 1455, 1366, 1097, 737, 699. $[\alpha]^{20}_D$: 17.3 (*c* 0.3, $CHCl_3$). HRMS: found 599.3478 $[M+H]^+$, calculated for $[C_{37}H_{46}O_5N_2+H]^+$ 599.3479.



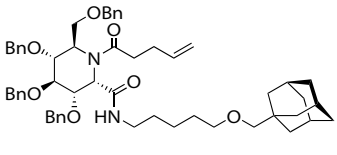
Pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*ido*-hexonamide (D1-III). R_F = 0.55 (1:1; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) 9:1 mixture of rotamers; major rotamer δ 7.65 (t, *J* = 5.8, 1H, C(O)NH), 7.43 – 7.15 (m, 15H, H_{Ar} Bn), 5.83 – 5.76 (m, 1H, =CH pentenyl), 5.05 – 4.97 (m, 3H, $=CH_2$ pentenyl, C*H*H Bn), 4.78 (d, *J* = 11.8, 1H, C*H*H Bn), 4.60 – 4.55 (m, 2H, H-2 (d, *J* = 6.9), CH*H* Bn), 4.53 (d, *J* = 11.2, 1H, CH*H* Bn), 4.45 – 4.39 (m, 2H, H-6a, C*H*H Bn), 4.25 – 4.21 (m, 3H, H-3, H-4, CH*H* Bn), 3.81 (d, *J* = 4.4, 1H, H-5), 3.48 (d, *J* = 10.6, 1H, H-6b), 2.69 (dt, *J* = 6.4, 13.4, 1H, NC*H*H-1 pentyl), 2.60 (dt, *J* = 6.1, 13.4, 1H, NCH*H*-1 pentyl), 2.41 – 2.32 (m, 3H, NC*H*H pentenyl, CH_2 pentenyl), 2.23 – 2.15 (m, 1H, NC*H*H pentenyl), 1.22 – 1.12 (m, 2H, CH_2-2 pentyl), 1.11 – 0.98 (m, 4H, 2×CH_2 pentyl), 0.81 (t, *J* = 7.4, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer δ 173.4 (NC=O pentenyl), 168.8 (NHC(O)-1), 138.2, 137.7, 137.1 (3×C_q Bn), 137.0 (=CH pentenyl), 128.8, 128.8, 128.6, 128.6, 128.6, 128.6, 128.5, 128.2, 128.1 (CH_{Ar} Bn), 115.7 ($=CH_2$ pentenyl), 82.1, 79.0 (C-3, C-4), 73.8, 73.4, 73.1 (3×CH_2 Bn), 66.5 (C-6), 63.4 (C-2), 60.2 (C-5), 39.2 (NCH_2-1 pentyl), 33.5 (CH_2 pentenyl), 29.6, 29.1, 28.8, 22.6 (CH_2 pentyl/pentenyl), 14.2 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3330, 2940, 1667, 1538, 1365, 1096, 737, 700. $[\alpha]^{20}_D$: 23.3 (*c* 0.3, $CHCl_3$). HRMS: found 599.3477 $[M+H]^+$, calculated for $[C_{37}H_{46}O_5N_2+H]^+$ 599.3479.



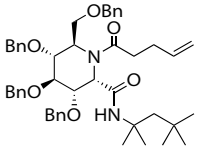
1-Cyclohexenyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*gulo*-hexonamide (C1-IV). Subjecting azido-aldehyde **15** (0.60 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1:2.4 mixture of **C1-IV** (49 mg, 0.08 mmol) and **D1-IV** (116 mg, 0.19 mmol) in a combined yield of 45%. R_F = 0.67 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) 2.5:1 mixture of rotamers; major rotamer δ 7.40 – 7.20 (m, 15H, H_{Ar} Bn), 7.07 (s, 1H, C(O)NH), 5.88 – 5.68 (m, 2H, =CH pentenyl, =CH-1 cyclohexenyl), 5.08 – 4.92 (m, 2H, $=CH_2$ pentenyl), 4.71 – 4.41 (m, 7H, H-5, 3×CH_2 Bn), 4.36 (s, 1H, H-2), 4.24 (s, 1H, H-3), 4.21 (s, 1H, H-4), 3.96 (dd, *J* = 4.4, 8.8, 1H, H-6a), 3.50 (dd, *J* = 9.1, 10.4, 1H, H-6b), 2.55 – 2.17 (m, 4H, 2×CH_2 pentenyl), 2.05 – 1.34 (m, 8H, 4×CH_2 cyclohexenyl). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 173.1 (NC=O pentenyl), 168.0 (NHC(O)-1), 138.5, 137.1, 137.0 (3×C_q Bn), 136.7 (=CH pentenyl), 132.2 (=C_q-1 cyclohexenyl), 128.7, 128.7, 128.6, 128.4, 128.2, 128.2, 128.1, 127.9, 127.8, 127.8 (CH_{Ar} Bn), 115.8 ($=CH_2$ pentenyl), 114.1 (=CH-2 cyclohexenyl), 85.9 (C-4), 81.0 (C-3), 73.3, 72.0, 71.9 (3×CH_2 Bn), 69.9 (C-2), 66.7 (C-6), 64.1 (C-5), 34.1 (NCH_2 pentenyl), 28.9 (CH_2 pentenyl), 27.4, 24.1, 22.5, 22.0 (4×CH_2 cyclohexenyl). IR ν_{max}(thin film)/ cm^{-1}: 2928, 1652, 1539, 1455, 1099, 737, 698, 668. $[\alpha]^{20}_D$: 2.0 (*c* 1.0, $CHCl_3$). HRMS: found 609.3322 $[M+H]^+$, calculated for $[C_{38}H_{44}O_5N_2+H]^+$ 609.3323.



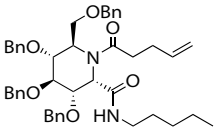
1-Cyclohexenyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*ido*-hexonamide (D1-IV). R_F = 0.54 (1:1; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) 5:1 mixture of rotamers; major rotamer δ 8.35 (s, 1H), 7.43 – 7.16 (m, 15H, H_{Ar} Bn), 5.89 – 5.72 (m, 2H, =CH pentenyl, =CH-1 cyclohexenyl), 5.09 – 4.93 (m, 3H, =CH_2 pentenyl, *CH*H Bn), 4.69 (d, *J* = 11.5, 1H, *CH*H Bn), 4.59 (d, *J* = 7.7, 1H, H-2), 4.58 – 4.35 (m, 4H, CH*H* Bn, CH_2 Bn), 4.30 (dd, *J* = 3.6, 9.8, 1H, H-6a), 4.23 (d, *J* = 7.5, 1H, H-3), 4.23 (d, *J* = 3.4, 1H, H-4), 3.89 – 3.86 (m, 1H, H-5), 3.50 (dd, *J* = 1.7, 9.6, 1H, H-6b), 2.43 – 2.22 (m, 4H, 2×CH_2 pentenyl), 2.12 – 1.92 (m, 4H, 2×CH_2 cyclohexenyl), 1.63 – 1.46 (m, 4H, 2×CH_2 cyclohexenyl). ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer δ 173.6 (NC=O pentenyl), 167.3 (NHC(O)-1), 138.0, 137.6, 137.3, 137.1, 132.7 (=C_q-1 cyclohexenyl), 128.7, 128.6, 128.5, 128.5, 128.5, 128.1, 128.0, 128.0, 127.9, 127.9, 127.7, 127.7 (CH_{Ar} Bn), 115.7 (=CH_2 pentenyl), 115.4 (=CH-2 cyclohexenyl), 82.2, 79.8 (C-3, C-4), 73.4, 73.4, 73.1 (3×CH_2 Bn), 66.1 (C-6), 64.1 (C-2), 60.5 (C-5), 33.6 (NCH_2 pentenyl), 28.8 (CH_2 pentenyl), 27.9, 24.2, 22.7, 21.9 (4×CH_2 cyclohexenyl). IR ν_{max}(thin film)/ cm^{-1}: 2928, 1668, 1540, 1455, 1102, 736, 697, 668. $[\alpha]^{20}_D$: 7.3 (*c* 2.3, $CHCl_3$). HRMS: found 609.3322 $[M+H]^+$, calculated for $[C_{38}H_{44}O_5N_2+H]^+$ 609.3323.



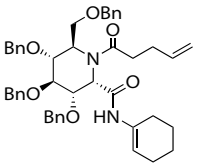
5-(Adamantan-1yl-methoxy)-pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-D-*glycero*-D-*ido*-heptonamide (E1-I). Subjecting azido-aldehyde **26** (1.01 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced **E1-I** (655 mg, 0.74 mmol) in a yield of 73%. R_F = 0.50 (1:2; EtOAc:toluene). ^{1}H NMR (500 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.44 – 7.16 (m, 21H, H_{Ar} Bn, C(O)NH), 5.85 – 5.74 (m, 1H, =CH pentenyl), 4.97 (dd, *J* = 13.5, 34.2, 2H, =CH_2 pentenyl), 4.86 – 3.43 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7), 3.25 (t, *J* = 6.6, 2H, CH_2-5 pentyl), 3.02 – 2.87 (m, 4H, NCH_2-1 pentyl, OCH_2-Ada), 2.50 – 2.21 (m, 4H, 2×CH_2 pentenyl), 1.95 (s, 3H, 3×CH Ada), 1.67 (dd, *J* = 11.9, 32.0, 6H, 3×CH_2 Ada), 1.52 (d, *J* = 1.9, 6H, 3×CH_2 Ada), 1.43 – 1.34 (m, 2H, CH_2 pentyl), 1.20 – 1.07 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (125 MHz, $CDCl_3$) collapsed iminosugar signals δ 174.5 (NC=O pentenyl), 168.2 (NHC(O)-1), 138.3, 137.8, 137.6, 137.2 (4×C_q Bn), 137.4 (=CH pentenyl), 128.5, 128.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 115.3 (=CH_2 pentenyl), 82.0 (OCH_2-Ada), 73.4, 73.2, 72.0, 71.5 (CH_2-5 pentyl), 70.9, 68.8 (C-7), 39.8 (CH_2 Ada), 39.4 (NCH_2-1 pentyl), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 33.2, 29.2, 29.2, 29.1 (2×CH_2 pentenyl, 2×CH_2 pentyl), 28.4 (CH Ada), 23.5 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3352, 2902, 2849, 1667, 1541, 1454, 1365, 1209, 1090, 909, 731, 697. $[\alpha]^{20}_D$: 11.1 (*c* 3.8, $CHCl_3$). HRMS: found 883.5263 $[M+H]^+$; calculated for $[C_{56}H_{70}N_2O_7+H]^+$ 883.5256.



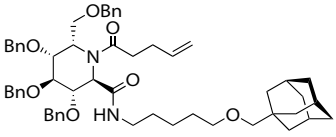
1,1,3,3-Tetramethylbutyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-D-*glycero*-D-*ido*-heptonamide (E1-II). Subjecting azido-aldehyde **26** (1.01 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced **E1-II** (625 mg, 0.82 mmol) in a yield of 81%. R_F = 0.48 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.44 – 7.22 (m, 20H, H_{Ar} Bn), 7.08 (s, 1H, C(O)NH), 5.95 – 5.80 (m, 1H, =CH pentenyl), 5.04 (dd, *J* = 13.1, 25.0, 2H, =CH_2 pentenyl), 4.86 – 3.53 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7), 2.50 – 2.26 (m, 4H, 2×CH_2 pentenyl), 1.88 – 1.52 (m, 2H, CH_2-2 tMB), 1.23 (s, 6H, 2×CH_3 tMB), 0.92 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, $CDCl_3$) collapsed iminosugar signals δ 174.7 (NC=O pentenyl), 167.0 (NHC(O)-1), 138.4, 137.7, 137.6, 137.4 (4×C_q Bn), 137.4 (=CH pentenyl), 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9 (CH_{Ar} Bn), 115.2 (=CH_2 pentenyl), 75.1, 73.7, 73.2, 71.5, 70.6, 68.8, 65.2, 55.3 (NHC_q-1 tMB), 51.3 (CH_2-2 tMB), 33.3 (CH_2 pentenyl), 31.5 (CH_3-4, 2×CH_3 tMB), 29.2 (CH_2 pentenyl), 29.4, 28.5 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3363, 2950, 1667, 1531, 1454, 1366, 1208, 1073, 1027, 911, 734, 697. $[\alpha]^{20}_D$: 6.6 (*c* 2.8, $CHCl_3$). HRMS: found 461.4529 $[M+H]^+$; calculated for $[C_{48}H_{60}N_2O_6+H]^+$ 761.4524.



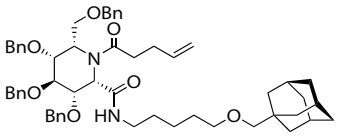
Pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-D-*glycero*-D-*ido*-heptonamide (E1-III). Subjecting azido-aldehyde **26** (1.01 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced **E1-III** (556 mg, 0.77 mmol) in a yield of 77%. R_F = 0.45 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.45 – 7.16 (m, 21H, H_{Ar} Bn, C(O)NH), 5.90 – 5.71 (m, 1H, =CH pentenyl), 4.97 (dd, *J* = 13.6, 28.1, 2H, =CH_2 pentenyl), 4.87 – 3.29 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7), 3.08 – 2.87 (m, 2H, NCH_2-1 pentyl), 2.56 – 2.20 (m, 4H, 2×CH_2 pentenyl), 1.24 – 0.97 (m, 6H, 3×CH_2 pentyl), 0.79 (t, *J* = 7.1, 3H, CH_3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) collapsed iminosugar signals δ 174.5 (NC=O pentenyl), 168.2 (NHC(O)-1), 138.3, 137.7, 137.6, 137.1 (4×C_q Bn), 137.4 (=CH pentenyl), 128.5, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.7, 127.6 (CH_{Ar} Bn), 115.3 (=CH_2 pentenyl), 77.7, 76.0, 73.4, 73.2, 71.9, 70.9, 68.8 (C-7), 39.4 (NCH_2-1 pentyl), 33.1 (NC(O)CH_2 pentenyl), 29.1, 29.0, 28.9, 22.3 (CH_2 pentenyl, 3×CH_2 pentyl), 14.1 (CH_3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3351, 2929, 1667, 1540, 1454, 1367, 1208, 1071, 1027, 910, 732, 696. $[\alpha]^{20}_D$: 16.0 (*c* 3.5, $CHCl_3$). HRMS: found 719.4060 $[M+H]^+$; calculated for $[C_{45}H_{54}N_2O_6+H]^+$ 719.4055.



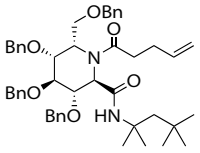
1-Cyclohexenyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-D-*glycero*-D-*ido*-heptonamide (E1-IV). Subjecting azido-aldehyde **26** (0.89 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced **E1-IV** (520 mg, 0.71 mmol) in a yield of 80%. R_F = 0.50 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) collapsed iminosugar signals δ 8.20 (s, 1H, C(O)NH), 7.43 – 7.10 (m, 20H, H_{Ar} Bn), 5.94 – 5.72 (m, 2H, =CH-2 cyclohexenyl, =CH pentenyl), 5.13 – 4.89 (m, 2H, =CH_2 pentenyl), 4.87 – 3.30 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7), 2.52 – 2.21 (m, 4H, 2×CH_2 pentenyl), 2.09 – 1.42 (m, 8H, 4×CH_2 cyclohexenyl). ^{13}C NMR (100 MHz, $CDCl_3$) collapsed iminosugar signals δ 176.4, 174.6 (2×C=O), 138.2, 137.7, 137.3, 137.1 (4×C_q Bn), 137.4 (=CH pentenyl), 132.3 (C_q-1 cyclohexenyl), 128.7, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6 (CH_{Ar} Bn), 115.3 (=CH_2 pentenyl), 113.3 (=CH-2 cyclohexenyl), 77.7, 75.6, 73.5, 73.2, 71.9, 70.9, 68.7 (C-7), 33.3, 33.1, 29.1, 28.8, 27.6, 24.0, 22.5, 21.9. IR ν_{max}(thin film)/ cm^{-1}: 3330, 2927, 1653, 1543, 1497, 1453, 1368, 1209, 1072, 911, 732, 696. $[\alpha]^{20}_D$: 25.4 (*c* 4.4, $CHCl_3$). HRMS: found 729.3902 $[M+H]^+$; calculated for $[C_{46}H_{52}N_2O_6+H]^+$ 729.3898.



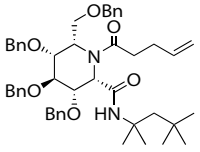
5-(Adamantan-1yl-methoxy)-pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*gulo*-heptonamide (F1-I). Subjecting azido-aldehyde **20** (1.16 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1.25:1 mixture of **G1-I** (314 mg, 0.36 mmol) and **F1-I** (248 mg, 0.28 mmol) in a combined yield of 55%. R_F = 0.27 (1:3; EtOAc:toluene). ^{1}H NMR (500 MHz, $CDCl_3$) 2.5:1 mixture of rotamers; major rotamer/ collapsed iminosugar signals δ 7.37 – 7.16 (m, 20H, H_{Ar} Bn), 6.18 (s, 1H, C(O)NH), 5.83 – 5.74 (m, 1H, =CH pentenyl), 5.03 – 4.91 (m, 2H, =CH_2 pentenyl), 4.81 – 3.60 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7), 3.30 (t, *J* = 6.6, 2H, CH_2-5 pentyl), 3.27 – 3.09 (m, 2H, NCH_2-1 pentyl), 2.92 (s, 2H, OCH_2-Ada), 2.71 – 2.40 (m, 2H, CH_2 pentenyl), 2.40 – 2.23 (m, 2H, CH_2 pentenyl), 1.95 (s, 3H, 3×CH Ada), 1.67 (dd, *J* = 11.8, 30.7, 6H, 3×CH_2 Ada), 1.56 – 1.13 (m, 12H, 3×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer/ collapsed iminosugar signals δ 174.1 (NC(O) pentenyl), 169.0 (NHC(O)-1), 138.3, 138.0, 138.0, 137.8, 137.6 (C_q Bn, =CH pentenyl), 128.6 – 127.7 (CH_{Ar} Bn), 115.0 (=CH_2 pentenyl), 82.0 (OCH_2-Ada), 78.1, 73.4, 71.9, 71.5 (CH_2-5 pentyl), 59.0, 54.8 (C-2, C-6), 39.9 (NCH_2-1 pentyl), 39.8 (CH_2 Ada), 37.3 (CH_2 Ada), 34.2 (C_q Ada), 29.4, 29.3, 29.0, 28.4 (CH Ada), 23.6 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2902, 2849, 1635, 1543, 1453, 1361, 1092, 910, 732, 696. $[\alpha]^{20}_D$: −11.7 (*c* 4.7, $CHCl_3$). HRMS: found 883.5265 $[M+H]^+$; calculated for $[C_{56}H_{70}N_2O_7+H]^+$ 883.5256.



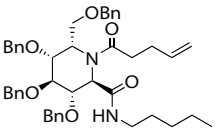
5-(Adamantan-1yl-methoxy)-pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*ido*-heptonamide (G1-I). R_F = 0.46 (1:3; EtOAc:toluene). ^{1}H NMR (500 MHz, $CDCl_3$) 3.5:1 mixture of rotamers; major rotamer δ 7.41 – 7.18 (m, 20H, H_{Ar} Bn), 6.69 (t, *J* = 5.7, 1H, C(O)NH), 5.80 – 5.68 (m, 1H, =CH pentenyl), 5.13 (d, *J* = 6.7, 1H, H-2), 5.00 – 4.91 (m, 2H, =CH_2 pentenyl), 4.89 – 4.59 (m, 7H, 3×CH_2 Bn, H-4), 4.45 (d, *J* = 11.9, 1H, C*H*H Bn), 4.38 (d, *J* = 11.9, 1H, CH*H* Bn), 4.26 – 4.19 (m, 1H, H-6), 4.07 (dd, *J* = 10.1, 1H, H-7a), 3.81 (dd, *J* = 4.3, 9.9, 1H, H-7b), 3.54 (dd, *J* = 6.5, 9.4, 1H, H-5), 3.48 (dd, *J* = 6.7, 9.3, 1H, H-3), 3.28 (t, *J* = 6.6, 2H, CH_2-5 pentyl), 3.26 – 3.13 (m, 1H, NC*H*H-1 pentyl), 2.97 – 2.84 (m, 3H, OCH_2-Ada, NCH*H*-1 pentyl), 2.66 – 2.17 (m, 4H, 2×CH_2 pentenyl), 1.94 (s, 3H, 3×CH Ada), 1.67 (dd, *J* = 11.7, 32.0, 6H, 3×CH_2 Ada), 1.51 (d, *J* = 2.4, 6H, 3×CH_2 Ada), 1.48 – 1.15 (m, 6H, 3×CH_2 pentyl). ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer δ 175.1 (NC(O) pentenyl), 169.1 (NHC(O)-1), 139.0, 138.5, 138.3, 138.1 (4×C_q Bn), 137.4 (=CH pentenyl), 128.8, 128.7, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.1 (CH_{Ar} Bn), 115.4 (=CH_2 pentenyl), 82.1 (OCH_2-Ada), 79.3 (C-5), 78.8 (C-4), 78.5 (C-3), 75.7, 74.0, 74.0, 73.1 (4×CH_2 Bn), 71.5 (CH_2-5 pentyl), 67.0 (C-7), 55.8 (C-6), 53.4 (C-2), 39.9 (CH_2 Ada), 39.5 (NCH_2-1 pentyl), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 33.0 (CH_2 pentenyl), 29.4, 29.4, 29.3 (CH_2 pentenyl, 2×CH_2 pentyl), 28.5 (CH Ada), 23.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3361, 2902, 2849, 1727, 1681, 1638, 1530, 1497, 1453, 1364, 1092, 1027, 911, 733, 697. $[\alpha]^{20}_D$: −45.4 (*c* 1.7, $CHCl_3$). HRMS: found 883.5265 $[M+H]^+$; calculated for $[C_{56}H_{70}N_2O_7+H]^+$ 883.5256.



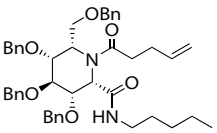
1,1,3,3-Tetramethylbutyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*gulo*-heptonamide (F1-II). Subjecting azido-aldehyde **20** (1.16 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 0.94:1 mixture of **G1-II** (260 mg, 0.34 mmol) and **F1-II** (278 mg, 0.37 mmol) in a combined yield of 61%. R_F = 0.59 (1:3; EtOAc:toluene). ^{1}H NMR (500 MHz, $CDCl_3$) complex mixture of rotamers; major signals δ 7.38 – 7.17 (m, 20H, H_{Ar} Bn), 5.89 – 5.75 (m, 1H, =CH pentenyl), 5.67 (s, 1H, C(O)NH), 5.12 – 3.65 (m, 17H, =CH_2 pentenyl, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7), 2.76 – 2.30 (m, 4H, 2×CH_2 pentenyl), 1.66 – 1.10 (m, 8H, CH_2-2 tMB, 2×CH_3 tMB), 0.94 – 0.82 (m, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (125 MHz, $CDCl_3$) major signals δ 174.3 (NC(O) pentenyl), 168.1 (NHC(O)-1), 138.2, 137.7 (C_q Bn), 136.7 (=CH pentenyl), 128.7 – 127.1 (CH_{Ar} Bn), 115.7 (=CH_2 pentenyl), 71.8, 65.4, 53.0, 33.4, 31.7 (CH_3-4, 2×CH_3 tMB), 29.3 (CH_2 pentenyl), 28.6, 28.3 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3347, 2953, 2869, 1725, 1682, 1636, 1537, 1454, 1365, 1276, 1209, 1073, 1027, 911, 734, 696. $[\alpha]^{20}_D$: −16.8 (*c* 3.2, $CHCl_3$). HRMS: found 461.4531 $[M+H]^+$; calculated for $[C_{48}H_{60}N_2O_6+H]^+$ 761.4524.



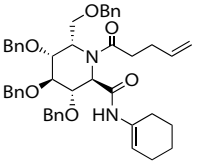
1,1,3,3-Tetramethylbutyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*ido*-heptonamide (G2-II). R_F = 0.67 (1:3; EtOAc:toluene). ^{1}H NMR (500 MHz, $CDCl_3$) 3.5:1 mixture of rotamers; major rotamer δ 7.35 – 7.22 (m, 20H, H_{Ar} Bn), 6.66 (s, 1H, C(O)NH), 5.86 – 5.70 (m, 1H, =CH pentenyl), 5.19 (d, *J* = 6.8, 1H, H-2), 5.01 – 4.35 (m, 11H, =CH_2 pentenyl, 4×CH_2 Bn, H-4), 4.23 – 4.16 (m, 1H, H-6), 4.05 (dd, *J* = 9.8, 1H, H-7a), 3.85 (dd, *J* = 3.7, 9.9, 1H, H-7b), 3.49 (dd, *J* = 6.5, 9.7, 1H, H-5), 3.44 (dd, *J* = 6.7, 9.6, 1H, H-3), 2.46 – 2.18 (m, 4H, 2×CH_2 pentenyl), 1.73 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.49 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.37 (s, 3H, CH_3 tMB), 1.27 (s, 3H, CH_3 tMB), 0.93 (s, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7 (NC(O) pentenyl), 167.9 (NHC(O)-1), 139.0, 138.6, 138.3, 138.1 (4×C_q Bn), 137.4 (=CH pentenyl), 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.6, 127.4 (CH_{Ar} Bn), 115.3 (=CH_2 pentenyl), 79.4 (C-5), 78.8, 78.7 (C-3, C-4), 75.8, 74.1, 73.9, 73.0 (4×CH_2 Bn), 67.1 (C-7), 56.6 (C-6), 55.2 (NHC_q-1 tMB), 54.0 (C-2), 52.7 (CH_2-2 tMB), 33.3 (C_q-3 tMB), 32.8 (CH_2 pentenyl), 31.6 (CH_3-4, 2×CH_3 tMB), 29.3 (CH_2 pentenyl), 28.8, 28.5 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 2952, 1726, 1683, 1638, 1532, 1454, 1365, 1227, 1091, 1027, 911, 734, 696. $[\alpha]^{20}_D$: −51.0 (*c* 3.0, $CHCl_3$). HRMS: found 461.4531 $[M+H]^+$; calculated for $[C_{48}H_{60}N_2O_6+H]^+$ 761.4524.



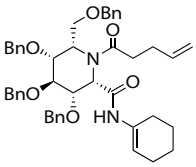
Pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*gulo*-heptonamide (F1-III). Subjecting azido-aldehyde **20** (1.16 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1.6:1 mixture of **G1-III** (297 mg, 0.41 mmol) and **F1-III** (182 mg, 0.25 mmol) in a combined yield of 57%. R_F = 0.27 (1:3; EtOAc:toluene). ^{1}H NMR (500 MHz, $CDCl_3$) complex mixture of rotamers; major signals δ 7.38 – 7.19 (m, 20H, H_{Ar} Bn), 5.82 – 5.74 (m, 1H, =CH pentenyl), 5.02 – 4.92 (m, 2H, =CH_2 pentenyl), 4.81 – 3.61 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7), 3.23 – 3.12 (m, 2H, NCH_2-1 pentyl), 2.68 – 2.22 (m, 4H, 2×CH_2 pentenyl), 1.73 – 0.97 (m, 6H, 3×CH_2 pentyl), 0.85 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (125 MHz, $CDCl_3$) major signals δ 174.2 (NC(O) pentenyl), 169.1 (NHC(O)-1), 138.4, 138.2, 138.2, 137.8 (4×C_q Bn), 138.0 (=CH pentenyl), 128.8 – 127.7 (CH_{Ar} Bn), 115.0 (=CH_2 pentenyl), 80.8, 78.7, 78.2, 73.6, 72.0, 70.1, 69.1, 64.5, 59.1, 54.9, 40.1 (NCH_2-1 pentyl), 33.3 (CH_2 pentenyl), 29.3, 29.2, 22.5 (CH_2 pentyl/pentenyl), 14.2 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3325, 2929, 2862, 1726, 1636, 1543, 1454, 1417, 1363, 1279, 1072, 1027, 911, 724, 967. $[\alpha]^{20}_D$: −12.4 (*c* 0.9, $CHCl_3$). HRMS: found 719.4058 $[M+H]^+$; calculated for $[C_{45}H_{54}N_2O_6+H]^+$ 719.4055.



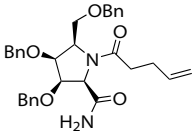
Pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*ido*-heptonamide (G1-III). R_F = 0.45 (1:3; EtOAc:toluene). ^{1}H NMR (500 MHz, $CDCl_3$) major rotamer; 3.5:1 mixture of rotamers δ 7.39 – 7.14 (m, 20H, H_{Ar} Bn), 6.67 (t, *J* = 5.7, 1H, C(O)NH), 5.79 – 5.68 (m, 1H, =CH pentenyl), 5.13 (d, *J* = 6.7, 1H, H-2), 5.03 – 4.50 (m, 9H, =CH_2 pentenyl, 3×CH_2 Bn, H-4), 4.45 (d, *J* = 11.8, 1H, C*H*H Bn), 4.38 (d, *J* = 11.8, 1H, CH*H* Bn), 4.27 – 4.19 (m, 1H, H-6), 4.07 (dd, *J* = 10.1, 1H, H-7a), 3.82 (dd, *J* = 4.3, 9.9, 1H, H-7b), 3.54 (dd, *J* = 6.5, 9.5, 1H, H-5), 3.48 (dd, *J* = 6.7, 9.4, 1H, H-3), 3.26 – 3.16 (m, 1H, NC*H*H-1), 2.97 – 2.85 (m, 1H, NCH*H*-1), 2.67 – 2.21 (m, 4H, 2×CH_2 pentenyl), 1.40 – 1.27 (m, 2H, CH_2 pentyl), 1.27 – 1.12 (m, 4H, 2×CH_2 pentyl), 0.82 (t, *J* = 7.1, 3H, CH_3-5 pentyl). ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer δ 175.0 (NC(O) pentenyl), 169.1 (NHC(O)-1), 139.0, 138.5, 138.3, 138.1 (4×C_q Bn), 137.4 (=CH pentenyl), 128.7, 128.6, 128.4, 128.3, 128.3, 127.9, 127.9, 127.8, 127.4, 127.1 (CH_{Ar} Bn), 115.3 (=CH_2 pentenyl), 79.3 (C-4), 78.8 (C-5), 78.5 (C-3), 75.7, 74.0, 74.0, 73.0 (4×CH_2 Bn), 67.0 (C-7), 55.8 (C-6), 53.4 (C-2), 39.5 (NCH_2-1 pentyl), 33.0 (CH_2 pentenyl), 29.2, 29.2, 29.2, 22.4 (CH_2 pentenyl, 3×CH_2 pentyl), 14.1 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3364, 2930, 2862, 1681, 1531, 1454, 1365, 1208, 1091, 1027, 911, 733, 696. $[\alpha]^{20}_D$: −58.1 (*c* 2.0, $CHCl_3$). HRMS: found 719.4059 $[M+H]^+$; calculated for $[C_{45}H_{54}N_2O_6+H]^+$ 719.4055.



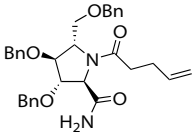
1-Cyclohexenyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*gulo*-heptonamide (F-IV). Subjecting azido-aldehyde **20** (0.93 mmol) to the tandem SAWU-3CR (General procedure B in MeOH) produced a separable 1.5:1 mixture of **G-IV** (210 mg, 0.29 mmol) and **F-IV** (140 mg, 0.19 mmol) in a combined yield of 41%. R_F = 0.52 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, CDCl3) complex mixture of rotamers; major signals δ 7.40 – 7.12 (m, 20H, H_{Ar} Bn), 6.90 – 6.82 (m, 1H, C(O)NH), 6.18 – 6.06 (m, 1H, =CH-2 cyclohexenyl), 5.89 – 5.71 (m, 1H, =CH pentenyl), 5.02 – 4.90 (m, 2H, =CH_2 pentenyl), 4.83 – 3.62 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7), 2.71 – 2.24 (m, 4H, 2×CH_2 pentenyl), 2.16 – 1.23 (m, 8H, 4×CH_2 cyclohexenyl). ^{13}C NMR (100 MHz, $CDCl_3$) major signals δ 138.1, 137.8 (Cq Bn, =CH pentenyl), 128.6 – 127.8 (CH_{Ar} Bn), 115.2 (=CH_2 pentenyl), 112.7 (=CH-2 cyclohexenyl), 80.9 (C-4), 79.4 (C-5), 78.2 (C-3), 73.8, 73.6, 73.4 (CH_2 Bn), 68.7 (C-7), 59.8 (C-6), 55.6 (C-2), 33.5, 29.4 (2×CH_2 pentenyl), 28.0, 24.2, 22.8, 22.2 (4×CH_2 cyclohexenyl). IR ν_{max}(thin film)/ cm^{-1}: 3312, 2928, 2860, 1730, 1695, 1622, 1556, 1453, 1367, 1208, 1072, 1027, 912, 734, 696. $[\alpha]^{20}_D$: −16.0 (*c* 2.7, $CHCl_3$). HRMS: found 751.3716 $[M+H]^+$; calculated for $[C_{46}H_{52}N_2O_6+Na]^+$ 751.3723.



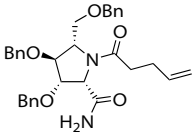
1-Cyclohexenyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*ido*-heptonamide (G-IV). R_F = 0.63 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) 3.5:1 mixture of rotamers; major rotamer δ 7.70 (s, 1H, C(O)NH), 7.42 – 7.14 (m, 20H, H_{Ar} Bn), 6.16 (s, 1H, =CH-2 cyclohexenyl), 5.90 – 5.61 (m, 1H, =CH pentenyl), 5.14 (d, *J* = 6.6, 1H, H-2), 5.04 – 4.58 (m, 9H, =CH_2 pentenyl, 3×CH_2 Bn, H-4), 4.44 (d, *J* = 11.8, 1H, C*H*H Bn), 4.35 (d, *J* = 11.8, 1H, CH*H* Bn), 4.26 – 4.16 (m, 1H, H-6), 4.01 (dd, *J* = 10.3, 1H, H-7a), 3.81 (dd, *J* = 4.3, 9.9, 1H, H-7b), 3.54 (dd, *J* = 6.4, 9.5, 1H, H-5), 3.46 (dd, *J* = 6.6, 9.5, 1H, H-3), 2.69 – 2.12 (m, 4H, 2×CH_2 pentenyl), 2.09 – 1.20 (m, 8H, 4×CH_2 cyclohexenyl). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 175.4 (NC(O) pentenyl), 167.3 (NHC(O)-1), 138.9, 138.5, 138.2, 138.1 (4×C_q Bn), 137.3 (=CH pentenyl), 132.6 (=C_q-1 cyclohexenyl), 128.6, 128.5, 128.4, 128.2, 128.2, 128.0, 127.9, 127.7, 127.6, 127.4, 127.0 (CH_{Ar} Bn), 115.3 (=CH_2 pentenyl), 112.0 (=CH-2 cyclohexenyl), 79.2 (C-4), 78.8 (C-4), 78.5 (C-3), 75.8, 74.0, 73.9, 73.0 (4×CH_2 Bn), 66.7 (C-7), 55.8 (C-6), 53.8 (C-2), 32.9, 29.2 (2×CH_2 pentenyl), 28.0, 24.0, 22.4, 22.0 (4×CH_2 cyclohexenyl). IR ν_{max}(thin film)/ cm^{-1}: 3321, 3032, 2929, 1695, 1635, 1542, 1497, 1454, 1366, 1273, 1235, 1208, 1091, 1027, 913, 734, 697. $[\alpha]^{20}_D$: −61.2 (*c* 4.2, $CHCl_3$). HRMS: found 729.3904 $[M+H]^+$; calculated for $[C_{46}H_{52}N_2O_6+H]^+$ 729.3898.



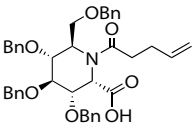
3,4,6-Tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-D-*galacto*-hexonamide (B1-VI). Compound **B1-VI** (81 mg, 0.15 mmol) was synthesized in 75% yield from **B1-IV** (0.20 mmol) by isomerization and hydrolysis of the 1-cyclohexene-amide moiety (general procedure C). R_F = 0.20 (4:1; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) 2:1 mixture of rotamers; major rotamer: δ 7.39 – 7.20 (m, 15H, H_{Ar} Bn), 5.91 (s, 1H, NH_2), 5.84 – 5.73 (m, 1H, =CH pentenyl), 5.06 – 4.90 (m, 2H, =CH-2 cyclohexenyl), 4.75 – 4.38 (m, 7H, 3×CH_2 Bn, H-2, H-4), 4.37 – 4.32 (m, 1H, H-5), 4.12 (dd, *J* = 10.1, 1H, H-6a), 3.89 (dd, *J* = 5.1, 6.4, 1H, H-3), 3.81 (dd, *J* = 3.4, 10.3, 1H, H-6b), 2.86 – 2.78 (m, 1H, NC*H*H pentenyl), 2.45 – 2.30 (m, 3H, NCH*H*, CH_2 pentenyl).^{13}C NMR (150 MHz, $CDCl_3$) major rotamer: δ 174.1 (NC=O pentenyl), 170.7 (NHC(O)-1), 138.3, 137.7 (3×C_q Bn), 137.6 (=CH pentenyl), 137.3 (C_q Bn), 128.8 – 127.7 (CH_{Ar} Bn), 115.4 (=CH_2 pentenyl), 79.0 (C-3), 76.7 (C-4), 75.0, 73.6, 72.6 (3×CH_2 Bn), 69.0 (C-6), 64.2 (C-2), 58.7 (C-5), 33.6 (NCH_2 pentenyl), 29.0 (CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3320, 3030, 2868, 1683, 1652, 1638, 1495, 1454, 1406, 1360, 1212, 1109, 1055, 1026, 913, 735, 698. $[\alpha]^{20}_D$: 21.2 (*c* 1.5, $CHCl_3$).HRMS: found 529.2693 $[M+H]^+$, calculated for $[C_{32}H_{36}O_5N_2+H]^+$ 529.2693.



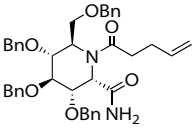
3,4,6-Tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*gulo*-hexonamide (C1-VI). Compound **C1-VI** (27 mg, 51 µmol) was synthesized in 73% yield from **C1-IV** (70 µmol) by isomerization and hydrolysis of the 1-cyclohexene-amide moiety (general procedure C). R_F = 0.50 (3:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.09 (m, 15H, H_{Ar} Bn), 5.88 – 5.70 (m, 1H, =CH pentenyl), 5.12 – 4.84 (m, 2H, =CH_2 pentenyl), 4.74 – 3.39 (m, 12H, H-2, H-3, H-4, H-5, CH_2-6, 3×CH_2 Bn), 2.55 – 208 (m, 4H, 2×CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 2924, 2855, 1638, 1454, 1409, 1206, 1095, 911, 736, 698. $[\alpha]^{20}_D$: 10.8 (*c* 0.5, $CHCl_3$). HRMS: found 529.2694 $[M+H]^+$, calculated for $[C_{32}H_{36}O_5N_2+H]^+$ 529.2697.



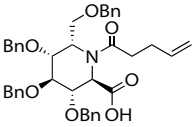
3,4,6-Tri-*O*-benzyl-2,5-dideoxy-2,5-(pent-4-enimido)-L-*ido*-hexonamide (D1-VI). Compound **D1-VI** (62 mg, 117 µmol) was synthesized in 73% yield from **D1-IV** (160 µmol) by isomerization and hydrolysis of the 1-cyclohexene-amide moiety (general procedure C). R_F = 0.57 (3:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.01 (m, 15H, H_{Ar} Bn), 5.94 – 5.67 (m, 1H, =CH pentenyl), 5.28 – 3.39 (m, 14H, =CH_2 pentenyl, H-2, H-3, H-4, H-5, CH_2-6, 3×CH_2 Bn), 2.73 – 1.91 (m, 4H, 2×CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 2924, 1651, 1454, 1402, 1363, 1208, 1094, 1026, 912, 736, 698. $[\alpha]^{20}_D$: 25.3 (*c* 1.2, $CHCl_3$). HRMS: found 529.2693 $[M+H]^+$, calculated for $[C_{32}H_{36}O_5N_2+H]^+$ 529.2693.



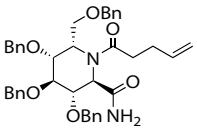
3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-D-*glycero*-D-*ido*-heptonic acid (E1-V). Compound **E1-V** (245 mg, 0.38 mmol) was synthesized in 82% yield from **E1-IV** (0.46 mmol) by isomerization and hydrolysis of the 1-cyclohexene-amide moiety (general procedure C). R_F = 0.36 (1:1; EtOAc:toluene+5% AcOH). ^{1}H NMR (400 MHz, $CDCl_3$) collapsed iminosugar signals δ 9.83 – 8.15 (m, 1H, COOH), 7.43 – 7.13 (m, 20H, H_{Ar} Bn), 5.79 (ddd, *J* = 6.2, 10.3, 16.7, 1H, =CH pentenyl), 4.97 (dd, *J* = 13.7, 23.2, 2H, =CH_2 pentenyl), 4.89 – 3.16 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7), 2.50 – 2.30 (m, 4H, 2×CH_2 pentenyl). ^{13}C NMR (100 MHz, $CDCl_3$) collapsed iminosugar signals δ 174.2 (NC=O pentenyl), 169.5 (NHC(O)-1), 137.6, 136.5 (C_q Bn), 137.1 (=CH pentenyl), 128.6, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.7 (CH_{Ar} Bn), 115.5 (=CH_2 pentenyl), 73.2, 56.1, 32.6 (C(O)NCH_2 pentenyl), 29.0 (CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2868, 1739, 1652, 1496, 1454, 1367, 1203, 1074, 1027, 912, 736, 698. $[\alpha]^{20}_D$: 11.6 (*c* 2.8, $CHCl_3$). HRMS: found 650.3114 $[M+H]^+$; calculated for $[C_{40}H_{43}NO_7+H]^+$ 650.3112.



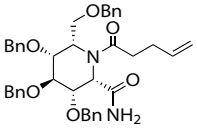
3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-D-*glycero*-D-*ido*-heptonamide (E1-VI). Ethyl chloroformate (25 µL, 0.25 mmol) was added to a cooled (0 °C) solution of **E1-IV** (100 mg, 0,15 mmol) and Et_3N (36 µL, 0.26 mmol) in THF (1.5 mL). After stirring for 1h at 0 °C, aqueous ammonia (0.2mL, 25%) was added and the reaction was stirred for an additional hour at 0 °C. The mixture was diluted with H_2O (20 mL) and extracted with Et_2O (3×30 mL). The combined organic layers were dried and concentrated. The residue was purified with silica gel column chromatography (0% » 50% EtOAc in toluene) to afford **E1-VI** (64 mg, 0.10 mmol) in 64% yield as a colorless oil. R_F = 0.52 (1:1; EtOAc:toluene+5% AcOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 20H, H_{Ar} Bn), 6.86 (s, 1H, C(O)NH), 5.80 (ddt, *J* = 6.5, 10.2, 16.8, 1H, =CH pentenyl), 5.06 – 4.93 (m, 3H, =CH_2 pentenyl, H-2), 4.87 – 4.39 (m, 8H, 4×CH_2 Bn), 4.36 (dd, *J* = 7.5, 9.8, 1H, H-3), 4.22 (t, *J* = 7.5, 1H, H-6), 3.67 (dd, *J* = 6.8, 9.8, 1H, H-4), 3.64 – 3.54 (m, 2H, H-5, C*H*H-7), 3.46 (dd, *J* = 6.7, 9.7, 1H, CH*H*-7), 2.59 – 2.51 (m, 2H, C(O)NCH_2 pentenyl), 2.42 – 2.33 (m, 2H, CH_2 pentenyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2 (NC=O pentenyl), 172.4 (NHC(O)-1), 138.4, 138.4, 137.8, 137.8 (4×C_q Bn), 137.3 (=CH pentenyl), 128.7, 128.6, 128.5, 128.5, 128.1, 128.1, 128.0, 127.8 (CH_{Ar} Bn), 115.5 (=CH_2 pentenyl), 81.9 (C-4), 80.3 (C-5), 75.5 (C-3), 74.8, 74.5, 73.4, 72.4 (4×CH_2 Bn), 70.1 (C-7), 59.5 (C-6), 58.3 (C-2), 32.7 (C(O)NCH_2 pentenyl), 29.2 (CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3033, 2867, 1695, 1639, 1496, 1454, 1365, 1070, 1028, 914, 735, 698. $[\alpha]^{20}_D$: 47.0 (*c* 1.3, $CHCl_3$). HRMS: found 649.3272 $[M+H]^+$; calculated for $[C_{40}H_{44}N_2O_6+H]^+$ 649.3272.



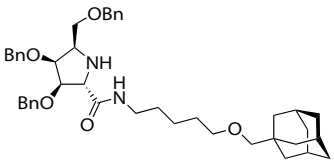
3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*gulo*-heptonic acid (F1-V). Compound **F1-V** (35 mg, 54 µmol) was produced in 31% yield together with **F1-VI** (40 mg, 62 µmol) in 36% yield from **F1-IV** (0.17 mmol) by isomerization and hydrolysis of the 1-cyclohexene-amide moiety (general procedure C). R_F = 0.13 (1:1; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) 4:1 mixture of rotamers; major rotamer δ 7.43 – 7.19 (m, 20H, H_{Ar} Bn), 5.84 – 5.67 (m, 1H, =CH pentenyl), 4.95 (dd, *J* = 13.7, 18.1, 2H, =CH_2 pentenyl), 4.66 (d, *J* = 5.0, 1H, H-2), 4.65 – 4.38 (m, 8H, 4×CH_2 Bn), 4.35 – 4.30 (m, 1H, H-6), 4.09 (dd, *J* = 2.6, 5.0, 1H, H-3), 4.04 (dd, *J* = 6.1, 7.5, 1H, H-5), 3.82 (dd, *J* = 3.8, 10.0, 1H, H-7a), 3.79 – 3.69 (m, 2H, H-4, H-7b), 2.80 – 2.18 (m, 4H, 2×CH_2 pentenyl). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 175.5 (NC(O) pentenyl), 172.5 (C(O)-1), 138.2, 138.0, 138.0, 137.6 (4×C_q Bn), 137.7 (=CH pentenyl), 128.6, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 115.2 (=CH_2 pentenyl), 80.3 (C-4), 77.8 (C-5), 77.5 (C-3), 73.5, 73.2, 72.7, 72.6 (4×CH_2 Bn), 69.2 (C-7), 56.4 (C-2), 55.1 (C-6), 32.9, 29.1 (2×CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3333, 2926, 1684, 1636, 1495, 1454, 1417, 1278, 1208, 1073, 1027, 911, 735, 698. $[\alpha]^{20}_D$: −22.9 (*c* 0.7, $CHCl_3$). HRMS: found 650.3114 $[M+H]^+$; calculated for $[C_{40}H_{43}NO_7+H]^+$ 650.3112.



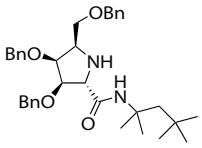
3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*gulo*-heptonamide (F1-VI). Compound **F1-VI** (40 mg, 62 µmol) was produced in 36% yield together with **F1-V** (35 mg, 54 µmol) in 31% yield from **F1-IV** (0.17 mmol) by isomerization and hydrolysis of the 1-cyclohexene-amide moiety (general procedure C). R_F = 0.07 (1:1; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.66 (m, 1H, C(O)N*H*H), 7.56 – 7.49 (m, 1H, C(O)NH*H*), 7.43 – 7.14 (m, 20H, H_{Ar} Bn), 5.89 – 5.68 (m, 1H, =CH pentenyl), 5.03 – 4.87 (m, 2H, =CH_2 pentenyl), 4.79 – 4.32 (m, 8H, 4×CH_2 Bn), 4.32 – 4.22 (m, 2H, H-2, H-6), 4.09 – 4.02 (m, 1H, H-3), 4.03 – 3.96 (m, 1H, H-5), 3.87 – 3.76 (m, 1H, H-7a), 3.75 – 3.69 (m, 2H, H-4, H-7b), 2.70 – 2.22 (m, 4H, 2×CH_2 pentenyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7 (NC(O) pentenyl), 172.3 (NH_2C(O)-1), 138.3, 138.1, 138.0, 137.7 (4×C_q Bn), 137.8 (=CH pentenyl), 129.0, 128.6, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8 (CH_{Ar} Bn), 115.3 (=CH_2 pentenyl), 80.6 (C-4), 78.9 (C-5), 78.0 (C-3), 73.6, 73.5, 73.5, 73.4 (4×CH_2 Bn), 68.6 (C-7), 58.4, 55.5 (C-2, C-6), 33.3, 29.2 (2×CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2860, 1739, 1652, 1454, 1365, 1205, 1092, 1027, 913, 736, 698. $[\alpha]^{20}_D$: −18.8 (*c* 0.8, $CHCl_3$). HRMS: found 649.3271 $[M+H]^+$; calculated for $[C_{40}H_{44}N_2O_6+H]^+$ 649.3272.



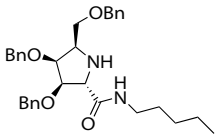
3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-(pent-4-enimido)-L-*glycero*-D-*ido*-heptonamide (G1-VI). Compound **G1-VI** (122 mg, 0.19 mmol) was synthesized in 72% yield from **G1-IV** (0.26 mmol) by isomerization and hydrolysis of the 1-cyclohexene-amide moiety (general procedure C). R_F = 0.52 (1:1; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) 3:1 mixture of rotamers; major rotamer δ 7.37 – 7.17 (m, 20H, H_{Ar} Bn), 6.70 (d, *J* = 2.2, 1H, C(O)N*H*H), 5.87 – 5.62 (m, 1H, =CH pentenyl), 5.49 (d, *J* = 2.8, 1H, C(O)NH*H*), 5.25 (d, *J* = 6.6, 1H, H-2), 4.99 – 4.58 (m, 8H, =CH_2 pentenyl, 3×CH_2 Bn), 4.51 (dd, *J* = 9.3, 1H, H-4), 4.48 – 4.36 (m, 2H, CH_2 Bn), 4.28 – 4.19 (m, 1H, H-6), 4.00 (dd, *J* = 10.0, 1H, H-7a), 3.81 (dd, *J* = 4.2, 9.9, 1H, H-7b), 3.63 – 3.48 (m, 2H, H-3, H-5), 2.67 – 2.19 (m, 4H, 2×CH_2 pentenyl). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 174.8 (NC(O) pentenyl), 171.5 (NH_2C(O)-1), 138.8, 138.4, 138.0, 138.0 (4×C_q Bn), 137.4 (=CH pentenyl), 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.9, 127.6, 127.5 (CH_{Ar} Bn), 115.3 (=CH_2 pentenyl), 79.3 (C-5), 78.6 (C-4), 78.2 (C-3), 75.5, 74.1, 73.9, 73.0 (4×CH_2 Bn), 66.9 (C-7), 55.7 (C-6), 52.6 (C-2), 32.9, 29.2 (2×CH_2 pentenyl). IR ν_{max}(thin film)/ cm^{-1}: 3428, 3032, 2869, 1695, 1650, 1495, 1454, 1366, 1274, 1209, 1092, 1027, 912, 736, 698. $[\alpha]^{20}_D$: −76.4 (*c* 2.4, $CHCl_3$). HRMS: found 649.3273 $[M+H]^+$; calculated for $[C_{40}H_{44}N_2O_6+H]^+$ 649.3272.



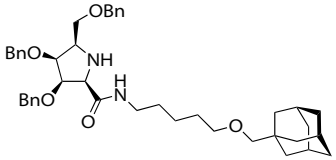
5-(Adamantan-1yl-methoxy)-pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-D-*talo*-hexonamide (A2-I). Compound **A2-I** (75 mg, 0.11 mmol) was synthesized in 75% yield from **A1-I** (0.15 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.46 (1:1; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (t, *J* = 5.8, 1H, C(O)NH), 7.38 – 7.24 (m, 15H, H_{Ar} Bn), 4.73 (d, *J* = 12.2, 1H, C*H*H Bn), 4.65 (d, *J* = 12.2, 1H, CH*H* Bn), 4.63 (d, *J* = 11.8, 1H, C*H*H Bn), 4.53 (d, *J* = 11.9, 1H, C*H*H Bn), 4.50 (d, *J* = 11.9, 1H, CH*H* Bn), 4.45 (d, *J* = 11.8, 1H, CH*H* Bn), 4.10 (dd, *J* = 4.0, 1H, H-3), 3.95 (dd, *J* = 5.1, 1H, H-4), 3.79 (d, *J* = 3.4, 1H, H-2), 3.77 (dd, *J* = 9.2, 1H, H-6a), 3.72 (dd, *J* = 5.0, 9.5, 1H, H-6b), 3.55 – 3.48 (m, 1H, H-5), 3.35 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 3.27 – 3.21 (m, 1H, NC*H*H-1 pentyl), 3.21 – 3.09 (m, 1H, NCH*H*-1 pentyl), 2.94 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.67 (dd, *J* = 12.1, 37.4, 6H, 3×CH_2 Ada), 1.58 – 1.49 (m, 8H, 3×CH_2 Ada, CH_2-4 pentyl), 1.49 – 1.41 (m, 2H, CH_2-2 pentyl), 1.38 – 1.29 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5 (C(O)-1), 138.4, 138.3, 138.2 (3×C_q Bn), 128.7, 128.6, 128.5, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8 (CH_{Ar} Bn), 82.1 (OCH_2-Ada), 81.7 (C-3), 78.9 (C-4), 73.5, 72.9, 72.0 (3×CH_2 Bn), 71.5 (CH_2-5 pentyl), 70.6 (C-6), 64.3 (C-2), 59.2 (C-5), 39.9 (CH_2 Ada), 39.3 (NCH_2-1 pentyl), 37.4 (CH_2 Ada), 34.3 (C_q Ada), 29.6 (CH_2-2 pentyl), 29.4 (CH_2-4 pentyl), 28.5 (CH Ada), 23.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2900, 2848, 1667, 1653, 1519, 1453, 1360, 1096, 1058, 1027, 734, 697. $[\alpha]^{20}_D$: −4.2 (*c* 0.6, $CHCl_3$). HRMS: found 681.4261 $[M+H]^+$, calculated for $[C_{43}H_{56}O_5N_2+H]^+$ 681.4262.



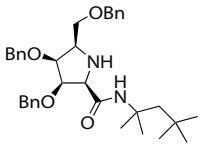
1,1,3,3-Tetramethylbutyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-D-*talo*-hexonamide (A2-II). Compound **A2-II** (212 mg, 0.38 mmol) was synthesized in 69% yield from **A1-II** (0.55 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.59 (1:2; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (s, 1H, C(O)NH), 7.39 – 7.21 (m, 15H, H_{Ar} Bn), 4.73 (d, *J* = 12.0, 1H, C*H*H Bn), 4.65 – 4.59 (m, 2H, CH*H* Bn, C*H*H Bn), 4.52 (d, *J* = 11.8, 1H, CH*H* Bn), 4.48 (d, *J* = 11.8, 1H, CH*H* Bn), 4.42 (d, *J* = 11.8, 1H, CH*H* Bn), 4.08 (dd, *J* = 3.2, 4.7, 1H, H-3), 3.91 (dd, *J* = 4.7, 6.0, 1H, H-4), 3.78 (dd, *J* = 9.3, 1H, H-6a), 3.72 (dd, *J* = 4.8, 9.6, 1H, H-6b), 3.67 (d, *J* = 3.2, 1H, H-2), 3.52 (ddd, *J* = 4.8, 5.9, 8.9, 1H, H-5), 2.55 (s, 1H, NH), 1.72 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.63 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.36 (d, *J* = 17.3, 6H, 2×CH_3 tMB), 0.94 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (C(O)-1), 138.1, 138.0, 137.8 (3×C_q Bn), 128.3, 128.2, 127.8, 127.7, 127.6, 127.4 (CH_{Ar} Bn), 81.1 (C-3), 78.2 (C-4), 73.2, 73.4, 71.5 (3×CH_2 Bn), 70.3 (C-6), 64.6 (C-2), 58.8 (C-5), 54.2 (NHC_q-1 tMB), 51.7 (CH_2-2 tMB), 31.5 (C_q-3 tMB), 31.3 (2×CH_3, CH_3-4 tMB), 29.1, 28.6 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3317, 2950, 1668, 1515, 1093, 734, 696. $[\alpha]^{20}_D$: –14.6 (*c* 3.7, $CHCl_3$). HRMS: found 559.3528 $[M+H]^+$, calculated for $[C_{35}H_{46}O_4N_2+H]^+$ 559.3530.



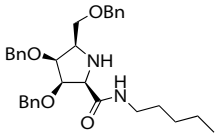
Pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-D-*talo*-hexonamide (A2-III). Compound **A2-III** (81 mg, 0.16 mmol) was synthesized in 80% yield from **A1-III** (0.20 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.85 (1:1; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 16H, C(O)NH, H_{Ar} Bn), 4.73 (d, *J* = 12.0, 1H, C*H*H Bn), 4.65 (d, *J* = 12.0, 1H, CH*H* Bn), 4.63 (d, *J* = 11.8, 1H, C*H*H Bn), 4.53 (d, *J* = 11.7, 1H, C*H*H Bn), 4.50 (d, *J* = 11.7, 1H, CH*H* Bn), 4.45 (d, *J* = 11.8, 1H, CH*H* Bn), 4.10 (dd, *J* = 3.6, 4.5, 1H, H-3), 3.95 (dd, *J* = 4.9, 5.5, 1H, H-4), 3.79 (d, *J* = 3.6, 1H, H-2), 3.77 – 3.71 (m, 2H, CH_2-6), 3.52 (dt, *J* = 5.3, 8.8, 1H, H-5), 3.26 – 3.11 (m, 2H, NCH_2-1 pentyl), 1.48 – 1.41 (m, 2H, CH_2-2 pentyl), 1.34 – 1.28 (m, 2H, CH_2 pentyl), 1.28 – 1.21 (m, 2H, CH_2 pentyl), 0.88 (t, *J* = 7.2, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5 (C(O)-1), 138.4, 138.3, 138.2 (3×C_q Bn), 128.6, 128.5, 128.2, 128.0, 127.9, 127.9, 127.8 (CH_{Ar} Bn), 81.7 (C-3), 78.9 (C-4), 73.6, 72.9, 72.0 (3×CH_2 Bn), 70.6 (C-6), 64.3 (C-2), 59.2 (C-5), 39.2 (NCH_2-1 pentyl), 29.5 (CH_2-2 pentyl), 29.2, 22.5 (2×CH_2 pentyl), 14.2 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3325, 2929, 2867, 1667, 1521, 1454, 1360, 1209, 1096, 1027, 735, 698. $[\alpha]^{20}_D$: –4.0 (*c* 0.8, $CHCl_3$). HRMS: found 517.3059 $[M+H]^+$, calculated for $[C_{32}H_{40}O_4N_2+H]^+$ 517.3061.



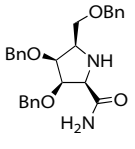
5-(Adamantan-1yl-methoxy)-pentyl3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-D-*galacto*-hexonamide (B2-I). Compound **B2-I** (385 mg, 0.57 mmol) was synthesized in 97% yield from **B1-I** (0.58 mmol) by deprotection of the pent-4-enamide (general procedure C). R_F = 0.25 (2:1; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (t, *J* = 5.5, 1H, C(O)NH), 7.38 – 7.18 (m, 15H, H_{Ar} Bn), 5.91 – 5.73 (s, NH), 4.95 (dd, *J* = 4.1, 5.8, 1H, H-3), 4.84 (d, *J* = 6.0, 1H, H-2), 4.74 (d, *J* = 11.3, 1H, C*H*H Bn), 4.70 (d, *J* = 11.3, 1H, CH*H* Bn), 4.62 – 4.46 (m, 4H, 2×CH_2 Bn), 4.35 (dd, *J* = 3.8, 6.4, 1H, H-4), 4.16 (dt, *J* = 5.4, 10.8, 1H, H-5), 3.96 (dd, *J* = 10.4, 1H, H-6a), 3.70 (dd, *J* = 4.6, 10.4, 1H, H-6b), 3.37 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.32 – 3.16 (m, 2H, CH_2-1 pentyl), 2.91 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.67 (dd, *J* = 12.4, 40.4, 6H, 3×CH Ada), 1.61 – 1.54 (m, 2H, CH_2-4 pentyl), 1.52 (d, *J* = 6.6, 6H, 3×CH Ada), 1.47 – 1.36 (m, 3H, CH_2-2, C*H*H-3 pentyl), 1.31 – 1.23 (m, 1H, CH*H*-3 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8 (C(O)-1), 137.3, 137.1, 136.9 (3×C_q Bn), 128.7, 128.7, 128.6, 128.3, 128.1, 128.1, 127.7, 127.7 (CH_{Ar} Bn), 82.1 (C-3), 82.0 (C-4), 78.7, 78.4, 74.7, 73.7, 73.7, 71.4, 71.4 (3×CH_2 Bn), 66.1 (C-6), 59.9 (C-2), 58.5 (C-5), 40.5 (CH_2-1 pentyl), 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 29.3 (CH_2 pentyl), 29.2, 29.0 (CH_2 pentyl), 28.4 (CH Ada), 23.7, 23.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3242, 2900, 2847, 1686, 1544, 1453, 1359, 1153, 1097, 1026, 734, 697. $[\alpha]^{20}_D$: 13.5 (*c* 1.8, $CHCl_3$). HRMS: found 681.4262 $[M+H]^+$, calculated for $[C_{43}H_{56}O_5N_2+H]^+$ 681.4262.



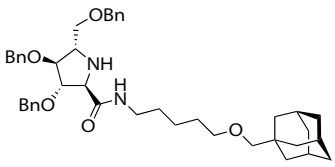
1,1,3,3-Tetramethylbutyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-D-*galacto*-hexonamide (B2-II). Compound **B2-II** (301 mg, 0.54 mmol) was synthesized in 92% yield from **B1-II** (0.58 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.40 (1:2; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (s, 1H, C(O)NH), 7.37 – 7.25 (m, 15H, H_{Ar} Bn), 5.56 – 5.19 (s, 1H, NH), 4.76 (d, *J* = 11.4, 1H, C*H*H Bn), 4.73 (d, *J* = 11.4, 1H, CH*H* Bn), 4.64 (d, *J* = 11.7, 1H, C*H*H Bn), 4.61 (dd, *J* = 3.8, 6.1, 1H, H-3), 4.57 (d, *J* = 11.7, 1H, C*H*H Bn), 4.55 – 4.49 (m, 2H, 2×CH*H* Bn), 4.28 (d, *J* = 6.3, 1H, H-2), 4.18 (dd, *J* = 3.8, 6.2, 1H, H-4), 3.89 – 3.84 (m, 1H, H-5), 3.81 (dd, *J* = 9.2, 1H, H-6a), 3.76 (dd, *J* = 4.6, 9.7, 1H, H-6b), 1.66 – 1.57 (m, 2H, CH_2-2 tMB), 1.33 (d *J* = 29.4, 6H, 2×CH_3 tMB), 0.95 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1 (C(O)-1), 137.8, 137.7, 137.5 (3×C_q Bn), 128.3, 128.1, 127.9, 127.7, 127.6, 127.5, 127.4 (CH_{Ar} Bn), 79.2 (C-3), 78.7 (C-4), 73.7, 73.2, 73.0 (3×CH_2 Bn), 69.2 (C-6), 60.9 (C-2), 57.9 (C-5), 55.2 (NHC_q-1 tMB), 52.4 (CH_2-2 tMB), 31.6 (C_q-3 tMB), 31.4 (2×CH_3, CH_3-4 tMB), 28.4 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3274, 2951, 1681, 1668, 1530, 1093, 732, 696. $[\alpha]^{20}_D$: 4.2 (*c* 6.0, $CHCl_3$). HRMS: found 559.3529 $[M+H]^+$, calculated for $[C_{35}H_{46}O_4N_2+H]^+$ 559.3530.



Pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-D-*galacto*-hexonamide (B2-III). Compound **B2-III** (341 mg, 0.66 mmol) was synthesized in 77% yield from **B1-III** (0.86 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.15 (1:1; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (s, 1H, C(O)NH), 7.38 – 7.19 (m, 15H, H_{Ar} Bn), 6.34 – 6.11 (s, 1H, NH), 4.74 – 4.48 (m, 7H, H-3, 3×CH_2 Bn), 4.47 (d, *J* = 5.6, 1H, H-2), 4.20 (dd, *J* = 3.9, 6.2, 1H, H-4), 3.92 – 3.86 (m, 1H, H-5), 3.83 (dd, *J* = 9.6, 1H, H-6a), 3.74 – 3.67 (m, 1H, H-6b), 3.16 – 3.10 (m, 2H, NCH_2-1 pentyl), 1.39 – 1.32 (m, 2H, CH_3-2 pentyl), 1.23 – 1.13 (m, 4H, 2×CH_2 pentyl), 0.80 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7 (C(O)-1), 137.8, 137.6, 137.4 (3×C_q Bn), 128.8, 128.4, 128.4, 128.3, 128.3, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 127.5, 127.2 (CH_{Ar} Bn), 79.1 (C-3), 78.8 (C-4), 74.0, 73.4, 73.2 (3×CH_2 Bn), 68.3 (C-6), 60.6 (C-2), 58.0 (C-5), 39.9 (NCH_2-1 pentyl), 29.0 (CH_2-2 pentyl), 28.8, 22.2 (2×CH_2 pentyl), 14.0 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3231, 2929, 2862, 1682, 1652, 1543, 1454, 1358, 1257, 1210, 1092, 1026, 734, 696. $[\alpha]^{20}_D$: 14.4 (*c* 5.5, $CHCl_3$). HRMS: found 517.3059 $[M+H]^+$, calculated for $[C_{32}H_{40}O_4N_2+H]^+$ 517.3061.

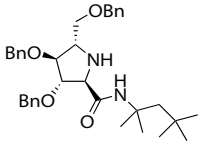


3,4,6-Tri-*O*-benzyl-2,5-dideoxy-2,5-imino-D-*galacto*-hexonamide (B2-VI). Compound **B2-VI** (40 mg, 90 µmol) was synthesized in 52% yield from **B1-VI** (173 µmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.36 (1:9; MeOH:EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 15H, H_{Ar} Bn), 5.38 (s, 1H, NH_2), 4.75 (d, *J* = 11.8, 1H, C*H*H Bn), 4.69 (d, *J* = 11.8, 1H, C*H*H Bn), 4.66 (d, *J* = 11.8, 1H, CH*H* Bn), 4.55 – 4.51 (m, 2H, CH*H* Bn, C*H*H Bn), 4.48 (d, *J* = 11.9, 1H, CH*H* Bn), 4.29 (dd, *J* = 3.9, 6.7, 1H, H-3), 3.99 (dd, *J* = 4.0, 5.9, 1H, H-4), 3.94 (d, *J* = 6.7, 1H, H-2), 3.76 (dd, *J* = 4.6, 9.4, 1H, H-6a), 3.66 (dd, *J* = 8.7, 1H, H-6b), 3.58 – 3.53 (m, 1H, H-5), 2.30 – 2.07 (m, 2H, NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9 (C(O)-1), 138.5, 138.5, 138.3 (3×C_q Bn), 128.6, 128.6, 128.5, 128.1, 127.9, 127.9, 127.7, 127.7, 127.7 (CH_{Ar} Bn), 80.1 (C-3), 79.5 (C-4), 73.8, 73.6, 73.1 (3×CH_2 Bn), 71.5 (C-6), 62.0 (C-2), 58.3 (C-5). IR ν_{max}(thin film)/ cm^{-1}: 3319, 2928, 2870, 1726, 1682, 1495, 1454, 1363, 1277, 1209, 1126, 1074, 1026, 735, 698. $[\alpha]^{20}_D$: 9.2 (*c* 0.2, $CHCl_3$). HRMS: found 447.2276 $[M+H]^+$, calculated for $[C_{27}H_{30}O_5N_2+H]^+$ 447.2278.

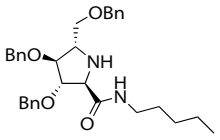


5-(Adamantan-1yl-methoxy)-pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-L-*gulo*-hexonamide (C2-I). Compound **C2-I** (54 mg, 79 µmol) was synthesized in 55% yield from **C1-I** (144 µmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.38 (1:1; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (t, *J* = 5.9, 1H, C(O)NH), 7.39 – 7.18 (m, 15H,

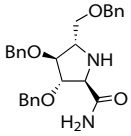
H_{Ar} Bn), 4.77 (d, *J* = 11.8, 1H, C*H*H Bn), 4.62 (d, *J* = 11.8, 1H, CH*H* Bn), 4.55 – 4.45 (m, 3H, C*H*H Bn, CH_2 Bn), 4.41 (d, *J* = 11.6, 1H, CH*H* Bn), 4.36 (dd, *J* = 2.9, 1H, H-3), 3.88 (dd, *J* = 3.2, 5.7, 1H, H-4), 3.74 (d, *J* = 2.3, 1H, H-2), 3.58 (dd, *J* = 4.0, 9.6, 1H, H-6a), 3.53 (dd, *J* = 5.6, 9.6, 1H, H-6b), 3.34 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 3.29 – 3.15 (m, 3H, H-5, NCH_2-1 pentyl), 2.93 (s, 2H, OCH_2-Ada), 2.66 (s, 1H, NH), 1.95 (s, 3H, 3×CH Ada), 1.67 (dd, *J* = 11.6, 36.7, 6H, 3×CH_2 Ada), 1.58 – 1.43 (m, 10H, 3×CH_2 Ada), 1.39 – 1.30 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9 (NHC(O)-1), 138.1, 137.9, 137.9 (3×C_q Bn), 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 87.2 (C-3), 84.9 (C-4), 81.9 (OCH_2-Ada), 73.2, 71.8, 71.6 (3×CH_2 Bn), 71.4 (CH_2-5 pentyl), 68.8 (C-6), 65.7 (C-2), 62.4 (C-5), 39.7 (CH_2 Ada), 39.1 (NCH_2-1 pentyl), 37.3 (CH_2 Ada), 34.1 (C_q Ada), 29.5, 29.2 (2×CH_2 pentyl), 28.3 (CH Ada), 23.6 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 1669, 1513, 1455, 1097, 735, 697. $[\alpha]^{20}_D$: –0.5 (*c* 0.8, $CHCl_3$). HRMS: found 681.4259 $[M+H]^+$, calculated for $[C_{43}H_{56}O_5N_2+H]^+$ 681.4262.



1,1,3,3-Tetramethylbutyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-L-*gulo*-hexonamide (C2-II). Compound **C2-II** (175 mg, 313 µmol) was synthesized in 95% yield from **C1-II** (330 µmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.69 (1:1; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 1H, C(O)NH)), 7.39 – 7.20 (m, 15H, H_{Ar} Bn), 4.78 (d, *J* = 11.8, 1H, C*H*H Bn), 4.62 (d, *J* = 11.8, 1H, CH*H* Bn), 4.59 – 4.41 (m, 4H, 2×CH_2 Bn), 4.34 (dd, *J* = 2.8, 3.3, 1H, H-3), 3.90 (dd, *J* = 3.4, 6.0, 1H, H-4), 3.61 (d, *J* = 2.6, 1H, H-2), 3.59 – 3.51 (m, 2H, CH_2-6), 3.20 – 3.13 (m, 1H, H-5), 2.74 – 2.61 (m, 1H, NH), 1.76 (d, *J* = 14.9, 1H, C*H*H-2 tMB), 1.60 (d, *J* = 13.7, 1H, CH*H*-2 tMB), 1.39 (d, *J* = 12.9, 6H, 2×CH_3 tMB), 0.98 (s, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (NHC(O)-1), 138.5, 138.2, 138.1 (3×C_q Bn), 128.6, 128.5, 128.5, 128.1, 128.1, 128.0, 128.0, 127.8, 127.7 (CH_{Ar} Bn), 87.7 (C-3), 85.2 (C-4), 73.4, 72.1, 71.9 (3×CH_2 Bn), 68.8 (C-6), 66.3 (C-2), 62.3 (C-5), 54.5 (NHC_q-1 tMB), 52.8 (CH_2-2 tMB), 31.8 (C_q-3 tMB), 31.7 (CH_3-4, 2×CH_3 tMB), 29.3, 28.6 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3322, 2948, 1670, 1516, 1092, 738, 698. $[\alpha]^{20}_D$: –1.5 (*c* 2.0, $CHCl_3$). HRMS: found 559.3525 $[M+H]^+$, calculated for $[C_{35}H_{46}O_4N_2+H]^+$ 559.3530.

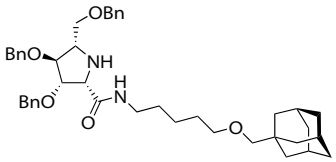


Pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-L-*gulo*-hexonamide (C2-III). Compound **C2-III** (220 mg, 0.43 mmol) was synthesized in 95% yield from **C1-III** (0.45 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.57 (1:1; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (t, *J* = 5.6, 1H, C(O)NH), 7.40 – 7.19 (m, 15H, H_{Ar} Bn), 4.77 (d, *J* = 11.8, 1H, C*H*H Bn), 4.62 (d, *J* = 11.8, 1H), CH*H* Bn, 4.54 – 4.39 (m, 4H, 2×CH_2 Bn), 4.36 (dd, *J* = 2.9, 1H, H-3), 3.89 (dd, *J* = 3.3, 5.6, 1H, H-4), 3.78 (d, *J* = 2.3, 1H, H-2), 3.58 (dd, *J* = 4.1, 9.6, 1H, H-6a), 3.55 (dd, *J* = 5.7, 9.6, 1H, H-6b), 3.28 – 3.15 (m, 3H, H-5, NCH_2-1 pentyl), 1.51 – 1.42 (m, 2H, CH_2-2 pentyl), 1.32 – 1.24 (m, 4H, 2×CH_2 pentyl), 0.87 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8 (NHC(O)-1), 138.3, 138.1, 138.0 (3×C_q Bn), 128.7, 128.6, 128.5, 128.2, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9 (CH_{Ar} Bn), 87.3 (C-3), 85.0 (C-4), 73.4, 72.1, 71.9 (3×CH_2 Bn), 68.9 (C-6), 65.8 (C-2), 62.7 (C-5), 39.3 (NCH_2-1 pentyl), 29.5, 29.3, 22.6 (3×CH_2 pentyl), 14.2 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3325, 2930, 2860, 1668, 1526, 1455, 1096, 736, 698. $[\alpha]^{20}_D$: –1.6 (*c* 4.4, $CHCl_3$). HRMS: found 517.3055 $[M+H]^+$, calculated for $[C_{32}H_{40}O_4N_2+H]^+$ 517.3061.

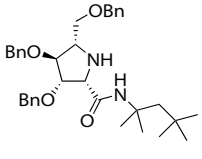


3,4,6-Tri-*O*-benzyl-2,5-dideoxy-2,5-imino-L-*gulo*-hexonamide (C2-VI). Compound **C2-VI** (6 mg, 13 µmol) was synthesized in 26% yield from **C1-VI** (50 µmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.23 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 3.5, 1H, C(O)N*H*H), 7.38 – 7.17 (m, 15H, H_{Ar} Bn), 5.51 (d, *J* = 3.9, 1H, C(O)NH*H*), 4.73 (d, *J* = 11.8, 1H, C*H*H Bn), 4.64 – 4.40 (m, 5H, CH*H* Bn, 2×CH_2 Bn), 4.38 (dd, *J* = 2.8, 1H, H-3), 3.90 (dd, *J* = 3.1, 5.4, 1H, H-4), 3.77 (d, *J* = 2.5, 1H, H-2), 3.62 – 3.50 (m, 2H, H-6a, H-5), 3.29 (dd, *J* = 5.4, 10.0, 1H, H-6b). ^{13}C NMR (101 MHz, CDCl3) δ 175.5 (NHC(O)-1), 138.2, 138.1, 138.1 (3×C_q Bn), 128.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9 (CH_{Ar} Bn), 87.3 (C-3), 85.1 (C-4), 73.4, 72.1, 71.9 (3×CH_2 Bn), 69.1 (C-6), 65.8

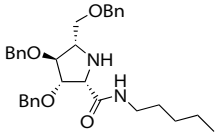
(C-2), 62.8 (C-5). IR ν_{max}(thin film)/ cm^{-1}: 3427, 295, 2856, 1682, 1454, 1364, 1093, 1027, 735, 698. $[\alpha]^{20}_D$: –2.0 (*c* 0.2, $CHCl_3$). HRMS: found 447.2275 $[M+H]^+$, calculated for $[C_{27}H_{30}O_5N_2+H]^+$ 447.2278.



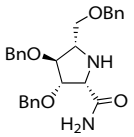
5-(Adamantan-1yl-methoxy)-pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-L-*ido*-hexonamide (D2-I). Compound **D2-I** (111 mg, 163 µmol) was synthesized in 62% yield from **D1-I** (262 µmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.16 (1:1; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (t, *J* = 5.6, 1H, C(O)NH), 7.37 – 7.19 (m, 15H, H_{Ar} Bn), 4.59 (d, *J* = 11.7, 1H, C*H*H Bn), 4.53 – 4.39 (m, 5H, CH*H* Bn, 2×CH_2 Bn), 4.29 (dd, *J* = 1.7, 5.6, 1H, H-3), 4.16 (d, *J* = 5.6, 1H, H-2), 3.85 (dd, *J* = 2.1, 1H, H-4), 3.56 – 3.47 (m, 3H, H-5, CH_2-6), 3.30 (t, *J* = 6.6, 2H, CH_2-5 pentyl), 3.23 – 3.18 (m, 2H, NCH_2-1 pentyl), 2.92 (s, 2H, OCH_2-Ada), 2.55 – 2.14 (m, 1H, NH), 1.95 (s, 3H, 3×CH Ada), 1.67 (dd, *J* = 11.6, 38.8, 6H, 3×CH_2 Ada), 1.54 – 1.37 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.34 – 1.26 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5 (NHC(O)-1), 138.2, 138.0, 137.8 (3×C_q Bn), 128.7, 128.4, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6 (CH_{Ar} Bn), 83.2 (C-4), 83.0 (C-3), 81.9 (OCH_2-Ada), 73.2, 72.9 (2×CH_2 Bn), 72.0 (C-6), 71.5 (CH_2 Bn), 71.4 (CH_2-5 pentyl), 64.5 (C-2), 62.3 (C-5), 39.8 (CH_2 Ada), 39.1 (NCH_2-1 pentyl), 37.3 (CH_2 Ada), 34.1 (C_q Ada), 29.5, 29.2 (2×CH_2 pentyl), 28.3 (CH Ada), 23.6 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3030, 2903, 1668, 1512, 1454, 1096, 735, 699. $[\alpha]^{20}_D$: –4.6 (*c* 2.2, $CHCl_3$). HRMS: found 681.4259 $[M+H]^+$, calculated for $[C_{43}H_{56}O_5N_2+H]^+$ 681.4262.



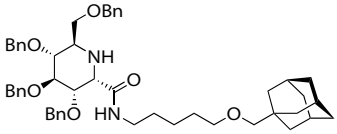
1,1,3,3-Tetramethylbutyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-L-*ido*-hexonamide (D2-II). Compound **D2-II** (151 mg, 270 µmol) was synthesized in 75% yield from **D1-II** (360 µmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.47 (1:1; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 16H, C(O)NH), H_{Ar} Bn), 4.62 (d, *J* = 11.7, 1H, C*H*H Bn), 4.56 (d, *J* = 12.0, 1H, C*H*H Bn), 4.53 – 4.45 (m, 3H, CH*H* Bn, CH*H* Bn, C*H*H Bn), 4.43 (d, *J* = 11.9, 1H, CH*H* Bn), 4.26 (dd, *J* = 1.4, 5.5, 1H, H-3), 4.02 (d, *J* = 5.5, 1H, H-2), 3.88 (dd, *J* = 1.7, 1H, H-4), 3.57 (dd, *J* = 5.5, 7.0, 1H, H-6a), 3.53 – 3.47 (m, 2H, H-5, H-6b), 2.33 (s, 1H, NH), 1.81 (d, *J* = 14.9, 1H, C*H*H-2 tMB), 1.51 (d, *J* = 14.9, 1H, CH*H*-2 tMB), 1.40 (d, *J* = 29.5, 6H, 2×CH_3 tMB), 0.98 (s, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5 (NHC(O)-1), 138.3, 138.1, 137.9 (3×C_q Bn), 128.4, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.7, 127.7, 127.7, 127.5 (CH_{Ar} Bn), 83.5 (C-4), 83.1 (C-3), 73.2, 72.9 (2×CH_2 Bn), 72.6 (C-6), 71.4 (CH_2 Bn), 65.4 (C-2), 62.5 (C-5), 54.4 (NHC_q-1 tMB), 53.0 (CH_2-2 tMB), 31.6 (C_q-3 tMB), 31.5 (CH_3-4, 2×CH_3 tMB), 28.9, 28.2 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3320, 2950, 1669, 1522, 1096, 738, 698. $[\alpha]^{20}_D$: –6.1 (*c* 2.1, $CHCl_3$). HRMS: found 559.3525 $[M+H]^+$, calculated for $[C_{35}H_{46}O_4N_2+H]^+$ 559.3530.



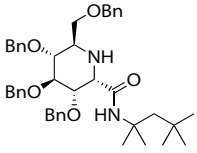
Pentyl 3,4,6-tri-*O*-benzyl-2,5-dideoxy-2,5-imino-L-*ido*-hexonamide (D2-III). Compound **D2-III** (410 mg, 0.79 mmol) was synthesized in 83% yield from **D1-III** (0.95 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.35 (1:1; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (t, *J* = 5.7, 1H, C(O)NH), 7.35 – 7.21 (m, 15H, H_{Ar} Bn), 4.60 (d, *J* = 11.7, 1H, C*H*H Bn), 4.52 – 4.40 (m, 5H, CH*H* Bn, 2×CH_2 Bn), 4.30 (dd, *J* = 1.5, 5.6, 1H, H-3), 4.17 (d, *J* = 5.7, 1H, H-2), 3.85 (s, 1H, H-4), 3.56 – 3.47 (m, 3H, H-5, CH_2-6), 3.26 – 3.12 (m, 2H, NCH_2-1 pentyl), 2.44 (s, 1H, NH), 1.46 – 1.38 (m, 2H, CH_2-2 pentyl), 1.29 – 1.19 (m, 4H, 2×CH_2 pentyl), 0.84 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7 (NHC(O)-1), 138.3, 138.2, 137.9 (3×C_q Bn), 128.8, 128.6, 128.6, 128.5, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8 (CH_{Ar} Bn), 83.4 (C-4), 83.2 (C-3), 73.4, 73.1 (2×CH_2 Bn), 72.1 (C-6), 71.7 (CH_2 Bn), 64.6 (C-2), 62.6 (C-5), 39.3 (NCH_2-1 pentyl), 29.5, 29.3, 22.5 (3×CH_2 pentyl), 14.2 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3325, 3032, 2929, 2861, 1668, 1532, 1497, 1455, 1363, 1208, 1093, 1028, 735, 698. $[\alpha]^{20}_D$: –5.8 (*c* 8.2, $CHCl_3$). HRMS: found 517.3056 $[M+H]^+$, calculated for $[C_{32}H_{40}O_4N_2+H]^+$ 517.3061.



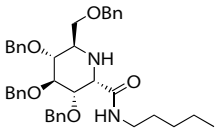
3,4,6-Tri-*O*-benzyl-2,5-dideoxy-2,5-imino-L-*ido*-hexonamide (D2-VI). Compound **D2-VI** (29 mg, 63 µmol) was synthesized in 55% yield from **D1-VI** (115 µmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.11 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 16H, H_{Ar} Bn, C(O)N*H*H), 5.50 (s, 1H, C(O)NH*H*), 4.62 (d, *J* = 11.7, 1H, C*H*H Bn), 4.55 – 4.39 (m, 5H, CH*H* Bn, 2×CH_2 Bn), 4.26 (dd, *J* = 2.1, 5.8, 1H, H-3), 4.11 (d, *J* = 5.8, 1H, H-2), 3.89 (dd, *J* = 2.3, 1H, H-4), 3.59 – 3.43 (m, 3H, H-5, CH_2-6), 2.30 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (NHC(O)-1), 138.4, 138.1, 138.0 (3×C_q Bn), 128.6, 128.6, 128.5, 128.0, 128.0, 127.9, 127.9 (CH_{Ar} Bn), 83.5, 83.3 (C-3, C-4), 73.4, 73.1 (2×CH_2 Bn), 72.4 (C-6), 71.8 (CH_2 Bn), 64.6 (C-2), 62.6 (C-5). IR ν_{max}(thin film)/ cm^{-1}: 3431, 2860, 1682, 1453, 1363, 1092, 1070, 1027, 735, 697. $[\alpha]^{20}_D$: –34.2 (*c* 0.4, $CHCl_3$). HRMS: found 447.2275 $[M+H]^+$, calculated for $[C_{27}H_{30}O_5N_2+H]^+$ 447.2278.



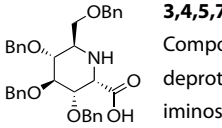
5-(Adamantan-1yl-methoxy)-pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptonamide (E2-I). Compound **E2-I** (585 mg, 0.73 mmol) was synthesized in 99% yield from **E1-I** (0.74 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.22 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 5.0, 1H, C(O)NH), 7.55 (s, 1H, NH), 7.41 – 7.00 (m, 20H, H_{Ar} Bn), 4.94 (d, *J* = 10.9, 1H, C*H*H Bn), 4.90 (d, *J* = 11.2, 1H, C*H*H Bn), 4.80 (d, *J* = 10.9, 1H, CH*H* Bn), 4.76 – 4.67 (m, 3H, H-2, CH*H* Bn, C*H*H Bn), 4.58 – 4.43 (m, 3H, H-3, CH_2 Bn), 4.36 (d, *J* = 11.0, 1H, CH*H* Bn), 3.80 – 3.64 (m, 4H,), 3.59 – 3.48 (m, 1H, H-6), 3.28 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 3.20 (dt, *J* = 6.8, 20.8, 2H, NCH_2-1 pentyl), 2.91 (s, 2H, OCH_2-Ada), 1.93 (s, 3H, 3×CH Ada), 1.65 (dd, *J* = 12.0, 27.5, 6H, 3×CH_2 Ada), 1.53 – 1.39 (m, 11H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.31 – 1.22 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (C(O)-1), 137.7, 137.2, 136.8, 136.6 (4×C_q Bn), 128.6, 128.4, 128.4, 128.4, 128.3, 128.1, 128.1, 127.9, 127.9, 127.8, 127.8 (CH_{Ar} Bn), 81.8 (OCH_2-Ada), 80.9, 76.9, 76.7 (C-3, C-4, C-5), 75.1, 74.6, 73.1 (CH_2 Bn), 71.2 (CH_2-5 pentyl), 66.6 (C-7), 55.8 (C-6), 54.5 (C-2), 39.8 (NCH_2-1 pentyl), 39.6 (CH_2 Ada), 37.1 (CH_2 Ada), 34.0 (C_q Ada), 29.1, 28.8, 28.2 (CH Ada), 23.5 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2848, 1679, 1545, 1497, 1453, 1362, 1210, 1155, 1067, 1027, 909, 730, 697. $[\alpha]^{20}_D$: 28.1 (*c* 9.1, $CHCl_3$). HRMS: found 801.4839 $[M+H]^+$; calculated for $[C_{51}H_{64}N_2O_6+H]^+$ 801.4837.



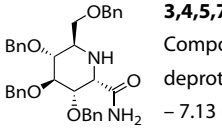
1,1,3,3-Tetramethylbutyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptonamide (E2-II). Compound **E2-II** (468 mg, 0.69 mmol) was synthesized in 90% yield from **E1-II** (0.77 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.34 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, CDCl3) δ 7.60 (s, 1H, C(O)NH), 7.43 – 7.01 (m, 20H, H_{Ar} Bn), 4.96 – 4.89 (m, 2H, 2×C*H*H Bn), 4.86 (d, *J* = 10.5, 1H, CH*H* Bn), 4.80 (d, *J* = 11.3, 1H, CH*H* Bn), 4.76 (d, *J* = 10.8, 1H, C*H*H Bn), 4.58 (d, *J* = 12.4, 1H, C*H*H Bn), 4.53 (d, *J* = 12.4, 1H, CH*H* Bn), 4.47 – 4.38 (m, 3H, CH*H* Bn, H-2, H-3), 3.75 – 3.70 (m, 3H, H-5, CH_2-7), 3.63 (dd, *J* = 8.8, 1H, H-4), 3.38 (dt, *J* = 5.5, 10.8, 1H, H-6), 1.70 (d, *J* = 14.9, 1H, C*H*H-2 tMB), 1.47 (d, *J* = 14.9, 1H, CH*H*-2 tMB), 1.27 (d, *J* = 10.0, 6H, 2×CH_3 tMB), 0.87 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (NHC(O)-1), 137.9, 137.2, 136.9, 136.6 (4×C_q Bn), 128.8, 128.7, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8 (4×C_q Bn), 81.9 (C-4), 77.7 (C-3), 77.5 (C-5), 75.5, 75.4, 75.2, 73.3 (4×CH_2 Bn), 67.2 (C-7), 56.1 (C-6), 56.0 (NHC_q-1 tMB), 55.1 (C-2), 51.8 (CH_2-2 tMB), 31.5 (CH_3-4, 2×CH_3 tMB), 29.4, 28.5 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3327, 3032, 2951, 1680, 1637, 1543, 1454, 1366, 1223, 1153, 1067, 1027, 910, 731, 697. $[\alpha]^{20}_D$: 33.7 (*c* 4.3, $CHCl_3$). HRMS: found 679.4105 $[M+H]^+$; calculated for $[C_{43}H_{54}N_2O_5+H]^+$ 679.4105.



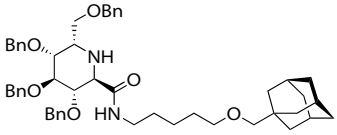
Pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-2,6-imino-D-*glycero*-D-*ido*-heptonamide (E2-III). Compound **E2-III** (459 mg, 0.72 mmol) was synthesized in 95% yield from **E1-III** (0.76 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.22 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (t, *J* = 5.5, 1H, C(O)NH), 7.33 – 7.12 (m, 20H, H_{Ar} Bn), 4.84 (d, *J* = 11.1, 1H, C*H*H Bn), 4.77 – 4.72 (m, 3H, 2×C*H*H Bn, CH*H* Bn), 4.68 (d, *J* = 11.3, 1H, CH*H* Bn), 4.58 (d, *J* = 12.1, 1H, C*H*H Bn), 4.47 – 4.41(m, 2H, CH*H* Bn, CH*H* Bn), 4.02 (dd, *J* = 5.0, 8.8, 1H, H-3), 3.70 (dd, *J* = 7.6, 8.9, 1H, H-4), 3.66 (d, *J* = 5.0, 1H, H-2), 3.62 (dd, *J* = 2.7, 9.7, 1H, H-7a), 3.51 (dd, *J* = 6.1, 9.7, 1H, H-7b), 3.41 (dd, *J* = 7.7, 9.7, 1H, H-5), 3.33 – 3.12 (m, 2H, CH_2-1 pentyl), 3.06 – 2.98 (m, 1H, H-6), 2.85 (s, 1H, NH), 1.47 – 1.38 (m, 2H, CH_2-2 pentyl), 1.32 – 1.17 (m, 4H, 2×CH_2 pentyl), 0.85 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (NHC(O)-1), 138.4, 138.3, 138.1, 137.4 (4×C_q Bn), 128.6, 128.4, 128.3, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6 (4×CH_2 Bn), 82.8 (C-4), 79.7 (C-3), 79.6 (C-5), 74.9, 74.5, 74.0, 72.9 (4×CH_2 Bn), 69.9 (C-7), 56.2 (C-2), 55.0 (C-6), 39.2 (CH_2-1 pentyl), 29.2 (CH_2-2 pentyl), 29.1, 22.3 (2×CH_2 pentyl), 14.0 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3344, 2929, 2861, 1667, 1532, 1497, 1454, 1362, 1209, 1066, 1027, 909, 733, 696. $[\alpha]^{20}_D$: 35.4 (*c* 4.9, $CHCl_3$). HRMS: found 637.3632 $[M+H]^+$; calculated for $[C_{40}H_{48}N_2O_5+H]^+$ 637.3636.



3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptonic acid (E2-V). Compound **E2-V** (58 mg, 73 µmol) was synthesized in 35% yield from **E1-V** (0.21 mmol) by deprotection of the pent-4-enamide (general procedure D). ^{1}H NMR (400 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.56 – 6.91 (m, 20H, H_{Ar} Bn), 4.82 – 3.48 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7). ^{13}C NMR (100 MHz, $CDCl_3$) collapsed iminosugar signals δ 138.0, 137.9, 137.8, 137.5 (4×C_q Bn), 128.7, 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9 (CH_{Ar} Bn), 73.8, 73.3 (CH_2 Bn), 55.9 (C-2), 54.1 (C-6). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2864, 1635, 1453, 1360, 1323, 1091, 1072, 1026, 910, 733, 697. $[\alpha]^{20}_D$: 26.0 (*c* 0.9, $CHCl_3$). HRMS: found 568.2690 $[M+H]^+$; calculated for $[C_{35}H_{37}NO_6+H]^+$ 568.2694.

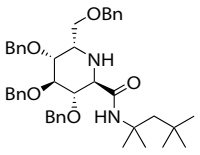


3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptonamide (E2-VI). Compound **E2-VI** (45 mg, 79 µmol) was synthesized in 79% yield from **E1-V1** (100 µmol) by deprotection of the pent-4-enamide (general procedure D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 20H, H_{Ar} Bn), 6.12 (d, *J* = 1.6, 1H, C(O)N*H*H), 5.78 (d, *J* = 1.9, 1H, C(O)NH*H*), 4.89 (s, 2H, CH_2 Bn), 4.86 (d, *J* = 10.6, 1H, C*H*H Bn), 4.81 (d, *J* = 10.9, 1H, C*H*H Bn), 4.63 (d, *J* = 10.6, 1H, CH*H* Bn), 4.55 – 4.47 (m, 2H, C*H*H Bn, CH*H* Bn), 4.43 (d, *J* = 11.9, 1H, CH*H* Bn), 3.64 (dd, *J* = 2.6, 9.0, 1H, H-7a), 3.62 – 3.54 (m, 3H, H-3, H-4, H-7b), 3.50 – 3.44 (m, 1H, H-5), 3.20 (d, *J* = 9.1, 1H, H-2), 2.77 (ddd, *J* = 2.6, 5.2, 9.6, 1H, H-6), 2.27 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (NHC(O)-1), 138.5, 138.2, 137.9, 137.8 (4×C_q Bn), 129.1, 128.7, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 87.6, 82.2 (C-3, C-4), 80.0 (C-5), 75.7, 75.3, 75.2, 73.4 (4×CH_2 Bn), 69.5 (C-7), 61.9 (C-2), 58.3 (C-6). IR ν_{max}(thin film)/ cm^{-1}: 3398, 3031, 2909, 2864, 1668, 1453, 1359, 1149, 1087, 1054, 1027, 735, 696. $[\alpha]^{20}_D$: 29.1 (*c* 0.9, $CHCl_3$). HRMS: found 567.2850 $[M+H]^+$; calculated for $[C_{35}H_{38}N_2O_5+H]^+$ 567.2853.

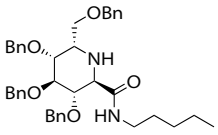


5-(Adamantan-1yl-methoxy)-pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-L-*glycero*-D-*gulo*-heptonamide (F2-I). Compound **F2-I** (108 mg, 0.14 mmol) was synthesized in 50% yield from **F1-I** (0.27 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.17 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 20H, H_{Ar} Bn), 6.86 (t, *J* = 5.7, 1H, C(O)NH), 4.72 – 4.45 (m, 8H, 4×CH_2 Bn), 4.01 (dd, *J* = 5.7, 1H, H-3), 3.77 (dd, *J* = 6.1, 1H, H-4), 3.63 – 3.52 (m, 3H, CH_2-7, H-5), 3.50 (d, *J* = 5.6, 1H, H-2), 3.39 (dt, *J* = 4.2, 8.3, 1H, H-6), 3.30 (t, *J* = 6.5,

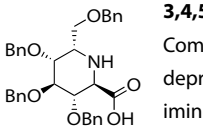
2H, CH_2-5 pentyl), 3.29 – 3.20 (m, 1H, NC*H*H-1 pentyl), 3.19 – 3.08 (m, 1H, NCH*H*-1 pentyl), 2.91 (s, 2H, OCH_2-Ada), 2.47 (s, 1H, NH), 1.94 (s, 3H, 3×CH Ada), 1.67 (dd, *J* = 12.1, 24.3, 6H, 3×CH_2 Ada), 1.55 – 1.36 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.36 – 1.24 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, CDCl3) δ 170.6 (C(O)-1), 138.5, 138.4, 138.3, 138.3 (4×C_q Bn), 128.6, 128.5, 128.4, 128.1, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 82.0 (OCH_2-Ada), 77.3 (C-4), 76.9 (C-5), 76.7 (C-3), 73.7, 73.6, 73.5, 72.3 (4×CH_2 Bn), 71.5 (CH_2-5 pentyl), 68.9 (C-7), 58.1 (C-2), 52.2 (C-6), 39.9 (CH_2 Ada), 39.5 (NCH_2-1 pentyl), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 29.5, 29.4 (2×CH_2 pentyl), 28.4 (CH Ada), 23.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3313, 2901, 2849, 1667, 1524, 1497, 1453, 1363, 1207, 1092, 1027, 908, 730, 696. $[\alpha]^{20}_D$: −8.4 (*c* 2.1, $CHCl_3$). HRMS: found 801.4840 $[M+H]^+$; calculated for $[C_{51}H_{64}N_2O_6+H]^+$ 801.4837.



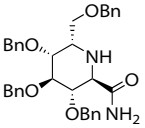
1,1,3,3-Tetramethylbutyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-L-*glycero*-D-*gulo*-heptonamide (F2-II). Compound **F2-II** (94 mg, 0.14 mmol) was synthesized in 40% yield from **F1-II** (0.35 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.37 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 20H, H_{Ar} Bn), 6.99 (s, 1H, C(O)NH), 4.71 – 4.43 (m, 8H, 4×CH_2 Bn), 4.11 (dd, *J* = 4.9, 1H, H-3), 3.78 (dd, *J* = 5.4, 1H, H-4), 3.61 – 3.48 (m, 3H, H-5, CH_2-7), 3.44 (d, *J* = 4.7, 1H, H-2), 3.41 – 3.33 (m, 1H, H-6), 2.38 (s, 1H, NH), 1.76 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.61 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.32 (d, *J* = 11.7, 6H, 2×CH_3 tMB), 0.94 (s, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C(O)-1), 138.4, 138.4, 138.3, 138.3 (4×C_q Bn), 128.4, 128.4, 128.3, 128.3, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6 (CH_{Ar} Bn), 75.9, 75.8 (C-4, C-5), 75.2 (C-3), 73.4, 73.1, 73.0, 72.0 (4×CH_2 Bn), 69.4 (C-7), 58.7 (C-2), 54.6 (NHC_q-1 tMB), 52.0 (CH_2-2 tMB), 51.6 (C-6), 31.6 (C_q-3 tMB), 31.5 (CH_3-4, 2×CH_3 tMB), 28.8, 28.7 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3329, 2867, 1671, 1517, 1454, 1366, 1208, 1093, 1027, 734, 697. $[\alpha]^{20}_D$: −4.6 (*c* 1.0, $CHCl_3$). HRMS: found 679.4102 $[M+H]^+$; calculated for $[C_{43}H_{54}N_2O_5+H]^+$ 679.4105.



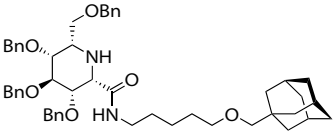
Pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-L-*glycero*-D-*gulo*-heptonamide (F2-III). Compound **F2-III** (98 mg, 0.15 mmol) was synthesized in 59% yield from **F1-III** (0.26 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.17 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, CDCl3) δ 7.36 – 7.18 (m, 20H, H_{Ar} Bn), 6.84 (t, *J* = 5.6, 1H, C(O)NH), 4.73 – 4.45 (m, 8H, 4×CH_2 Bn), 4.02 (dd, *J* = 5.7, 1H, H-3), 3.78 (dd, *J* = 6.1, 1H, H-4), 3.60 (dd, *J* = 8.4, 9.6, 1H, H-7a) 3.57 – 3.52 (m, 2H, H-5, H-7b), 3.50 (d, *J* = 5.7, 1H, H-2), 3.40 (dt, *J* = 4.2, 8.4, 1H, H-6), 3.32 – 3.21 (m, 1H, NC*H*H-1 pentyl), 3.20 – 3.06 (m, 1H, NCH*H*-1 pentyl), 2.35 (s, 1H, NH), 1.48 – 1.32 (m, 2H, CH_2-2 pentyl), 1.32 – 1.13 (m, 4H, 2×CH_2 pentyl), 0.84 (t, *J* = 6.9, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (C(O)-1), 138.5, 138.5, 138.4, 138.3 (4×C_q Bn), 128.5, 128.5, 128.4, 128.1, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 77.3 (C-4), 76.9 (C-5), 76.7 (C-3), 73.6, 73.6, 73.5, 72.3 (4×CH_2 Bn), 68.9 (C-7), 58.1 (C-2), 52.2 (C-3), 39.5 (NCH_2-1 penty), 29.3, 29.2, 22.5 (3×CH_2 pentyl), 14.1 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3306, 2928, 2861, 1725, 1653, 1527, 1497, 1454, 1365, 1208, 1069, 1027, 908, 733, 696. $[\alpha]^{20}_D$: −9.9 (*c* 1.5, $CHCl_3$). HRMS: found 637.3633 $[M+H]^+$; calculated for $[C_{40}H_{48}N_2O_5+H]^+$ 637.3636.



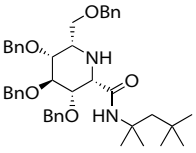
3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-L-*glycero*-D-*gulo*-heptonic acid (F2-V). Compound **F2-V** (19 mg, 34 µmol) was synthesized in 63% yield from **F1-V** (54 µmol) by deprotection of the pent-4-enamide (general procedure D). ^{1}H NMR (400 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.38 – 6.97 (m, 20H, H_{Ar} Bn), 4.88 – 3.45 (m, 15H, 4×CH_2 Bn, H-2, H-3, H-4, H-5, H-6, CH_2-7). ^{13}C NMR (100 MHz, $CDCl_3$) collapsed iminosugar signals δ 137.9, 137.4, 137.2, 137.1 (4×C_q Bn), 128.6, 128.6, 128.5, 128.2, 128.0 (CH_{Ar} Bn), 73.8, 73.8, 72.3 (CH_2 Bn). IR ν_{max}(thin film)/ cm^{-1}: 2866, 1636, 1454, 1395, 1208, 1073, 910, 734, 698. $[\alpha]^{20}_D$: −5.3 (*c* 0.4, $CHCl_3$). HRMS: found 568.2691 $[M+H]^+$; calculated for $[C_{35}H_{37}NO_6+H]^+$ 568.2694.



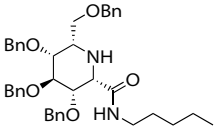
3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-L-*glycero*-D-*gulo*-heptonamide (F2-VI). Compound **F2-VI** (23 mg, 41 µmol) was synthesized in 66% yield from **F1-VI** (62 µmol) by deprotection of the pent-4-enamide (general procedure D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 20H, H_{Ar} Bn), 6.75 (d, *J* = 2.7, 1H, C(O)N*H*H), 5.53 (d, *J* = 1.8, 1H, C(O)NH*H*), 4.75 – 4.46 (m, 8H, 4×CH_2 Bn), 3.97 (dd, *J* = 5.9, 1H, H-3), 3.79 (dd, *J* = 6.2, 1H, H-4), 3.64 – 3.52 (m, 4H, H-2 (d, *J* = 4.6), H-5, CH_2-7), 3.48 – 3.42 (m, 1H, H-6), 2.30 (s, 2H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (C(O)-1), 138.5, 138.4, 138.3, 138.2 (4×C_q Bn), 128.6, 128.6, 128.5, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8 (CH_{Ar} Bn), 77.7 (C-4), 76.9 (C-5), 76.8 (C-3), 73.9, 73.8, 73.6, 72.5 (4×CH_2 Bn), 68.6 (C-7), 57.8 (C-2), 52.3 (C-6).IR ν_{max}(thin film)/ cm^{-1}: 2923, 1682, 1495, 1454, 1365, 1069, 1027, 734, 697. $[\alpha]^{20}_D$: −9.6 (*c* 0.5, $CHCl_3$). HRMS: found 567.2850 $[M+H]^+$; calculated for $[C_{35}H_{38}N_2O_5+H]^+$ 567.2853.



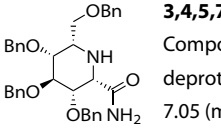
5-(Adamantan-1yl-methoxy)-pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-L-*glycero*-D-*ido*-heptonamide (G2-I). Compound **G2-I** (130 mg, 0.16 mmol) was synthesized in 65% yield from **G1-I** (0.25 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.20 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.12 (m, 20H, H_{Ar} Bn), 7.05 (t, *J* = 5.9, 1H, C(O)NH), 4.62 (d, *J* = 11.7, 1H, C*H*H Bn), 4.55 – 4.25 (m, 7H, CH*H* Bn, 3×CH_2 Bn), 4.18 – 4.13 (m, 1H, H-3), 3.67 (dd, *J* = 2.6, 1H, H-4), 3.60 (d, *J* = 1.9, 1H, H-2), 3.53 (dd, *J* = 6.7, 9.2, 1H, H-7a), 3.45 (dd, *J* = 7.5, 9.2, 1H, H-7b), 3.43 – 3.40 (m, 1H, H-5), 3.33 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 3.30 – 3.23 (m, 2H, NCH_2-1 pentyl), 3.20 (dt, *J* = 2.3, 7.2, 1H, H-6), 2.93 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.90 (s, 1H, NH), 1.67 (dd, *J* = 12.2, 24.6, 6H, 3×CH_2 Ada), 1.58 – 1.46 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.40 – 1.28 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (C(O)-1), 138.8, 138.4, 138.4, 138.0 (4×C_q Bn), 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 82.1 (OCH_2-Ada), 73.7, 73.4 (2×CH_2 Bn), 73.3 (C-3), 73.1 (C-5), 72.3, 72.2 (2×CH_2 Bn), 71.7 (C-4), 71.5 (CH_2-5 pentyl), 70.6 (C-7), 60.1 (C-2), 56.0 (C-6), 39.9 (CH_2 Ada), 39.3 (NCH_2-1 pentyl), 37.4 (CH_2 Ada), 34.3 (C_q Ada), 29.7, 29.4 (2×CH_2 pentyl), 28.5 (CH Ada), 23.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2902, 2849, 1726, 1670, 1454, 1363, 1288, 1208, 1093, 1028, 909, 735, 698. $[\alpha]^{20}_D$: 0.4 (*c* 0.9, $CHCl_3$). HRMS: found 801.4839 $[M+H]^+$; calculated for $[C_{51}H_{64}N_2O_6+H]^+$ 801.4837.



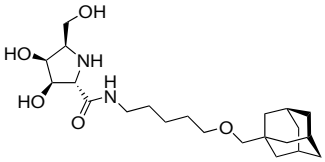
1,1,3,3-Tetramethylbutyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-L-*glycero*-D-*ido*-heptonamide (G2-II). Compound **G2-II** (120 mg, 0.18 mmol) was synthesized in 55% yield from **G1-II** (0.32 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.59 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 20H, H_{Ar} Bn), 7.05 (s, 1H, C(O)NH), 4.62 (d, *J* = 11.5, 1H, C*H*H Bn), 4.56 – 4.28 (m, 7H, CH*H* Bn, 3×CH_2 Bn), 4.20 – 4.17 (m, 1H, H-3), 3.68 (dd, *J* = 2.7, 1H, H-4), 3.54 – 3.48 (m, 2H, CH_2-7), 3.47 (d, *J* = 2.0, 1H. H-2), 3.44 (s, 1H, H-5), 3.19 (dt, *J* = 2.1, 7.3, 1H, H-6), 1.90 (s, 1H, NH), 1.79 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.65 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.40 (d, *J* = 11.9, 6H, 2×CH_3 tMB), 0.96 (s, 9H, CH_3-4, 2×CH_3 tMB).^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C(O)-1), 138.9, 138.6, 138.5, 138.1 (4×C_q Bn), 128.6, 128.6, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.8, 127.6 (CH_{Ar} Bn), 73.6, 73.4 (2×CH_2 Bn), 73.1, 73.0 (C-3, C-5), 72.3, 72.2 (2×CH_2 Bn), 71.9 (C-4), 70.5 (C-7), 60.5 (C-2), 56.2 (C-6), 54.7 (NHC_q-1 tMB), 52.3 (CH_2-2 tMB), 31.8 (C_q-3 tMB), 31.7 (CH_3-4, 2×CH_3 tMB), 29.1, 29.0 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3371, 2868, 1678, 1518, 1454, 1365, 1208, 1071, 1028, 911, 724, 698. $[\alpha]^{20}_D$: 4.7 (*c* 0.4, $CHCl_3$). HRMS: found 679.4102 $[M+H]^+$; calculated for $[C_{43}H_{54}N_2O_5+H]^+$ 679.4105.



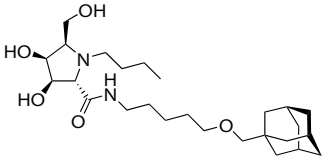
Pentyl 3,4,5,7-tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-L-*glycero*-D-*ido*-heptonamide (G2-III). Compound **G2-III** (181 mg, 0.28 mmol) was synthesized in 77% yield from **G1-III** (0.37 mmol) by deprotection of the pent-4-enamide (general procedure D). R_F = 0.20 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.12 (m, 20H, H_{Ar} Bn), 7.04 (t, *J* = 5.9, 1H, C(O)NH), 4.62 (d, *J* = 11.7, 1H, C*H*H Bn), 4.54 – 4.27 (m, 7H, CH*H* Bn, 3×CH_2 Bn), 4.18 – 4.16 (m, 1H, H-3), 3.67 (dd, *J* = 2.7, 1H, H-4), 3.60 (d, *J* = 2.0, 1H, H-2), 3.53 (dd, *J* = 6.7, 9.3, 1H, H-7a), 3.45 (dd, *J* = 7.2, 9.3, 1H, H-7b), 3.43 – 3.40 (m, 1H, H-5), 3.31 – 3.17 (m, 3H, NCH_2-1 pentyl, H-6), 2.01 (s, 1H, NH), 1.53 – 1.44 (m, 2H, CH_2-2 pentyl), 1.35 – 1.22 (m, 4H, 2×CH_2 pentyl), 0.87 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (C(O)-1), 138.8, 138.4, 138.4, 138.0 (4×C_q Bn), 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 73.7, 73.4 (2×CH_2 Bn), 73.3 (C-3), 73.1 (C-5), 72.3, 72.2 (2×CH_2 Bn), 71.7 (C-4), 70.6 (C-7), 60.2 (C-2), 56.0 (C-6), 39.3 (NCH_2-1 penty), 29.6, 29.3, 22.6 (3×CH_2 pentyl), 14.2 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3387, 2927, 2862, 1725, 1668, 1521, 1497, 1454, 1364, 1288, 1208, 1070, 908, 735, 698. $[\alpha]^{20}_D$: 2.1 (*c* 0.6, $CHCl_3$). HRMS: found 637.3633 $[M+H]^+$; calculated for $[C_{40}H_{48}N_2O_5+H]^+$ 637.3636.



3,4,5,7-Tetra-*O*-benzyl-2,6-dideoxy-2,6-imino-L-*glycero*-D-*ido*-heptonamide (G2-VI). Compound **G2-VI** (77 mg, 136 µmol) was synthesized in 72% yield from **G1-VI** (188 µmol) by deprotection of the pent-4-enamide (general procedure D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.05 (m, 21H, H_{Ar} Bn, C(O)N*H*H), 5.83 (s, 1H, C(O)NH*H*), 4.60 (d, *J* = 11.6, 1H, C*H*H Bn), 4.52 – 4.43 (m, 5H, CH_2 Bn, 2×C*H*H Bn, CH*H* Bn), 4.36 (d, *J* = 12.2, 1H, CH*H* Bn), 4.26 (d, *J* = 11.7, 1H, CH*H* Bn), 4.24 – 4.21 (m, 1H, H-3), 3.79 (d, *J* = 1.5, 1H, H-2), 3.70 (dd, *J* = 2.6, 1H, H-4), 3.60 (dd, *J* = 6.7, 9.4, 1H, H-7a), 3.48 (dd, *J* = 7.4, 9.6, 1H, H-7b), 3.46 – 3.43 (m, 1H, H-5), 3.33 (dt, *J* = 1.7, 6.7, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (C(O)-1), 138.2, 138.2, 138.0, 137.8 (4×C_q Bn), 128.6, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8 (CH_{Ar} Bn), 73.6, 73.4 (2×CH_2 Bn), 73.2 (C-3), 72.6 (C-5), 72.5, 72.2 (2×CH_2 Bn), 70.9 (C-4), 69.8 (C-7), 59.8 (C-2), 55.5 (C-6). IR ν_{max}(thin film)/ cm^{-1}: 3031, 2865, 1682, 1495, 1454, 1366, 1208, 1071, 1027, 909, 734, 698. $[\alpha]^{20}_D$: −4.6 (*c* 1.5, $CHCl_3$). HRMS: found 567.2850 $[M+H]^+$; calculated for $[C_{35}H_{38}N_2O_5+H]^+$ 567.2853.

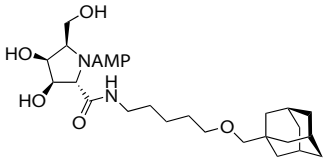


5-(Adamantan-1yl-methoxy)-pentyl 2,5-dideoxy-2,5-imino-D-*talo*-hexonamide (A3-I). Compound **A3-I** (11 mg, 27 µmol) was synthesized in 82% yield from **A2-I** (33 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.16 (1:9; MeOH:DCM+2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 4.07 (t, *J* = 4.1, 1H, H-4), 4.02 (dd, *J* = 4.3, 7.1, 1H, H-3), 3.77 (dd, *J* = 5.9, 10.9, 1H, H-6a), 3.65 (dd, *J* = 6.3, 10.9, 1H, H-6b), 3.52 (d, *J* = 7.1, 1H, H-2), 3.38 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.30 – 3.27 (m, 1H, H-5), 3.23 (t, *J* = 7.0, 2H, NCH_2-1 pentyl), 2.96 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.9, 45.9, 6H, 3×CH_2 Ada), 1.61 – 1.51 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.44 – 1.36 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 175.5 (C(O)-1), 83.2 (OCH_2-Ada), 78.6 (C-3), 74.3 (C-4), 72.6 (CH_2-5 pentyl), 65.9 (C-2), 62.7 (C-5), 62.5 (C-6), 41.0 (CH_2 Ada), 40.5 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.5, 30.5 (2×CH_2 pentyl), 29.9 (CH Ada), 24.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3319, 2902, 2849, 1652, 1543, 1454, 1112. $[\alpha]^{20}_D$: −1.0 (*c* 0.2, MeOH). HRMS: found 411.2851 $[M+H]^+$, calculated for $[C_{22}H_{38}O_5N_2+H]^+$ 411.2853.

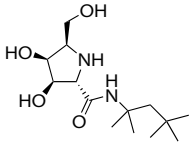


5-(Adamantan-1yl-methoxy)-pentyl 2,5-butylimino-2,5-dideoxy-D-*talo*-hexonamide (A4-I). Compound **A4-I** (11 mg, 24 µmol) was synthesized in 67% yield over two steps from **A2-I** (36 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general

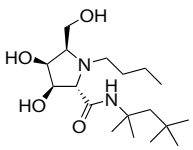
procedure F). R_F = 0.30 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.85 (1:1; EtOAc:toluene+2% Et_3N). ^1H NMR (600 MHz, MeOD) δ 4.31 (dd, *J* = 5.7, 6.5, 1H, H-4), 3.87 (dd, *J* = 1.0, 5.7, 1H, H-3), 3.80 (d, *J* = 8.2, 1H, H-6a), 3.70 (dd, *J* = 1.4, 11.6, 1H, H-6b), 3.39 – 3.37 (m, 3H, H-2, CH_2-5 pentyl), 3.35 – 3.32 (m, 1H, H-5), 3.28 – 3.20 (m, 1H, NC*H*H-1 pentyl), 3.20 – 3.11 (m, 1H, NCH*H*-1 pentyl), 2.96 (s, 2H, OCH_2-Ada), 2.93 – 2.85 (m, 1H, NC*H*H butyl), 2.60 – 2.47 (m, 1H, NCH*H* butyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 12.1, 46.3, 8H, 3×CH_2 Ada), 1.62 – 1.27 (m, 16H, 3×CH_2 Ada, 5×CH_2 pentyl/butyl), 0.94 (t, *J* = 7.4, 3H, CH_3 butyl). ^{13}C NMR (150 MHz, MeOD) δ 175.8 (C(O)-1), 83.2 (OCH_2-Ada), 76.2 (C-3), 76.2 (C-2), 72.7 (C-4), 72.6 (CH_2-5 pentyl), 64.9 (C-5), 58.3 (C-6), 50.7 (NCH_2 butyl), 41.0 (CH_2 Ada), 40.0 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.2, 30.6, 30.5 (3×CH_2 pentyl/butyl), 29.9 (CH Ada), 25.0 (CH_2-3 pentyl), 21.9 (CH_2 butyl), 14.6 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2903, 2850, 1652, 1456, 1097, 1016. $[\alpha]^{20}_D$: −29.7 (*c* 0.2, MeOH). HRMS: found 467.3475 $[M+H]^+$, calculated for $[C_{26}H_{46}O_5N_2+H]^+$ 467.3479.



5-(Adamantan-1yl-methoxy)-pentyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-D-*talo*-hexonamide (A5-I). Compound **A5-I** (17 mg, 26 μmol) was synthesized in 72% yield over two steps from **A2-I** (36 μmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.37 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.88 (1:1; EtOAc:toluene+2% Et_3N). ^1H NMR (600 MHz, MeOD) δ 4.31 (dd, *J* = 6.0, 7.1, 1H, H-4), 3.88 (dd, *J* = 1.5, 5.8, 1H, H-3), 3.81 (dd, *J* = 3.5, 11.7, 1H, H-6a), 3.71 (dd, *J* = 1.9, 11.7, 1H, H-6b), 3.41 – 3.36 (m, 5H, H-2, 2×CH_2-5 pentyl), 3.35 – 3.32 (m, 1H, H-5), 3.26 (dt, *J* = 7.0, 13.8, 1H, C(O)NC*H*H-1 pentyl), 3.16 (dt, *J* = 6.9, 13.5, 1H, C(O)NCH*H*-1 pentyl), 2.98 – 2.95 (m, 4H, 2×OCH_2-Ada), 2.94 – 2.87 (m, 1H, NC*H*H pentyl), 2.53 (ddd, *J* = 7.1, 9.3, 12.3, 1H, NCH*H* pentyl), 1.95 (s, 6H, 6×CH Ada), 1.72 (dd, *J* = 11.9, 46.7, 12H, 6×CH_2 Ada), 1.63 – 1.47 (m, 20H, 6×CH_2 Ada, 4×CH_2 pentyl), 1.47 – 1.31 (m, 4H, 2×CH_2-3 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 175.8 (C(O)-1), 83.3, 83.2 (2×OCH_2-Ada), 76.3 (C-3), 76.2 (C-2), 72.7 (C-4), 72.6, 72.5 (2×CH_2-5 pentyl), 64.8 (C-5), 58.3 (C-6), 50.9 (NCH_2-1 pentyl), 41.0, 41.0 (2×CH_2 Ada), 40.1 (C(O)NCH_2-1 pentyl), 38.5 (2×CH_2 Ada), 35.3, 35.3 (2×C_q Ada), 29.9 (2×CH Ada), 30.8, 30.6, 30.5, 29.8 (4×CH_2 pentyl), 25.4, 25.0 (2×CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3332, 2902, 2848, 1652, 1454, 1361, 1158, 1112. $[\alpha]^{20}_D$: −14.6 (*c* 0.3, MeOH). HRMS: found 645.4834 $[M+H]^+$, calculated for $[C_{38}H_{64}O_6N_2+H]^+$ 645.4837.

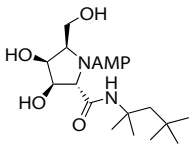


1,1,3,3-Tetramethylbutyl 2,5-dideoxy-2,5-imino-D-*talo*-hexonamide (A3-II). Compound **A3-II** (15 mg, 52 μmol) was synthesized in 93% yield from **A2-II** (56 μmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.16 (1:9; MeOH:DCM+2% NH_4OH). ^1H NMR (600 MHz, MeOD) δ 4.06 (dd, *J* = 4.1, 1H, H-4), 4.02 (dd, *J* = 4.2, 6.8, 1H, H-4), 3.76 (dd, *J* = 5.9, 10.9, 1H, H-6a), 3.65 (dd, *J* = 6.1, 10.9, 1H, H-6b), 3.45 (d, *J* = 6.8, 1H, H-2), 3.24 (dd, *J* = 5.8, 10.1, 1H, H-5), 1.83 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.75 (d, *J* = 14.9, 1H, CH*H*-2 tMB), 1.40 (d, *J* = 8.2, 6H, 2×CH_3 tMB), 1.02 (s, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (150 MHz, MeOD) δ 174.4 (C(O)-1), 78.2 (C-3), 74.4 (C-4), 66.3 (C-2), 62.6 (C-5), 62.4 (C-6), 55.9 (NHC_q-1 tMB), 52.4 (CH_2-2 tMB), 32.7 (C_q-3 tMB), 32.1 (CH_3-4, 2×CH_3 tMB), 29.8, 29.7 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3309, 2970, 2904, 1652, 1529, 1391, 1366, 1227, 1050. $[\alpha]^{20}_D$: −7.1 (*c* 0.3, MeOH). HRMS: found 289.2123 $[M+H]^+$, calculated for $[C_{14}H_{28}O_4N_2+H]^+$ 289.2122.

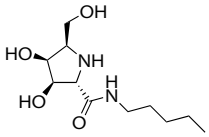


1,1,3,3-Tetramethylbutyl 2,5-butylimino-2,5-dideoxy-D-*talo*-hexonamide (A4-II). Compound **A4-II** (23 mg, 67 μmol) was synthesized in 85% yield over two steps from **A2-II** (79 μmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.29 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.93

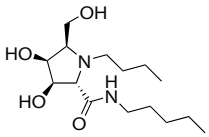
(1.5:1; EtOAc:toluene+2% Et_3N). ^1H NMR (600 MHz, MeOD) δ 4.23 (dd, *J* = 5.8, 6.8, 1H, H-4), 3.92 (d, *J* = 5.3, 1H, H-3), 3.83 (dd, *J* = 3.5, 11.9, 1H, H-6a), 3.75 (d, *J* = 10.9, 1H, H-6b), 3.41 (s, 1H, H-5), 3.31 (s, 1H, H-1), 3.03 – 2.95 (m, 1H, NC*H*H butyl), 2.61 – 2.51 (m, 1H, NCH*H* butyl), 1.83 (d, *J* = 14.9, 1H, C*H*H-2 tMB), 1.73 (d, *J* = 14.9, 1H, CH*H*-2 tMB), 1.61 – 1.27 (m, 10H, 2×CH_2 butyl, 2×CH_3 tMB), 1.02 (s, 9H, 2×CH_3, CH_3-4 tMB), 0.96 (t, *J* = 7.4, 3H, CH_3 butyl). ^{13}C NMR (150 MHz, MeOD) collapsed iminosugar signals δ 76.7 (C-2), 75.9 (C-3), 72.7 (C-4), 65.1 (C-5), 57.9 (C-6), 56.0 (NHC_q-1 tMB), 52.8 (CH_2-2 tMB), 50.9 (NCH_2 butyl), 32.6 (C_q-3 tMB), 32.1 (CH_3-4, 2×CH_3 tMB), 30.9 (CH_2 butyl), 29.9, 29.1 (2×CH_3 tMB), 22.0 (CH_2 butyl), 14.6 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2957, 2929, 1652, 1432, 1366, 1227, 1166, 1046. $[\alpha]^{20}_D$: −33.6 (*c* 0.5, MeOH). HRMS: found 345.2748 $[M+H]^+$, calculated for $[C_{18}H_{36}O_4N_2+H]^+$ 345.2748.



1,1,3,3-Tetramethylbutyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-D-*talo*-hexonamide (A5-II). Compound **A5-II** (34 mg, 65 µmol) was synthesized in 72% yield over two steps from **A2-II** (90 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.32 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.89 (1:2; EtOAc:toluene+2% Et_3N). ^1H NMR (600 MHz, MeOD) δ 4.22 (dd, *J* = 5.9, 7.2, 1H, H-4), 3.89 (dd, *J* = 1.6, 5.8, 1H, H-4), 3.83 (dd, *J* = 3.4, 11.8, 1H, H-6a), 3.72 (dd, *J* = 2.1, 11.8, 1H, H-6b), 3.39 (t, *J* = 6.2, 2H, CH_2-5 pentyl), 3.37 – 3.33 (m, 1H, H-5), 3.25 (d, *J* = 1.6, 1H, H-2), 3.00 – 2.94 (m, 3H, OCH_2-Ada, NC*H*H-1 pentyl), 2.49 (dt, *J* = 8.2, 12.5, 1H, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.86 (d, *J* = 14.9, 1H, C*H*H-2 tMB), 1.79 – 1.66 (m, 7H, 3×CH_2 Ada, CH*H*-2 tMB), 1.64 – 1.45 (m, 11H, 3×CH_2 Ada, 2×CH_2 pentyl, C*H*H-3 pentyl), 1.44 – 1.37 (m, 7H, CH*H*-3pentyl, 2×CH_3 tMB), 1.03 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (150 MHz, MeOD) δ 174.3 (C(O)-1), 83.2 (OCH_2-Ada), 77.2 (C-2), 75.9 (C-3), 72.7 (C-4), 72.4 (CH_2-5 pentyl), 64.3 (C-5), 57.9 (C-6), 56.0 (NHC_q-1 tMB), 52.8 (CH_2-2 tMB), 50.9 (NCH_2-1 pentyl), 41.1 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.7 (C_q-3 tMB), 32.1 (CH_3-4, 2×CH_3 tMB), 30.8, 30.0 (2×CH_2 pentyl), 29.9 (CH Ada), 30.1, 29.2 (2×CH_3 tMB), 25.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2903, 2849, 1652, 1429, 1366, 1228, 1159, 1109. $[\alpha]^{20}_D$: −34.2 (*c* 0.5, MeOH). HRMS: found 523.4100 $[M+H]^+$, calculated for $[C_{30}H_{54}O_5N_2+H]^+$ 523.4105.

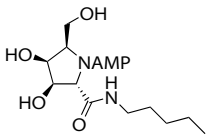


Pentyl 2,5-dideoxy-2,5-imino-D-*talo*-hexonamide (A3-III). Compound **A3-III** (10 mg, 41 µmol) was synthesized in 89% yield from **A2-III** (46 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.09 (1:9; MeOH:DCM+2% NH_4OH). ^1H NMR (600 MHz, MeOD) δ 4.10 (dd, *J* = 4.0, 1H, H-4), 4.05 (dd, *J* = 4.2, 7.2, 1H, H-3), 3.79 (dd, *J* = 5.8, 11.0, 1H, H-6a), 3.69 (dd, *J* = 6.4, 11.0, 1H, H-6b), 3.58 (d, *J* = 7.2, 1H, H-2), 3.39 – 3.33 (m, 1H, H-5), 3.22 (t, *J* = 7.1, 2H, NCH_2-1 pentyl), 1.57 – 1.49 (m, 2H, CH_2-2 pentyl), 1.41 – 1.28 (m, 4H, 2×CH_2 pentyl), 0.92 (t, *J* = 6.9, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 174.7 (C(O)-1), 78.4 (C-3), 74.1 (C-4), 65.5 (C-2), 63.0 (C-5), 62.1 (C-6), 40.6 (NCH_2-1 pentyl), 30.3, 23.6 (3×CH_2 pentyl), 14.5 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3350, 2930, 2857, 1652, 1544, 1464, 1317, 1127. $[\alpha]^{20}_D$: −2.0 (*c* 0.2, MeOH). HRMS: found 247.1654 $[M+H]^+$, calculated for $[C_{11}H_{22}O_4N_2+H]^+$ 247.1652.

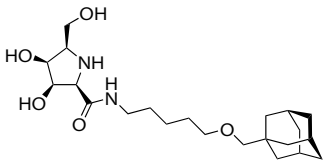


Pentyl 2,5-butylimino-2,5-dideoxy-D-*talo*-hexonamide (A4-III). Compound **A4-III** (7 mg, 23 µmol) was synthesized in 44% yield over two steps from **A2-III** (52 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.23 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.83 (1:1; EtOAc:toluene+2% Et_3N). ^1H NMR (600 MHz, MeOD) δ 4.32 (dd, *J* = 5.8, 7.2, 1H, H-4), 3.87 (dd, *J* = 1.7, 5.8, 1H, H-3), 3.80 (dd, *J* = 3.6, 11.6, 1H, H-6a), 3.71 (dd, *J* = 2.1, 11.6, 1H, H-6b), 3.39 (d, *J* = 1.4, 1H, H-2), 3.35 – 3.32 (m, 1H, H-5),

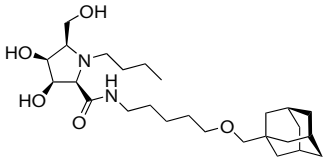
3.26 – 3.19 (m, 1H, NC*H*H-1 pentyl), 3.19 – 3.11 (m, 1H, NCH*H*-1 pentyl), 2.88 (ddd, *J* = 4.8, 9.5, 12.6, 1H, NC*H*H butyl), 2.54 (ddd, *J* = 6.8, 9.8, 12.5, 1H, NCH*H* butyl), 1.56 – 1.26 (m, 10H, 5×CH_2 pentyl/butyl), 0.96 – 0.90 (m, 6H, 2×CH_3 pentyl/butyl). ^{13}C NMR (150 MHz, MeOD) δ 175.8 (C(O)-1), 76.2 (C-3), 76.0 (C-2), 72.7 (C-4), 65.0 (C-5), 58.4 (C-6), 50.7 (NCH_2 butyl), 40.1 (NCH_2-1 pentyl), 32.2, 30.5, 30.4, 23.6, 21.9 (5×CH_2 pentyl/butyl), 14.6, 14.5 (2×CH_3 pentyl/butyl).IR ν_{max}(thin film)/ cm^{-1}: 3312, 2927, 2856, 1652, 1528, 1461, 1167. $[\alpha]^{20}_D$: −32.3 (*c* 0.1, MeOH). HRMS: found 303.2279 $[M+H]^+$, calculated for $[C_{15}H_{30}O_4N_2+H]^+$ 303.2278.



Pentyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-D-*talo*-hexonamide (A5-III). Compound **A5-III** (17 mg, 35 μmol) was synthesized in 73% yield over two steps from **A2-III** (48 μmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.29 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.87 (1:1; EtOAc:toluene+2% Et_3N). ^{1}H NMR (600 MHz, MeOD) δ 4.31 (dd, *J* = 5.8, 7.4, 1H, H-4), 3.87 (dd, *J* = 1.6, 5.8, 1H, H-3), 3.81 (dd, *J* = 3.4, 11.5, 1H, H-6a), 3.70 (d, *J* = 11.5, 1H, H-6b), 3.39 – 3.37 (m, 3H, H-2, CH_2-5 pentyl AMP), 3.36 – 3.32 (m, 1H, H-5), 3.27 – 3.20 (m, 1H, NC*H*H-1 pentyl AMP), 3.19 – 3.11 (m, 1H, NCH*H*-1 pentyl AMP), 2.96 (s, 2H, OCH_2-Ada), 2.94 – 2.85 (m, 1H, NC*H*H pentyl), 2.58 – 2.50 (m, 1H, NCH*H* pentyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 12.1, 48.4, 6H, 3×CH_2 Ada), 1.60 – 1.27 (m, 18H, 3×CH_2 Ada, 6×CH_2 pentyl/pentyl AMP), 0.93 (t, *J* = 7.1, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 175.8 (C(O)-1), 83.2 (OCH_2-Ada), 76.3 (C-3), 76.2 (C-2), 72.7 (C-4), 72.6 (CH_2-5 pentyl AMP), 64.9 (C-5), 58.3 (C-6), 50.9 (NCH_2 pentyl), 41.0 (CH_2 Ada), 40.1 (NCH_2 pentyl AMP), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 30.7, 30.5, 30.4, 29.7, 25.4, 23.6 (6×CH_2 pentyl/pentyl AMP), 14.6 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3319, 2902, 2849, 1652, 1458, 1112. $[\alpha]^{20}_D$: −17.3 (*c* 0.3, MeOH). HRMS: found 481.3631 $[M+H]^+$, calculated for $[C_{27}H_{48}O_5N_2+H]^+$ 481.3636.

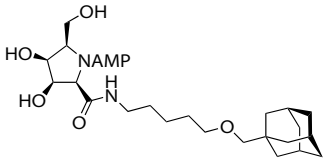


5-(Adamantan-1yl-methoxy)-pentyl 2,5-dideoxy-2,5-imino-D-*galacto*-hexonamide (B3-I). Compound **B3-I** (20 mg, 49 μmol) was synthesized in 37% yield from **B2-I** (131 μmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.14 (1:9; MeOH:DCM+2% NH_4OH). ^{1}H NMR (500 MHz, MeOD) δ 4.27 – 4.21 (m, 2H, H-3, H-4), 3.75 (d, *J* = 5.3, 1H, H-2), 3.69 (dd, *J* = 5.1, 11.1, 1H, H-6a), 3.63 (dd, *J* = 4.3, 11.1, 1H, H-6b), 3.42 – 3.35 (m, 4H, H-5, CH_2-5 pentyl), 3.24 (dt, *J* = 1.4, 7.0, 2H, NCH_2-1 pentyl), 2.97 (s, 2H, OCH_2-Ada), 1.94 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.7, 38.7, 6H, 3×CH_2 Ada), 1.62 – 1.51 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.45 – 1.37 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (125 MHz, MeOD) δ 174.6 (C(O)-1), 83.2 (OCH_2-Ada), 74.4 (C-3), 74.2 (C-4), 72.7 (CH_2-5 pentyl), 63.8 (C-2), 62.7 (C-6), 61.5 (C-5), 41.0 (CH_2 Ada), 40.2 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.5, 30.5 (2×CH_2 pentyl), 29.9 (CH Ada), 24.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3320, 2902, 2848, 1637, 1543, 1456, 1114. $[\alpha]^{20}_D$: 27.1 (*c* 0.3, MeOH). HRMS: found 411.2851 $[M+H]^+$, calculated for $[C_{22}H_{38}O_5N_2+H]^+$ 411.2853.

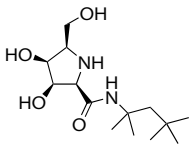


5-(Adamantan-1yl-methoxy)-pentyl 2,5-butylimino-2,5-dideoxy-D-*galacto*-hexonamide (B4-I). Compound **B4-I** (36 mg, 77 μmol) was synthesized in 48% yield over two steps from **B2-I** (161 μmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.31 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.61 (1:1; EtOAc:toluene+2% Et_3N). ^{1}H NMR (600 MHz, MeOD) δ 4.30 (dd, *J* = 4.5, 7.9, 1H, H-4), 4.18 (dd, *J* = 4.9, 1H, H-3), 3.72 (dd, *J* = 2.8, 11.2, 1H, H-6a), 3.62 (dd, *J* = 4.3, 11.2, 1H, H-6b), 3.41 – 3.31 (m, 4H, H-2, CH_2-5, NC*H*H-1 pentyl), 3.22 – 3.15 (m, 1H, NCH*H*-1 pentyl), 3.04 – 2.99 (m, 1H, H-5), 2.96 (s, 1H, OCH_2-Ada), 2.68 – 2.61 (m, 1H, NC*H*H butyl), 2.57

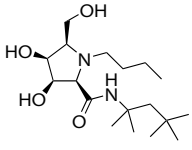
– 2.49 (m, 1H, NCH*H* butyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.6, 46.0, 6H, 3×CH_2 Ada), 1.62 – 1.26 (m, 16H, 3×CH_2 Ada, 5×CH_2 pentyl/butyl), 0.94 (t, *J* = 7.4, 3H, CH_3 butyl). ^{13}C NMR (150 MHz, MeOD) δ 174.4 (C(O)-1), 83.2 (OCH_2-Ada), 74.2 (C-3), 73.2 (C-4), 72.7 (CH_2-5 pentyl), 72.3 (C-2), 67.8 (C-5), 61.7 (C-6), 57.4 (NCH_2 butyl), 41.0 (CH_2 Ada), 40.1 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 32.0, 30.6, 30.5, 24.9, 21.7 (5×CH_2 pentyl/butyl), 14.6 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3319, 2902, 2849, 1651, 1637, 1458, 1113. $[\alpha]^{20}_D$: 34.7 (*c* 0.7, MeOH). HRMS: found 467.3475 $[M+H]^+$, calculated for $[C_{26}H_{46}O_5N_2+H]^+$ 467.3479.



5-(Adamantan-1yl-methoxy)-pentyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-D-*galacto*-hexonamide (B5-I). Compound **B5-I** (56 mg, 87 µmol) was synthesized in 59% yield over two steps from **B2-I** (148 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.37 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.69 (1:1; EtOAc:toluene+2% Et_3N). ^{1}H NMR (500 MHz, MeOD) δ 4.29 (dd, *J* = 4.5, 7.9, 1H, H-4), 4.18 (dd, *J* = 4.5, 5.5, 1H, H-3), 3.72 (dd, *J* = 3.0, 11.2, 1H, H-6a), 3.64 (dd, *J* = 4.5, 11.2, 1H, H-6b), 3.41 – 3.36 (m, 2H, 2×CH_2-5 pentyl), 3.37 – 3.34 (m, 1H, C(O)NC*H*H-1 pentyl), 3.33 (d, *J* = 5.5, 1H, H-2), 3.18 (dt, *J* = 6.8, 13.5, 1H, C(O)NCH*H*-1 pentyl), 3.02 (ddd, *J* = 3.0, 4.5, 7.6, 1H, H-5), 2.97 (s, 4H, 2×OCH_2-Ada), 2.70 – 2.62 (m, 1H, NC*H*H-1 pentyl), 2.54 (ddd, *J* = 6.3, 9.3, 12.5, 1H, NCH*H*-1 pentyl), 1.95 (s, 6H, 3×CH_2 Ada), 1.72 (dd, *J* = 11.8, 39.2, 12H, 6×CH_2 Ada), 1.63 – 1.30 (m, 24H, 6×CH_2 Ada, 6×CH_2 pentyl). ^{13}C NMR (125 MHz, MeOD) δ 174.4 (C(O)-1), 83.2 (2×OCH_2-Ada), 74.2 (C-3), 73.3 (C-4), 72.7, 72.6 (2×CH_2-5 pentyl), 72.3 (C-2), 67.9 (C-5), 61.8 (C-6), 57.6 (NCH_2-1 pentyl), 41.0, 41.0 (2×CH_2 Ada), 40.1 (C(O)NCH_2-1 pentyl), 38.5 (2×CH_2 Ada), 35.3, 35.3 (2×C_q Ada), 30.8, 30.6, 30.6, 29.7 (4×CH_2 pentyl), 29.9 (2×CH Ada), 25.3, 24.9 (2×CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3319, 2902, 2848, 1651, 1455, 1361, 1113. $[\alpha]^{20}_D$: 24.3 (*c* 0.7, MeOH). HRMS: found 645.4834 $[M+H]^+$, calculated for $[C_{38}H_{64}O_6N_2+H]^+$ 645.4837.

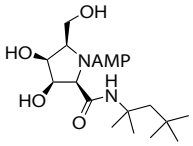


1,1,3,3-Tetramethylbutyl 2,5-dideoxy-2,5-imino-D-*galacto*-hexonamide (B3-II). Compound **B3-II** (14 mg, 47 µmol) was synthesized in 53% yield from **B2-II** (90 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.15 (1:9; MeOH:DCM+2% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 4.25 – 4.18 (m, 2H, H-3, H-4), 3.71 – 3.61 (m, 2H, CH_2-6), 3.59 (d, *J* = 5.9, 1H, H-2), 3.37 – 3.32 (m, 1H, H-5), 1.87 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.65 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.41 (d, *J* = 20.5, 6H, 2×CH_3 tMB), 1.03 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (150 MHz, MeOD) δ 173.8 (C(O)-1), 74.6, 74.2 (C-3, C-4), 63.9 (C-2), 62.8 (C-6), 61.3 (C-5), 55.9 (NHC_q-1 tMB), 53.1 (CH_2-2 tMB), 32.6 (C_q-3 tMB), 32.1 (CH_3-4, 2×CH_3 tMB), 29.7, 29.4 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3325, 2952, 1651, 1537, 1452, 1390, 1366, 1227, 1120, 1034. $[\alpha]^{20}_D$: 33.1 (*c* 0.3, MeOH). HRMS: found 289.2123 $[M+H]^+$, calculated for $[C_{14}H_{28}O_4N_2+H]^+$ 289.2122.

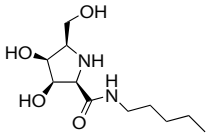


1,1,3,3-Tetramethylbutyl 2,5-butylimino-2,5-dideoxy-D-*galacto*-hexonamide (B4-II). Compound **B4-II** (27 mg, 78 µmol) was synthesized in 87% yield over two steps from **B2-II** (90 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.31 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.82 (1.5:1; EtOAc:toluene+2% Et_3N). ^{1}H NMR (600 MHz, MeOD) δ 4.27 (dd, *J* = 4.5, 7.7, 1H, H-4), 4.20 – 4.12 (m, 1H, H-3), 3.71 (dd, *J* = 2.6, 10.8, 1H, H-6a), 3.63 (dd, *J* = 4.8, 10.8, 1H, H-6b), 3.18 (d, *J* = 5.7, 1H, H-2), 3.03 – 2.99 (m, 1H, H-5), 2.66 – 2.59 (m, 1H, NC*H*H butyl), 2.57 – 2.49 (m, 1H, NCH*H* butyl), 1.93 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.63 (d, *J* = 14.9, 1H, CH*H*-2 tMB), 1.55 – 1.26 (m, 10H, 2×CH_2 butyl, 2×CH_3 tMB), 1.04 (s, 9H, 2×CH_3, CH_3-4 tMB), 0.94 (t,

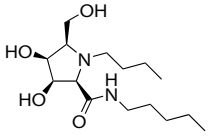
J = 7.4, 3H, CH_3 butyl). ^{13}C NMR (150 MHz, MeOD) δ 173.5 (C(O)-1), 74.4 (C-3), 73.3 (C-4), 72.5 (C-2), 67.5 (C-5), 61.9 (C-6), 57.4 (NCH_2 butyl), 56.2 (NHC_q-1 tMB), 53.6 (CH_2-2 tMB), 32.6 (C_q-3 tMB), 32.3 (CH_2 butyl), 32.2 (CH_3-4, 2×CH_3 tMB), 29.4, 29.3 (2×CH_3 tMB), 21.8 (CH_2 butyl), 14.6 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3292, 2957, 2928, 1639, 1461, 1440, 1366, 1229, 1149, 1128, 1034. $[\alpha]^{20}_D$: 37.8 (*c* 0.5, MeOH). HRMS: found 345.2748 $[M+H]^+$, calculated for $[C_{18}H_{36}O_4N_2+H]^+$ 345.2748.



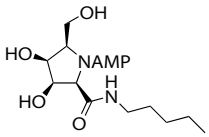
1,1,3,3-Tetramethylbutyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-D-*galacto*-hexonamide (B5-II). Compound **B5-II** (35 mg, 67 µmol) was synthesized in 74% yield over two steps from **B2-II** (90 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.35 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.84 (1.5:1; EtOAc:toluene+2% Et_3N). ^1H NMR (600 MHz, MeOD) δ 4.28 (dd, J = 4.5, 7.7, 1H, H-4), 4.17 (t, J = 5.0, 1H, H-3), 3.72 (dd, J = 1.6, 10.5, 1H, H-6a), 3.64 (dd, J = 4.5, 10.5, 1H, H-6b), 3.39 (t, J = 6.3, 2H, CH_2-5 pentyl), 3.20 (d, J = 3.4, 1H, H-2), 3.07 – 3.01 (m, 1H, H-5), 2.96 (s, 2H, OCH_2-Ada), 2.70 – 2.61 (m, 1H, NC*H*H-1 pentyl), 2.60 – 2.48 (m, 1H, NCH*H*-1 pentyl), 1.98 – 1.91 (m, 4H, 3×CH Ada, C*H*H-2 tMB), 1.80 – 1.65 (m, 7H, 3×CH_2 Ada, CH*H* tMB), 1.65 – 1.31 (m, 18H, 3×CH_2 Ada, 3×CH_2 pentyl, 2×CH_3 tMB), 1.04 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (150 MHz, MeOD) δ 173.3 (C(O)-1), 83.2 (OCH_2-Ada), 74.3 (C-3), 73.3 (C-4), 72.5 (C-2), 72.5 (CH_2-5 pentyl), 67.5 (C-5), 61.9 (C-6), 57.7 (NCH_2-1), 56.2 (NHC_q-1 tMB), 53.6 (CH_2-2 tMB), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.6 (C_q-3 tMB), 32.3 (CH_3-4, 2×CH_3 tMB), 30.8 (CH_2 pentyl), 29.9 (CH Ada), 29.5, 29.4 (2×CH_3 tMB, CH_2 pentyl), 25.4 (CH_2-1 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3325, 2903, 2850, 1651, 1454, 1366, 1228, 1110, 1055. $[\alpha]^{20}_D$: 28.4 (*c* 0.7, MeOH). HRMS: found 523.4101 $[M+H]^+$, calculated for $[C_{30}H_{54}O_5N_2+H]^+$ 523.4105.



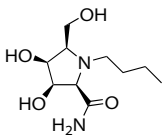
Pentyl 2,5-dideoxy-2,5-imino-D-*galacto*-hexonamide (B3-III). Compound **B3-III** (22 mg, 89 µmol) was synthesized in 66% yield from **B2-III** (135 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.08 (1:9; MeOH:DCM+2% NH_4OH). ^1H NMR (500 MHz, MeOD) δ 4.28 – 4.21 (m, 2H, H-3, H-4), 3.76 (d, J = 5.4, 1H, H-2), 3.69 (dd, J = 5.2, 11.1, 1H, H-6a), 3.63 (dd, J = 4.4, 11.1, 1H, H-6b), 3.37 (dd, J = 5.1, 11.6, 1H, H-5), 3.28 – 3.17 (m, 2H, NCH_2-1 pentyl), 1.58 – 1.50 (m, 2H, CH_2-2 pentyl), 1.39 – 1.30 (m, 4H, 2×CH_2 pentyl), 0.92 (t, J = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (151 MHz, MeOD) δ 174.4 (C(O)-1), 74.3 (C-3), 74.1 (C-4), 63.8 (C-2), 62.6 (C-6), 61.5 (C-5), 40.3 (NCH_2-1 pentyl), 30.3, 23.6 (3×CH_2 pentyl), 14.5 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3325, 2959, 2930, 1636, 1543, 1456, 1408, 1251, 1118, 1048. $[\alpha]^{20}_D$: 53.6 (*c* 0.3, MeOH). HRMS: found 247.1654 $[M+H]^+$, calculated for $[C_{11}H_{22}O_4N_2+H]^+$ 247.1652.



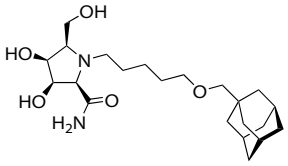
Pentyl 2,5-butylimino-2,5-dideoxy-D-*galacto*-hexonamide (B4-III). Compound **B4-III** (55 mg, 182 µmol) was synthesized in 86% yield over two steps from **B2-III** (212 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.24 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.56 (1:1; EtOAc:toluene+2% Et_3N). ^1H NMR (600 MHz, MeOD) δ 4.32 (dd, J = 4.6, 8.0, 1H, H-4), 4.20 (dd, J = 4.6, 5.4, 1H, H-3), 3.75 (dd, J = 2.9, 11.2, 1H, H-6a), 3.64 (dd, J = 4.4, 11.2, 1H, H-6b), 3.37 – 3.30 (m, 2H, H-2, NC*H*H-1 pentyl), 3.25 – 3.16 (m, 1H, NCH*H*-1 pentyl), 3.06 – 3.00 (m, 1H, H-5), 2.72 – 2.62 (m, 1H, NC*H*H butyl), 2.59 – 2.50 (m, 1H, NCH*H* butyl), 1.60 – 1.29 (m, 10H, 5×CH_2 pentyl/butyl), 0.99 – 0.90 (m, 6H, 2×CH_3 pentyl/butyl). ^{13}C NMR (150 MHz, MeOD) δ 174.4 (C(O)-1), 74.2 (C-3), 73.2 (C-4), 72.4 (C-2), 67.8 (C-5), 61.7 (C-6), 57.4 (NCH_2 butyl), 40.1 (NCH_2-1 pentyl), 32.0, 30.4, 30.4, 23.6, 21.7 (5×CH_2 pentyl/butyl), 14.6, 14.5(2×CH_3 pentyl/butyl). IR ν_{max}(thin film)/ cm^{-1}: 3327, 2957, 2930, 2862, 1650, 1636, 1539, 1463, 1141, 1030, 1011. $[\alpha]^{20}_D$: 60.6 (*c* 0.9, MeOH). HRMS: found 303.2279 $[M+H]^+$, calculated for $[C_{15}H_{30}O_4N_2+H]^+$ 303.2278.



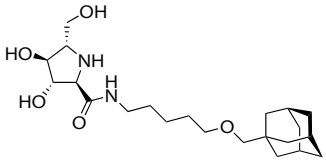
Pentyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-D-*galacto*-hexonamide (B5-III). Compound **B5-III** (71 mg, 148 µmol) was synthesized in 69% yield over two steps from **B2-III** (213 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.26 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.62 (1:1; EtOAc:toluene+2% Et_3N). ^{1}H NMR (600 MHz, MeOD) collapsed iminosugar signals δ 4.50 – 4.03 (m, 2H), 4.03 – 3.55 (m, 2H), 3.38 (t, *J* = 6.3, 2H, CH_2-5 pentyl AMP), 3.27 – 3.00 (m, 2H), 2.96 (s, 2H, OCH_2-Ada), 2.84 – 2.48 (m, 1H), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 12.1, 48.0, 6H, 3×CH_2 Ada), 1.63 – 1.32 (m, 18H, 3×CH_2 Ada, 6×CH_2 pentyl/pentyl AMP), 0.93 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (150 MHz, MeOD) collapsed iminosugar signals δ 83.2 (OCH_2-Ada), 72.4 (CH_2-5 pentyl AMP), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 30.6, 30.5, 30.4, 30.3, 25.3, 23.6 (6×CH_2 pentyl/pentyl AMP), 14.6 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3280, 1638, 1471, 1360, 1114, 1010. $[\alpha]^{20}_D$: 22.2 (*c* 0.2, MeOH). HRMS: found 481.3631 $[M+H]^+$, calculated for $[C_{27}H_{48}O_5N_2+H]^+$ 481.3636.



2,5-Butylimino-2,5-dideoxy-D-*galacto*-hexonamide (B4-VI). Compound **B4-VI** (11 mg, 47 µmol) was synthesized in 78% yield over two steps from **B2-VI** (60 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.29 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.51 (1.5:1; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) δ 4.30 (dd, *J* = 4.5, 7.9, 1H, H-4), 4.18 (dd, *J* = 4.5, 5.3, 1H, H-3), 3.72 (dd, *J* = 2.9, 11.3, 1H, H-6a), 3.62 (dd, *J* = 4.4, 11.3, 1H, H-6b), 3.30 – 3.29 (m, 1H, H-2), 3.02 (ddd, *J* = 3.0, 4.3, 7.6, 1H, H-5), 2.71 – 2.50 (m, 2H, NCH_2-1 butyl), 1.53 – 1.43 (m, 2H, CH_2-2 butyl), 1.40 – 1.26 (m, 2H, CH_2-3 butyl), 0.93 (t, *J* = 7.3, 3H, CH_3-4 butyl). ^{13}C NMR (100 MHz, MeOD) δ 178.0 (C(O)-1), 74.2 (C-3), 73.3 (C-4), 72.3 (C-2), 67.9 (C-5), 61.7 (C-6), 57.2 (NCH_2-1 butyl), 31.8 (CH_2-2 butyl), 21.7 (CH_2-3 butyl), 14.5 (CH_3-4 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3288, 2930, 1667, 1460, 1127. $[\alpha]^{20}_D$: 4.6 (*c* 0.3, MeOH). HRMS: found 233.1499 $[M+H]^+$, calculated for $[C_{10}H_2O_4N_2+H]^+$ 233.1496.

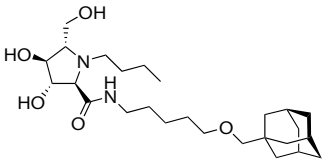


2,5-[5-(Adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-D-*galacto*-hexonamide (B5-VI). Compound **B5_VI** (14 mg, 34 µmol) was synthesized in 57% yield over two steps from **B2-VI** (60 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.46 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.59 (1.5:1; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) δ 4.33 (dd, *J* = 4.4, 7.9, 1H, H-4), 4.20 (dd, *J* = 4.4, 8.8, 1H, H-3), 3.75 (dd, *J* = 2.9, 11.3, 1H, H-6a), 3.65 (dd, *J* = 4.4, 11.3, 1H, H-6b), 3.40 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.37 – 3.34 (m, 1H, H-2), 3.09 – 3.03 (m, 1H, H-5), 2.99 (s, 2H, OCH_2-Ada), 2.74 – 2.56 (m, 2H, NCH_2-1 pentyl), 1.97 (s, 3H, 3×CH Ada), 1.75 (dd, *J* = 11.6, 32.2, 6H, 3×CH_2 Ada), 1.65 – 1.47 (m, 11H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.44 – 1.35 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 176.2 (C(O)-1), 81.7 (OCH_2-Ada), 72.6 (C-3), 71.7 (C-4), 71.1 (CH_2-5 pentyl), 70.7 (C-2), 66.3 (C-5), 60.1 (C-6), 55.9 (NCH_2-1 pentyl), 39.4 (CH_2 Ada), 36.9 (CH_2 Ada), 33.8 (C_q Ada), 29.1 (CH_2 pentyl), 28.4 (CH Ada), 27.7 (CH_2 pentyl), 23.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3290, 2902, 2849, 1668, 1453, 1114. $[\alpha]^{20}_D$: 15.0 (*c* 0.2, MeOH). HRMS: found 411.2852 $[M+H]^+$, calculated for $[C_{22}H_{38}O_5N_2+H]^+$ 411.2853.

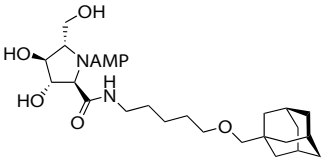


5-(Adamantan-1yl-methoxy)-pentyl 2,5-dideoxy-2,5-imino-L-*gulo*-hexonamide (C3-I). Compound **C3-I** (7 mg, 17 µmol) was synthesized in 85% yield from **C2-I** (20 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.29 (1:9; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.02 (dd, *J* = 5.2, 1H,

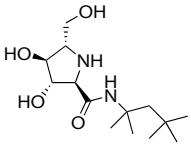
H-3), 3.79 (dd, *J* = 5.7, 1H, H-4), 3.70 (dd, *J* = 4.1, 11.1, 1H, H-6a), 3.60 (dd, *J* = 5.8, 11.1, 1H, H-6b), 3.49 (d, *J* = 5.3, 1H, H-2), 3.38 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.22 (t, *J* = 7.0, 2H, NCH_2-1 pentyl), 3.08 (dd, *J* = 5.8, 10.2, 1H, H-5), 2.97 (s, 2H, OCH_2-Ada), 1.94 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.9, 31.5, 6H, 3×CH_2 Ada), 1.63 – 1.49 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.46 – 1.35 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 175.0 (C(O)-1), 83.2 (OCH_2-Ada), 82.6 (C-3), 80.0 (C-4), 72.7 (CH_2-5 pentyl), 67.0 (C-2), 66.0 (C-5), 63.3 (C-6), 41.0 (CH_2 Ada), 40.4 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.5, 30.4 (2×CH_2 pentyl), 29.9 (CH Ada), 24.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3313, 2902, 2849, 1652, 1452, 1109. $[\alpha]^{20}_D$: 1.5 (*c* 0.1, MeOH). HRMS: found 411.2851 $[M+H]^+$, calculated for $[C_{22}H_{38}O_5N_2+H]^+$ 411.2853.



5-(Adamantan-1yl-methoxy)-pentyl 2,5-butylimino-2,5-dideoxy-L-*gulo*-hexonamide (C4-I). Compound **C4-I** (7 mg, 15 µmol) was synthesized in 75% yield over two steps from **C2-I** (20 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.76 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.80 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) δ 3.96 (dd, *J* = 1.7, 1H, H-4), 3.89 (dd, *J* = 1.8, 1H, H-3), 3.79 (dd, *J* = 5.0, 11.4, 1H, H-6a), 3.69 (dd, *J* = 3.2, 11.4, 1H, H-6b), 3.40 (s, 1H, H-2), 3.38 (t, *J* = 5.6, 2H, CH_2-5 pentyl), 3.28 – 3.11 (m, 3H, H-5, C(O)NCH_2-1 pentyl), 2.97 (s, 2H, OCH_2-Ada), 2.88 – 2.79 (m, 1H, NC*H*H-1 pentyl), 2.65 – 2.55 (m, 1H, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.7, 31.6, 6H, 3×CH_2 Ada), 1.64 – 1.23 (m, 16H, 3×CH_2 Ada, 3×CH_2 pentyl, 2×CH_2 butyl), 0.94 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 83.3 (OCH_2-Ada), 82.3 (C-3), 81.5 (C-4), 76.3 (CH_2-5 pentyl), 72.7 (C-2), 70.9 (C-5), 61.0 (C-6), 49.8 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 40.2 (C(O)NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 32.1, 30.5, 30.5, 24.9, 21.8 (3×CH_2 pentyl, 2×CH_2 butyl), 14.6 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3324, 2904, 2851, 1651, 1457, 1057. $[\alpha]^{20}_D$: 14.3 (*c* 0.1, MeOH). HRMS: found 467.3476 $[M+H]^+$, calculated for $[C_{26}H_{46}O_5N_2+H]^+$ 467.3479.

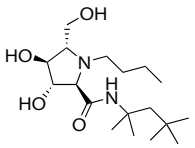


5-(Adamantan-1yl-methoxy)-pentyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-L-*gulo*-hexonamide (C5-I). Compound **C5-I** (8 mg, 13 µmol) was synthesized in 65% yield over two steps from **C2-I** (20 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.80 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.82 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) δ 3.96 (dd, *J* = 1.6, 1H, H-4), 3.89 (dd, *J* = 1.7, 1H, H-3), 3.80 (dd, *J* = 5.0, 11.4, 1H, H-6a), 3.69 (dd, *J* = 3.2, 11.4, 1H, H-6b), 3.42 – 3.35 (m, 5H, H-2, 2×CH_2-5 pentyl), 3.27 – 3.16 (m, 3H, H-5, C(O)NCH_2-1 pentyl), 2.97 (s, 4H, 2×OCH_2-Ada), 2.88 – 2.79 (m, 1H, NC*H*H-1 pentyl), 2.65 – 2.53 (m, 1H, NCH*H*-1 pentyl), 1.95 (s, 6H, 6×CH Ada), 1.72 (dd, *J* = 12.1, 31.4, 12H, 6×CH_2 Ada), 1.63 – 1.52 (m, 20H, 6×CH_2 Ada, 4×CH_2 pentyl), 1.49 – 1.34 (m, 4H, 2×CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.3, 83.3 (2×OCH_2-Ada), 82.4 (C-3), 81.6 (C-4), 76.5 (C-2), 72.7, 72.7 (2×CH_2-5 pentyl), 70.8 (C-5), 61.0 (C-6), 50.0 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 40.2 (C(O)NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.4, 35.3 (2×C_q Ada), 29.9 (CH Ada), 30.8, 30.5, 30.5, 29.7, 25.4 (CH_2 pentyl), 24.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2902, 2849, 1651, 1454, 1157, 1111. $[\alpha]^{20}_D$: 13.8 (*c* 0.2, MeOH). HRMS: found 645.4834 $[M+H]^+$, calculated for $[C_{38}H_{64}O_6N_2+H]^+$ 645.4837.

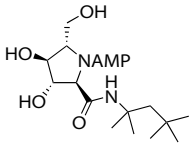


1,1,3,3-Tetramethylbutyl 2,5-dideoxy-2,5-imino-L-*gulo*-hexonamide (C3-II). Compound **C3-II** (10 mg, 35 µmol) was synthesized in 58% yield from **C2-II** (60 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.43 (1:4; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.02 (dd, *J* = 5.2, 1H, H-3), 3.78 (dd, *J* = 5.4, 6.1, 1H, H-4), 3.69 (dd, *J* = 4.1, 11.2, 1H, H-6a), 3.60 (dd, *J* = 5.7, 11.2, 1H,

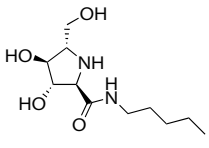
H-6b), 3.39 (d, *J* = 5.2, 1H, H-2), 3.02 (dt, *J* = 4.1, 6.0, 1H, H-5), 1.81 (d, *J* = 14.9, 1H, C*H*H-2 tMB), 1.74 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.41 (s, 6H, 2×CH_3 tMB), 1.02 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, MeOD) δ 174.1 (C(O)-1), 82.4 (C-3), 80.0 (C-4), 67.4 (C-2), 65.9 (C-5), 63.2 (C-6), 55.8 (NHC_q-1 tMB), 52.9 (CH_2-2 tMB), 32.6 (C_q-3 tMB), 32.1 (2×CH_3, CH_3-4 tMB), 29.6, 29.4 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3304, 2954, 1652, 1453, 1366, 1227, 1055. $[\alpha]^{20}_D$: 8.0 (*c* 0.2, MeOH). HRMS: found 289.2123 $[M+H]^+$, calculated for $[C_{14}H_{28}O_4N_2+H]^+$ 289.2122.



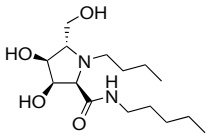
1,1,3,3-Tetramethylbutyl 2,5-butylimino-2,5-dideoxy-L-*gulo*-hexonamide (C4-II). Compound **C4-II** (11 mg, 32 µmol) was synthesized in 53% yield over two steps from **C2-II** (60 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.85 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.95 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) δ 3.97 (s, 1H, H-4), 3.89 (s, 1H, H-3), 3.81 (dd, *J* = 5.1, 11.5, 1H, H-6a), 3.69 (dd, *J* = 3.0, 11.5, 1H, H-6b), 3.29 (s, 2H, H-2, H-5), 2.94 – 2.82 (m, 1H, NC*H*H butyl), 2.67 – 2.51 (m, 1H, NCH*H* butyl), 1.88 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.73 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.63 – 1.25 (m, 10H, 2×CH_3 tMB, 2×CH_2 butyl), 1.02 (s, 9H, 2×CH_3, CH_3-4 tMB), 0.95 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 82.1 (C-3), 81.5 (C-4), 77.5, 70.5 (C-2, C-5), 60.8 (C-6), 52.8 (CH_2-2 tMB), 49.9 (NCH_2 butyl), 32.6 (C_q-3 tMB), 32.2 (2×CH_3, CH_3-4 tMB), 29.6, 29.4 (2×CH_3 tMB), 21.9 (CH_2 butyl), 14.6 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3312, 2957, 1651, 1439, 1366, 1226, 1155, 1066. $[\alpha]^{20}_D$: 20.9 (*c* 0.2, MeOH). HRMS: found 345.2748 $[M+H]^+$, calculated for $[C_{18}H_{36}O_4N_2+H]^+$ 345.2748.



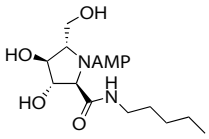
1,1,3,3-Tetramethylbutyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-L-*gulo*-hexonamide (C5-II). Compound **C5-II** (13 mg, 25 µmol) was synthesized in 42% yield over two steps from **C2-II** (60 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.85 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.83 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) δ 3.97 (s, 1H, H-4), 3.89 (s, 1H, H-3), 3.81 (dd, *J* = 5.1, 11.5, 1H, H-6a), 3.68 (dd, *J* = 3.1, 11.5, 1H, H-6b), 3.39 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.30 – 3.23 (m, 2H, H-2, H-5), 2.97 (s, 2H, OCH_2-Ada), 2.93 – 2.84 (m, 1H, NC*H*H pentyl), 2.61 – 2.53 (m, 1H, NCH*H* pentyl), 1.95 (s, 3H, 3×CH Ada), 1.89 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.81 – 1.65 (m, 7H, CH*H*-2 tMB, 3×CH_2 Ada), 1.64 – 1.37 (m, 18H, 3×CH_2 Ada, 2×CH_3 tMB, 3×CH_2 pentyl), 1.03 (s, 9, 2×CH_3, CH_3-4 tMBH). ^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 82.1 (C-3), 81.6 (C-4), 77.7 (C-2), 72.6 (CH_2-5 pentyl), 70.4 (C-5), 60.9 (C-6), 56.1 (NHC_q-1 tMB), 52.8 (CH_2-2 tMB), 50.1 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.6 (C_q-3 tMB), 32.2 (2×CH_3, CH_3-4 tMB), 30.9 (CH_2 pentyl), 29.9 (CH Ada), 29.7, 29.4 (2×CH_3 tMB), 25.5 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3342, 2903, 2850, 1651, 1440, 1227, 1064. $[\alpha]^{20}_D$: 24.6 (*c* 0.3, MeOH). HRMS: found 523.4101 $[M+H]^+$, calculated for $[C_{30}H_{54}O_5N_2+H]^+$ 523.4105.



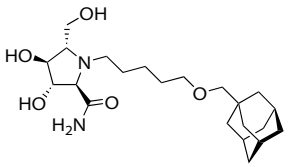
Pentyl 2,5-dideoxy-2,5-imino-L-*gulo*-hexonamide (C3-III). Compound **C3-III** (19 mg, 77 µmol) was synthesized in 51% yield from **C2-III** (150 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.24 (1:5; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.24 – 4.11 (m, 1H, H-3), 4.06 – 3.94 (m, 1H, H-4), 3.91 – 3.81 (m, 1H, H-6a), 3.81 – 3.71 (m, 2H, H-2, H-6b), 3.43 – 3.36 (m, 3H, H-5, NCH_2-1 pentyl), 1.68 – 1.55 (m, 2H, CH_2-2 pentyl), 1.51 – 1.33 (m, 4H, 2×CH_2 pentyl), 1.07 – 0.91 (m, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 172.3 (C(O)-1), 81.7 (C-3), 78.8 (C-4), 66.2, 66.1 (C-2, C-5), 61.9 (C-6), 40.7 (NCH_2-1 pentyl), 30.3, 30.2, 23.5 (3×CH_2 pentyl), 14.5 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3290, 2930, 1652, 1544, 1377, 1055. $[\alpha]^{20}_D$: 1.1 (*c* 0.4, MeOH). HRMS: found 247.1653 $[M+H]^+$, calculated for $[C_{11}H_{22}O_4N_2+H]^+$ 247.1652.



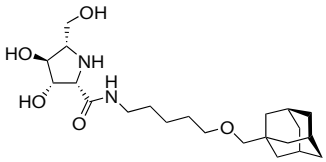
Pentyl 2,5-butylimino-2,5-dideoxy-L-*gulo*-hexonamide (C4-III). Compound **C4-III** (13 mg, 43 µmol) was synthesized in 31% yield over two steps from **C2-III** (140 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.69 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.77 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) δ 4.01 (s, 1H, H-4), 3.94 (s, 1H, H-3), 3.85 (dd, *J* = 4.5, 11.8, 1H, H-6a), 3.75 (dd, *J* = 3.1, 11.8, 1H, H-6b), 3.61 – 3.51 (m, 1H, H-2), 3.41 – 3.33 (m, 1H, H-5), 3.23 (t, *J* = 7.0, 2H, NCH_2-1 pentyl), 3.04 – 2.90 (m, 1H, NC*H*H-1 butyl), 2.83 – 2.67 (m, 1H, NCH*H*-1 butyl), 1.59 – 1.48 (m, 4H, 2×CH_2-2 pentyl/butyl), 1.43 – 1.28 (m, 6H, 3×CH_2 pentyl/butyl), 0.98 – 0.90 (m, 6H, 2×CH_3 butyl/pentyl). ^{13}C NMR (100 MHz, MeOD) δ 81.9 (C-3), 80.7 (C-4), 75.5 (C-2), 71.3 (C-5), 60.3 (C-6), 50.4 (NCH_2 butyl), 40.4 (NCH_2-1 pentyl), 31.4, 30.3, 30.3, 23.5, 21.7 (5×CH_2 pentyl/butyl), 14.5, 14.4 (2×CH_3 pentyl/butyl). IR ν_{max}(thin film)/ cm^{-1}: 3294, 2959, 2930, 2871, 1652, 1461, 1378, 1066. $[\alpha]^{20}_D$: 27.7 (*c* 0.3, MeOH). HRMS: found 303.2279 $[M+H]^+$, calculated for $[C_{15}H_{30}O_4N_2+H]^+$ 303.2278.



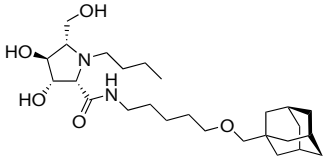
Pentyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-L-*gulo*-hexonamide (C5-III). Compound **C5-III** (15 mg, 31 µmol) was synthesized in 22% yield over two steps from **C2-III** (140 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.37 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.80 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) δ 3.96 (dd, *J* = 1.7, 1H, H-4), 3.89 (dd, *J* = 1.8, 1H, H-3), 3.80 (dd, *J* = 5.0, 11.4, 1H, H-6a), 3.69 (dd, *J* = 3.2, 11.4, 1H, H-6b), 3.40 (s, 1H, H-2), 3.38 (t, *J* = 4.9, 2H, CH_2-5 pentyl), 3.28 – 3.12 (m, 3H, H-5, C(O)NCH_2-1 pentyl), 2.97 (s, 2H, OCH_2-Ada), 2.90 – 2.78 (m, 1H, NC*H*H-1 pentyl), 2.66 – 2.52 (m, 1H, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 12.1, 32.1, 6H, 3×CH_2 Ada), 1.64 – 1.26 (m, 18H, 3×CH Ada, 6×CH_2 pentyl), 0.93 (t, *J* = 6.9, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 175.9 (C(O)-1), 83.2 (OCH_2-Ada), 82.4 (C-3), 81.6 (C-4), 76.4 (C-2), 72.7 (CH_2-5 pentyl), 70.8 (C-5), 61.0 (C-6), 50.0 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 40.2 (C(O)NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 30.8, 30.4, 30.4, 29.7, 25.4, 23.6 (6×CH_2 pentyl), 14.5 (CH_3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3297, 2902, 2849, 1651, 1456, 1361, 1157, 1111. $[\alpha]^{20}_D$: 11.4 (*c* 0.3, MeOH). HRMS: found 481.3632 $[M+H]^+$, calculated for $[C_{27}H_{48}O_5N_2+H]^+$ 481.3636.



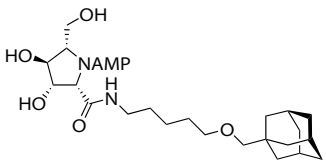
2,5-[5-(Adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-L-*gulo*-hexonamide (C5-VI). Compound **C5-VI** (5 mg, 12 µmol) was synthesized in 92% yield over two steps from **C2-VI** (13 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.45 (14% MeOH in DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.74 (1% MeOH in EtOAc+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.98 – 3.96 (m, 1H, H-4), 3.95 – 3.93 (m, 1H, H-3), 3.80 (dd, *J* = 5.0, 11.4, 1H, H-6a), 3.68 (dd, *J* = 3.2, 11.4, 1H, H-6b), 3.40 (s, 1H, H-2), 3.38 (t, *J* = 4.8, 2H, CH_2-5 pentyl), 3.23 (s, 1H, H-5), 2.97 (s, 2H, OCH_2-Ada), 2.89 – 2.80 (m, 1H, NC*H*H pentyl), 2.66 – 2.58 (m, 1H, NCH*H* pentyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.7, 31.3, 6H, 3×CH_2 Ada), 1.64 – 1.31 (m, 12H, 3×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 82.6 (C-3), 81.7 (C-4), 76.1 (C-2), 72.7 (CH_2-5 pentyl), 70.8 (C-5), 61.0 (C-6), 49.9 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2 pentyl), 29.9 (CH Ada), 29.6 (CH_2 pentyl), 25.3 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3312, 2903, 1669, 1410, 1056. $[\alpha]^{20}_D$: 23.4 (*c* 0.1, MeOH). HRMS: found 411.2852 $[M+H]^+$, calculated for $[C_{22}H_{38}O_5N_2+H]^+$ 411.2853.



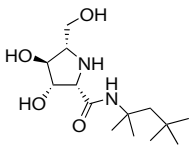
5-(Adamantan-1yl-methoxy)-pentyl 2,5-dideoxy-2,5-imino-L-*ido*-hexonamide (D3-I). Compound **D3-I** (12 mg, 29 µmol) was synthesized in 55% yield from **D2-I** (53 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.10 (1:9; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.17 (dd, *J* = 2.1, 5.1, 1H, H-3), 4.04 (d, *J* = 5.1, 1H, H-2), 3.92 (dd, *J* = 2.4, 1H, H-4), 3.71 – 3.68 (m, 2H, CH_2-6), 3.38 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.27 – 3.22 (m, 3H, H-5, NCH_2-1 pentyl), 2.97 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 12.1, 31.7, 7H, 3×CH_2 Ada), 1.62 – 1.52 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.46 – 1.37 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 175.0 (C(O)-1), 83.2 (OCH_2-Ada), 79.8 (C-4), 79.0 (C-3), 72.7 (CH_2-5 pentyl), 67.9 (C-5), 65.8 (C-2), 63.5 (C-6), 41.0 (CH_2 Ada), 40.4 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.5, 30.4 (2×CH_2 pentyl), 29.9 (CH Ada), 24.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3326, 2902, 2849, 1652, 1454, 1050. $[\alpha]^{20}_D$: −22.4 (*c* 0.1, MeOH). HRMS: found 411.2851 $[M+H]^+$, calculated for $[C_{22}H_{38}O_5N_2+H]^+$ 411.2853.



5-(Adamantan-1yl-methoxy)-pentyl 2,5-butylimino-2,5-dideoxy-L-*ido*-hexonamide (D4-I). Compound **D4-I** (18 mg, 39 µmol) was synthesized in 74% yield over two steps from **D2-I** (53 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.54 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.85 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.19 – 3.49 (m, 5H), 3.38 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.22 (s, 1H), 2.97 (s, 2H, OCH_2-Ada), 2.91 – 2.55 (m, 3H), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 12.1, 32.0, 6H, 3×CH_2 Ada), 1.64 – 1.25 (m, 16H, 3×CH_2 Ada, 3×CH_2 pentyl, 2×CH_2 butyl), 0.94 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) collapsed iminosugar signals δ 83.3 (OCH_2-Ada), 79.3 (CH), 78.4 (CH), 72.7 (CH_2-5 pentyl), 41.0 (CH_2 Ada), 40.3 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.5 (CH_2), 29.9 (CH Ada), 24.9 (CH_2), 21.8 (CH_2), 14.5 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3295, 2902, 2849, 1637, 1456, 1360, 1110, 756. $[\alpha]^{20}_D$: −16.7 (*c* 0.4, MeOH). HRMS: found 467.3476 $[M+H]^+$, calculated for $[C_{26}H_{46}O_5N_2+H]^+$ 467.3479.

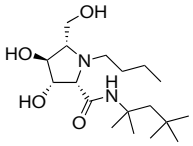


5-(Adamantan-1yl-methoxy)-pentyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-L-*ido*-hexonamide (D5-I). Compound **D5-I** (27 mg, 42 µmol) was synthesized in 79% yield over two steps from **D2-I** (53 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.56 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.72 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.47 – 3.50 (m, 5H), 3.39 (t, *J* = 6.4, 4H, 2×CH_2-5 pentyl), 3.27 – 3.16 (m, 1H), 2.97 (s, 4H, 2×OCH_2-Ada), 2.94 – 2.49 (m, 2H), 1.95 (s, 6H, 6×CH Ada), 1.72 (dd, *J* = 12.0, 32.1, 12H, 6×CH_2 Ada), 1.65 – 1.48 (m, 20H, 6×CH_2 Ada, 4×CH_2 pentyl), 1.48 – 1.32 (m, 4H, 2×CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) collapsed iminosugar signals δ 83.3 (OCH_2-Ada), 78.4 (CH), 72.7 (CH_2-5 pentyl), 41.0 (CH_2 Ada), 40.3 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3, 35.3 (2×C_q Ada), 30.7, 30.5, 30.5 (CH_2), 29.9 (CH Ada), 25.2, 24.9 (2×CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3295, 2900, 2848, 1652, 1453, 1361, 1157, 1109, 755. $[\alpha]^{20}_D$: −18.1 (*c* 0.5, MeOH). HRMS: found 645.4835 $[M+H]^+$, calculated for $[C_{38}H_{64}O_6N_2+H]^+$ 645.4837.

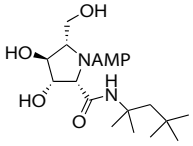


1,1,3,3-Tetramethylbutyl 2,5-dideoxy-2,5-imino-L-*ido*-hexonamide (D3-II). Compound **D3-II** (14 mg, 49 µmol) was synthesized in 78% yield from **D2-II** (63 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.38 (1:4; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.11 (dd, *J* = 2.4, 5.4, 1H, H-3), 3.90 (dd, *J* = 2.7, 1H, H-4), 3.81 (d, *J* = 5.4, 1H, H-2), 3.66 (dd, *J* = 4.1, 10.1, 1H, H-6a),

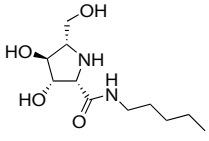
3.62 (dd, *J* = 4.3, 10.1, 1H, H-6b), 3.14 (dt, *J* = 2.9, 4.9, 1H, H-5), 1.83 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.69 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.41 (d, *J* = 6.0, 6H, 2×CH_3 tMB), 1.03 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, MeOD) δ 172.9 (C(O)-1), 80.3 (C-4), 79.4 (C-3), 67.3 (C-5), 66.2 (C-2), 64.6 (C-6), 56.0 (NHC_q-1 tMB), 53.2 (CH_2-2 tMB), 32.6 (C_q-3 tMB), 32.1 (2×CH_3, CH_3-4 tMB), 29.6 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2955, 2481, 1667, 1559, 1454, 1367, 1226, 1042. $[\alpha]^{20}_D$: −44.1 (*c* 0.3, MeOH). HRMS: found 289.2123 $[M+H]^+$, calculated for $[C_{14}H_{28}O_4N_2+H]^+$ 289.2122.



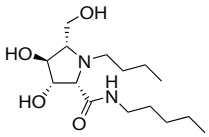
1,1,3,3-Tetramethylbutyl 2,5-butylimino-2,5-dideoxy-L-*ido*-hexonamide (D4-II). Compound **D4-II** (12 mg, 35 µmol) was synthesized in 55% yield over two steps from **D2-II** (63 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.66 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.88 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.15 – 4.07 (m, 1H, H-3), 4.02 (dd, *J* = 2.6, 1H, H-4), 3.68 (s, 2H, CH_2-6), 3.41 (s, 1H, H-2), 2.88 – 2.57 (m, 3H, H-5, NCH_2 butyl), 1.87 (d, *J* = 14.7, 1H, C*H*H-2 tMB), 1.70 (d, *J* = 14.2, 1H, CH*H*-2 tMB), 1.65 – 1.21 (m, 10H, 2×CH_2 butyl, 2×CH_3 tMB), 1.06 (s, 9H, 2×CH_3, CH_3-4 tMB), 0.97 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) collapsed iminosugar signals δ 79.7 (C-4), 78.7 (C-3), 74.2 (C-2), 73.4 (C-5), 63.7 (C-6), 57.5 (NCH_2 butyl), 56.2 (C_q-3 tMB), 53.9 (CH_2-2 tMB), 32.6 (C_q-3 tMB), 32.3 (CH_2 butyl), 32.2 (2×CH_3, CH_3-4 tMB), 29.7, 29.1 (2×CH_3 tMB), 21.9 (CH_2 butyl), 14.4 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3290, 2957, 2420, 1651, 1458, 1366, 1227, 1072, 756. $[\alpha]^{20}_D$: −30.7 (*c* 0.3, MeOH). HRMS: found 345.2748 $[M+H]^+$, calculated for $[C_{18}H_{36}O_4N_2+H]^+$ 345.2748.



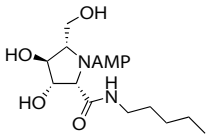
1,1,3,3-Tetramethylbutyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-L-*ido*-hexonamide (D5-II). Compound **D5-II** (28 mg, 54 µmol) was synthesized in 86% yield over two steps from **D2-II** (63 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.25 (1:9; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.83 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.72 – 3.44 (m, 6H), 3.39 (t, *J* = 6.2, 2H, CH_2-5 pentyl), 3.26 – 3.02 (m, 1H), 2.97 (s, 2H, OCH_2-Ada), 2.94 – 2.47 (m, 1H), 2.20 – 1.31 (m, 23H, CH_2-2 tMB, 3×CH Ada, 6×CH_2 Ada, 3×CH_2 pentyl), 1.04 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (101 MHz, MeOD) collapsed iminosugar signals δ 83.2 (OCH_2-Ada), 78.4 (CH), 72.3 (CH_2-5 pentyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.6 (C_q-3 tMB), 32.2 (2×CH_3, CH_3-4 tMB), 30.7 (CH_2 pentyl), 29.9 (CH Ada), 29.6 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3291, 2902, 2849, 2409, 1668, 1452, 1366, 1225, 1156, 1110, 755. $[\alpha]^{20}_D$: −21.4 (*c* 0.6, MeOH). HRMS: found 523.4101 $[M+H]^+$, calculated for $[C_{30}H_{54}O_5N_2+H]^+$ 523.4105.



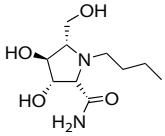
Pentyl 2,5-dideoxy-2,5-imino-L-*ido*-hexonamide (D3-III). Compound **D3-III** (52 mg, 211 µmol) was synthesized in 78% yield from **D2-III** (270 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.15 (1:4; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.29 (dd, *J* = 2.1, 4.9, 1H, H-3), 4.25 (d, *J* = 4.9, 1H, H-2), 3.99 (dd, *J* = 2.4, 1H, H-4), 3.79 (d, *J* = 6.0, 2H, CH_2-6), 3.41 (dt, *J* = 2.7, 6.0, 1H, H-5), 3.25 (t, *J* = 7.1, 2H, NCH_2-1 pentyl), 1.61 – 1.49 (m, 2H, CH_2-2 pentyl), 1.40 – 1.31 (m, 4H, 2×CH_2 pentyl), 0.92 (t, *J* = 6.9, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 169.5 (C(O)-1), 79.0 (C-4), 78.4 (C-3), 68.5 (C-5), 65.3 (C-2), 62.0 (C-6), 40.7 (NCH_2-1 pentyl), 30.3, 30.2, 23.5 (3×CH_2 pentyl), 14.5 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3287, 2957, 2931, 2871, 1666, 1638, 1652, 1560, 1470, 1377, 1310, 1066, 1034. $[\alpha]^{20}_D$: −54.5 (*c* 1.0, MeOH). HRMS: found 247.1654 $[M+H]^+$, calculated for $[C_{11}H_{22}O_4N_2+H]^+$ 247.1652.



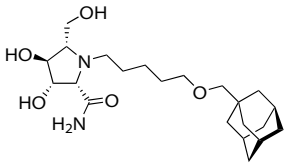
Pentyl 2,5-butylimino-2,5-dideoxy-L-*ido*-hexonamide (D4-III). Compound **D4-III** (24 mg, 79 µmol) was synthesized in 49% yield over two steps from **D2-III** (160 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.58 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.75 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) δ 4.08 (dd, *J* = 3.2, 6.1, 1H, H-3), 3.96 (dd, *J* = 3.2, 1H, H-4), 3.67 (d, *J* = 4.0, 2H, CH_2-6), 3.51 (d, *J* = 6.2, 1H, H-2), 3.35 – 3.25 (m, 1H, NC*H*H-1 pentyl), 3.17 (dt, *J* = 6.9, 13.5, 1H, NCH*H*-1 pentyl), 2.80 (dd, *J* = 3.7, 7.2, 1H, H-5), 2.70 (ddd, *J* = 5.9, 9.3, 12.5, 1H, NC*H*H-1 butyl), 2.59 (ddd, *J* = 6.4, 9.3, 12.5, 1H, NCH*H*-1 butyl), 1.59 – 1.26 (m, 10H, 5×CH_2 pentyl/butyl), 0.96 – 0.89 (m, 6H, 2×CH_3 butyl/pentyl). ^{13}C NMR (100 MHz, MeOD) δ 174.6 (C(O)-1), 79.3 (C-4), 78.4 (C-3), 73.3, 73.2 (C-2, C-5), 63.0 (C-6), 57.1 (NCH_2-1 butyl), 40.1 (NCH_2-1 pentyl), 31.9, 30.4, 23.6, 21.8 (5×CH_2 pentyl/butyl), 14.5 (2×CH_3 butyl/pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3274, 2959, 2931, 2871, 1637, 1464, 1376, 1118, 1069, 754. $[\alpha]^{20}_D$: −39.3 (*c* 0.3, MeOH). HRMS: found 303.2279 $[M+H]^+$, calculated for $[C_{15}H_{30}O_4N_2+H]^+$ 303.2278.



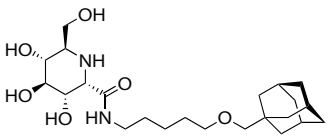
Pentyl 2,5-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-L-*ido*-hexonamide (D5-III). Compound **D5-III** (40 mg, 83 µmol) was synthesized in 52% yield over two steps from **D2-III** (160 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.69 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.80 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, MeOD) δ 4.08 (dd, *J* = 3.2, 6.1, 1H, H-3), 3.97 (dd, *J* = 3.1, 1H, H-4), 3.69 – 3.66 (m, 2H, CH_2-6), 3.51 (d, *J* = 6.1, 1H, H-2), 3.38 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.35 – 3.26 (m, 1H, C(O)NC*H*H-1 pentyl), 3.17 (dt, *J* = 6.9, 13.5, 1H, C(O)NCH*H*-1 pentyl), 2.96 (s, 2H, OCH_2-Ada), 2.80 (dd, *J* = 3.6, 7.1, 1H, H-5), 2.70 (ddd, *J* = 5.8, 9.1, 12.5, 1H, NC*H*H-1 pentyl), 2.59 (ddd, *J* = 6.5, 9.1, 12.5, 1H, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.9, 32.3, 6H, 3×CH_2 Ada), 1.60 – 1.29 (m, 18H, 3×CH_2 Ada, 6×CH_2 pentyl), 0.92 (t, *J* = 6.9, 3H, CH_3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 174.6 (C(O)-1), 83.2 (OCH_2-Ada), 79.4 (C-4), 78.4 (C-3), 73.4 (C-2), 73.2 (C-5), 72.6 (CH_2-5 pentyl), 63.1 (C-6), 57.4 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 40.1 (C(O)NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 30.7, 30.4, 30.4, 29.5, 25.3, 23.6 (6×CH_2 pentyl), 14.6 (CH_3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3343, 2903, 2850, 1637, 1457, 1374, 1157, 1072. $[\alpha]^{20}_D$: −32.1 (*c* 0.7, MeOH). HRMS: found 481.3632 $[M+H]^+$, calculated for $[C_{27}H_{48}O_5N_2+H]^+$ 481.3636.



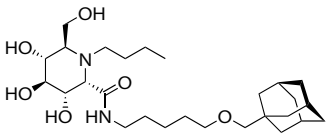
2,5-Butylimino-2,5-dideoxy-L-*ido*-hexonamide (D4-VI). Compound **D4-VI** (6 mg, 25 µmol) was synthesized in 92% yield over two steps from **D2-VI** (30 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.21 (14% MeOH in DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.62 (1% MeOH in EtOAc+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.08 (dd, *J* = 3.1, 6.0, 1H, H-3), 3.99 (dd, *J* = 3.1, 1H, H-4), 3.70 – 3.63 (m, 2H, CH_2-6), 3.50 (d, *J* = 6.0, 1H, H-2), 2.83 – 2.77 (m, 1H, H-5), 2.76 – 2.55 (m, 2H, NCH_2-1 butyl), 1.55 – 1.42 (m, 2H, CH_2-2 butyl), 1.41 – 1.27 (m, 2H, CH_2-3 butyl), 0.93 (t, *J* = 7.3, 3H, CH_3-4 butyl). ^{13}C NMR (100 MHz, MeOD) δ 79.4 (C-4), 78.4 (C-3), 73.4, 73.3 (C-2, C-5), 63.2 (C-6), 57.0 (NCH_2-1 butyl), 31.6 (CH_2-2 butyl), 21.7 (CH_2-3 butyl), 14.5 (CH_3-4 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3314, 2972, 2931, 1652, 1380, 1086, 1048, 881. $[\alpha]^{20}_D$: −33.3 (*c* 0.1, MeOH). HRMS: found 233.1499 $[M+H]^+$, calculated for $[C_{10}H_2O_4N_2+H]^+$ 233.1496.



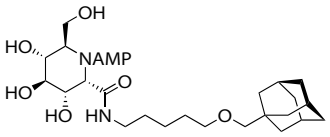
2,5-[5-(Adamantan-1yl-methoxy)-pentyl]imino-2,5-dideoxy-L-*ido*-hexonamide (D5-VI). Compound **D5-VI** (12 mg, 29 µmol) was synthesized in 97% yield over two steps from **D2-VI** (30 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.40 (14% MeOH in DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.67 (1% MeOH in EtOAc+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.09 (dd, *J* = 3.0, 6.0, 1H, H-3), 3.99 (dd, *J* = 2.8, 1H, H-4), 3.73 – 3.62 (m, 2H, CH_2-6), 3.52 (d, *J* = 6.0, 1H, H-2), 3.38 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 2.96 (s, 2H, OCH_2-Ada), 2.84 – 2.79 (m, 1H, H-5), 2.76 – 2.57 (m, 2H, NCH_2-1 pentyl), 1.94 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 12.0, 31.6, 6H, 3×CH_2 Ada), 1.62 – 1.46 (m, 12H, 3×CH_2 Ada, 3×CH_2 pentyl), 1.43 – 1.34 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 79.4 (C-4), 78.5 (C-3), 73.3 (C-2, C-5), 72.6 (CH_2-5 pentyl), 63.2 (C-6), 57.2 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2 pentyl), 29.9 (CH Ada), 29.1 (CH_2 pentyl), 25.2 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3340, 2902, 2849, 1666, 1452, 1158, 1111, 1056. $[\alpha]^{20}_D$: −17.2 (*c* 0.2, MeOH). HRMS: found 411.2850 $[M+H]^+$, calculated for $[C_{22}H_{38}O_5N_2+H]^+$ 411.2853.



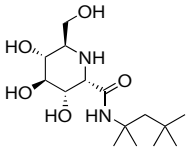
5-(Adamantan-1yl-methoxy)-pentyl 2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptonamide (E3-I). Compound **E3-I** (23 mg, 52 µmol) was synthesized in 36% yield from **E1-I** (144 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.14 (1:6.6; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 8.06 – 8.03 (m, 1H, (C(O)N)), 3.86 (dd, *J* = 3.1, 11.2, 1H, H-7a), 3.79 (d, *J* = 5.7, 1H, H-2), 3.72 (dd, *J* = 5.7, 9.5, 1H, H-3), 3.63 (dd, *J* = 6.4, 11.2, 1H, H-7b), 3.51 (dd, *J* = 8.7, 9.5, 1H, H-4), 3.39 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.29 – 3.19 (m, 3H, H-5, NCH_2-1 pentyl), 2.97 (s, 2H, OCH_2-Ada), 2.92 (ddd, *J* = 3.1, 6.4, 9.6, 1H, H-6), 1.94 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.8, 31.8, 6H, 3×CH_2 Ada), 1.63 – 1.51 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.46 – 1.36 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 172.4 (C(O)-1), 83.2 (OCH_2-Ada), 76.2 (C-4), 73.0 (C-3), 72.6 (CH_2-5 pentyl), 72.6 (C-5), 62.3 (C-7), 59.3 (C-6), 58.3 (C-2), 41.0 (CH_2 Ada), 40.3 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.4, 30.4 (2×CH_2 pentyl), 29.9 (CH Ada), 24.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3304, 2902, 2848, 1643, 1454, 1052. $[\alpha]^{20}_D$: 18.7 (*c* 0.5, MeOH). HRMS: found 441.2956 $[M+H]^+$; calculated for $[C_{23}H_{40}N_2O_6+H]^+$ 441.2959.



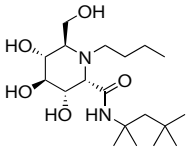
5-(Adamantan-1yl-methoxy)-pentyl 2,6-butylimino-2,6-dideoxy-D-*glycero*-D-*ido*-heptonamide (E4-I). Compound **E4-I** (66 mg, 133 µmol) was synthesized in 92% yield over two steps from **E2-I** (144 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F *N*-alkylated penultimate = 0.64 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.18 – 2.92 (m, 15H, H-2, H-3, H-4, H-5, H-6, CH_2-7, 2×NCH_2, OCH_2-Ada, CH_2-5 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.82 – 1.51 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl/butyl), 1.51 – 1.25 (m, 4H, 2×CH_2 pentyl/butyl), 1.06 – 0.93 (m, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) collapsed iminosugar signals δ 83.2 (OCH_2-Ada), 74.8, 74.8, 72.7 (CH_2-5 pentyl), 70.1, 70.0, 64.1, 41.0 (CH_2 Ada), 40.6 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 30.4, 30.2, 24.9, 21.3 (CH_2 pentyl/butyl), 14.2 (CH_3 butyl). $[\alpha]^{20}_D$: 8.6 (*c* 0.7, MeOH). IR ν_{max}(thin film)/ cm^{-1}: 3344, 2901, 2848, 1668, 1652, 1456, 1360, 1093, 1027. HRMS: found 497.3581 $[M+H]^+$; calculated for $[C_{27}H_{48}N_2O_6+H]^+$ 497.3585.



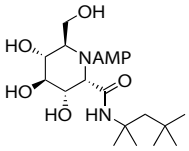
5-(Adamantan-1yl-methoxy)-pentyl 2,6-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-D-*glycero*-D-*ido*-heptonamide (E5-I). Compound **E5-I** (59 mg, 87 µmol) was synthesized in 60% yield over two steps from **E2-I** (145 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F *N*-alkylated penultimate = 0.69 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 3.94 – 3.33 (m, 11H, H-2, H-3, H-4, H-5, H-6, CH_2-7, 2×CH_2-5 pentyl), 3.29 – 3.08 (m, 2H, C(O)NCH_2-1 penty), 2.98 – 2.91 (s, 5H, 2×OCH_2-Ada, NC*H*H-1 pentyl), 2.88 – 2.78 (m, 1H, NCH*H*-1 pentyl), 1.94 (s, 6H, 6×CH Ada), 1.81 – 1.47 (m, 20H, 6×CH_2 Ada, 4×CH_2 pentyl), 1.46 – 1.31 (m, 4H, 2× CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) collapsed iminosugar signals δ 83.2, 83.2 (2×OCH_2-Ada), 76.0 (C-4), 72.7, 72.6 (2×CH_2-5 pentyl), 71.4 (C-3), 71.1 (C-5), 64.5 (C-2), 63.9 (C-6), 59.1 (C-7), 50.9 (NCH_2-1 pentyl), 41.0 (2×CH_2 Ada), 40.3 (C(O)NCH_2-1 pentyl), 38.5 (2×CH_2 Ada), 35.3 (2×C_q Ada), 30.7, 30.5, 30.4 (CH_2), 29.9 (2×CH Ada), 28.3 (CH_2), 25.1, 24.9 (2×CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3367, 2901, 2848, 1638, 1455, 1109. $[\alpha]^{20}_D$: 12.8 (*c* 0.5, MeOH). HRMS: found 675.4942 $[M+H]^+$; calculated for $[C_{39}H_{66}N_2O_7+H]^+$ 675.4943.



1,1,3,3-Tetramethylbutyl 2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptonamide (E3-II). Compound **E3-II** (20 mg, 63 µmol) was synthesized in 67% yield from **E2-II** (94 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.21 (1:6.6; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.88 (dd, *J* = 3.2, 11.3, 1H, H-7a), 3.79 (dd, *J* = 5.7, 9.4, 1H, H-3), 3.75 (d, *J* = 5.7, 1H, H-2), 3.67 (dd, *J* = 6.4, 11.3, 1H, H-7b), 3.47 (dd, *J* = 8.7, 9.4, 1H, H-4), 3.27 (d, *J* = 8.7, 1H, H-5), 2.94 – 2.86 (m, 1H, H-6), 1.86 (d, *J* = 14.9, 1H, C*H*H-2 tMB), 1.70 (d, *J* = 14.9, 1H, CH*H*-2 tMB), 1.43 (d, *J* = 11.8, 6H, 2×CH_3 tMB), 1.03 (s, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (100 MHz, MeOD) δ 169.9 (C(O)-1), 76.1 (C-4), 72.3 (C-3), 72.0 (C-5), 61.7 (C-7), 59.4 (C-6), 58.5 (C-1), 56.6 (NHC_q-1 tMB), 53.0 (CH_2-2 tMB), 32.6 (C_q-3 tMB), 32.1 (CH_3-4, 2×CH_3 tMB), 29.6, 29.5 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3304, 2955, 2362, 1726, 1651, 1559, 1419, 1366, 1272, 1227, 1119, 1073, 1040. $[\alpha]^{20}_D$: 47.7 (*c* 0.3, MeOH). HRMS: found 319.2229 $[M+H]^+$; calculated for $[C_{15}H_{30}N_2O_5+H]^+$ 319.2222.

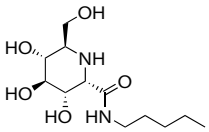


1,1,3,3-Tetramethylbutyl 2,6-butylimino-2,6-dideoxy-D-*glycero*-D-*ido*-heptonamide (E4-II). Compound **E4-II** (30 mg, 80 µmol) was synthesized in 82% yield over two steps from **E2-II** (97 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F *N*-alkylated penultimate = 0.70 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.01 – 3.39 (m, 7H, H-2, H-3, H-4, H-5, H-6, CH_2-7), 3.06 – 3.02 (s, 2H, NCH_2 butyl), 1.84 – 1.73 (m, 2H, CH_2-2 tMB), 1.71 – 1.24 (m, 8H, 2×CH_3 tMB, 2×CH_2 butyl), 1.03 (s, 9H, CH_3-4, 2×CH_3 tMB), 0.98 (t, *J* = 7.4, 3H, CH_3 butyl). ^{13}C NMR (101 MHz, MeOD) collapsed iminosugar signals δ 70.4, 64.8, 63.2, 56.9 (NHC_q-1 tMB), 54.0, 53.7, 52.9 (CH_2-2 tMB), 33.7 (CH_2 butyl), 32.5 (C_q-3 tMB), 32.1 (CH_3-4, 2×CH_3 tMB), 29.4, 29.3 (2×CH_3 tMB), 21.4 (CH_2 butyl), 14.3 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3327, 2959, 1668, 1652, 1458, 1366, 1227, 1051. $[\alpha]^{20}_D$: 22.2 (*c* 0.4, MeOH). HRMS: found 375.2854 $[M+H]^+$; calculated for $[C_{19}H_{38}N_2O_5+H]^+$ 375.2853.

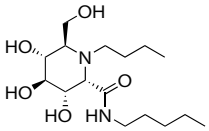


1,1,3,3-Tetramethylbutyl 2,6-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-D-*glycero*-D-*ido*-heptonamide (E5-II). Compound **E5-II** (33 mg, 60 µmol) was synthesized in 54% yield over two steps from **E2-II** (111 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F *N*-alkylated penultimate = 0.74 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) δ 3.89 (dd, *J* = 3.5, 11.8, 1H, H-7a), 3.78 (dd, *J* = 6.4, 11.8,

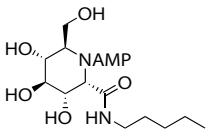
1H, H-7b), 3.68 (dd, *J* = 6.0, 9.6, 1H, H-3), 3.62 (d, *J* = 5.9, 1H, H-2), 3.58 – 3.51 (m, 1H, H-4), 3.39 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.37 – 3.32 (m, 1H, H-5), 3.06 – 2.98 (m, 1H, H-6), 2.97 (s, 2H, OCH_2-Ada), 2.91 – 2.81 (m, 1H, NC*H*H-1 pentyl), 2.76 – 2.65 (m, 1H, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.85 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.80 – 1.64 (m, 7H, 3×CH_2 Ada, CH*H*-2 tMB), 1.64 – 1.51 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.47 – 1.34 (m, 8H, CH_2-3 pentyl, 2×CH_3 tMB), 1.03 (s, 9H, CH_3-4, 2×CH_3 tMB). ^{13}C NMR (101 MHz, MeOD) δ 83.3 (OCH_2-Ada), 77.7 (C-4), 72.7 (CH_2-5 pentyl), 71.6, 71.4 (C-3, C-5), 63.6 (C-6), 63.1 (C-2), 60.0 (C-7), 56.3 (NHC_q-1 tMB), 53.0 (CH_2-2 tMB), 48.9 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 33.6 (C_q-3 tMB), 32.6 (CH_2 pentyl), 32.2 (CH_3-4, 2×CH_3 tMB), 30.8 (CH_2 pentyl), 29.9 (CH Ada), 29.5, 29.2 (2×CH_3 tMB), 25.2 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3377, 2902, 2849, 1651, 1424, 1366, 1227, 1157, 1098. $[\alpha]^{20}_D$: 24.8 (*c* 0.4, MeOH). HRMS: found 553.4208 $[M+H]^+$; calculated for $[C_{31}H_{56}N_2O_6+H]^+$ 553.4211.



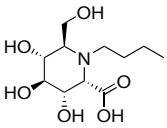
Pentyl 2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptonamide (E3-III). Compound **E3-III** (20 mg, 72 µmol) was synthesized in 77% yield from **E2-III** (93 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.13 (1:6.6; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.90 (d, *J* = 5.7, 1H, H-2), 3.87 (dd, *J* = 3.2, 11.4, 1H, H-7a), 3.78 (dd, *J* = 5.7, 9.4, 1H, H-3), 3.74 – 3.70 (dd, *J* = 6.1, 11.4, 1H, H-7b), 3.52 (dd, *J* = 8.5, 9.4, 1H, H-4), 3.35 – 3.30 (m, 1H, H-5), 3.30 – 3.17 (m, 2H, NCH_2-1 pentyl), 3.09 (ddd, *J* = 3.2, 6.1, 9.6, 1H, H-6), 1.59 – 1.50 (m, 2H, CH_2-2 pentyl), 1.40 – 1.27 (m, 4H, 2×CH_2 pentyl), 0.92 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 169.4 (C(O)-1), 74.3 (C-4), 70.6 (C-3), 70.2 (C-5), 59.9 (C-7), 57.9 (C-6), 56.5 (C-2), 38.9 (NCH_2-1 pentyl), 28.8, 28.7, 22.0 (3×CH_2 pentyl), 12.9 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3289, 2957, 2929, 1729, 1651, 1558, 1454, 1274, 1074, 1037. $[\alpha]^{20}_D$: 35.9 (*c* 0.4, MeOH). HRMS: found 277.1759 $[M+H]^+$; calculated for $[C_{12}H_{24}N_2O_5+H]^+$ 277.1758.



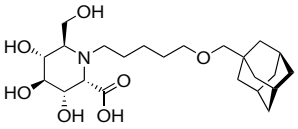
Pentyl 2,6-butylimino-2,6-dideoxy-D-*glycero*-D-*ido*-heptonamide (E4-III). Compound **E4-III** (23 mg, 69 µmol) was synthesized in 71% yield over two steps from **E2-III** (97 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F *N*-alkylated penultimate = 0.64 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.18 – 3.44 (m, 7H, H-2, H-3, H-4, H-5, H-6, CH_2-7), 3.30 – 2.87 (m, 4H, 2×NCH_2 pentyl/butyl), 1.84 – 1.28 (m, 10H, 5×CH_2 pentyl/butyl), 0.98 (t, *J* = 7.4, 3H, CH_3 butyl), 0.92 (t, *J* = 6.2, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) collapsed iminosugar signals δ 73.3, 68.6, 63.7, 62.6, 39.1, 39.0, 28.8, 28.5, 22.0, 19.8, 12.9 (CH_3-5 pentyl), 12.7 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3323, 2960, 1652, 1460, 1030. $[\alpha]^{20}_D$: 13.0 (*c* 0.2, MeOH). HRMS: found 333.2385 $[M+H]^+$; calculated for $[C_{16}H_{32}N_2O_5+H]^+$ 333.2384.



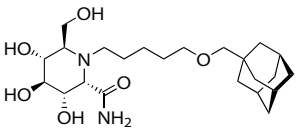
Pentyl 2,6-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-D-*glycero*-D-*ido*-heptonamide (E5-III). Compound **E5-III** (40 mg, 78 µmol) was synthesized in 71% yield over two steps from **E2-III** (110 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F *N*-alkylated penultimate = 0.69 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.31 – 2.99 (m, 13H, H-2, H-3, H-4, H-5, H-6, CH_2-7, CH_2-5 pentyl, 2×NCH_2), 2.97 (s, 2H, OCH_2 Ada), 1.94 (s, 3H, 3×CH Ada), 1.87 – 1.28 (m, 18H, 3×CH_2 Ada, 6×CH_2 pentyl), 0.97 – 0.85 (m, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) collapsed iminosugar signals δ 83.2 (OCH_2 Ada), 74.7, 72.2 (CH_2-5 pentyl), 69.9, 65.5, 64.0, 41.0 (CH_2 Ada), 40.6 (C(O)NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 30.4, 30.4, 30.1, 26.6, 24.8, 23.6 (6×CH_2 pentyl), 14.5 (CH_3-5 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3328, 2903, 2849, 1668, 1652, 1455, 1093, 1028. $[\alpha]^{20}_D$: 6.8 (*c* 0.8, MeOH). HRMS: found 511.3738 $[M+H]^+$; calculated for $[C_{28}H_{50}N_2O_6+H]^+$ 511.3742.



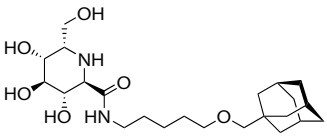
2,6-Butylimino-2,6-dideoxy-D-*glycero*-D-*ido*-heptonic acid (E4-V). Compound **E4-V** (19 mg, 72 µmol) was synthesized in 69% yield over two steps from **E2-V** (104 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.04 (1:3; MeOH:DCM). ^{1}H NMR (400 MHz, MeOD) δ 4.10 (d, *J* = 5.5, 1H, H-2), 4.00 (d, *J* = 4.0, 2H, CH_2-7), 3.90 – 3.80 (m, 2H, H-3, H-6), 3.66 (dd, *J* = 8.4, 1H, H-4), 3.59 (dd, *J* = 8.0, 10.0, 1H, H-5), 3.53 – 3.32 (m, 2H, NCH_2 butyl), 1.81 – 1.65 (m, 2H, CH_2-2 butyl), 1.54 – 1.37 (m, 4H, 2×CH_2 butyl), 0.99 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 75.8 (C-4), 70.0 (C-3), 69.5 (C-5), 65.1 (C-6), 63.4 (C-2), 56.8 (C-7), 51.7 (NCH_2 butyl), 28.5, 21.1 (2×CH_2 butyl), 14.1 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3265, 2962, 1622, 1380, 1100, 1025. $[\alpha]^{20}_D$: 9.3 (*c* 0.2, MeOH). HRMS: found 264.1444 $[M+H]^+$; calculated for $[C_{11}H_{21}NO_6+H]^+$ 264.1442.



2,6-[5-(Adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptonic acid (E5-V). Compound **E5-V** (6 mg, 14 µmol) was synthesized in 30% yield over two steps from **E5-V** (45 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.10 (1:3; MeOH:DCM). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.12 – 3.32 (m, 11H, H-2, H-3, H-4, H-5, H-6, CH_2-7, CH_2-5 pentyl, NCH_2), 2.97 (s, 2H, OCH_2-Ada), 1.95 (s, 3H), 1.82 – 1.36 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (100 MHz, MeOD) collapsed iminosugar signals δ 83.3 (OCH_2-Ada), 72.3 (CH_2-5 pentyl), 70.1, 69.6, 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.3, 29.9 (CH Ada), 24.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3311, 2902, 2848, 1651, 1456, 1398, 1053. $[\alpha]^{20}_D$: 2.3 (*c* 0.1, MeOH). HRMS: found 442.2801 $[M+H]^+$; calculated for $[C_{23}H_{39}NO_7+H]^+$ 442.2799.

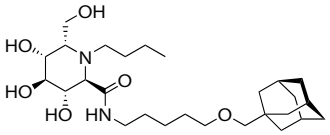


2,6-[5-(Adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptonamide (E5-VI). Compound **E5-VI** (12 mg, 27 µmol) was synthesized in 39% yield over two steps from **E2-VI** (70 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.31 (1:6.5; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.88 (dd, *J* = 3.4, 11.8, 1H, H-7a), 3.79 (dd, *J* = 5.2, 11.8, 1H, H-7b), 3.73 (d, *J* = 5.7, 1H, H-2), 3.71 – 3.60 (m, 2H, H-3, H-4), 3.39 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.35 – 3.31 (m, 1H, H-5), 3.15 – 3.08 (m, 1H, H-6), 2.97 (s, 2H, OCH_2-Ada), 2.79 – 2.74 (m, 2H, NCH_2-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.6, 31.4, 6H, 3×CH_2 Ada), 1.64 – 1.52 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.44 – 1.33 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 178.1 (C(O)-1), 83.2 (OCH_2-Ada), 76.8 (C-4), 72.7 (CH_2-5 pentyl), 72.2 (C-5), 71.6 (C-3), 63.8 (C-2), 63.1 (C-6), 60.6 (C-7), 49.9 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2 pentyl), 29.9 (CH Ada), 29.4 (CH_2 pentyl), 25.2 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3326, 2902, 2848, 1650, 1451, 1158, 1096. $[\alpha]^{20}_D$: 17.5 (*c* 0.2, MeOH).HRMS: found 441.2956 $[M+H]^+$; calculated for $[C_{23}H_{40}N_2O_6+H]^+$ 441.2959.

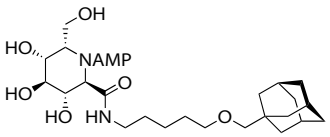


5-(Adamantan-1yl-methoxy)-pentyl 2,6-dideoxy-2,6-imino-L-*glycero*-D-*gulo*-heptonamide (F3-I). Compound **F3-I** (7 mg, 16 µmol) was synthesized in 41% yield from **F2-I** (39 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.01 – 3.35 (m, 9H, H-2, H-3, H-4, H-5, H-6, CH_2-7, CH_2-5 pentyl), 3.28 – 3.22 (m, 2H, NCH_2-1 pentyl), 2.96 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.72 (d, *J* = 21.1, 6H, 3×CH_2 Ada, 1.63 – 1.49 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.49 – 1.35 (m, 2H, CH_2-5

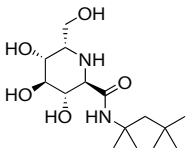
pentyl). ^{13}C NMR (100 MHz, MeOD) δ 171.8 (C(O)-1), 83.2 (OCH_2-Ada), 74.3, 73.3, 71.9 (C-3, C-4, C-5), 72.6 (CH_2-3 pentyl), 59.2 (C-7), 59.1, 57.7 (C-2, C-6), 41.0 (CH_2 Ada), 40.7 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.5, 30.3 (2×CH_2 pentyl), 29.9 (CH Ada), 24.8 (CH_2-3 pentyl). $[\alpha]^{20}_D$: −3.0 (*c* 1.0, MeOH). IR ν_{max}(thin film)/ cm^{-1}: 3312, 2901, 2848, 1652, 1455, 1099. HRMS: found 441.2957 $[M+H]^+$; calculated for $[C_{23}H_{40}N_2O_6+H]^+$ 441.2959.



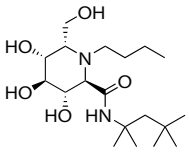
5-(Adamantan-1yl-methoxy)-pentyl 2,6-butylimino-2,6-dideoxy-L-*glycero*-D-*gulo*-heptonamide (F4-I). Compound **F4-I** (17 mg, 34 μmol) was synthesized in 83% yield over two steps from **F2-I** (41 μmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.36 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.62 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 4.16 – 3.47 (m, 6H, H-2, H-3, H-4, H-5, CH_2-7), 3.39 (t, *J* = 6.4, 3H, H-6, CH_2-5 pentyl), 3.30 – 3.17 (m, 2H, NCH_2-1 pentyl), 3.10 – 2.86 (m, 3H, OCH_2-Ada, NC*H*H butyl), 2.81 – 2.57 (m, 1H, NCH*H* butyl), 1.95 (s, 3H, 3×CH Ada), 1.80 – 1.26 (m, 22H, 6×CH_2 Ada, 3×CH_2 pentyl, 2×CH_2 butyl), 0.94 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 83.3 (OCH_2-Ada), 75.3, 73.1 (C-3, C-4, C-5), 72.6 (CH_2-5 pentyl), 68.1, 62.9 (C-2, C-5), 56.2 (C-7), 52.2 (NCH_2 butyl), 41.0 (CH_2 Ada), 40.7 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.5, 30.2 (CH_2 pentyl/butyl), 29.9 (CH Ada), 24.9 (CH_2-3 pentyl), 21.4 (CH_2 butyl), 14.3 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3316, 2903, 2849, 1652, 1458, 1074. $[\alpha]^{20}_D$: −1.0 (*c* 0.2, MeOH). HRMS: found 497.3581 $[M+H]^+$; calculated for $[C_{27}H_{48}N_2O_6+H]^+$ 497.3585.



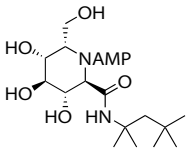
5-(Adamantan-1yl-methoxy)-pentyl 2,6-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-L-*glycero*-D-*gulo*-heptonamide (F5-I). Compound **F5-I** (22 mg, 33 μmol) was synthesized in 79% yield over two steps from **F2-I** (42 μmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F *N*-alkylated penultimate = 0.66 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) δ 3.96 – 3.82 (m, 2H, CH_2-7), 3.77 – 3.69 (m, 1H, H-5), 3.67 – 3.53 (m, 1H, H-3), 3.53 – 3.43 (m, 1H, H-4), 3.43 – 3.34 (m, 5H, 2×CH_2-5 pentyl, H-2), 3.33 – 3.12 (m, 3H, H-5, C(O)NCH_2-1 pentyl), 3.00 – 2.95 (m, 3H, 2×OCH_2-Ada), 2.86 – 2.73 (m, 1H, NC*H*H pentyl), 2.61 – 2.49 (m, 1H, NCH*H* pentyl), 1.95 (s, 6H, 6×CH Ada), 1.82 – 1.26 (m, 24H, 6×CH_2 Ada, 6×CH_2 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.3, 83.2 (2×OCH_2-Ada), 75.9 (C-4), 73.6 (C-3), 72.7, 72.6 (2×CH_2-5 pentyl), 71.8(C-5), 68.0 (C-2), 62.5 (C-6), 56.9 (C-7), 51.7 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 40.6 (C(O)NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7, 30.6, 30.3 (CH_2 pentyl), 29.9 (CH Ada), 25.1, 25.0 (2×CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3366, 2901, 2848, 1652, 1455, 130, 1157, 1110. $[\alpha]^{20}_D$: −2.3 (*c* 0.4, MeOH). HRMS: found 675.4941 $[M+H]^+$; calculated for $[C_{39}H_{66}N_2O_7+H]^+$ 675.4943.



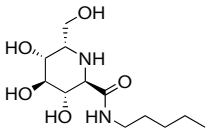
1,1,3,3-Tetramethylbutyl 2,6-dideoxy-2,6-imino-L-*glycero*-D-*gulo*-heptonamide (F3-II). Compound **F3-II** (17 mg, 53 μmol) was synthesized in 88% yield from **F2-II** (60 μmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.30 (1:4; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.95 – 3.55 (m, 7H, H-2, H-3, H-4, H-5, H-6, CH_2-7), 1.88 (s, 1H, C*H*H-2 tMB), 1.72 (s, 1H, CH*H*-2 tMB), 1.41 (s, 6H, 2×CH_3 tMB), 1.02 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, MeOD) δ 166.5 (C(O)-1), 72.2, 70.9, 69.0 (C-3, C-4, C-5), 57.3 (C-2), 57.0 (C-7), 56.0 (C-6), 55.3 (NHC_q-1 tMB), 51.2 (CH_2-2 tMB), 31.0 (C_q-3 tMB), 30.5 (2×CH_3, CH_3-4 tMB), 28.0, 27.7 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3319,2953, 2438, 1667, 1444, 1366, 1226, 1062. $[\alpha]^{20}_D$: −13.6 (*c* 0.8, MeOH). HRMS: found 319.2229 $[M+H]^+$; calculated for $[C_{15}H_{30}N_2O_5+H]^+$ 319.2222.



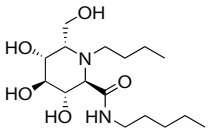
1,1,3,3-Tetramethylbutyl 2,6-butylimino-2,6-dideoxy-L-*glycero*-D-*gulo*-heptonamide (F4-II). Compound **F4-II** (11 mg, 29 µmol) was synthesized in 59% yield over two steps from **F2-II** (49 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.47 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated penultimate = 0.74 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) δ 3.87 (dd, *J* = 4.1, 11.8, 1H, H-7a), 3.79 (dd, *J* = 6.8, 11.7, 1H, H-7b), 3.70 (dd, *J* = 5.6, 9.7, 1H, H-5), 3.59 (dd, *J* = 9.2, 1H, H-3), 3.40 (dd, *J* = 9.1, 1H, H-4), 3.23 – 3.17 (m, 1H, H-6), 3.16 (d, *J* = 9.5, 1H, H-2), 2.71 (ddd, *J* = 5.5, 9.6, 12.6, 1H, NC*H*H-1 pentyl), 2.54 (ddd, *J* = 5.6, 9.7, 12.6, 1H, NCH*H*-1 pentyl), 1.92 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.68 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.61 – 1.38 (m, 8H, 2×CH_3 tMB, CH_2 butyl), 1.36 – 1.24 (m, 2H, CH_2 butyl), 1.03 (s, 9H, 2×CH_3, CH_3-4 tMB), 0.92 (t, *J* = 7.3, 3H). ^{13}C NMR (100 MHz, MeOD) δ 173.1 (C(O)-1), 76.1 (C-4), 73.6 (C-3), 71.8 (C-5), 67.8 (C-2), 62.2 (C-6), 57.4 (C-7), 56.5 (NHC_q-1 tMB), 52.9 (CH_2-2 tMB), 51.1 (NCH_2 butyl), 32.6 (C_q-3 tMB), 32.2 (2×CH_3, CH_3-4 tMB), 32.0 (CH_2 butyl), 29.6, 29.2 (2×CH_3 tMB), 21.6 (CH_2 butyl), 14.6 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3374, 2957, 2497, 1728, 1652, 1434, 1366, 1276, 1228, 1122, 1072. $[\alpha]^{20}_D$: −7.8 (*c* 0.2, MeOH). HRMS: found 375.2854 $[M+H]^+$; calculated for $[C_{19}H_{38}N_2O_5+H]^+$ 375.2853.



1,1,3,3-Tetramethylbutyl 2,6-[5-(adamantan-1yl-methoxy)-pentyl]imino- 2,6-dideoxy-L-*glycero*-D-*gulo*-heptonamide (F5-II). Compound **F5-II** (20 mg, 36 µmol) was synthesized in 69% yield over two steps from **F2-II** (52 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F *N*-alkylated penultimate = 0.77 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) δ 3.98 – 3.80 (m, 2H, CH_2-7), 3.80 – 3.65 (m, 1H, H-4), 3.65 – 3.50 (m, 1H, H-3), 3.50 – 3.21 (m, 5H, CH_2-5 pentyl, H-2, H-4, H-6), 3.03 – 2.91 (m, 2H, OCH_2-Ada), 2.89 – 2.74 (m, 1H, NC*H*H-1 pentyl), 2.73 – 2.53 (m, 1H, NCH*H*-1 pentyl), 2.03 – 1.17 (m, 27H, 3×CH Ada, CH_2-2 tMB, 6×CH_2 Ada, 3×CH_2 pentyl, 2×CH_3 tMB), 1.03 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, MeOD) δ 81.6 (OCH_2-Ada), 74.3 (C-4), 71.9 (C-3), 71.0 (CH_2-5 pentyl), 70.0 (C-5), 66.5 (C-2), 60.8 (C-6), 55.5 (NHC_q-1 tMB), 55.1 (C-7), 51.4 (CH_2-2 tMB), 50.1 (NCH_2-1 pentyl), 39.5 (CH_2 Ada), 36.9 (CH_2 Ada), 33.7 (C_q Ada), 31.0, 30.7, 29.2, 28.4 (CH Ada), 28.0, 27.7 (2×CH_3 tMB), 23.6 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3342, 2902, 2849, 1652, 1449, 1366, 1227, 1157, 1111. $[\alpha]^{20}_D$: −3.1 (*c* 0.4, MeOH). HRMS: found 553.4208 $[M+H]^+$; calculated for $[C_{31}H_{56}N_2O_6+H]^+$ 553.4211.

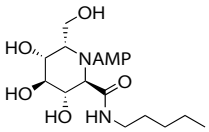


Pentyl 2,6-dideoxy-2,6-imino-L-*glycero*-D-*gulo*-heptonamide (F3-III). Compound **F3-III** (13 mg, 46 µmol) was synthesized in 92% yield from **F2-III** (50 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.85 (1:4; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.89 (dd, *J* = 4.5, 11.7, 1H, H-7a), 3.86 – 3.75 (m, 3H, H-2, H-5, H-7b), 3.73 (t, *J* = 7.3, 1H, CH), 3.67 (t, *J* = 7.3, 1H, CH), 3.57 (dt, *J* = 4.7, 9.0, 1H, H-6), 3.24 (dt, *J* = 2.7, 7.0, 2H, NCH_2-1 pentyl), 1.61 – 1.47 (m, 2H, CH_2-2 pentyl), 1.46 – 1.23 (m, 4H, 2×CH_2 pentyl), 0.92 (t, *J* = 6.8, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 170.0 (C(O)-1), 73.7, 72.7, 70.9 (C-3, C-4, C-5), 58.9 (C-2), 58.8 (C-7), 57.7 (C-6), 40.9 (NCH_2-1 pentyl), 30.3, 30.1, 23.6 (3×CH_2 pentyl), 14.5 (CH_3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3312, 2931, 1652, 1460, 1062. $[\alpha]^{20}_D$: −7.5 (*c* 0.8, MeOH). HRMS: found 277.1759 $[M+H]^+$; calculated for $[C_{12}H_{24}N_2O_5+H]^+$ 277.1758.

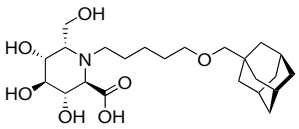


Pentyl 2,6-butylimino-2,6-dideoxy-L-*glycero*-D-*gulo*-heptonamide (F4-III). Compound **F4-III** (10 mg, 30 µmol) was synthesized in 64% yield over two steps from **F2-III** (47 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.37 (1:4; MeOH:DCM+2% NH_4OH); R_F *N*-alkylated

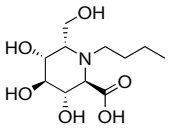
penultimate = 0.59 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) δ 3.88 (dd, *J* = 4.2, 11.8, 1H, H-7a), 3.82 (dd, *J* = 6.4, 11.8, 1H, H-7b), 3.76 – 3.69 (m, 1H, H-5), 3.63 – 3.57 (m, 1H, H-3), 3.41 (dd, *J* = 8.9, 9.9, 1H, H-4), 3.29 – 3.14 (m, 4H, H-2, H-6, NCH_2-1 pentyl), 2.70 (ddd, *J* = 5.4, 9.6, 12.5, 1H, NC*H*H butyl), 2.47 (ddd, *J* = 5.7, 9.7, 12.5, 1H, NCH*H* butyl), 1.62 – 1.23 (m, 10H, 3×CH_2 pentyl, 2×CH_2 butyl), 0.96 – 0.88 (m, 6H, 2×CH_3 pentyl/butyl). ^{13}C NMR (100 MHz, MeOD) δ 174.2 (C(O)-1), 76.1 (C-4), 73.8 (C-3), 72.1 (C-5), 67.9 (C-2), 62.3 (C-6), 57.1 (C-7), 51.1 (NCH_2 butyl), 40.6 (NCH_2-1 pentyl), 31.6, 30.5, 30.2, 23.6, 21.6 (3×CH_2 pentyl, 2×CH_2 butyl), 14.5, 14.5 (2×CH_3 butyl/pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3329, 2958, 2931, 2871, 1730, 1637, 1462, 1378, 1278, 1122, 1073. $[\alpha]^{20}_D$: −7.8 (*c* 0.2, MeOH). HRMS: found 333.2385 $[M+H]^+$; calculated for $[C_{16}H_{32}N_2O_5+H]^+$ 333.2384.



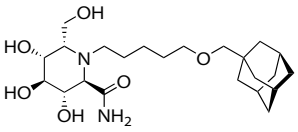
Pentyl 2,6-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-L-*glycero*-D-*gulo*-heptonamide (F5-III). Compound **F5-III** (13 mg, 25 μmol) was synthesized in 51% yield over two steps from **F2-III** (49 μmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F *N*-alkylated penultimate = 0.62 (1:2; EtOAc:toluene). ^{1}H NMR (400 MHz, MeOD) δ 3.89 (dd, *J* = 2.8, 11.6, 1H, H-7a), 3.84 (dd, *J* = 6.1, 11.7, 1H, H-7b), 3.72 (dd, *J* = 5.6, 9.8, 1H, H-5), 3.60 (dd, *J* = 9.2, 1H, H-3), 3.46 – 3.39 (m, 1H, H-4), 3.36 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.30 – 3.09 (m, 4H, H-2, H-6, C(O)NCH_2-1 pentyl), 2.96 (s, 2H, OCH_2-Ada), 2.83 – 2.68 (m, 1H, NC*H*H pentyl), 2.56 – 2.43 (m, 1H, NCH*H* pentyl), 1.94 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 12.2, 33.0, 6H, 3×CH_2 Ada), 1.64 – 1.26 (m, 18H, 3×CH_2 Ada, 6×CH_2 pentyl), 0.92 (t, *J* = 6.2, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 81.7 (OCH_2-Ada), 74.5 (C-4), 72.2 (C-3), 71.1 (CH_2-5 pentyl), 70.4 (C-5), 66.4 (C-2), 60.9 (C-6), 55.5 (C-7), 49.9 (NCH_2-1 pentyl), 39.5 (CH_2 Ada), 39.1 (C(O)NCH_2-1 pentyl), 36.9 (CH_2 Ada), 33.8 (C_q Ada), 28.4 (CH Ada), 29.2, 28.9, 28.7, 27.5, 23.5, 22.1 (6×CH_2 pentyl), 13.0 (CH_3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3342, 2903, 2849, 1651, 1458, 1157, 1051. $[\alpha]^{20}_D$: −1.1 (*c* 0.2, MeOH). HRMS: found 511.3738 $[M+H]^+$; calculated for $[C_{28}H_{50}N_2O_6+H]^+$ 511.3742.



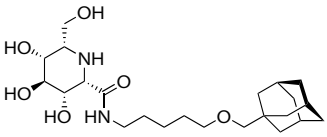
2,6-Butylimino-2,6-dideoxy-L-*glycero*-D-*gulo*-heptonic acid (F4-V). Compound **F4-V** (8 mg, 30 μmol) was synthesized in 88% yield over two steps from **F2-V** (34 μmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.04 (1:3; MeOH:DCM). ^{1}H NMR (400 MHz, MeOD) δ 4.19 – 3.70 (m, 7H, H-2, H-3, H-4, H-5, H-6, CH_2-7), 3.48 – 3.38 (m, 2H, NCH_2 butyl), 1.74 (s, 2H, CH_2 butyl), 1.49 – 1.39 (m, 2H, CH_2 butyl), 0.98 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 72.4, 71.8, 69.8, 68.6 (C-2, C-3, C-4, C-5), 61.7 (C-6), 57.3 (C-7), 52.7 (NCH_2 butyl), 28.8 (CH_2 butyl), 20.9 (CH_2 butyl), 14.1. IR ν_{max}(thin film)/ cm^{-1}: 3224, 2927, 1622, 1404, 1067. $[\alpha]^{20}_D$: −0.6 (*c* 0.4, MeOH). HRMS: found 264.1444 $[M+H]^+$; calculated for $[C_{11}H_{21}NO_6+H]^+$ 264.1442.



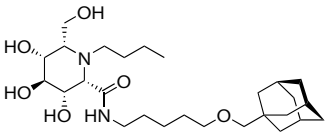
2,6-Butylimino-2,6-dideoxy-L-*glycero*-D-*gulo*-heptonamide (F4-VI). Compound **F4-VI** (5 mg, 19 μmol) was synthesized in 95% yield over two steps from **F2-VI** (20 μmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.21 (1:3; MeOH:DCM). ^{1}H NMR (400 MHz, MeOD) δ 3.95 – 3.80 (m, 2H, CH_2-7), 3.73 (dd, *J* = 5.5, 9.8, 1H, H-5), 3.60 (dd, *J* = 9.3, 1H, H-3), 3.45 (dd, *J* = 9.4, 1H, H-4), 3.37 – 3.20 (m, 2H, H-2, H-6), 2.82 – 2.71 (m, 1H, NC*H*H butyl), 2.62 – 2.46 (m, 1H, NCH*H* butyl), 1.70 – 1.22 (m, 4H, 2×CH_2 butyl), 1.01 – 0.87 (m, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 76.0, 73.7, 71.9, 67.5, 62.3 (C-2, C-3, C-4, C-5, C-6), 57.1 (C-7), 51.2 (NCH_2 butyl), 38.3 (CH_2 butyl), 21.5 (CH_2 butyl), 14.5 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3262, 2960, 1641, 1460, 1072. $[\alpha]^{20}_D$: 0.5 (*c* 0.1, MeOH). HRMS: found 263.1603 $[M+H]^+$; calculated for $[C_{11}H_{22}N_2O_5+H]^+$ 263.1601.



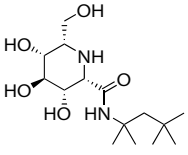
2,6-[5-(Adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-L-*glycero*-D-*gulo*-heptonamide (F5-VI). Compound **F5-VI** (7 mg, 16 µmol) was synthesized in 80% yield over two steps from **F2-VI** (20 µmol) via a reductive amination with the appropriate aldehyde (general procedure E) and a subsequent benzyl-ether deprotection (appropriate method in general procedure F). R_F = 0.43 (1:3; MeOH:DCM). ^{1}H NMR (400 MHz, MeOD) δ 3.89 (dd, *J* = 4.1, 11.9, 1H, H-7a), 3.83 (dd, *J* = 6.3, 11.6, 1H, H-7b), 3.73 (dd, *J* = 5.7, 9.6, 1H, H-5), 3.59 (dd, *J* = 9.2, 1H, H-3), 3.49 – 3.28 (m, 4H, H-2, H-4, CH_2-5 pentyl), 3.23 (dd, *J* = 5.5, 10.4, 1H, H-6), 2.98 – 2.95 (m, 2H, OCH_2-Ada), 2.81 – 2.71 (m, 1H, NC*H*H-1 pentyl), 2.60 – 2.50 (m, 1H, NCH*H*-1 pentyl), 1.94 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.8, 33.6, 6H, 3×CH_2 Ada), 1.65 – 1.46 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.40 – 1.28 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 76.1 (C-4), 73.8 (C-3), 72.8 (CH_2-5 pentyl), 72.0 (C-5), 67.6 (C-2), 62.3 (C-6), 57.2 (C-7), 51.3 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 38.5(CH_2 Ada), 36.0 (C_q Ada), 30.7 (CH_2 pentyl), 29.9 (CH Ada), 29.2 (CH_2 pentyl), 25.0 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3327, 2903, 2849, 1641, 1452, 1158, 1112. $[\alpha]^{20}_D$: 4.6 (*c* 0.1, MeOH). HRMS: found 441.2957 $[M+H]^+$; calculated for $[C_{23}H_{40}N_2O_6+H]^+$ 441.2959.



5-(Adamantan-1yl-methoxy)-pentyl 2,6-dideoxy-2,6-imino-L-*glycero*-D-*ido*-heptonamide (G3-I). Compound **G3-I** (14 mg, 32 µmol) was synthesized in 71% yield from **G2-I** (45 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). ^{1}H NMR (400 MHz, MeOD) δ 4.10 (s, 1H, H-3), 3.97 (dd, *J* = 3.1, 1H, H-4), 3.90 (s, 1H, H-2), 3.86 – 3.73 (m, 3H, H-5, CH_2-7), 3.39 (t, *J* = 6.4, 2, CH_2-5 pentyl), 3.34 – 3.23 (m, 3H, H-6, NCH_2-1 pentyl), 2.97 (s, 2H, OCH_2-Ada), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.7, 32.5, 6H, 3×CH_2 Ada), 1.63 – 1.52 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.47 – 1.37 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 171.3 (C(O)-1), 83.2 (OCH_2-Ada), 72.6 (CH_2-5 pentyl), 71.3 (C-3), 69.7, 69.7 (C-4, C-5), 62.2 (C-7), 59.9 (C-2), 57.6 (C-6), 41.0 (CH_2 Ada), 40.6 (NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.5, 30.3 (2×CH_2 pentyl), 29.9 (CH Ada), 24.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3304, 2902, 2848, 1652, 1453, 1056. $[\alpha]^{20}_D$: −11.3 (*c* 0.3, MeOH). HRMS: found 441.2957 $[M+H]^+$; calculated for $[C_{23}H_{40}N_2O_6+H]^+$ 441.2959.

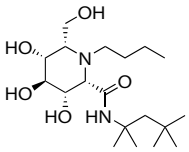


5-(Adamantan-1yl-methoxy)-pentyl 2,6-butylimino-2,6-dideoxy-L-*glycero*-D-*ido*-heptonamide (G4-I). Compound **G4-I** (6 mg, 12 µmol) was synthesized in 41% yield from **G2-I** (29 µmol) via a reductive amination with the appropriate aldehyde (general procedure G). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 3.99 – 3.60 (m, 6H, H-3, H-4, H-5, H-6, CH_2-7), 3.53 (d, *J* = 3.4, 1H, H-2), 3.39 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.34 – 3.15 (m, 4H, H-5, NCH_2-1 pentyl), 2.97 (s, 2H, OCH_2-Ada), 2.84 – 2.64 (m, 2H, NCH_2 butyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 12.0, 31.0, 6H, 3×CH_2 Ada), 1.62 – 1.23 (m, 16H, 3×CH_2 Ada, 3×CH_2 pentyl, 2×CH_2 butyl), 0.94 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 81.7 (OCH_2-Ada), 71.8, 71.7, 70.0 (C-3, C-4, C-5), 71.1 (CH_2-5 pentyl), 63.8 (C-2), 60.3 (C-7), 59.5 (C-6), 52.7 (NCH_2 butyl), 39.5 (CH_2 Ada), 38.8 (NCH_2-1 pentyl), 36.9 (CH_2 Ada), 35.3 (C_q Ada), 28.4 (CH Ada), 29.0, 28.7, 23.5, 20.1 (3×CH_2 pentyl, 2×CH_2 butyl), 12.9 (CH_3 butyl).IR ν_{max}(thin film)/ cm^{-1}: 3315, 2904, 2850, 1651, 1590, 1456, 1065. $[\alpha]^{20}_D$: −6.7 (*c* 0.1, MeOH). HRMS: found 497.3580 $[M+H]^+$; calculated for $[C_{27}H_{48}N_2O_6+H]^+$ 497.3585.

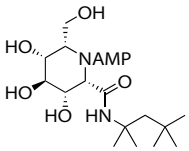


1,1,3,3-Tetramethylbutyl 2,6-dideoxy-2,6-imino-L-*glycero*-D-*ido*-heptonamide (G3-II). Compound **G3-II** (12 mg, 37 µmol) was synthesized in 81% yield from **G2-II** (46 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.41 (1:4; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.13 (s, 1H, CH), 3.97 (s, 1H, CH), 3.87 (s, 1H, CH), 3.82 (s, 3H, CH_2-7, CH), 3.33 (s, 1H, H-6), 1.81 (s, 2H, CH_2-2 tMB), 1.42 (s, 6H, 2×CH_3 tMB), 1.02 (d, *J* = 4.6, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, MeOD) δ 71.1, 69.6, 69.5 (C-3,

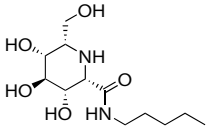
C-4, C-5), 61.8 (C-7), 60.1 (C-2), 57.7 (C-5), 56.7 (NHC_q-1 tMB), 52.4 (CH_2-2 tMB), 32.6 (C_q-3 tMB), 32.0 (2×CH_3, CH_3-4 tMB), 29.8, 29.5 (2×CH_3 tMB). IR ν_{max}(thin film)/ cm^{-1}: 3311, 2955, 2409, 1667, 1752, 1453, 1391, 1366, 1225, 1056. $[\alpha]^{20}_D$: −4.5 (*c* 0.6, MeOH). HRMS: found 319.2229 $[M+H]^+$; calculated for $[C_{15}H_{30}N_2O_5+H]^+$ 319.2222.



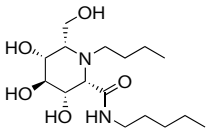
1,1,3,3-Tetramethylbutyl 2,6-butylimino-2,6-dideoxy-L-*glycero*-D-*ido*-heptonamide (G4-II). Compound **G4-II** (7 mg, 19 µmol) was synthesized in 49% yield from **G2-II** (39 µmol) via a reductive amination with the appropriate aldehyde (general procedure G). ^{1}H NMR (400 MHz, MeOD) δ 3.88 – 3.78 (m, 2H, H-7a, CH), 3.77 – 3.70 (m, 2H, 2×CH), 3.66 (dd, *J* = 6.6, 11.3, 1H, H-7b), 3.40 (d, *J* = 3.3, 1H, H-2), 2.97 (dd, *J* = 5.9, 9.8, 1H, H-6), 2.88 – 2.65 (m, 2H, NCH_2-1 butyl), 1.86 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.72 (d, *J* = 14.8, 1H, CH*H*-2 tMB), 1.59 – 1.46 (m, 2H, CH_2 butyl), 1.42 (d, *J* = 1.7, 6H, 2×CH_3 tMB), 1.37 – 1.26 (m, 2H, CH_2 butyl), 1.03 (s, 9H, 2×CH_3, CH_3-4 tMB), 0.94 (t, *J* = 7.4, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 73.2, 73.1, 71.8 (C-3, C-4, C-5), 65.0 (C-2), 61.9 (C-6), 61.4 (C-7), 56.4 (NHC_q-1 tMB), 54.9 (NCH_2 butyl), 53.0 (CH_2-2 tMB), 32.6 (C_q-3 tMB), 32.1 (2×CH_3, CH_3-4 tMB), 29.3 (CH_2 butyl), 29.1, 29.1 (CH_2-2 tMB), 21.6 (CH_2 butyl), 14.5 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3339, 2955, 1638, 1434, 1366, 1227, 1048. $[\alpha]^{20}_D$: −1.4 (*c* 0.1, MeOH). HRMS: found 375.2856 $[M+H]^+$; calculated for $[C_{19}H_{38}N_2O_5+H]^+$ 375.2853.



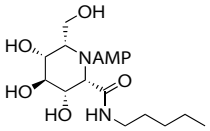
1,1,3,3-Tetramethylbutyl 2,6-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-L-*glycero*-D-*ido*-heptonamide (G5-II). Compound **G5-II** (5 mg, 9 µmol) was synthesized in 21% yield from **G2-II** (43 µmol) via a reductive amination with the appropriate aldehyde (general procedure G). ^{1}H NMR (400 MHz, MeOD) δ 3.85 (dd, *J* = 5.7, 11.4, 1H, H-7a), 3.82 – 3.79 (m, 1H, H-5), 3.77 – 3.71 (m, 2H, H-3, H-4), 3.68 (dd, *J* = 6.4, 11.4, 1H, H-7b), 3.42 (d, *J* = 3.3, 1H, H-2), 3.39 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.02 – 2.95 (m, 3H, H-6, OCH_2-Ada), 2.90 – 2.64 (m, 2H, NCH_2-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.87 (d, *J* = 14.8, 1H, C*H*H-2 tMB), 1.81 – 1.64 (m, 7H, 3×CH_2 Ada, CH*H*-2 tMB), 1.63 – 1.50 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.42 (d, *J* = 1.9, 6H, 2×CH_3 tMB), 1.39 – 1.25 (m, 2H, CH_2-3 pentyl), 1.03 (s, 9H, 2×CH_3, CH_3-4 tMB). ^{13}C NMR (100 MHz, MeOD) δ 81.7 (OCH_2-Ada), 71.1 (CH_2-5 pentyl), 71.5, 71.5, 70.1 (C-3, C-4, C-5), 63.5 (C-2), 60.3 (C-6), 60.0 (C-7), 54.9 (NHC_q-1 tMB), 53.5 (NCH_2-1 pentyl), 51.4 (CH_2-2 tMB), 39.5 (CH_2 Ada), 36.9 (CH_2 Ada), 33.8 (CH Ada), 31.0 (C_q-3 tMB), 30.6 (2×CH_3, CH_3-4 tMB), 29.2 (CH_2 pentyl), 28.4 (CH Ada), 27.8, 27.6 (2×CH_3 tMB), 25.1 (CH_2 pentyl), 23.6 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3367, 2903, 2849, 1638, 1451, 1227, 1056. $[\alpha]^{20}_D$: −2.0 (*c* 0.1, MeOH). HRMS: found 553.4207 $[M+H]^+$; calculated for $[C_{31}H_{56}N_2O_6+H]^+$ 553.4211.



Pentyl 2,6-dideoxy-2,6-imino-L-*glycero*-D-*ido*-heptonamide (G3-III). Compound **G3-III** (13 mg, 46 µmol) was synthesized in 79% yield from **G2-III** (58 µmol) by deprotection of the benzyl-ethers (appropriate method in general procedure F). R_F = 0.29 (1:4; MeOH:DCM+2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.13 – 4.10 (m, 1H, H-3), 3.98 (dd, *J* = 3.4, 1H, H-4), 3.92 (d, *J* = 2.1, 1H, H-2), 3.86 – 3.80 (m, 1H, H-7a), 3.80 – 3.75 (m, 2H, H-7b, H-5), 3.36 – 3.32 (m, 1H, H-6), 3.24 (dt, *J* = 0.9, 7.0, 2H, $NHCH_2$-1 pentyl), 1.60 – 1.50 (m, 2H, CH_2-2 pentyl), 1.39 – 1.29 (m, 4H, 2×CH_2 pentyl), 0.92 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 169.1 (C(O)-1), 69.8 (C-3), 68.1, 67.9 (C-4, C-5), 60.4 (C-7), 58.3 (C-2), 56.2 (C-6), 39.1 (NCH_2-1 pentyl), 28.8, 28.7, 22.0 (3×CH_2 pentyl), 12.9 (CH_3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3259, 2929, 1652, 1460, 1058. $[\alpha]^{20}_D$: −9.8 (*c* 0.8, MeOH). HRMS: found 277.1758 $[M+H]^+$; calculated for $[C_{12}H_{24}N_2O_5+H]^+$ 277.1758.



Pentyl 2,6-butylimino-2,6-dideoxy-L-*glycero*-D-*ido*-heptonamide (G4-III). Compound **G4-III** (5 mg, 15 µmol) was synthesized in 33% yield from **G2-III** (45 µmol) via a reductive amination with the appropriate aldehyde (general procedure G). ^{1}H NMR (400 MHz, MeOD) δ 3.98 (dd, *J* = 3.9, 8.0, 1H, H-7a), 3.91 – 3.52 (m, 5H, H-2, H-3, H-4, H-5, H-7b), 3.29 – 3.10 (m, 2H, NCH_2-1 pentyl), 3.10 – 2.94 (m, 1H, H-6), 2.94 – 2.64 (m, 2H, NCH_2 butyl), 1.76 – 1.25 (m, 10H, 3×CH_2 pentyl, 2×CH_2 butyl), 0.97 – 0.88 (m, 6H, 2×CH_3 pentyl/butyl). ^{13}C NMR (100 MHz, MeOD) δ 71.7, 71.6, 71.1 (C-3, C-4, C-5), 63.7 (C-2), 60.2 (C-7), 59.8 (C-6), 52.6 (NCH_2 butyl), 38.8 (NCH_2-1 pentyl), 36.4 (CH_2 butyl), 28.9, 28.7 (2×CH_2 pentyl), 22.0 (CH_2 pentyl), 20.0 (CH_2 butyl), 12.9, 12.7 (2×CH_3 pentyl/butyl). IR ν_{max}(thin film)/ cm^{-1}: 3344, 2959, 2931, 2872, 1638, 1461, 1061. $[\alpha]^{20}_{D}$: −2.0 (*c* 0.1, MeOH). HRMS: found 333.2385 $[M+H]^+$; calculated for $[C_{16}H_{32}N_2O_5+H]^+$ 333.2384.



Pentyl 2,6-[5-(adamantan-1yl-methoxy)-pentyl]imino-2,6-dideoxy-L-*glycero*-D-*ido*-heptonamide (G5-III). Compound **G5-III** (6 mg, 12 µmol) was synthesized in 24% yield from **G2-III** (50 µmol) via a reductive amination with the appropriate aldehyde (general procedure G). ^{1}H NMR (400 MHz, MeOD) δ 3.90 – 3.81 (m, 2H, H-5, H-7a), 3.80 – 3.68 (m, 3H, H-3, H-4, H-7b), 3.53 (d, *J* = 3.5, 1H, H-2), 3.38 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.30 – 3.12 (m, 2H, C(O)NCH_2-1 pentyl), 3.00 – 2.93 (m, 3H, H-6, OCH_2-Ada), 2.85 – 2.63 (m, 2H, NCH_2-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.8, 31.6, 6H, 3×CH_2 Ada), 1.65 – 1.49 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl/butyl), 1.42 – 1.26 (m, 6H, 3×CH_2 pentyl/butyl), 0.93 (t, *J* = 7.0, 3H, CH_3-5 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 72.7 (CH_2-5 pentyl), 73.3, 73.3, 71.5 (C-3, C-4, C-5), 65.4 (C-2), 61.9 (C-7), 61.1 (C-6), 54.5 (NCH_2-1 pentyl), 41.0 (CH_2 Ada), 40.4 (C(O)NCH_2-1 pentyl), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 29.9 (CH Ada), 30.7, 30.5, 30.2, 25.9, 25.2, 23.6 (6×CH_2 pentyl), 14.5 (CH_3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3327, 2903, 2850, 1649, 1638, 1455, 1362, 1157, 1096, 1057. $[\alpha]^{20}_{D}$: −1.7 (*c* 0.1, MeOH). HRMS: found 511.3737 $[M+H]^+$; calculated for $[C_{28}H_{50}N_2O_6+H]^+$ 511.3742.

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(16) *Note on selective reduction of tertiary amides*: The post-Ugi $LiAlH_4$ reduction as employed by Davis and co-workers for reduction of the endocyclic tertiary amide of pyrrolidine Ugi products resulted in low yields and difficultly separable mixtures of starting compound, the reduced amide and the free secondary amide. Prior to the start of the here presented study several other reduction methods of the tertiary amide were evaluated on a model SAWU-3CR product from **6**. However, also reductions with diisobutylaluminium hydride, borane dimethylsulfide or the tertiary amide selective lithium diisopropylaminoborohydride[38] were unsuccessful and all produced complex mixtures in low yields.

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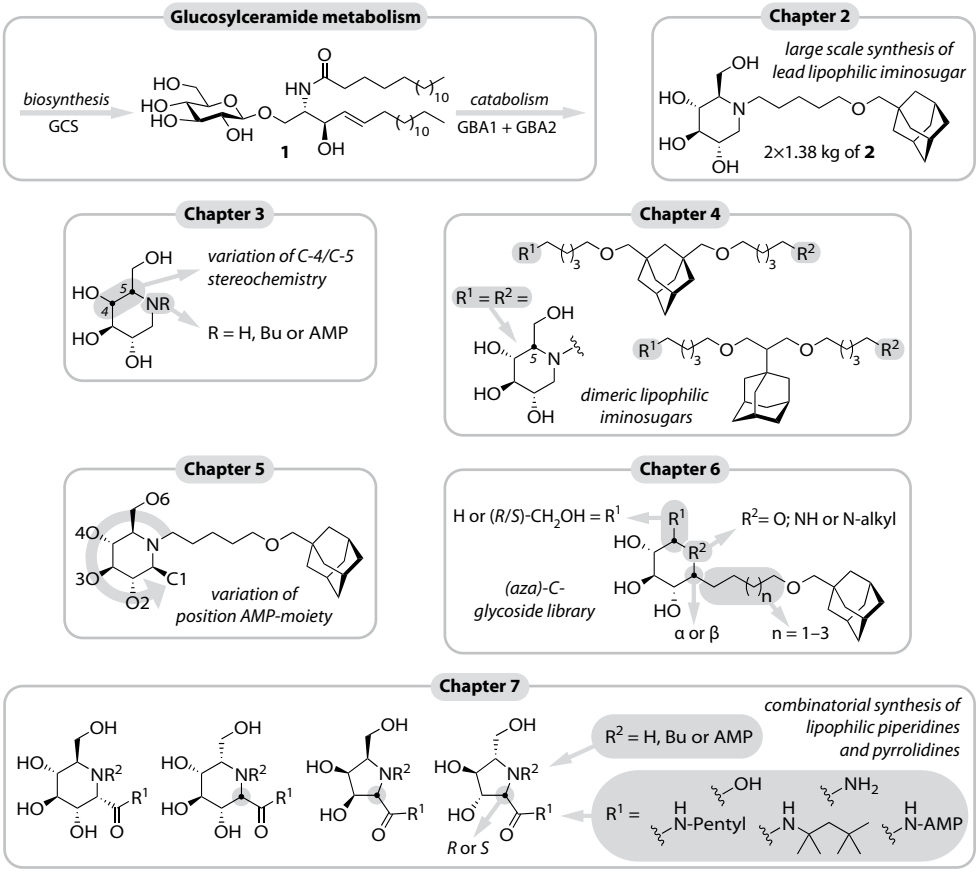
8 Summary, Work in Progress and Prospects

Summary

The primary goal of the research described in this thesis was to develop selective inhibitors for each of the three enzymes associated with glucosylceramide metabolism (Figure 1). Glucosylceramide (**1**) and its more complexly glycosylated derivatives are called glycosphingolipids (GSLs). They are components of the outer cellular membrane and are involved in many (patho)physiological processes in humans. The exact functions and influence of GSLs in these processes however is often still not fully understood. Manipulation of the cellular levels of GSL is one of the ways to investigate their functions. Control of GSL levels can be achieved by targeted inhibition of the enzymes that carry out their biosynthesis and degradation that is their metabolism. The enzymes involved in the metabolism of **1** are an ideal target to accomplish this, because **1** represents the most basic GSL from which almost all more complex GSLs are made in their biosynthesis. Consequently, **1** also represents the substrate in the final step of the degradation of most GSLs. Biosynthesis of **1** is carried out by the glycosyltransferase, glucosylceramide synthase (GCS). The primary catabolism of **1** is achieved by the glycosidase, glucocerebrosidase (GBA1). A second glycosidase, β-glucosidase 2 (GBA2), is also capable of cleaving the glycosidic bond in **1**, but has an unknown function as of yet. Lipophilic iminosugar **2** is a known potent inhibitor of all three these enzymes, but also inhibits several other glycosidases not involved in the metabolism of **1** (Figure 1 and Table 1). More selective inhibitors for each of the three enzymes are needed in order to achieve more accurate

control of the metabolism of **1**. Additionally, the effects on biological processes resulting from selective inhibition of one of the enzymes will be better interpretable due to a decrease in side effects. In this study, **2** was chosen as the lead compound for developing more selective inhibitors through the design, synthesis and evaluation of analogs.

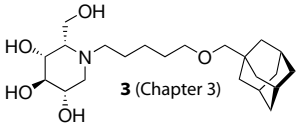
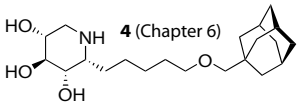
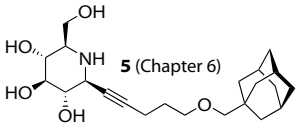
Figure 1. Overview of glucosylceramide metabolism and the research chapters presented in this thesis.



The general introduction of this thesis (**Chapter 1**) discusses the biological background of the study from a historical point of view. First, the metabolism of GSLs is discussed with a focus on GCS, GBA1 and GBA2. Next, the known functions of GSLs in health and disease are discussed together with the therapeutic uses of inhibitors of the metabolism of **1** in treating various GSL related diseases. Finally, an overview of all currently known inhibitors of GCS, GBA1 and GBA2 is provided. The here presented study started with the development and optimization of a route for the large-scale synthesis of **2** in order to obtain a sufficient supply of **2** needed for the principal biological studies (**Chapter 2**; Figure 1). One of these studies investigated the effect of **2** on improvement of glycemic control in type 2 diabetes animal models under the influence of **2**. The research described in **Chapter 3** investigated the mechanism by which **2** achieves this. Evaluation of

derivatives of **2** with altered C-4/C-5 stereochemistry and *N*-alkylation showed that the C-5 epimerized L-*ido*-analogue **3** is a more selective inhibitor of GCS (Table 1). Head to head comparison of this **3** and **2** in rodent models of type 2 diabetes revealed that the improvement of insulin resistance by **2** is due to its dual action as both an inhibitor of GCS and intestinal glycosidases. The synthesis of dimeric derivatives of **2** and **3** is described in **Chapter 4**. Four distinct dimeric compounds were evaluated for bivalent-type inhibition of GCS, GBA1 and GBA2. This was found not to be the case, but all compounds did still showed appreciable inhibition of these enzymes. **Chapter 5** describes the synthesis of derivatives of **2** in which the 5-(adamantan-1yl-methoxy)-pentyl (AMP) moiety is moved to five alternate positions on the 1-deoxynojirmycin ring. Their evaluation showed that moving the AMP moiety to alternate positions causes the loss of inhibition of GCS except in the case of the β-aza-*C*-1-glycoside derivatives. In **Chapter 6**, the structure–activity relationship (SAR) of these aza-*C*-glycoside derivatives was further investigated through the synthesis of a small library. This showed that the β-AMP derivative from chapter 5 already represented the optimal GCS inhibitor for this class and that α-D-*xylo*-derivatives are very potent and selective GBA1 inhibitors (*e.g.* **4** in Table 1). β-Aza-*C*-1-glycoside **5** proved to be a selective inhibitor of GBA2.

Table 1. Enzyme inhibition profiles of **2** and optimized derivatives: IC_{50} values in μM.

Compound	GCS	GBA1	GBA2	Non-related glycosidases
Lead lipophilic iminosugar **2**	0.2	0.2	0.001	0.4–35
 **3** (Chapter 3)	0.1	2	0.001	> 100
 **4** (Chapter 6)	> 10	0.001	10	≥ 100
 **5** (Chapter 6)	> 10	20	0.075	≥ 100

The research described in the chapters leading up to chapter 7 mainly relied on long linear synthetic routes to prepare the various target compounds. In a different approach, the tandem Staudinger/aza-Wittig/Ugi three-component reaction was used to prepare four diverse libraries of pyrrolidine and piperidine iminosugars in a combinatorial fashion (**Chapter 7**). Evaluation of these libraries yielded several inhibitors of GBA1 and GBA2 and a GCS inhibitor. The second part of this **Chapter (8)** presents work in

progress on new classes of lipophilic iminosugar inhibitors of GCS, GBA1 and GBA2. It also discusses some prospects for the development of inhibitors and their applications for future research.

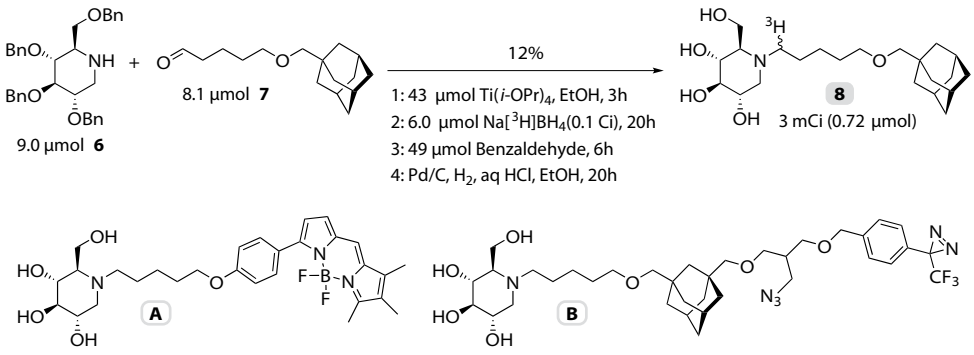
The research described in this thesis has resulted in many novel inhibitors of GCS, GBA1 and GBA2, among which several that improve upon the inhibition profile of lead compound **2** (Table 1). A remaining challenge here lies in the development of a lipophilic iminosugar that solely inhibits GCS without also inhibiting GBA2. The successful use of lipophilic iminosugars in type 2 diabetes models and the partial elucidation of their mechanism of action therein provide prospects for their development towards therapeutics for diabetes type 2. Finally, the evaluation of all the here presented iminosugars for inhibition of GCS, GBA1, GAB2 and several other relevant glycosidases has resulted in extensive additional knowledge on the selectivity of lipophilic iminosugar based inhibitors in general.

Work in Progress and Prospects

The research described in this thesis has led to the development of several potent and selective inhibitors of GCS, GBA1 or GBA2. As discussed in Chapter 1 such compounds hold potential for the treatment of various diseases and as small-molecule tools in the study of GSL functioning. The next stage in the research of these lipophilic iminosugars and a way to facilitate both their potential clinical development and their functionality in fundamental research is to adapt them to molecular probes. These probes can be used to more closely study the behavior of the inhibitor itself in the body and its targets. A pilot study in this direction has already led to the development of probe **8** (Scheme 1). This tritium ($t_{½}$ = 12.3 years) labeled version of lead compound **2** can be used in animal studies to determine with high accuracy and sensitivity the lifetime and distribution of **8** in the body after administration. The use of Na[^{3}H]BH_4 to reduce the imine of **6** and **7** in its synthesis also represents an economic alternative to the use of Na[^{3}H]$CNBH_3$ by Butters *et al.* in the preparation of similar tritiated labels.[1]

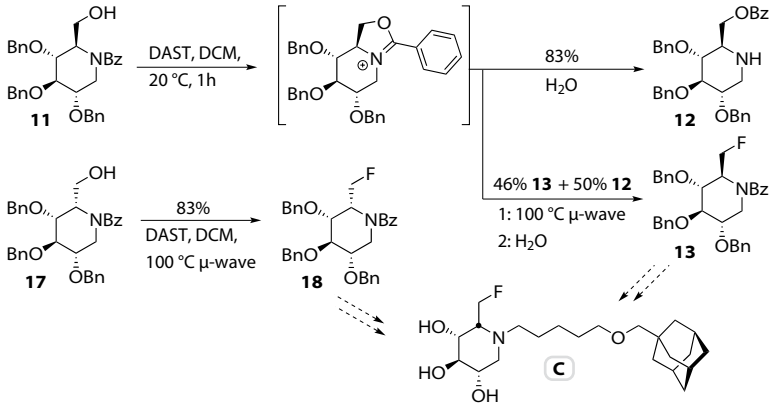
Swapping the adamantane group in **2** for a hydrophobic and fluorescent BODIPY would – if still an inhibitor of the targeted enzymes – produce visual probe **A** (Scheme 1) that could be used to study the localization of lipophilic iminosugars in various cells and tissues.[2] Finally, it would be helpful to investigate more precisely which proteins have an affinity for lipophilic iminosugar based on **2**. The dimeric compounds of Chapter 4 have shown that attachment of a substantial second group to the adamantane does not abolish inhibition of the target enzymes. This fact might be used in the development of probe **B** (Scheme 1) that is equipped with a diazirine photophore.[3] In a living cell or cell lysate this group can be activated to create a nitrene that creates a covalent bond with the protein to which **B** is bound. The azide in **B** can then be used as a post labeling tag to visualize or isolate these proteins as has been successfully demonstrated in various proteomics studies.[4-6]

Scheme 1. Synthesis of tritiated probe **8** and structure of potential probes **A** and **B**.



Although several promising compounds with improved selectivity for one of the three enzymes have been developed during the research described in the previous chapters there are many possibilities left to explore. In Chapter 3 it was revealed that epimerization of the C-5 position in **2** produced a more potent and selective GCS inhibitor. However, this derivative also still inhibited GBA1 and GBA2. A study is ongoing to further explore the SAR of the C-5 and C-6 position of **2** with respect to GCS, GBA1 and GBA2 inhibition. One target herein is to evaluate C-6 fluorinated derivatives (**C**) of **2** and its L-*ido* epimer (**3**) (Scheme 2). Introduction of a fluorine atom has found widespread application in drug development in enhancing binding and selectivity in potential pharmaceuticals.

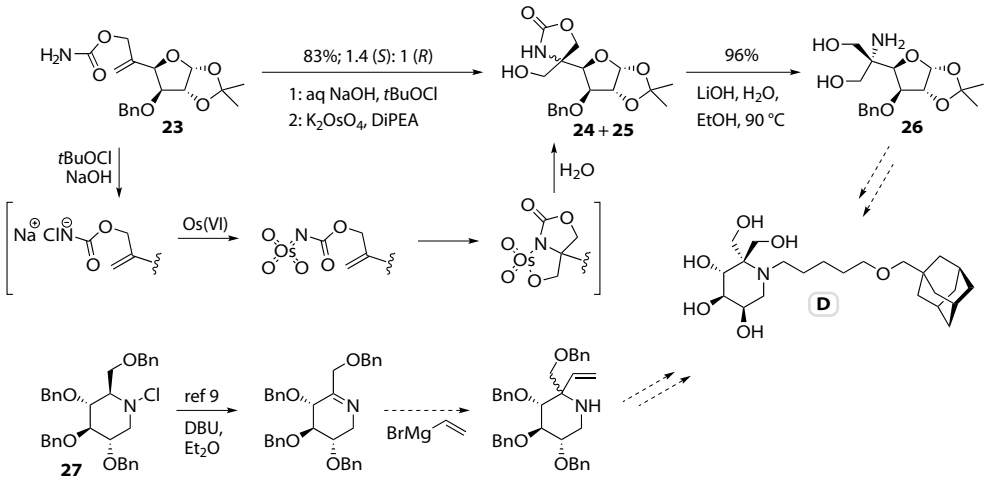
Scheme 2. Synthesis of C-6 fluorinated building blocks **13** and **18** and general structure of target (**C**).



Treatment of building block **11** with DAST at rt resulted in efficient but unwanted benzoyl migration to give **12** that presumably proceeds via an oxazolinium intermediate (Scheme 2).[7] Treatment of **17** with DAST at room temperature only led to retrieval of the starting material. However, heating **11** or **17** to a 100 °C in the presence of DAST did produce fluorinated **13** and **18** that with additional steps can lead to the target derivatives (**C**).

Another C-5 derivative of **2** in development is **D** that contains two hydromethylene groups (Scheme 3). A tethered aminohydroxylation was chosen to simultaneously introduce the required C-5 amino and additional C-5 hydroxymethylene onto a D-glucose starting material.[8] To this end the allylic primary carbamate **23** was prepared in 37% yield over 8 steps from diacetonglucose. In a one-pot procedure the amide of **23** is first chlorinated and deprotonated to yield an intermediate that reacts with and oxidizes the subsequently added potassium osmate (VI) to produce a tethered osmium(VIII)tetraoxide intermediate. This intermediate underwent intramolecular aminohydroxylation and hydrolysis to produce a diastereoisomeric mixture of **24** and **25** in 83% yield. Hydrolysis of the cyclic carbamate produced **26** that with a few additional steps might be advanced to target **D**. Alternatively, C-5 selective elimination of chloro-amine **27**[9] as reported by Davis *et al.* and a subsequent Grignard on the cyclic imine with vinyl magnesiumbromide might represent a quicker route to **D**.

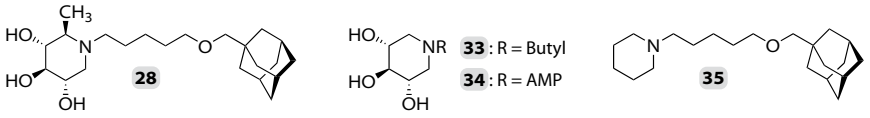
Scheme 3. Synthesis of a C-5 bis(hydroxymethylene)derivative (**D**) of **2**.



6-Deoxy derivative **28** was isolated as a byproduct in the research described in Chapter 2 and has since been analyzed in an enzyme assay for inhibition of GCS, GBA1 and GBA2 (Figure 2 and Table 2 on page 288). These results show that removal of the C-6 hydroxyl has relatively little impact on the inhibition of the three enzymes. D-*Xylo*-derivatives **33** and **34** that completely lack the C-5 hydroxymethylene were synthesized and they no longer inhibited GCS but still inhibited GBA1 and GBA2 (Figure 2 and Table 2).

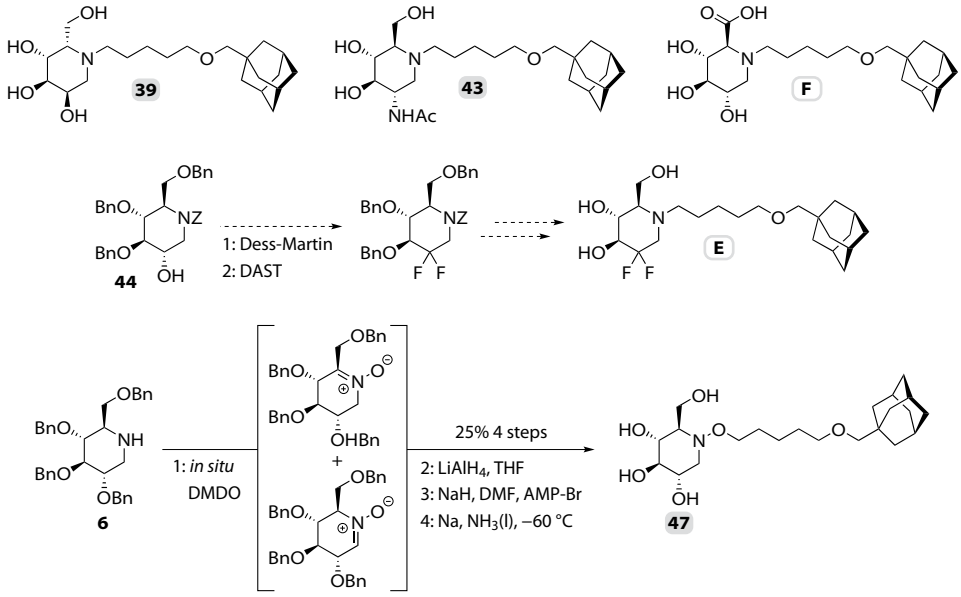
These results indicate that further exploration of deoxygenated derivatives of **2** on other positions of the 1-deoxynojirimycin ring might represent a handle to modify the selectivity of inhibition of GCS, GBA1 and GBA2. The fact that piperidine derivative **35** is still capable of inhibiting GBA1 shows that this enzyme tolerates a lot of structural modifications in this respect (Figure 2 and Table 2).

Figure 2. Structures of C-6-deoxy (**28**), D-*xylo* (**33** and **34**); and piperidine (**35**) derivatives of **2**.



The substitution pattern can of course also be explored beyond the C-4/C-5 position of Chapter 3. For a more comprehensive SAR of the stereochemistry of the iminosugar core in **2**, all remaining twelve stereochemical possibilities should also be synthesized. A start in this direction was made by the synthesis and evaluation of derivative **39** with L-*gulo*-stereochemistry that showed diminished inhibition of GCS, GBA1 and GBA2 (Scheme 4 and Table 2).

Scheme 4. Derivatives of **2** with an altered substitution pattern of the iminosugar core and synthesis of **47**.



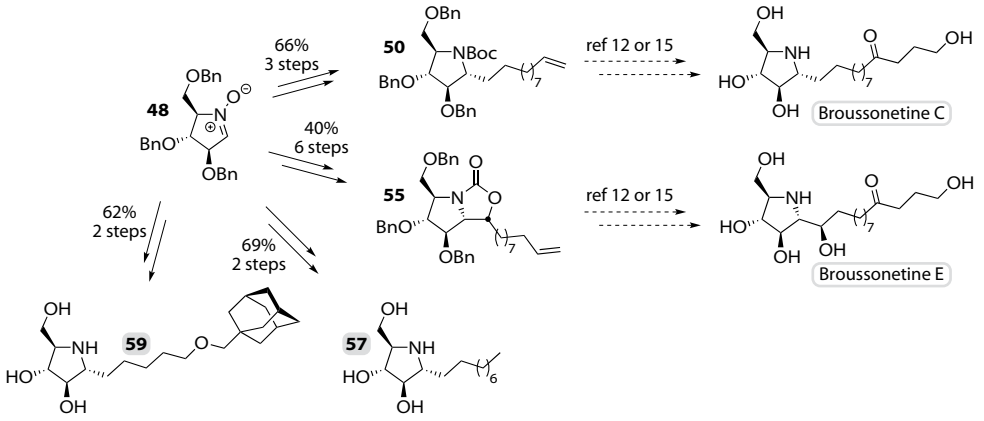
Alternatively, leaving the stereochemistry of **2** unchanged and introducing an acetamide at C-2 (**43**) abolished all inhibition of these enzymes. Finally, another variation of the substitution pattern that should be easily accessible is a difluorinated derivative (*e.g.* **E** in Scheme 4). These can be made straightforward by oxidation and DAST treatment of the C-2 (**44** in Scheme 4), C-3, C-4 and C-6 hydroxyl building blocks from Chapter 5.

The presence of a basic nitrogen function is a prerequisite for inhibition of GCS, GBA1 or GBA2. Therefore modifications at this site could also have an effect on inhibition. For a pilot study in this area aminoxy-derivative **47** was designed, which should posses a less basic nitrogen function. Its synthesis commenced with the generation of the mixed C1-N/C-5-N cyclic nitrones by oxidation of **6** as reported by van den Broek (Scheme 4).[10]

Subsequent reduction of this mixture yielded a hydroxylamine intermediate that could be alkylated and debenzylated by a Birch reduction to provide target **47**. Evaluation of **47** in an enzyme assay showed substantial loss in inhibitory potency for all three enzymes and no improvement in selectivity. Another potential target with a modified nitrogen could be C-6 oxidized **F** that would protonate the nitrogen function and form an intramolecular salt (Scheme 4). A similar compound from Chapter 7, an α-aza-C1-carboxylate of **2**, proved to still inhibit GCS, GBA1 and GBA2.

The results from Chapter 7 have shown that lipophilic pyrrolidine iminosugars can also be inhibitors of GCS, GBA1 and probably also GBA2. A specific class of plant alkaloids and known glycosidase inhibitors represents a naturally occurring source of lipophilic pyrrolidines. They are called Broussonetines and have been isolated from the Asian indigenous *Broussonetia kazinoki* tree that is related to the mulberry tree.[11] Up till now total syntheses for only two of the over thirty known broussonetines have been reported in literature.[12-15] In order to evaluate this class of compounds as inhibitors of GCS, GBA1 and GBA2 it was decided to synthesize two representative members, Broussonetine C and E. Known cyclic nitrone **48** was chosen as a novel and convenient building block for the start of the total synthesis of both.[16-18]

Scheme 5. Synthesis of Broussonetine C and E intermediates **50** and **55**; and Broussonetine analogs **57** and **59**.

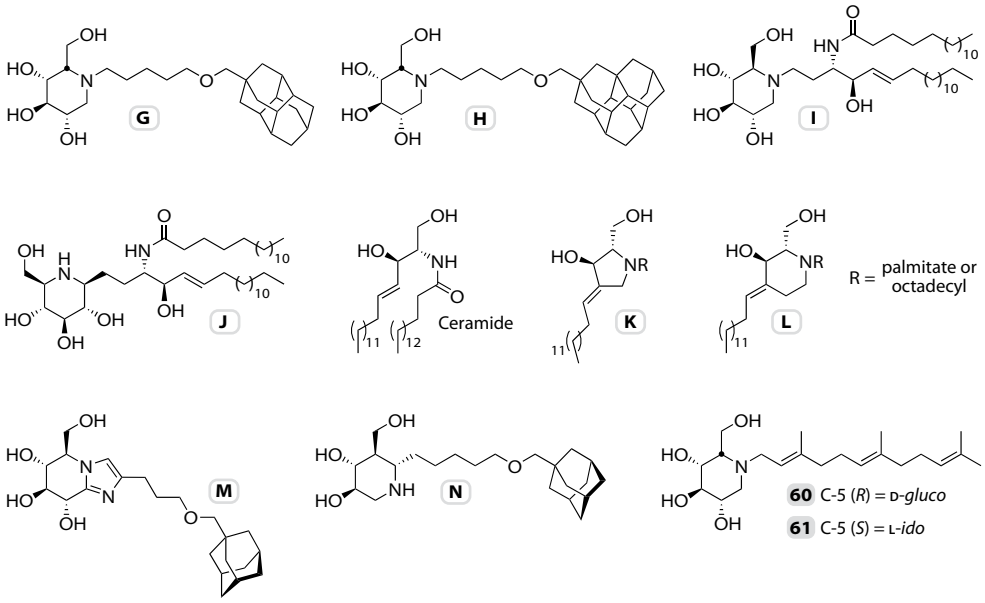


Reaction of **48** with undecenyl magnesiumbromide stereoselectively produced an intermediate hydroxylamine that could be reduced and protected as Boc-carbamate **50** (Scheme 5). This intermediate will be further transformed into Broussonetine C via either of two previously reported syntheses of Broussonetine C that share this intermediate. A similar sequence of reactions with **48** produced a vinyl intermediate that was successively cleaved by ozonolysis, subjected to a second Grignard and transformed into cyclic carbamate **55**. This intermediate will be transformed into Boussontine E via the same steps as planned for Broussonetine C from **50**. Reaction of **48** with either nonyl magnesiumbromide or the acetylene anion from 5-(adamantan-1yl-methoxy-pentyn and

subsequent hydrogenolysis produced Broussonetine derivatives **57** and **59** (Scheme 5). These were evaluated as inhibitors of the three enzymes and both proved to be inhibitors of GBA1 with **59** also moderately inhibiting GCS (Table 2).

With the exception of Chapter 7, the research described in this thesis has mostly left the AMP hydrophobic tail of lead compound **2** untouched. Several alternatives to the pentyl spacer and adamantane moiety have already been investigated in previous studies, but provided less potent or non-active inhibitors. As discussed in Chapter 4, one of the functions of the adamantane group in **2** might be to target, concentrate and stabilize the inhibitor in the cellular membrane by binding hydrophobic pockets created by unsaturated lipids. Synthesis and evaluation of the more bulky diamantine and triamantane derivatives **G** and **H** might function to further elucidate this (Figure 3).

Figure 3. Structures of derivatives of **2** with an alternate hydrophobic tail or iminosugar core.



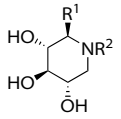
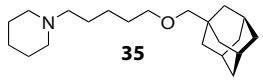
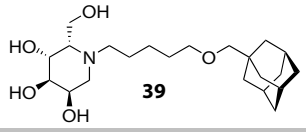
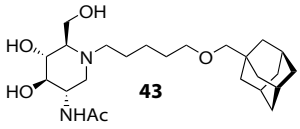
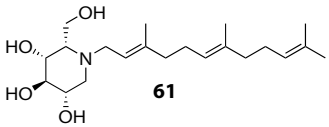
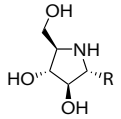
The AMP moiety should however not be viewed as the optimal or only suitable option for a hydrophobic tail. *N*-Alkylation of 1-deoxynojirmycin and L-*ido*-1-deoxynojirmycin with a *trans*,*trans*-farnesylbromide produced **60** and **61** that upon evaluation proved to inhibit GCS, GBA1 and GBA2 to an almost similar extent as **2** and **3** (Table 2).

Another direction for the development of other hydrophobic tails for **2** and new inhibitors in general lies in more closely mimicking the natural substrates and products of the three targeted enzymes. If the 1-deoxynojirmycin core in **2** is viewed as a mimic of glucose and the AMP-moiety as a mimic of ceramide than the development of derivatives of **2** with a ceramide tail such as **I** or **J** might provide new inhibitors (Figure 3). On the other hand if the *N*-alkylated iminosugar as a whole is viewed as a ceramide mimic – as advocated by Butters – then ceramide mimicking structures such as pyrrolidine **K** or

piperidine **L** might represent targets for the further development of inhibitors.

Extensive kinetic analysis studies of the inhibition of glycosidases by 1-deoxynojirmycin-based iminosugars have shown that they are not true transition-state mimics.[19] To achieve this and the associated tighter binding of the active site an iminosugar requires sp^2-hybridization at its pseudo anomeric center (C-1). Modification of **2** to incorporate this as in **M**, its design based on work by Vasella,[20] could result in more potent and selective inhibitors of GBA1 and GBA2 (Figure 3). Finally, lipophilic isofagomines have so far resulted in the most potent inhibitors of GBA1 reported to date.[21] Based on their design, isofagomine **N** might represent an interesting target for a GBA1 inhibitor (Figure 3).

Table 2. Enzyme inhibition assay results for : apparent IC_{50} values in μM.[a,b]

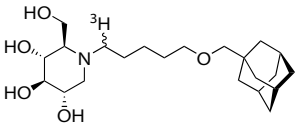
Compound	GCS *in vivo*	GBA1	GBA2	Lysosomal α-glucosidase
 **2**: $R^1 = CH_2OH$; R^2 = AMP	0.2	0.2	0.001	0.4
28: $R^1 = CH_3$; R^2 = AMP	0.8	0.33	0.03	150
33: R^1 = H (D-*xylo*); R^2 = Butyl	-	500	6.0	-
34: R^1 = H (D-*xylo*); R^2 = AMP	> 30	2.2	0.8	-
47: $R^1 = CH_2OH$; R^2 = -O-AMP	20; 35%	75	0.5	500
60: $R^1 = CH_2OH$; R^2 = *trans*,*trans*-Farnesyl	0.35	0.28	0.013	3.7
 **35**	> 100	11	-	3.7
 **39**	15	100	2	> 1000
 **43**	> 100	160	100	> 1000
 **61**	0.15	5	0.011	450
 **57**: R = Nonyl	> 100	6.5	50	> 1000
59: R = AMP	60	3.0	-	> 1000

[a]AMP = 5-(adamantan-1-yl-methoxy)-pentyl; [b]Except for GCS all other enzyme assays are *in vitro*.

Experimental section

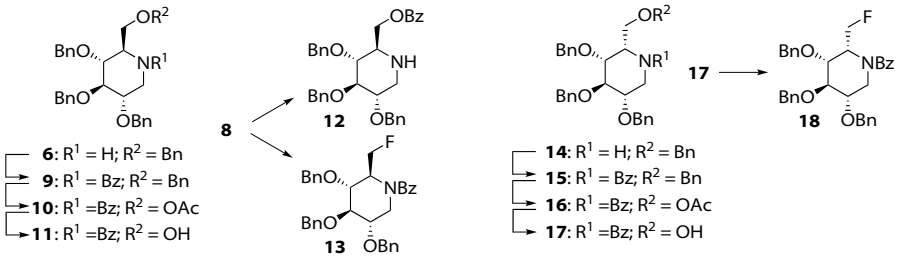
General methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at ambient temperatures unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere. Residual water was removed from starting compounds by repeated coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. Reaction grade acetonitrile and methanol were stored on 3Å molecular sieves. Other reaction grade solvents were stored on 4Å molecular sieves. THF was distilled prior to use from $LiAlH_4$. Ethanol was purged of acetaldehyde contamination by distillation from zinc/KOH. DCM was distilled prior to use from P_2O_5. R_F values were determined from TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by spraying with a solution of $(NH_4)_6Mo_7O_{24}\times4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times2H_2O$ (10 g/L) in 10% sulfuric acid or a solution of phosphomolybdic acid hydrate (7.5 wt% in ethanol) followed by charring at ~150 °C. Visualization of all deprotected iminosugar compounds during TLC analysis was accomplished by exposure to iodine vapour. Column chromatography was performed on silica gel (40–63 µm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker DMX 600 (600/150 MHz), Bruker DMX 500 (500/125 MHz), or Bruker AV 400 (400/100 MHz) spectrometer in $CDCl_3$ or MeOD. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard (^1H NMR in $CDCl_3$) or the signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. All presented ^{13}C-APT spectra are proton decoupled. High resolution mass spectra were recorded by direct injection (2 µL of a 2 µM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150–2000) and dioctylpthalate (m/z = 391.28428) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Low resolution mass spectra were recorded on a Perkin Elmer Sciex API 165 equipped with an electron spray interface (ESI). Optical rotations were measured on a Propol automatic polarimeter (Sodium D-line, λ = 589 nm). ATR-IR spectra were recorded on a Shimadzu FTIR-8300 fitted with a single bounce Durasample IR diamond crystal ATR-element and are reported in cm^{-1}.

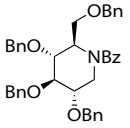
General procedure A – Hydrogenolysis at atmospheric H_2 pressure: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (4 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C (~50 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 minutes and the reaction was stirred for 20 h under atmospheric hydrogen pressure. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene. In the case of incomplete reduction hydrogenolysis was repeated after workup and coevaporation (3×) with 'acetaldehyde free' EtOH), at atmospheric pressure in the presence of Pd/C (~50 mg) and Pd black (~5 mg) or at higher H_2 pressure in a Parr-apparatus. *Hydrogenolysis in Parr-apparatus*: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (50 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C (50 mg, 10 wt % on act. carbon) was added. The reaction vessel was placed under vacuum and subsequently ventilated with hydrogen gas. This cycle was repeated one more time after which the vessel was placed under 4 bar of hydrogen gas and mechanically shaken for 20 h.



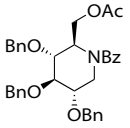
(1'-*R*/*S*)-*N*-[5-(Adamantan-1-yl-methoxy)-1-tritium-pentyl]-1-deoxynojirimycin (8). Stock solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**6**: 104.8 mg in 2 mL EtOH; synthesis described in Chapter 2) and 5-(adamantan-1yl-methoxy)-pentanal (**7**: 38.1 mg in 1.7 mL EtOH, synthesis described in Chapter 2) were prepared and stored under argon (ethanol absolute AR Biosolve; distilled from zinc/KOH and stored on 3Å molecular sieves before use). 90 µL of the stock solutions of **6** (9.0 µmol) and **7** (8.1 µmol) were combined in a vial (Supelco vial, screw top, clear glass, 1.5 mL) with a stirring magnet. Under stirring titanium(IV)isopropoxide (13 µL; 43.2 µmol; 99.999% from Aldrich) was added to the mixture and the vial was flushed with argon and closed with a screw cap. The mixture was stirred for 3 h during which it turned turbid. An ampoule with sodium boro[^{3}H]hydride (purple solid, 100±20 mCi, 6.0±1.2 µmol; 16.7 Ci/mmol ±15% specific activity; MW 39 g/mol; from Amersham Biosciences) was opened and EtOH (60 µ L) was added. The content was transferred to the reaction vial. The ampoule was rinsed with EtOH (1: 60 µL; 2: 30 µL) and both portions were transferred to the reaction vial. The reaction vial was flushed with argon, closed with a screw cap and stirred for 20 h. TLC analysis indicated the formation of the radiolabeled penultimate (R_F penultimate = 0.60; **6** = 0.05; **7** = 0.70; alcohol of **7** = 0.30; TLC eluent: 25% EtOAc in PE; TLC staining: molecular iodine vapour). Benzaldehyde (5 µ L, 49 µmol, ≥99.5% from Fluka) was added to the reaction vial and the reaction mixture was stirred for 6h whilst enclosed. Aqueous 1M HCl (75 µL) and EtOH (200 µL) were added to the vial. The reaction vial was enclosed with a suitable rubber septa and argon gas (from a filled balloon) was bubbled trough the reaction mixture via 0.8 mm needle (0.3 mm needle as outlet) for 10 min (gas from outlet was passed through container with 20 ml water). Palladium on activated charcoal (15 mg, 10% Pd basis from Fluka) was added to the vial and it was enclosed with a new septa. Hydrogen gas was bubbled through the reaction mixture for 10 min via the same method as used for argon. The hydrogen balloon was replaced with a newly filled one, the gas-outlet was removed and the reaction vial was sealed with parafilm. The reaction set-up was left stirring for 20 h after which the balloon and septa were removed. The reaction mixture was filtered over a 2 mL filter syringe fitted with 2 layers of glass fibre material (GF/T from Whatman). The reaction vial was rinsed with MeOH (4×1 mL) and the resulting Pd/C pellet was also rinsed with MeOH (4×1 mL). The combined filtrate was collected in 100 mL round-bottom flask. The flask was placed in a water bath (40 °C) and the content was concentrated by a gentle air-flow. The residue was suspended in 0.2 mL of 10% MeOH in $CHCl_3$ and transferred to a filter syringe (2 mL) that contained packed silica gel (0.8 cm^3 in 10% MeOH in $CHCl_3$ + 5% NH_4OH). The flask was rinsed a further 4 times with the same mixture. The silica gel column was eluted with 30 mL of eluent (10% MeOH in $CHCl_3$ + 5% NH_4OH) and 0.5 mL fractions were collected. The product eluted in fractions 5–16 (as determined by triple spotting and elution on TLC) and was collected in a 100 mL round-bottom flask (R_F **8** = 0.30; TLC eluent: 20% MeOH in $CHCl_3$ + 2% NH_4OH; TLC staining: molecular iodine vapour). The collected fractions were concentrated via the same method as mentioned previously to yield compound **8** as a colourless oil. In cold runs of the above procedure a stock solution of $NaBH_4$ (30 µL, 6.2 µmol in EtOH) was added instead of the radiolabel. This produced cold **2** in yields of 30-40% with a purity of 90–95% as judged by ^{1}H-NMR. A 3 mL DMSO stock solution of **8** was analyzed for radioactivity by performing a scintillation counting of various dilutions in water of the stock solution. From these measurements the activity of the 3 mL DMSO solution of **8** was determined to be 3 mCi ±15%. If it is assumed that a maximum of 25% of the specific activity of the sodium boro[^{3}H]hydride was transferred to **8** then 3 mCi equates to 0.72 µmol of **8** and 12% yield over the two steps. The lower yield might be caused by the extra amount of EtOH (120 µL) needed to transfer the sodium boro[^{3}H]hydride from the ampoule to the reaction vial. The specific activity of **8** is not yet known and can only be determined if the chemical concentration of **8** in the DMSO stock solution is determined by either ^{1}H-NMR or HPLC.

Synthesis of C-6 fluorinated iminosugars 13 and 18:

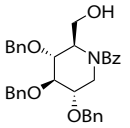




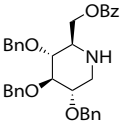
***N*-Benzoyl-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (9).** Benzoylchloride (2.25 mL, 19.38 mmol) was added to a dry solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**6**: 6.76 g, 12.92 mmol; synthesis described in Chapter 2) in pyridine (80 mL). The reaction mixture was stirred at rt over a period of 45 min. The reaction mixture was concentrated and coevaporated with toluene. The residue was dissolved in EtOAc (50 mL) and washed with sat aq $NaHCO_3$ (50 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (25% » 33% EtOAc in PE) to provide **9** (6.52 g, 10.46 mmol) in 80% yield as a colourless oil. R_F = 0.86 (40% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.45 – 7.12 (m, 25H, H_{Ar} Bn/Bz), 4.85 – 3.26 (m, 16H, 4×CH_2 Bn, CH_2-1, H-2, H-3, H-4, H-5, CH_2-6). ^{13}C NMR (150 MHz, $CDCl_3$) collapsed iminosugar signals δ 172.0 (C=O Bz), 138.4, 138.2, 138.1, 138.1 (4×C_q Bn), 136.4 (C_q Bz), 129.3, 128.6, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6 (CH_{Ar} Bn/Bz), 74.1(CH), 73.2, 70.8 (CH_2 Bn), 68.1 (C-6). MS (ESI): found 628.2 $[M+H]^+$, calculated for $[C_{41}H_{41}NO_5+H]^+$ 628.3.



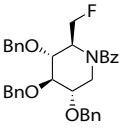
6-*O*-Acetyl-*N*-benzoyl-2,3,4-tri-*O*-benzyl-1-deoxynojirimycin (10). Zinc chloride (13.96 g, 102.4 mmol) was added to a dry solution of **9** (6.42 g, 10.24 mmol) in a mixture of Ac_2O/AcOH (102.4 mL, 2/1, v/v). The reaction mixture was stirred at rt over a period of 20 hr. The reaction was quenched (water, 5 mL) and stirred for 30 min. The reaction mixture was poured into sat aq Na_2CO_3 (100 mL) and extracted with DCM (3×50 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried ($MgSO_4$) and concentrated. After coevaporation with toluene the residue was purified by silica gel column chromatography (20% » 50% EtOAc in PE) to afford **10** (5.29 g, 9.12 mmol) in 89% yield as a colourless oil. R_F = 0.17 (25% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.43 – 7.20 (m, 20H, H_{Ar} Bn/Bz), 4.51 (dd, *J* = 7.8, 11.5, 1H, H-6a), 4.73 – 3.26 (m, 13H, 3×CH_2 Bn, CH_2-1, H-2, H-3, H-4, H-5, H-6b), 2.01 (s, 3H, CH_3 Ac). ^{13}C NMR (150 MHz, $CDCl_3$) collapsed iminosugar signals δ 172.3 (C=O Bz), 170.6 (C=O Ac), 137.9, 137.8, 137.6 (C_q Bn), 136.1 C_q Bz), 129.3, 128.6, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.4 (CH_{Ar} Bn/Bz), 73.7 (CH), 72.9, 70.7 (CH_2 Bn), 61.6 (C-6), 20.9 (CH_3 Ac).



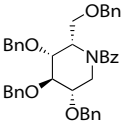
***N*-Benzoyl-2,3,4-tri-*O*-benzyl-1-deoxynojirimycin (11).** A sodium methoxide solution (169 µL, 0.9 mmol; 30 wt%) was added to a dry solution of **10** (5.24 g, 9.04 mmol) in MeOH (90 mL). The reaction mixture was stirred at rt for 20 h. The reaction was quenched by addition of amberlite H^+ resin (IR-50). The reaction mixture was filtered and the resin was rinsed with MeOH (3×5 mL). The combined filtrate was concentrated and the resulting residue was purified by silica gel column chromatography (33% » 67% EtOAc in PE) to produce **11** (2.56 g, 4.77 mmol) in 53% yield as a white crystalline solid. R_F = 0.31 (50% EtOAc in PE). ^{1}H NMR (300 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.46 – 7.06 (m, 20H, H_{Ar} Bn, H_{Ar} Bz), 4.70 – 3.23 (m, 14H, 3×CH_2 Bn, CH_2-1, H-2, H-3, H-4, H-5, CH_2-6), 1.67 (s, 1H, OH-6). ^{13}C NMR (75 MHz, $CDCl_3$) collapsed iminosugar signals δ 172.9 (C=O Bz), 138.0, 137.7 (C_q Bn), 135.8 (C_q Bz), 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{Ar} Bn/Bz), 74.7 (CH), 73.3, 71.0 (CH_2 Bn), 61.3 (C-6), 58.6 (C-5).



6-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-1-deoxynojirimycin (12). A dry and cooled (0 °C) solution of **11** (107 mg, 0.2 mmol) in DCM (2 mL) was charged with DAST (37 µL 0.3 mmol). The reaction mixture was stirred for 20 h and allowed to warm to rt. The mixture was quenched by addition of MeOH and diluted with EtOAc (20 mL). The organic phase was washed successively with sat aq $NaHCO_3$ (10 mL) and sat aq NaCl (10 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (isocratic 25% EtOAc in PE) to yield **12** (89 mg, 0.17 mmol) in 83% yield as a colourless oil and 7% of starting material **11** (8 mg, 0.02 mmol). R_F = 0.44 (50% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2, 2H, H_{Ar} Bz), 7.51 – 7.10 (m, 18H, H_{Ar} Bn/Bz), 5.01 (d, *J* = 10.8, 1H, C*H*H Bn), 4.93 (d, *J* = 10.9, 1H, C*H*H Bn), 4.86 (d, *J* = 10.8, 1H, CH*H* Bn), 4.68 (d, *J* = 11.3, 1H, C*H*H Bn), 4.65 (d, *J* = 11.3, 1H, CH*H* Bn), 4.62 (d, *J* = 10.9, 1H, CH*H* Bn), 4.57 (dd, *J* = 2.3, 11.2, 1H, H-6a), 4.39 (dd, *J* = 5.3, 11.3, 1H, H-6b), 3.62 (dd, *J* = 8.9, 1H, H-3), 3.53 (ddd, *J* = 5.0, 9.4, 10.4, 1H, H-2), 3.44 (dd, *J* = 8.9, 9.7, 1H, H-4), 3.26 (dd, *J* = 5.1, 12.3, 1H, H-1a), 2.88 (ddd, *J* = 2.4, 5.2, 9.8, 1H, H-5), 2.53 (dd, *J* = 10.3, 12.3, 1H, H-1b), 2.49 – 2.33 (m, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2 (C=O Bz), 138.7, 138.4, 138.0 (C_q Bn), 129.8 (C_q Bz), 129.5, 128.4, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.4 (CH_{Ar} Bn/Bz), 87.2 (C-3), 80.5 (C-2), 79.5 (C-4), 75.7, 75.2, 72.6 (CH_2 Bn), 64.8 (C-6), 59.1 (C-5), 48.1 (C-1).

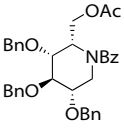


***N*-Benzoyl-2,3,4-tri-*O*-benzyl-6-fluoro-1,6-dideoxynojirimycin (13).** DAST (24 µL, 200 µmol) was added to a dry solution of **11** (54 mg, 100 µmol) in DCM (1 mL) and stirred at rt over a period of 30 min. The reaction mixture was heated in a sealed tube in the microwave at 70 °C for 30 min, after which TLC analysis indicated ~50% conversion into a higher running product. The reaction mixture was heated for an additional 30 min at 100 °C. The reaction mixture was quenched with MeOH, diluted with EtOAc (50 mL) and washed successively with sat aq $NaHCO_3$ (20 mL) and sat aq NaCl (20 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (25% EtOAc in PE) to produce **13** (25 mg, 46 µmol) in 46% yield as a colorless oil and **12** (27 mg, 50 µmol) in 50% yield. R_F = 0.90 (1:1; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.53 – 7.16 (m, 20H, H_{Ar} Bn/Bz), 4.98 – 3.22 (m, 14H, 3×CH_2 Bn, CH_2-1, H-2, H-3, H-4, H-5, CH_2-6). ^{13}C NMR (126 MHz, $CDCl_3$) collapsed iminosugar signals δ 172.3, 138.1, 138.0, 137.9, 136.0, 128.7, 128.6, 128.5, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7, 73.7, 73.5, 70.9. MS (ESI): found 540.2 $[M+H]^+$, calculated for $[C_{34}H_{34}FNO_4+H]^+$ 540.3.

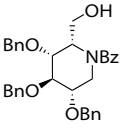


***N*-Benzoyl-2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (15).** Benzoylchloride (2.07 mL, 17.85 mmol) was added to a dry solution of 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin **14** (6.24 g, 11.90 mmol; synthesis described in Chapter 3) in pyridine (70 mL). The reaction mixture was stirred at rt for 20 h. The reaction mixture was concentrated and coevaporated with toluene. The residue was dissolved in EtOAc (50 mL) and washed with sat aq $NaHCO_3$ (2×50 mL), dried ($MgSO_4$) and concentrated. The residue was purified with silica gel column chromatography (25% » 50% EtOAc in PE) to provide **15** (6.43 g, 10.25 mmol) in 86% yield as a light yellow oil. R_F = 0.90 (50% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) mixture of (A/B; 1/0.6) rotamers δ 7.47 – 7.16 (m, 50H, H_{Ar} Bn/Bz a/b), 5.42 – 5.37 (m, 1H, H-5 B), 4.92 – 4.40 (m, 17H, CH_2 Bn/Bz A/B, H-1a A), 4.25 – 4.20 (m, 1H, H-5 A), 3.95 (dd, *J* = 8.1, 10.5, 1H, H-6a B), 3.91 (dd, *J* = 9.2, 1H, H-3 B), 3.85 (dd, *J* = 3.4, 10.5, 1H, H-6b B), 3.76 (dd, *J* = 10.1, 1H, H-6a A), 3.74 – 3.63 (m, 4H, H-3 A, H-4 A, H-1a B, H-4 B), 3.64 (dd, *J* = 3.3, 10.1, 1H, H-6b A), 3.62 – 3.56 (m, 1H, H-2 A), 3.52 (dd, *J* = 6.2, 9.5, 1H, H-4 A), 3.41 – 3.36 (m, 1H, H-2 B), 3.22 (dd, *J* = 11.6, 12.8, 1H, H-1b B), 2.81 (dd, *J* = 11.5, 12.9, 1H, H-1b A). ^{13}C NMR (150 MHz, $CDCl_3$) mixture of (A/B; 1/0.6) rotamers δ 172.4, 171.5 (C=O Bz A/B), 138.9, 138.8, 138.3, 138.2, 138.0, 137.6 (C_q Bn A/B), 135.9, 135.8 (C_q Bz A/B), 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.7, 127.6, 127.2 (H_{Ar} Bn/Bz A/B), 82.9 (C-3 B), 82.8 (C-3 A), 79.1 (C-4 B), 78.6 (C-4 A), 78.3 (C-2 A), 78.2 (C-2 B), 75.9, 75.8, 73.4, 73.3, 73.2, 73.1, 73.1 (CH_2 Bn A/B), 66.4 (C-6 B), 64.8 (C-6 A), 56.9 (C-5 A), 49.9 (C-5 B), 46.3 (C-1 B), 39.4 (C-1 A). IR ν_{max}(thin film)/ cm^{-1}: 2853,

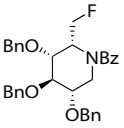
1636, 1541, 1454, 1364, 1256, 1088, 1072, 1026, 733, 694, 652, 611. $[\alpha]^{20}_{D}$: 8.9 (*c* 0.4, $CHCl_3$). MS (ESI): found 628.2 $[M+H]^+$, calculated for $[C_{41}H_{41}NO_5+H]^+$ 628.3.



6-*O*-Acetyl-*N*-benzoyl-2,3,4-tri-*O*-benzyl-L-*ido*-1-deoxynojirimycin (16). Zinc chloride (13.97 g, 102.5 mmol) was added in to a dry solution of **15** (6.41 g, 10.25 mmol) in a mixture of Ac_2O/AcOH (102.5 mL, 2/1, v/v). The mixture was stirred at rt over a period of 24 h. The reaction was quenched (water, 5 mL) and stirred for 30 min. The reaction mixture was poured into sat aq Na_2CO_3 (100 mL) and extracted with DCM (3×50 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried ($MgSO_4$) and concentrated. After coevaporation with toluene the residue was purified by silica gel column chromatography (20% » 33% EtOAc in PE) to provide **16** (2.63 g, 4.53 mmol) in 80% yield as a colourless oil. R_F = 0.25 (25% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 7.49 – 7.11 (m, 40H, H_{Ar} Bn/Bz A/B), 5.51 – 5.45 (m, 1H, H-5 B), 4.96 – 4.68 (m, 10H, CH_2 Bn A/B, H-1a A), 4.63 (dd, *J* = 11.1, 1H, H-6a B), 4.60 – 4.51 (m, 2H, CH*H* Bn A/B, C*H*H Bn A/B), 4.48 (dd, *J* = 2.9, 12.1, 1H, H-6b B), 4.44 (d, 1H, *J* = 11.7, 1H, CH*H* Bn A/B) 4.39 (dd, *J* = 11.2, 1H, H-6a A), 4.32 (dd, *J* = 2.6, 11.9, 1H, H-6b A), 4.30 – 4.24 (m, 1H, H-5 A), 3.73 – 3.67 (m, 3H, H-1a B, H-3 B, H-4 B), 3.62 – 3.55 (m, 2H, H-2 A, H-4 A), 3.40 – 3.33 (m, 1H, H-2 B), 3.18 (dd, *J* = 11.8, 13.1, 1H, H-1b B), 2.83 (dd, *J* = 11.8, 12.8, 1H, H-1b A), 2.06 (s, 3H, CH_3 Ac A/B), 2.03 (s, 3H, CH_3 Ac A/B). ^{13}C NMR (150 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 172.0, 171.7, 171.3, 170.5 (C=O Bz/Ac A/B), 138.7, 138.1, 137.9, 137.8, 137.5 (C_q Bn A/B), 135.5 (C_q Bz A/B), 130.2, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 126.8 (H_{Ar} Bn/Bz A/B), 82.6, 78.5 (C-3 A, C-3 B, C-4 B), 78.1, 78.0 (C-2 A, C-4 A), 77.9 (C-2 B), 76.0, 75.9, 73.3, 73.2 (CH_2 Bn A/B), 59.2 (C-6 B), 59.1 (C-6 A), 56.0 (C-5 A), 50.0 (C-5 B), 45.6 (C-1 B), 39.3 (C-1 A), 21.1, 21.1 (CH_3 Ac A/B). MS (ESI): found 580.1 $[M+H]^+$, calculated for $[C_{36}H_{37}NO_6+H]^+$ 580.3.



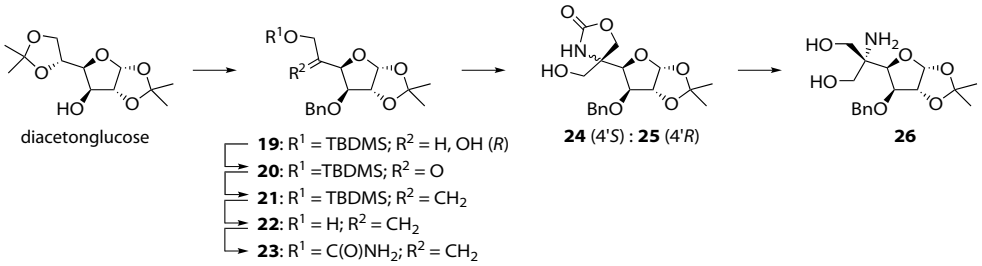
***N*-Benzoyl-2,3,4-tri-*O*-benzyl-L-*ido*-1-deoxynojirimycin (17).** A sodium methoxide solution (82 µL, 0.44 mmol; 30 wt%) was added to a dry solution of **16** (2.53 g, 4.36 mmol) in MeOH (43.6 mL). The reaction mixture was stirred at rt over a period of 20 h. The reaction was quenched by addition of Amberlite H^+ resin (IR-50). The reaction mixture was filtered and the resin was rinsed with MeOH (3×5 mL). The combined filtrate was concentrated and the resulting residue was purified by silica gel column chromatography (33% » 67% EtOAc in PE) to afford **17** (2.16 g, 4.01 mmol) in 92% yield as a white crystalline solid. R_F = 0.40 (50% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 7.55 – 7.10 (m, 40H, H_{Ar} Bn/Bz A/B), 5.27 – 5.19 (m, 1H, H-5 B), 4.91 – 4.41 (m, 13H, H-1a A, CH_2 Bn A/B), 4.16 – 4.05 (m, 3H, H-6a A, H-4 B, H-6b B), 3.92 (dd, *J* = 9.9, 1H, H-6a B), 3.86 – 3.76 (m, 3H, H-4 A/B, H-5 A, H-6b A), 3.76 – 3.65 (m, 3H, H-1b B, H-3 A, H-3 B), 3.62 – 3.54 (m, 1H, H-2 A), 3.54 – 3.49 (m, 1H, H-4 A/B), 3.48 – 3.39 (m, 1H, H-2 B), 3.13 (dd, *J* = 12.1, 1H, H-1a B), 3.02 (s, 1H, OH-6), 2.77 (dd, *J* = 11.9, 1H, H-1b A). ^{13}C NMR (150 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 172.7, 172.4 (C=O Bz A/B), 138.7, 138.1, 137.8, 137.7, 137.4 (C_q Bn A/B), 135.5, 135.3 (C_q Bz A/B), 128.6, 128.4, 128.1, 128.0, 127.9, 127.7 (CH_{Ar} Bn/Bz A/B), 82.6 (C-3 A/B), 82.4 (C-4 A/B), 79.1 (C-3 A/B), 78.8 (C-4 A/B), 78.1 (C-2 A), 77.8 (C-2 B), 75.8, 75.7, 73.3, 73.3, 73.1, 72.9 (CH_2 Bn A/B), 59.3 (C-6 B), 58.2 (C-5 A), 58.1 (C-6 A), 52.4 (C-5 B), 45.7 (C-1 B), 39.3 (C-1 A).

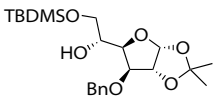


***N*-Benzoyl-2,3,4-tri-*O*-benzyl-6-fluoro-L-*ido*-1,6-dideoxynojirimycin (18).** DAST (24 µL, 200 µmol) was added to a dry solution of **17** (54 mg, 100 µmol) in DCM (1 mL) and stirred at rt over a period of 30 min. The reaction mixture was heated in a sealed tube in the microwave at 70 °C for 30 min, after which TLC analysis indicated ~50% conversion into a higher running product. The reaction mixture was heated for an additional 30 min at 100 °C. The mixture was quenched with MeOH, diluted with EtOAc (50 mL) and washed successively with sat aq $NaHCO_3$ (20 mL) and sat aq NaCl (20 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (25%

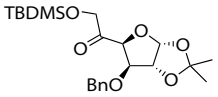
EtOAc in PE) to produce **18** (44 mg, 83 µmol) in 83% yield. R_F = 0.85 (1:1; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) mixture of (A/B; 0.8/1) rotamers δ 7.48 – 7.08 (m, 40H), 5.21 (d, *J* = 32.6, 1H, H-5 B), 5.08 – 4.41 (m, 18H, H-1a A, CH_2-6 A ($J_{H\text{-}F}$ = 113.2), CH_2-6 B ($J_{H\text{-}F}$ = 90.1), CH_2 Bn A/B), 4.15 (d, *J* = 20.8, 1H, H-5 A), 3.89 (dd, *J* = 8.7, 1H, H-3 B), 3.82 – 3.65 (m, 3H, H-1a B, H-3 A, H-4 B), 3.61 – 3.55 (m, 1H, H-2 A), 3.55 – 3.49 (m, 1H, H-4 A), 3.47 – 3.36 (m, 1H, H-2 B), 3.24 (dd, *J* = 12.3, 1H, H-1b B), 2.89 (dd, *J* = 12.1, 1H, H-1b A). ^{13}C NMR (125 MHz, $CDCl_3$) mixture of (A/B; 0.8/1) rotamers δ 172.0, 171.6 (C=O Bz A/B), 138.9, 138.7, 138.4, 138.1, 137.9 (C_q Bn A/B), 135.4, 135.3 (C_q Bz A/B), 128.9, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.0, 126.8, 126.7, 83.4 (C-3 B), 83.0 (C-3 A), 82.4 (d, $J_{C\text{-}F}$ = 174.1, C-6 B), 79.7 (d, $J_{C\text{-}F}$ = 171.8, C-6 A), 78.4 (C-4 B), 78.1 (C-2 A, C-4 A), 77.9 (C-2 B), 75.9, 73.8, 73.2, 73.2, 72.5, 72.0 (CH_2 Bn A/B), 57.1 (d, $J_{C\text{-}F}$ = 17.9, C-5 A), 50.8 (d, $J_{C\text{-}F}$ = 18.2, C-5 B), 47.1 (d, $J_{C\text{-}F}$ = 2.2, C-1 B), 39.8 (C-1 A). MS (ESI): found 540.2 $[M+H]^+$, calculated for $[C_{34}H_{34}FNO_4+H]^+$ 540.3.

Synthesis of a precursor towards C-5 bis(hydroxymethylene)-1-deoxynojirimycin:

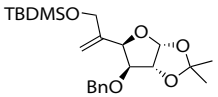




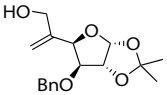
3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-glucofuranose (19). Sodium hydride (1.73 g, 43.2 mmol, 60% in mineral oil) was added in portions over 2 min to a dry and cooled (0 °C) solution of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (10.33 g, 39.7 mmol) and benzylbromide (5.2 mL, 43.2 mmol) in DMF (118 mL). The reaction mixture was stirred for 20 h and allowed to warm to rt. The reaction mixture was cooled to 0 °C and poured into water (500 mL). The aqueous mixture was extracted with Et_2O (3×150 mL) and the combined organic phases were evaporated. The crude benzylated product (R_F = 0.8 (25% EtOAc in PE) was dissolved in a mixture of acetic acid/water (200 mL, 3/1, v/v). The resulting mixture was stirred for 20 h at rt. The reaction mixture was washed with PE (3×100 mL) to remove excess benzylbromide. The washed mixture was concentrated and coevaporated with toluene (3×). The residue was dissolved in DCM (100 mL) and washed with a mixture of sat aq $NaHCO_3$ (100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated to provide the 3-*O*-benzylated-5,6-diol (~40 mmol) that was used crude in the next reaction (R_F = 0.35 (50% EtOAc in DCM). *Tert*-butyldimethylsilylchloride (6.63g, 44 mmol) was added to a dry solution of the crude diol (~40 mmol) and DMAP (10 mg) in pyridine (227 mL). The reaction mixture was stirred for 20 h at rt after which the mixture was concentrated and coevaporated with toluene (3×). The residue was dissolved in EtOAc (100 mL) and washed successively with 1M aq HCl (2×100 mL), sat aq $NaHCO_3$ (2×100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (5% » 20% EtOAc in PE) to produce **19** (14.8 g, 34.9 mmol) in 88% yield over three steps as a colorless oil. R_F = 0.37 (16% EtOAc in toluene). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 – 7.24 (m, 5H, H_{Ar} Bn), 5.89 (d, *J* = 3.7, 1H, H-1), 4.70 (d, *J* = 11.8, 1H, C*H*H Bn), 4.63 (d, *J* = 11.8, 1H, CH*H* Bn), 4.57 (d, *J* = 3.8, 1H, H-2), 4.17 – 4.06 (m, 2H, H-3, H-4), 4.06 – 3.89 (m, 1H, H-5), 3.80 (dd, *J* = 3.7, 10.2, 1H, H-6a), 3.72 (dd, *J* = 4.9, 10.2, 1H, H-6b), 2.66 (d, *J* = 6.4, 1H, 5-OH), 1.45 (s, 3H, CH_3 isoprop), 1.29 (s, 3H, CH_3 isoprop), 0.88 (s, 9H, 3×CH_3 *t*-Bu TBDMS), 0.06 (s, 6H, 2×CH_3 TBDMS).^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8 (C_q Bn), 128.6 (CH_{Ar}-3,5 Bn), 128.0 (CH_{Ar}-4 Bn), 127.9 (CH_{Ar}-2,6 Bn), 111.7 (C_q isoprop), 105.3 (C-1), 82.6, 82.0, 79.6 (C-2, C-3, C-4), 72.6 (CH_2 Bn), 68.6 (C-6), 64.6 (C-5), 26.8, 26.4 (2×CH_3 isoprop), 26.0 (CH_3 *t*-Bu TBDMS), 18.4 (C_q *t*-Bu), -5.3 (CH_3 TBDMS).



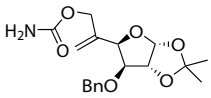
3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-ulose (20). Dess-Martin periodinane (4.98 g, 12 mmol, synthesis described in Chapter 6) was added to a dry and cooled (0 °C) solution of **19** (4.14 g, 9.77 mmol) in DCM (50 mL). The reaction mixture was stirred for 3 h and allowed to warm to rt. A mixture of sat aq $NaHCO_3$ (20 mL) and 1M aq $Na_2S_2O_3$ (20 mL) was added to the reaction and stirred vigorously for 15 min. The organic phase was separated and washed with sat aq NaCl (2×50 mL). The organic phase was dried and concentrated. The resulting ketone **20** was used crude in the next reaction. A small sample was purified by silica gel column chromatography (5% » 25% EtOAc in PE) for characterization to yield **20** as a colourless oil. R_F = 0.69 (16% EtOAc in toluene). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 5H, H_{Ar} Bn), 6.05 (d, *J* = 3.6, 1H, H-1), 4.89 (d, *J* = 3.6, 1H, H-2), 4.75 – 4.30 (m, 6H, H-3, H-4, CH_2-6, CH_2 Bn), 1.47 (s, 3H, CH_3 isoprop), 1.32 (s, 3H, CH_3 isoprop), 0.90 (s, 9H, 3×CH_3 *t*-Bu TBDMS), 0.04 (s, 6H, 2×CH_3 TBDMS).^{13}C NMR (50 MHz, $CDCl_3$) δ 205.2 (C(O)-5), 136.9 (C_q Bn), 128.6 (CH_{Ar}-3,5 Bn), 128.1 (CH_{Ar}-4 Bn), 127.8 (CH_{Ar}-2,6 Bn), 112.4 (C_q isoprop), 105.8 (C-1), 84.7, 83.5, 81.8 (C-2, C-3, C-4), 72.5 (CH_2 Bn), 68.9 (C-6), 27.0, 26.4 (2×CH_3 isoprop), 25.9 (CH_3 *t*-Bu TBDMS), 18.4 (C_q *t*-Bu), -5.3 (CH_3 TBDMS).



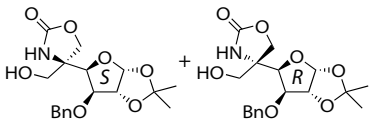
3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-methylene-α-D-*xylo*-hexofuranose (21).[22] A solution of butyllithium (6.49 mL, 10.38 mmol, 1.6M in hexane) was added to a dry and cooled (−50 °C) suspension of methyltriphenylphosphonium bromide (4.05 g, 11.33 mmol; dried *in vacuo* for 20 h at 140 °C) in THF (28 mL). The bright yellow suspension was allowed to warm to 0 °C. The suspension was cooled to −50 °C and a dry solution of crude **20** (9.44 mmol) in THF (20 mL) was added over a period of 1 min. The resulting thick suspension was allowed to warm to rt and stirred for 20 h. The mixture poured into sat aq NH_4Cl (200 mL) and EtOAc (100 mL). The organic phase was washed successively with water (2×100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (0% » 15% EtOAc in toluene) to produce **21** (2.03 g, 4.82 mmol) in 49% yield over two steps as a colorless oil. The silylether in **21** hydrolyzes to **22** over time (3 months) when stored on the bench. R_F = 0.52 (16% EtOAc in PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 5H, H_{Ar} Bn), 5.98 (d, *J* = 3.8, 1H, H-1), 5.29 (s, 2H, =CH_2), 4.84 – 4.74 (m, 1H, H-4), 4.63 (d, *J* = 3.8, 1H, H-2), 4.63 (d, *J* = 11.9, 1H, C*H*H Bn), 4.52 (d, *J* = 11.9, 1H, CH*H* Bn), 4.16 (s, 2H, CH_2-6), 3.97 (d, *J* = 3.1, 1H, H-3), 1.50 (s, 3H, CH_3 isoprop), 1.33 (s, 3H, CH_3 isoprop), 0.90 (s, 9H, 3×CH_3 *t*-Bu TBDMS), 0.04 (s, 3H, CH_3 TBDMS), 0.02 (s, 3H, CH_3 TBDMS). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.8 (=C_q-5), 137.7 (C_q Bn), 128.6 (CH_{Ar}-3,5 Bn), 128.1 (CH_{Ar}-4 Bn), 128.0 (CH_{Ar}-2,6 Bn), 111.6, 111.6 (=CH_2, C_q isoprop), 104.5 (C-1), 82.8, 82.7, 80.5 (C-2, C-3, C-4), 72.2 (CH_2 Bn), 64.5 (C-6), 26.9, 26.5 (2×CH_3 isoprop), 26.1 (CH_3 *t*-Bu TBDMS), 18.5 (C_q *t*-Bu), -5.3 (CH_3 TBDMS).



3-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-methylene-α-D-*xylo*-hexofuranose (22). A solution of tetrabutylammoniumfluoride (0.5 mL, 0.5 mmol, 1M in THF) was added to a dry solution of **21** (136 mg, 0.32 mmol) in THF (1.6 mL). The reaction mixture was stirred for 3h after which it was poured into EtOAc (50 mL) and washed with sat aq NaCl (3×20 mL). The organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (20% » 66% EtOAc in PE) to produce **22** (90 mg, 0.29 mmol) in 91% yield as a colorless oil that crystallized over time. R_F = 0.32 (33% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H, H_{Ar} Bn), 5.98 (d, *J* = 3.9, 1H, H-1), 5.30 – 5.25 (m, 2H, =CH_2), 4.81 (d, *J* = 3.4, 1H, H-4), 4.65 (d, *J* = 12.0, 1H, C*H*H Bn), 4.64 (d, *J* = 3.9, 1H, H-2), 4.49 (d, *J* = 12.0, 1H, CH*H* Bn), 4.12 (d, *J* = 13.0, 1H, H-6a), 4.07 (d, *J* = 13.0, 1H, H-6b), 3.98 (d, *J* = 3.4, 1H, H-3), 2.23 (s, 1H, OH-6), 1.50 (s, 3H, CH_3 isoprop), 1.33 (s, 3H, CH_3 isoprop). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (=C_q-5), 137.2 (C_q Bn), 128.7 (CH_{Ar}-3,5 Bn), 128.2 (CH_{Ar}-4 Bn), 128.0 (CH_{Ar}-2,6 Bn), 114.5 (=CH_2), 111.8 (C_q isoprop), 104.7 (C-1), 83.4 (C-3), 82.4 (C-2), 81.5 (C-4), 72.1 (CH_2 Bn), 64.3 (C-6), 26.9, 26.4 (2×CH_3 isoprop).

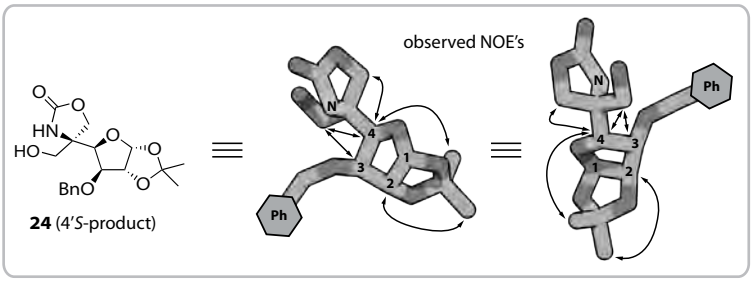


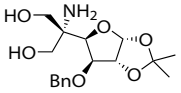
3-*O*-Benzyl-6-*O*-carbamoyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-methylene-α-D-*xylo*-hexofuranose (23). Trichloroacetyl isocyanate (479 µL, 4.04 mmol) was added over a 1 min period to a dry and cooled (0 °C) solution of **22** (1.03 g, 3.37 mmol) in DCM (5 mL). The reaction mixture was stirred for 1h after which it was concentrated to provide the crude intermediate (R_F = 0.70 in 33% EtOAc in PE). The intermediate was immediately dissolved in MeOH (7 mL) and cooled to 0 °C. An aqueous 2M potassium carbonate solution (1.4 g, 10.1 mmol in 5 mL) was added to the methanolic solution and the reaction mixture was stirred for 4 h (warming to rt). The reaction mixture was concentrated until most methanol had evaporated and the suspension was diluted with water (20 mL) and extracted with DCM (3×25 mL). The organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (5% » 40% EtOAc in PE) to produce **23** (1.12 g, 3.21 mmol) in 95% yield as a colourless oil. R_F = 0.25 (33% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 5H, H_{Ar} Bn), 5.96 (d, *J* = 3.8, 1H, H-1), 5.36 (d, *J* = 34.2, 2H, =CH_2), 5.02 (s, 2H, NH_2), 4.72 (d, *J* = 3.0, 1H, H-4), 4.62 (d, *J* = 3.8, 1H, H-2), 4.62 (d, *J* = 12.0, 1H, C*H*H Bn), 4.57 (s, 2H, CH_2-6), 4.50 (d, *J* = 12.0, 1H, CH*H* Bn), 3.96 (d, *J* = 3.3, 1H, H-3), 1.48 (s, 3H, CH_3 isoprop), 1.31 (s, 3H, CH_3 isoprop).^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9 (C=O), 138.6 (=C_q-5), 137.4 (C_q Bn), 128.5 (CH_{Ar}-3,5 Bn), 128.0 (CH_{Ar}-4 Bn), 127.8 (CH_{Ar}-2,6 Bn), 115.2 (=CH_2), 111.7 (C_q isoprop), 104.6 (C-1), 82.6 (C-3), 82.5 (C-2), 80.5 (C-4), 72.0 (CH_2 Bn), 65.5 (C-6), 26.8, 26.3 (2×CH_3 isoprop).



(4*R*, 4′*S*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-*C*-[4-(hydroxymethyl)-2-oxooxazolidin-4-yl]-α-D-erythofuranose (24) and (4*R*, 4′*R*)-3-*O*-benzyl-1,2-*O*-isopropylidene-4-*C*-[4-(hydroxymethyl)-2-oxooxazolidin-4-yl]-α-D-erythofuranose (25). A freshly prepared aqueous solution of NaOH (109 mg, 2.72 mmol in 34 mL; 0.5 mL was held back) was added to a solution of **23** (1.0 g, 2.86 mmol) in *n*-propanol (34 mL). The mixture was stirred for 5 min after which the reaction vessel was darkened by wrapping it in aluminium foil. *Tert*-butyl hypochlorite (341 µL, 2.86 mmol; prepared according to a reported[23] procedure) was added and the mixture was allowed to stir for 5 min after which diisopropylethylamine (30 µL, 0.14 mmol) was added. The reaction mixture was allowed to stir for 5 min after which a suspension of potassium osmate(VI) dihydrate (53 mg, 0.14 mmol) in aq NaOH (0.5 mL) was added. The reaction mixture colored green, which disappeared quickly and left pale yellow solution. The still darkened reaction mixture was stirred for 20 h during which it slowly colored black. Aqueous 1M Na_2SO_3 (50 mL) was added and the mixture was stirred vigorously for 30 min. The mixture was further diluted with aq 1M Na_2SO_3 (50 mL) and extracted with EtOAc (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (33% » 75% EtOAc in PE) to produce **24** (508 mg, 1.39 mmol) and **25** (364 mg, 1.0 mmol) in a combined yield of 83% as off-white foams. R_F **24** = 0.45; **25** = 0.32 (8% MeOH in DCM + 2% NH_4OH). **24 (4′*S*-product)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 5H, H_{Ar} Bn), 5.96 (d, *J* = 3.8, 1H, H-1), 5.87 (s, 1H, NH-3′), 4.66 (d, *J* = 11.4, 1H, C*H*H Bn), 4.63 (d, *J* = 3.8, 1H, H-2), 4.45 (d, *J* = 11.4, 1H, CH*H* Bn), 4.44 (d, *J* = 8.4, 1H, C*H*H-5′), 4.33 (d, *J* = 8.4, 1H, CH*H*-5′), 4.13 (d, *J* = 3.5, 1H, H-4), 4.05 (d, *J* = 3.5, 1H, H-3), 3.54 (d, *J* = 11.3, 1H, HO-C*H*H), 3.43 (d, *J* = 11.3, 1H, HO-CH*H*), 3.20 – 2.80 (m, 1H, OH), 1.47 (s, 3H, CH_3 isoprop), 1.32 (s, 3H, CH_3 isoprop). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1 (C(O)-2′), 136.2 (C_q Bn), 129.1 (CH_{Ar}-3,5 Bn), 128.9 (CH_{Ar}-4 Bn), 128.7 (CH_{Ar}-2,6 Bn), 112.1 (C_q isoprop), 104.7 (C-1), 82.4 (C-3), 81.9 (C-2), 79.5 (C-4), 72.4 (CH_2 Bn), 70.6 (C-5′), 64.8 (CH_2-OH), 62.3 (C_q-4′), 26.9, 26.3 (2×CH_3 isoprop). MS (ESI): found 366.1 $[M+H]^+$, calculated for $[C_{18}H_{23}O_7N+H]^+$ 366.2. **25 (4′*R*-product)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 5H, H_{Ar} Bn), 6.55 (s, 1H, NH-3′), 5.97 (d, *J* = 3.8, 1H, H-1), 4.63 (d, *J* = 3.9, 1H, H-2), 4.62 (d, *J* = 11.2, 1H, C*H*H Bn), 4.55 (d, *J* = 9.3, 1H, C*H*H-5′), 4.42 (d, *J* = 11.2, 1H, CH*H* Bn), 4.41 (d, *J* = 3.4, 1H, H-4), 4.02 (d, *J* = 9.3, 1H, CH*H*-5′), 3.98 (d, *J* = 3.4, 1H, H-3), 3.97 – 3.89 (m, 1H, OH), 3.53 (s, 2H, HO-CH_2), 1.50 (s, 3H, CH_3 isoprop), 1.32 (s, 3H, CH_3 isoprop). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 (C(O)-2′), 136.6 (C_q Bn), 128.9 (CH_{Ar}-3,5 Bn), 128.5 (CH_{Ar}-4 Bn), 128.1 (CH_{Ar}-2,6 Bn), 112.4 (C_q isoprop), 104.9 (C-1), 81.9 (C-2, C-3),

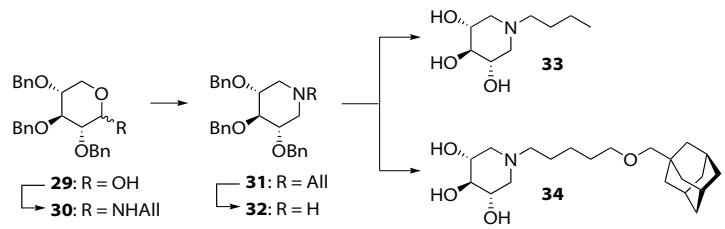
80.2 (C-4), 72.1 (CH_2 Bn), 69.0 (C-5′), 65.3 (CH_2-OH), 63.6 (C_q-4′), 26.9, 26.5 (2×CH_3 isoprop). MS (ESI): found 366.1 $[M+H]^+$, calculated for $[C_{18}H_{23}O_7N+H]^+$ 366.2.

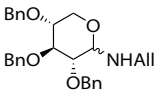




(4*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-*C*-(2-amino-1,3-dihydroxy-propane-2-yl)-α-D-erythofuranose (26). Lithium hydroxide (232 mg, 9.65 mmol) was added to a mixture of **24** and **25** (70 mg, 0.19 mmol) in EtOH/water (5 mL, 7/3, v/v). The suspension was refluxed (95 °C) for 4 h after which TLC analysis indicated complete consumption of the starting material. The mixture was passed over glass fibre filter and the filtrate was concentrated. The residue was purified by silica gel column chromatography (5% » 20% MeOH in DCM + 2% NH_4OH) to afford **26** (63 mg, 0.19 mmol) in 96% yield as a colourless oil. R_F = 0.20 (8% MeOH in DCM + 2% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 5H, H_{Ar} Bn), 5.86 (d, *J* = 3.8, 1H, H-1), 4.62 (d, *J* = 11.2, 1H, C*H*H Bn), 4.55 (d, *J* = 11.2, 1H, CH*H* Bn), 4.53 (d, *J* = 3.8, 1H, H-2), 4.21 (s, 4H, OH-1′, OH-2′, NH_2-2′), 4.13 (d, *J* = 3.1, 1H, H-3), 4.06 (d, *J* = 3.1, 1H, H-4), 3.75 – 3.57 (m, 4H, CH_2-1′, CH_2-3′), 1.45 (s, 3H, CH_3 isoprop), 1.29 (s, 3H, CH_3 isoprop).^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6 (C_q Bn), 129.0 (CH_{Ar}-3,5 Bn), 128.6 (CH_{Ar}-4 Bn), 128.6 (CH_{Ar}-2,6 Bn), 112.1 (C_q isoprop), 104.5 (C-1), 83.3 (C-3), 81.7 (C-4), 79.4 (C-4), 72.3 (CH_2 Bn), 64.2, 63.0 (CH_2-1′, CH_2-3′), 59.5 (C_q-2′), 26.9, 26.4 (2×CH_3 isoprop).

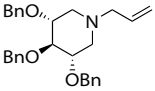
Synthesis of D-*xylo*-derivatives 33 and 34:



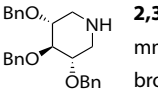


α/β-Mixture of *N*-allyl-2,3,4-tri-*O*-benzyl-D-xylopyranosylamine (30). A suspension of **29** (2.1 g, 5 mmol), allylamine (3.76 mL, 50 mmol), (±)-camphor-10-sulfonic acid (1.16 g, 5 mmol) and Na_2SO_4 (3.40 g, 24 mmol) in toluene (50 mL) was refluxed for 3 h, after which TLC analysis indicated complete consumption of **29**. The reaction mixture was cooled to rt, diluted with EtOAc (200 mL) and successively washed with sat aq $NaHCO_3$ (2×100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 20% EtOAc in PE) to provide **30** (2.07 g, 4.51 mmol) in 90% yield as a white solid. R_F = 0.61 (25% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) 0.75:1 α/β-mixture δ 7.39 – 7.22 (m, 15H, H_{Ar} Bn α/β), 5.96 – 5.80 (m, 1H, =CH allyl α/β), 5.24 – 5.01 (m, 2H, =CH_2 allyl α/β), 4.96 – 4.56 (m, 6H, 3×CH_2 Bn), 4.46 (d, *J* = 4.0, 1H, H-1α), 3.93 (d, *J* = 8.5, 1H, H-1β), 3.91 – 3.12 (m, 7H, H-2, H-3, H-4, CH_2-5 α/β), 1.96 (s, 1H, NH).^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.8, 138.6, 138.6, 138.4, 138.3 (C_q Bn α/β), 136.9, 136.8 (=CH allyl α/β), 128.6 – 127.7 (CH_{Ar} Bn α/β), 115.9, 115.8 (=CH_2 allyl α/β), 90.8 (C-1 β), 85.2

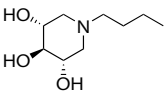
(CH β), 84.4 (C-1 α), 81.9 (CH β), 79.4 (CH α), 79.0 (CH α), 78.6 (CH β), 77.3 (CH α), 75.8, 75.2, 74.8 (3×CH_2 Bn α), 73.4, 73.3, 72.8 (3×CH_2 Bn β), 65.1 (C-5 β), 60.4 (C-5 α), 48.6 (NCH_2 allyl β), 48.2 (NCH_2 allyl α). MS (ESI): found 460.4 $[M+H]^+$, calculated for $[C_{29}H_{33}NO_4+H]^+$ 460.2.



***N*-Allyl-2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-xylitol (31).** Lithium aluminum hydride (291 mg, 7.65 mmol) was added to a dry and cooled (0 °C) solution of **30** (1.17 g, 2.55 mmol) in THF (26 mL). The reaction mixture was stirred for 20 h and allowed to warm to rt. The mixture was cooled to 0 °C and quenched by slow addition of EtOAc. The mixture was stirred for 1 h and subsequently poured into a mixture of sat aq NH_4Cl and sat aq NaCl (200 mL, 1/1, v/v). The mixture was extracted with EtOAc (3×150 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was used crude in subsequent reactions (R_F = 0.24 in 100% EtOAc + 2% NH_4OH). Diethyl azodicarboxylate (0.28 mL, 0.61 mmol; 2.2M in toluene) was added over a 1 min period to a dry solution of crude aminoalcohol (~0.55 mmol) and PPh_3 (161 mg, 0.61mmol) in DCM (5.5 mL). The reaction mixture was stirred for 20 h and subsequently quenched by addition of water. The mixture was concentrated and purified by silica gel column chromatography (0% » 20% EtOAc in toluene) to produce **31** (178 mg, 0.40 mmol) in 73% yield as a colorless oil. R_F = 0.73 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 15H, H_{Ar} Bn), 5.79 (ddt, *J* = 6.5, 10.2, 16.8, 1H, =CH allyl), 5.19 – 5.08 (m, 2H, =CH_2 allyl), 4.88 (s, 2H, CH_2 Bn), 4.70 (d, *J* = 11.6, 2H, 2×C*H*H Bn), 4.64 (d, *J* = 11.6, 2H, 2×CH*H* Bn), 3.64 – 3.54 (m, 2H, H-2, H-4), 3.41 (dd, *J* = 8.7, 1H, H-3), 3.07 (dd, *J* = 3.7, 10.8, 2H, H-1a, H-5a), 3.01 (d, *J* = 6.5, 2H, NCH_2 allyl), 1.94 (t, *J* = 10.8, 2H, H-1b, H-5b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (C_q Bn), 138.7 (2×C_q Bn), 134.5 (=CH allyl), 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{Ar} Bn), 118.4 (=CH_2 allyl), 86.4 (C-3), 78.8 (C-2, C-4), 75.5 (CH_2 Bn), 73.1 (2×CH_2 Bn), 60.9 (NCH_2 allyl), 56.1 (C-1, C-5). MS (ESI): found 444.3 $[M+H]^+$, calculated for $[C_{29}H_{33}NO_3+H]^+$ 444.3.

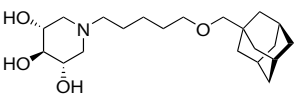


2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-xylitol (32). Potassium *tert*-butoxide (32 mg, 0.29 mmol) was added to a solution of **31** (170 mg, 0.38 mmol) in DMSO (2 mL) and the resulting brown reaction mixture was heated at 100 °C for 30 minutes. The reaction mixture was charged with 1M aq HCl (2 mL) and stirred vigorously for 15 minutes. The mixture was poured into sat aq $NaHCO_3$ (50 mL) and extracted with Et_2O (3×50 mL). The organic phase was isolated, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (33% » 100% EtOAc in PE+2% NH_4OH) to produce **32** (106 mg, 0.26 mmol) in 69% yield as a yellow oil. R_F = 0.37 (EtOAc+2% NH_4OH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.28 (15H, m, H_{Ar} Bn), 4.91 – 4.58 (6H, m, 3×CH_2 Bn), 3.61 3.54 (m, 2H, H-2, H-4), 3.39 (dd, *J* = 7.1, 1H, H-3), 3.04 (2H, dd, *J* = 10.8, 4.2, 1H, H-1a, H-5a), 2.41 (2H, dd, *J* = 10.8, 8.4, 1H, H-1b, H-5b), 1.93 (s, 1H, NH). MS (ESI): found 404.5 $[M+H]^+$, calculated for $[C_{26}H_{29}NO_3+H]^+$ 404.2.

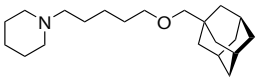


***N*-Butyl-1,5-dideoxy-1,5-imino-D-xylitol (33).** A mixture of **32** (50 mg, 124 µmol), butyraldehyde (56 µL, 0.62 mmol) and Na_2SO_4 (50 mg, 0.35 mmol) in CH_3CN/MeOH/AcOH (2 mL, 20/20/1, v/v) was charged with $NaCNBH_3$ (39 mg, 0.62 mmol). The reaction mixture was stirred for 20 h after which it was poured into a mixture of sat aq $NaHCO_3$ (25 mL) and sat aq NaCl (25 mL). The mixture was extracted with EtOAc (3×50 mL), dried ($MgSO_4$) and concentrated (R_F *N*-alkylated intermediate = 0.55 in 3:1; PE:EtOAc). The crude residue was subjected to Pd-catalyzed hydrogenation as described in general procedure A to provide **33** (17 mg, 88 µmol) in 71% yield as a crystalline white solid after silica gel column purification (1% » 20% MeOH in $CHCl_3$ + 2% NH_4OH). R_F = 0.33 (25% MeOH in $CHCl_3$ + 2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.54 – 3.45 (m, 2H, H-2, H-4), 3.09 (d, *J* = 8.9, 1H, H-3), 3.01 – 2.94 (m, 2H, H-1b, H-5b), 2.41 (dd, *J* = 6.7, 8.8, 2H, NCH_2-1 butyl), 1.92 (dd, *J* = 10.8, 2H, H-1b, H-5b), 1.55 – 1.43 (m, 2H, CH_2-2 butyl), 1.42 – 1.27 (m, 2H, CH_2-3 butyl), 0.94 (t, *J* = 7.3, 3H, CH_3 butyl).^{13}C NMR (100 MHz, MeOD) δ 80.6 (C-3), 71.5 (C-2, C-4), 59.6 (C-1,

C-5), 58.9 (NCH_2-1 butyl), 30.1, 21.8 (2×CH_2 butyl), 14.5 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3288, 2932, 2876, 1636, 1456, 1067, 1036, 976, 878. MS (ESI): found 190.0 $[M+H]^+$, calculated for $[C_9H_{19}NO_3+H]^+$ 190.1.

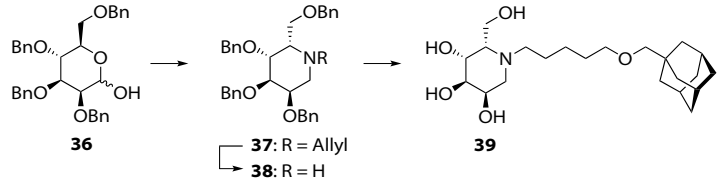


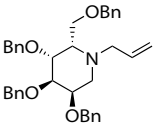
***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1,5-dideoxy-1,5-imino-D-xylitol (34).** Compound **34** (8 mg, 22 µmol) was obtained in 31% yield as a colourless oil from **32** (70 µmol) after silica gel column purification (1% » 15% MeOH in $CHCl_3$ + 2% NH_4OH) via the same 2 step procedure as described for **33**, but now with 5-(adamantane-1-yl-methoxy)-1-pentanal (**7**). R_F **34** = 0.72 (25% MeOH in $CHCl_3$ + 2% NH_4OH); R_F *N*-alkylated intermediate = 0.44 in 3:1; PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$/MeOD; 1/1; 40 °C) δ 3.72 (dd, *J* = 3.9, 10.9, 1H), 3.52 (dd, *J* = 7.8, 10.9, 1H), 3.52 – 3.41 (m, 1H), 3.37 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.20 (dd, *J* = 7.7, 1H, H-3), 3.06 – 2.99 (m, 1H), 2.98 – 2.91 (m, 3H, OCH_2-Ada, CH), 2.66 – 2.52 (m, 2H), 2.36 – 2.27 (m, 1H), 1.93 (s, 3H, 3×CH Ada), 1.76 – 1.37 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). MS (ESI): found 368.2 $[M+H]^+$, calculated for $[C_{21}H_{37}NO_4+H]^+$ 368.3.



***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-piperidine (35).** Formic acid (30 µL, 0.8 mmol) was added to a solution of piperidine (79 µL, 0.8 mmol) in DCM (5 mL). The solution was concentrated and coevaporated with dichloroethane. The residue was dissolved in EtOH (1 mL) and a solution 5-(adamantan-1yl-methoxy)-pentanal (70 mg, 0.28 mmol, synthesis described in Chapter 2) in EtOH (0.4 mL) and 3Å molecular sieves were added. The mixture was stirred for 15 min after which $NaCNBH_3$ (38 mg, 0.6 mmol) was added and the reaction mixture was stirred for 20h at rt. The mixture was filtered and the filtrate was concentrated and redissolved in EtOAc (50 mL). The solution was washed successively with sat aq $NaHCO_3$ (50 mL) and sat aq NaCl (50 mL). The organic phase was dried and concentrated. The residue was purified by silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ + 1% NH_4OH) to afford **32** (58 mg, 0.18 mmol) in 64% yield as a colourless oil. R_F = 0.44 (100% EtOAc + 2% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 2.95 (s, 2H, OCH_2-Ada), 2.71 – 2.59 (m, 4H, NCH_2-2/6 piperidine), 2.54 (d, *J* = 16.7, 1H, NC*H*H-1 pentyl), 2.54 (t, *J* = 2.9, 1H, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.78 – 1.51 (m, 16H, 3×CH_2 Ada, 3×CH_2 piperidine, 2×CH_2 pentyl), 1.52 (d, *J* = 2.6, 6H, 3×CH_2 Ada), 1.44 – 1.32 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.1 (OCH_2-Ada), 71.5 (CH_2-5 pentyl), 59.0 (NCH_2-1 pentyl), 54.3 (NCH_2-2/6 piperidine), 40.0 (CH_2 Ada), 37.4 (CH_2 Ada), 34.3 (C_q Ada), 29.5 (CH_2-4 pentyl), 28.5 (CH Ada), 25.6 (CH_2-2 pentyl), 24.8 (CH_2-3/5 piperidine), 24.3 (CH_2-3 pentyl), 23.6 (CH_2-4 piperidine). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1651, 1450, 1119. HRMS: found 320.2948 $[M+H]^+$, calculated for $[C_{21}H_{37}NO+H]^+$ 320.2956.

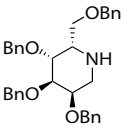
Synthesis of L-*gulo*-derivative 39:



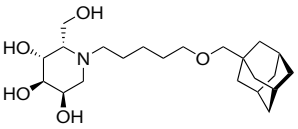


***N*-Allyl-2,3,4,6-tetra-*O*-benzyl-L-*gulo*-1-deoxynojirimycin (37).** A solution of $LiAlH_4$ (4.4 mL, 10.6 mmol, 2.4M in THF) was added in portions to a cooled (0 °C) and dry solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**36**, 1.64 g, 3.0 mmol; prepared according to a known procedure[24]) in THF (15 mL). The reaction mixture was stirred for 20 h, allowing it to warm to rt. The excess $LiAlH_4$ was quenched successively with EtOAc (5 mL, 1 h of stirring) and water at 0 °C. The mixture was diluted with EtOAc (100 mL) and washed with sat aq NH_4Cl (2×100 mL) and sat aq NaCl (100 mL). The

organic phase was dried ($MgSO_4$) and concentrated to yield the mannitol derivative, which was used crude in the next reaction (R_F mannitol der. = 0.25; **36** = 0.46 in 33% EtOAc in PE). Methanesulfonyl chloride (0.59 mL, 7.58 mmol) was added dropwise to a cooled (0 °C) solution of the crude mannitol deribative (~3 mmol) in pyridine (6 mL). After TLC analysis indicated complete consumption of starting material (2 hours), water (2 mL) was added and the reaction mixture was concentrated. The residue was dissolved in EtOAc (50 mL) and washed successively with 1M aq HCl (2×50 mL), sat aq $NaHCO_3$ (50 mL) and sat aq NaCl (50 mL). The organic phase was isolated, dried (Na_2SO_4) and concentrated to yield the mesylate as a yellow oil, which was used crude in the next step. (R_F mesylate = 0.74 in 1:1; PE:EtOAc). The crude mesylate (~3 mmol) was coevaporated with toluene, dissolved in allylamine (15 mL) and refluxed for 20 hours. The reaction mixture was concentrated, dissolved in EtOAc (50 mL) and washed successively with sat aq $NaHCO_3$ (2×50 mL) and sat aq NaCl (50 mL). The organic phase was isolated, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (isocratic 15% EtOAc in PE) to produce **37** (943 mg, 1.67 mmol) in 56% yield over three steps as an orange oil. R_F = 0.45 (16% EtOAc in PE). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32 – 7.13 (m, 20H, H_{Ar} Bn), 6.05 – 5.84 (m, 1H, =CH allyl), 5.16 – 5.08 (m, 2H, $=CH_2$ allyl), 4.68 – 4.42 (m, 8H, 4×CH_2 Bn), 3.90 – 3.78 (m, 1H, H-2), 3.77 – 3.67 (m, 2H, H-4, H-6a), 3.63 (dd, *J* = 3.2, 4.2, 1H, H-3), 3.49 (dd, *J* = 5.8, 9.5, 1H, H-6b), 3.33 (dd, *J* = 6.3, 14.2, 1H, NC*H*H allyl), 3.13 (dd, *J* = 7.2, 14.2, 1H, NCH*H* allyl), 3.00 (td, *J* = 1.8, 5.8, 1H, H-5), 2.80 (dd, *J* = 4.5, 10.9, 1H, H-1a), 2.68 (dd, *J* = 9.8, 10.9, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0, 138.8, 138.4, 138.3 (4×C_q Bn), 134.4 (=CH allyl), 128.4, 128.3, 128.0, 127.8, 127.6, 127.5 (CH_{Ar} Bn), 118.2 ($=CH_2$ allyl), 76.6 (C-4), 74.2 (C-2), 73.8 (C-3), 73.2, 72.5, 72.6, 71.2 (4×CH_2 Bn), 69.3 (C-6), 58.4 (C-5), 57.4 (NCH_2 allyl), 50.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3026, 2860, 1497, 1454, 1364, 1205, 1072, 1026, 995, 914, 733, 694. $[\alpha]^{20}_D$: −0.8 (*c* 0.98, $CHCl_3$). MS (ESI): found 564.3 $[M+H]^+$, calculated for $[C_{37}H_{41}NO_4+H]^+$ 564.3.



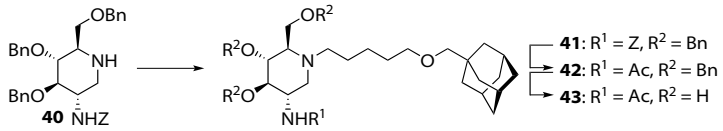
2,3,4,6-Tetra-*O*-benzyl-L-*gulo*-1-deoxynojirimycin (38). Potassium *tert*-butoxide (181 mg, 1.61 mmol) was added to a solution of **37** (1.20 g, 2.12 mmol) in DMSO (10 mL) and the resulting brown reaction mixture was heated at 100 °C for 60 minutes. The reaction mixture was charged with 1M aq HCl (6 mL) and stirred vigorously for 15 minutes. The mixture was poured into sat aq $NaHCO_3$ (100 mL) and extracted with Et_2O (3×100 mL). The organic phase was isolated, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (1: 33% » 100% EtOAc in PE+1% NH_4OH; 2: isocratic 10% MeOH in EtOAc) to furnish **38** (1.00 g, 1.91 mmol) in 90% yield as a yellow oil. R_F = 0.14 (50% EtOAc in PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 20H, H_{Ar} Bn), 4.79 – 4.26 (m, 8H, 4×CH_2 Bn), 3.80 (dd, *J* = 2.7, 4.0, 1H, H-3), 3.78 – 3.67 (m, 1H, H-2), 3.54 (dd, *J* = 1.7, 4.0, 1H, H-4), 3.47 (dd, *J* = 7.4, 8.6, 1H, H-6a), 3.41 – 3.22 (m, 2H, H-5, H-6b), 3.01 (d, *J* = 8.1, 2H, CH_2-1), 2.15 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 138.9, 138.3, 138.2 (4×C_q Bn), 128.4, 128.3, 128.1, 127.9, 127.6, 127.3, 127.1 (CH_{Ar} Bn), 75.6 (C-4), 75.2 (C-2), 73.4 (C-3), 73.3, 72.9, 72.7, 71.0 (4×CH_2 Bn), 70.6 (C-6), 53.7 (C-5), 44.4 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3034, 2862, 1495, 1452, 1366, 1205, 1092, 1059, 1026, 733, 694. $[\alpha]^{20}_D$: 0.2 (*c* 1.14, $CHCl_3$). MS (ESI): found 524.6 $[M+H]^+$, calculated for $[C_{34}H_{37}NO_4+H]^+$ 524.3.

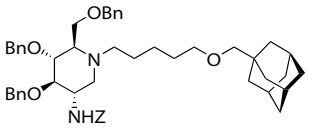


***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-L-*gulo*-1-deoxynojirimycin (39).** A solution of **38** (100 mg, 0.19 mmol) and 5-(adamantane-1-yl-methoxy)-1-pentanal **7** (53 mg, 0.21 mmol) in EtOH/AcOH (50 mL, 9/1, v/v) was purged of oxygen by bubbling argon through the solution. Pd/C (10 wt%, 50 mg) was added to the solution and the reaction mixture was exposed to 4 bar of hydrogen for 20 hours. Removal of Pd/C by filtration over a glass micro fibre filter and concentration of the filtrate provided the crude *N*-alkylated intermediate (R_F = ~0.5 in 4:1; PE:EtOAc) as a light yellow oil. A solution of crude intermediate in EtOH (50 mL) was acidified with 2M aq HCl (5 mL) and purged of oxygen by bubbling argon through the solution. Pd/C (10 wt%, 50 mg) was added to the solution and the reaction mixture was exposed to 4 bar of

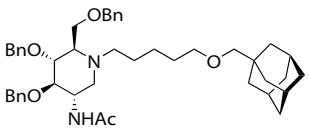
hydrogen for 20 hours. After removal of Pd/C and concentration, the residue was purified by silica gel column chromatography (0% » 20% MeOH in $CHCl_3$ + 1% NH_4OH) to afford **39** (48 mg, 0.12 mmol) in 61% yield over two steps as white foam. R_F = 0.2 (4:1; $CHCl_3$:MeOH + 1% NH_4OH). ^1H NMR (400 MHz, MeOD) δ 3.98 (ddd, *J* = 3.3, 4.4, 9.7, 1H, H-2), 3.92 (dd, *J* = 2.6, 4.7, 1H, H-4), 3.84 (dd, *J* = 5.3, 11.5, 1H, H-6a), 3.79 (dd, *J* = 4.7, 11.5, 1H, H-6b), 3.76 (dd, *J* = 3.3, 4.7, 1H, H-3), 3.39 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 2.97 (s, 2H, OCH_2-Ada), 2.79 – 2.76 (m, 1H, H-5), 2.75 – 2.69 (m, 2H, H-1a, NC*H*H-1 pentyl), 2.66 – 2.57 (m, 2H, H-1b, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.7, 30.9, 6H, 3×CH_2 Ada), 1.63 – 1.50 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.39 – 1.27 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 73.1 (C-4), 72.7 (CH2-5 pentyl), 72.3 (C-3), 67.6 (C-2), 61.7 (C-6), 60.9 (C-5), 55.0, 53.2 (C-1, NCH_2-1 pentyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2-4 pentyl), 29.9 (CH Ada), 25.5 (CH_2-2 pentyl), 25.4 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3359, 2902, 2848, 1453, 1065, 1057. $[\alpha]^{20}_D$: 24.5 (*c* 0.4, MeOH). HRMS: found 398.2899 $[M+H]^+$, calculated for $[C_{22}H_{39}O_5N_1+H]^+$ 398.2901.

Synthesis of C-2 acetamido derivative 43:



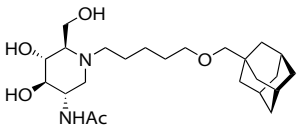


***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-2-(benzyloxycarbonyl) amino-3,4,6-tri-*O*-benzyl-1,2-deoxynojirimycin (41).** A dry mixture of 2-(benzyloxycarbonyl)amino-3,4,6-tri-*O*-benzyl-1,2-dideoxynojirimycin (**40**: 180 mg, 0.32 mmol; prepared according to a known procedure[25]), 5-(adamantane-1-yl-methoxy)-1-pentanal (160 mg, 0.64 mmol) and Na_2SO_4 (91 mg, 0.64 mmol) in MeOH/AcOH (3 mL, 20/1, v/v) was charged with $NaCNBH_3$ (41 mg, 0.64 mmol). The reaction mixture was stirred for 20 h after which it was poured into a mixture of sat aq $NaHCO_3$ (25 mL) and sat aq NaCl (25 mL). The mixture was extracted with EtOAc (3×50 mL), dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 33% EtOAc in PE) to produce **41** (233 mg, 0.29 mmol) in 91% yield as a colorless oil. R_F = 0.22 (25% EtOAc in PE). ^1H NMR (300 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.37 – 7.16 (m, 20H, H_{Ar} Bn/Z), 5.25 (s, 1H, NH), 5.13 – 5.00 (m, 2H, CH_2 Z), 4.73 – 4.38 (m, 6H, 3×CH_2 Bn), 3.90 – 3.78 (m, 1H, H-2), 3.76 – 3.68 (m, 2H, CH_2-6), 3.68 – 3.59 (m, 1H, H-3/4), 3.45 – 3.27 (m, 3H, H-3/4, CH_2-5 pentyl), 3.05 (dd, *J* = 3.4, 11.7, 1H, H-1a), 2.97 – 2.90 (m, 2H, OCH_2-Ada), 2.81 – 2.72 (m, 1H, H-5), 2.65 – 2.50 (m, 2H, NCH_2-1 pentyl), 2.37 – 2.24 (m, 1H, H-1b), 1.95 (s, 3H, 3×CH Ada), 1.75 – 1.21 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) collapsed iminosugar signals δ 156.1 (C=O Z), 138.5, 138.4, 138.4, 136.9 (C_q Bn/Z), 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5 (CH_{Ar} Bn/Z), 82.1 (OCH_2 Ada), 79.7, 77.3 (C-3, C-4), 73.4, 71.7, 66.6, 65.5 (CH_2 Z, CH_2 Bn, C-6, CH_2-5 pentyl), 62.3 (C-5), 53.4, 51.1 (C-1, NCH_2-1 pentyl), 50.0 (C-2), 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 28.5 (CH Ada), 29.6, 25.9, 24.0 (3×CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2897, 2847, 1699, 1539, 1497, 1454, 1362, 1094, 1070, 1028, 733, 696. $[\alpha]^{20}_D$: 12.9 (*c* 2.8, $CHCl_3$). MS (ESI): found 801.4 $[M+H]^+$, calculated for $[C_{51}H_{64}O_6N_2+H]^+$ 801.5.



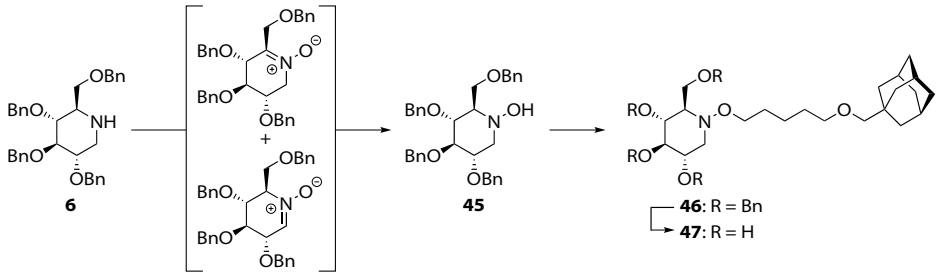
2-Acetamide-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-3,4,6-tri-*O*-benzyl-1,2-deoxynojirimycin (42). A solution of compound **41** (233 mg, 0.29 mmol) in EtOAc (5 mL) was acidified with AcOH (0.1 mL). Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C Degussa-type (50 mg) was added. A gentle flow of hydrogen gas was passed through the reaction mixture for 2 h after which TLC analysis indicated complete consumption of **41**. Pd/C was removed by

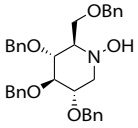
filtration over a glass micro fibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene. The residue was dissolved in pyridine (5 mL) and Ac_2O (0.2 mL) was added. The reaction mixture was stirred for 20 h. The mixture was concentrated and purified by silica gel column chromatography (0% » 5% MeOH in DCM) to provide **42** (144 mg, 0.20 mmol) in 70% yield as a colourless oil. R_F = 0.85 (5% MeOH in DCM). ^{1}H NMR (200 MHz, $CDCl_3$/MeOD, 2/1) δ 7.41 – 7.20 (m, 15H, H_{Ar} Bn), 4.72 – 4.47 (m, 6H, 3×CH_2 Bn), 4.09 – 3.98 (m, 1H, H-2), 3.85 – 3.39 (m, 2H, H-3, H-4, CH_2-6), 3.35 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 2.99 (dd, *J* = 3.7, 11.7, 1H, H-1a), 2.96 (s, 2H, OCH_2-Ada), 2.89 – 2.70 (m, 1H, H-5), 2.62 – 2.53 (m, 1H, NCH_2-1 pentyl), 2.23 (dd, *J* = 7.3, 11.7, 1H, H-1b), 1.96 (s, 3H, 3×CH Ada), 1.79 (s, 3H, CH_3 Ac), 1.76 – 1.26 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). MS (ESI): found 709.3 $[M+H]^+$, calculated for $[C_{45}H_{60}O_5N_2+H]^+$ 709.5.



2-Acetamide-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1,2-deoxynojirimycin (43). Compound **42** (78 mg, 0.18 mmol) was obtained after silica gel column chromatography (5% » 20% MeOH in DCM + 2% NH_4OH) in 90% yield by subjecting **43** (0.20 mmol) to Pd-catalyzed hydrogenation according to general procedure A. R_F = 0.47 (20% MeOH in DCM+2% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$/MeOD, 1/1) δ 3.90 – 3.84 (m, 2H, CH_2-6), 3.98 (dd, *J* = 4.4, 10.4, 1H, H-2), 3.46 (dd, *J* = 9.1, 1H, H-3/4), 3.40 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.21 (dd, *J* = 8.9, 10.2, 1H, H-3/4), 3.08 (dd, *J* = 4.3, 11.3, 1H, H-1a), 2.98 (s, 2H, OCH_2-Ada), 2.81 – 2.73 (m, 1H, NC*H*H-1 pentyl), 2.59 – 2.52 (m, 1H, NCH*H*-1 pentyl), 2.19 – 2.11 (m, 2H, H-1b, H-5), 1.98 (s, 3H, CH_3 Ac), 1.96 (s, 3H, 3×CH Ada), 1.71 (dd, *J* = 11.7, 30.9, 6H, 3×CH_2 Ada), 1.61 – 1.48 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.35 – 1.27 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$/MeOD, 1/1) δ 173.1 (C=O Ac), 82.8 (OCH_2 Ada), 77.2, 72.5 (C-3, C-4), 72.4 (CH_2-5 pentyl), 66.2 (C-5), 59.4 (C-6), 55.2, 53.1 (C-1, NCH_2-1 pentyl), 51.5 (C-2), 40.5 (CH_2 Ada), 37.9 (CH_2 Ada), 34.8 (C_q Ada), 29.1 (CH Ada), 30.1, 25.1, 24.8 (3×CH_2 pentyl), 22.9 (CH_3 Ac). MS (ESI): found 439.4 $[M+H]^+$, calculated for $[C_{24}H_{42}O_5N_2+H]^+$ 439.3.

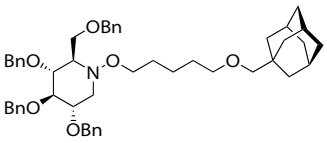
Synthesis of aminoxy-derivative 47:



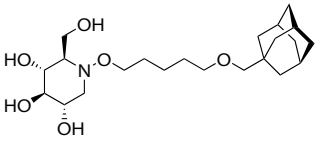


***N*-Hydroxy-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (45).** An aqueous solution of $NaHCO_3$ (378 mg, 4.5 mmol, 5 mL H_2O) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**6**: 522 mg, 1.0 mmol; synthesis described in Chapter 2) in DCM/acetone (10 mL, 1/1, v/v) and the resulting two-phase mixture was cooled to 0 °C. A solution of Oxone (potassium peroxymonosulfate, 1.54 g, 2.5 mmol) in water (5 mL) was added dropwise to the vigorously stirred mixture. The reaction mixture was stirred for 90 min at 0 °C after which TLC analysis indicated complete consumption of **6**. The mixture was diluted with DCM (50 mL) and successively washed with 5% aq $KHSO_4$ (50 mL) and sat aq $NaHCO_3$ (50 mL). The organic phase was dried (Na_2SO_4) and concentrated at ~30 °C to yield the crude intermediate cyclic nitrone (R_F = 0.29 in 25% PE in EtOAc+ 2% Et_3N). A dry and cooled (0 °C) solution of the cyclic nitrone in THF (20 mL) was charged in a dropwise fashion with $LiAlH_4$ (2 mL, 2.8 mmol, 2.4M in THF). After stirring for 1h at 0 °C the reaction mixture was quenched by slow addition of EtOAc (5 mL). After stirring for 1h

at 0 °C the mixture was poured into sat aq NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The residue was purified by silica gel column chromatography (25% » 75% EtOAc in PE + 1% Et_3N) to produce **45** (416 mg, 0.77 mmol) in 77% yield over two steps as an off-white solid. R_F = 0.85 (25% PE in EtOAc+ 2% Et_3N). ^1H NMR (400 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.35 – 7.10 (m, 20H, H_{Ar} Bn), 6.63 (s, 1H, N–OH), 4.95 (d, *J* = 11.0, 1H, C*H*H Bn), 4.87 – 4.78 (m, 2H, CH*H* Bn, C*H*H Bn), 4.71 – 4.38 (m, 5H), 3.99 – 3.77 (m, 1H), 3.81 – 3.51 (m, 5H), 2.63 (t, *J* = 11.0, 1H), 2.65 – 2.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) collapsed iminosugar signals δ 138.9, 138.4, 138.3, 137.9 (4×C_q Bn), 128.6, 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 76.5, 75.6, 75.5, 73.4, 73.1. MS (ESI): found 540.2 $[M+H]^+$, calculated for $[C_{34}H_{37}NO_5+H]^+$ 540.3.



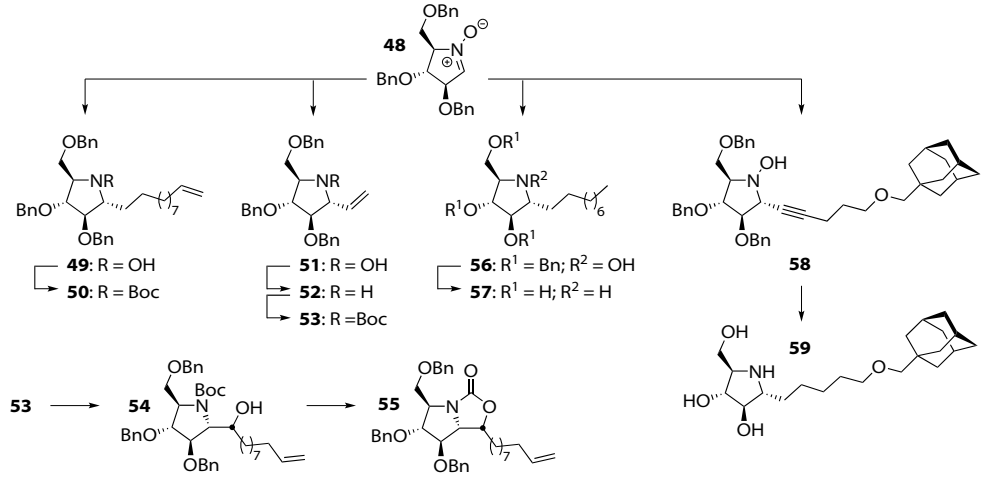
***N*-[5-(Adamantan-1-yl-methoxy)-pentyloxy]-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (46).** Sodium hydride (17 mg, 0.42 mmol, 60% in mineral oil) was added to a dry and cooled (0 °C) solution of **45** (225 mg, 0.417 mmol) in DMF (2 mL). The mixture was stirred for 10 min at 0 °C after which a solution of 5-(adamantan-1yl-methoxy)-1-bromo-pentane (132 mg, 0.42 mmol, synthesis described in Chapter 5) in DMF (0.5 mL) was added. The reaction mixture was stirred for 2h at rt after which TLC indicated ~50% conversion. The mixture was cooled to 0 °C and an additional equivalent of NaH and bromide were successively added. After stirring for 1h at rt the reaction mixture was quenched by addition of water. The mixture was diluted with water (50 mL) and extracted with Et_2O (3×50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (5% » 20% EtOAc in PE) to produce **46** (190 mg, 0.25 mmol) in 60% yield as a colourless oil. R_F = 0.53 (25% EtOAc in PE). ^1H NMR (200 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.49 – 7.07 (m, 20H, H_{Ar} Bn), 4.95 (d, *J* = 11.1, 1H, CHH Bn), 4.89 – 4.77 (m, 2H, CH*H* Bn, C*H*H Bn), 4.71 (d, *J* = 11.6, 1H, C*H*H Bn), 4.64 (d, *J* = 11.6, 1H, CH*H* Bn), 4.57 – 4.40 (m, 3H, CH*H* Bn, CH_2 Bn), 3.95 – 3.43 (m, 9H, H-1a, H-2, H-3, H-4, H-5, CH_2-6, $NOCH_2$-1 pentyl), 3.37 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 2.96 (s, 2H, OCH_2-Ada), 2.48 (dd, *J* = 10.8, 1H, H-1b), 1.95 (s, 3H, 3×CH Ada), 1.82 – 1.11 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl).^{13}C NMR (50 MHz, $CDCl_3$) collapsed iminosugar signals δ 139.0, 138.5, 138.5, 138.0 (4×C_q Bn), 128.5, 128.0, 128.0, 127.9, 127.9, 127.7, 127.6 (CH_{Ar} Bn), 82.1 (OCH_2-Ada), 76.4 (CH), 75.5, 73.6, 73.2, 73.1, 71.6, 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 28.4 (CH Ada), 29.6, 28.6, 23.1 (3×CH_2 pentyl). MS (ESI): found 774.7 $[M+H]^+$, calculated for $[C_{50}H_{63}NO_6+H]^+$ 774.5.

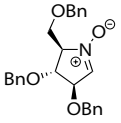


***N*-[5-(Adamantan-1-yl-methoxy)-pentyloxy]-1-deoxynojirimycin (47).** A dry (100 mL) three-neck roundbottom flask was cooled to –60 °C and ammonia gas (via a CaO filled drying column) was passed through it until 20-30 mL ammonia has condensed. The ammonia gasflow was stopped and sodium (50–100 mg, rinsed beforehand with heptane) was added to the liquid ammonia. After stirring the dark blue mixture at –60 °C for 1 min, a solution of the **46** (95 mg, 120 µmol) in *t*BuOH/ THF (0.2 mL/1 mL) was added. The reaction mixture was stirred for 1-2 h at –60 °C and additional sodium was added if the blue color of the mixture disappears. The reaction was quenched by slow addition of sat aq NH_4HCOOH (1 mL). The ammonia was evaporated and the resulting residue was coevaporated with dioxane. The solid residue was redissolved in MeOH and concentrated in the presence of celite. The celite-compound mixture was purified by silica gel column chromatography (10% » 20% MeOH in $CHCl_3$+5% NH_4OH) to afford **47** (26 mg, 63 µmol) in 53% yield as a colourless oil. R_F = 0.39 (3:1; EtOAc:MeOH +1% NH_4OH). ^1H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 3.93 (dd, *J* = 3.1, 11.2, 1H, H-6a), 3.87 – 3.78 (m, 1H, H-6b), 3.75 (t, *J* = 6.3, 2H, $NOCH_2$-1 pentyl), 3.50 – 3.44 (m, 1H)3.47 (dd, *J* = 4.5, 11.4, 1H, H-1a), 3.39 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.19 (dd, *J* = 8.9, 1H), 2.97 (s, 2H, OCH_2-Ada), 2.50 – 2.36 (m, 1H, H-1b), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.6, 30.4, 6H, 3×CH_2 Ada), 1.63 – 1.52 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.47 – 1.38 (m, 2H, CH_2-3 pentyl). ^{13}C

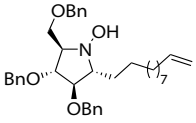
NMR (100 MHz, MeOD) collapsed iminosugar signals δ 83.2 (OCH_2-Ada), 80.4 (CH), 74.0 ($NOCH_2$-1 pentyl), 72.7 (CH_2-5 pentyl), 70.6 (CH), 69.2 (CH), 61.4 (C-1), 60.2 (C-6), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7, 29.8 (2×CH_2 pentyl), 29.9 (CH Ada), 24.3 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3359, 2902, 2849, 1453, 1105, 1043. $[\alpha]^{20}_D$: 1.0 (*c* 0.4, MeOH). HRMS: found 414.2848 $[M+H]^+$, calculated for $[C_{22}H_{39}O_6N_1+H]^+$ 414.2850.

Synthesis of Broussonetine C and E intermediates 50 and 55; and Broussonetine analogs 57 and 59:



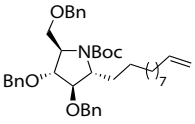


1,4-Anhydro-2,3,5-tri-*O*-benzyl-1-deoxy-1-imino-D-arabinitol *N*-oxide (48). Cyclic nitrone **48** was prepared according to a procedure reported[16] by Vogel *et al.* from D-arabinose and obtained as a white solid that was stable for several weeks when stored at −20 °C. R_F = 0.50 (5% MeOH in Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 15H, H_{Ar} Bn), 6.88 (t, *J* = 1.9, 1H, H-1), 4.66 (td, *J* = 0.8, 2.2, 1H, H-2), 4.61 (d, *J* = 12.0, 1H, C*H*H Bn), 4.55 (s, 2H, CH_2 Bn), 4.54 (s, 2H, CH_2 Bn), 4.51 (d, *J* = 12.0, 1H, CH*H* Bn), 4.37 (dd, *J* = 2.1, 3.7, 1H, H-3), 4.04 (dd, *J* = 5.1, 10.0, 1H, C*H*H-5), 4.01 (ddd, *J* = 1.1, 2.3, 5.1, 1H, H-4), 3.77 (dd, *J* = 2.8, 10.0, 1H, CH*H*-5). ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.9, 137.4, 137.3 (C_q Bn), 133.1 (C-1), 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9 (CH_{Ar} Bn), 83.0, 80.6, 77.7 (C-2), 73.7 (C-3), 72.1 (C-4), 71.9 (CH_2 Bn), 66.3 (C-5). MS (ESI): found 418.2 $[M+H]^+$, calculated for $[C_{26}H_{28}NO_4+H]^+$ 418.2.

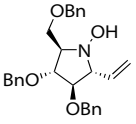


(1*R*)-2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-hydroxylimino-1-*C*-(undec-1-en-11-yl)-D-arabinitol (49). A solution of undec-1-en-11-ylmagnesium bromide was prepared by combining 'dry stirrred'[26] magnesium (350 mg, 14.4 mmol), 11-bromoundec-1-ene (2.61 mL, 12 mmol) and two drops of ethylenedibromide in THF (12 mL). The reaction was stirred for 1h with optional heating if the reaction stalled and cooled to rt when finished. The solution of the undec-1-en-11-ylmagnesium bromide was added over a period of 1 min to a dry and cooled (−50 °C) solution of **48** (1.42 g, 3.41 mmol) in THF (34 mL). The reaction mixture was stirred for 1h at −50 °C after which sat aq NH_4Cl was added carefully. The mixture was poured into sat aq NH_4Cl (200 mL) and extracted with EtOAc (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 20% EtOAc in PE) to afford **49** (1.61 g, 2.82 mmol) in 82% as an off-white solid. R_F = 0.36 (25% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 15H, H_{Ar} Bn), 6.67 (s, 1H, N-OH), 5.80 (ddt, *J* = 6.7, 10.2, 16.9, 1H,=CH undecenyl), 5.06 – 4.86 (m, 2H, =CH_2 undecenyl), 4.60 – 4.38 (m, 6H, 3×CH_2 Bn), 3.94 (dd, *J* = 2.8, 3.8, 1H, H-3), 3.82 – 3.76 (m, 2H, H-2, H-5a), 3.58 (dd, *J* = 6.9, 9.3, 1H, H-5b), 3.55 – 3.48 (m, 1H, H-4), 3.16 (dt, *J* = 8.1, 5.4, 1H, H-1a), 2.07 – 1.98 (m, 2H, CH_2-9 undecenyl), 1.93 – 1.78 (m, 1H, C*H*H-1 undecenyl), 1.57

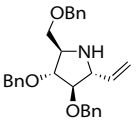
– 1.42 (m, 1H, CH*H*-1 undecenyl), 1.42 – 1.19 (m, 14H, 7×CH_2 undecenyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5 (=CH undecenyl), 138.4, 138.3 (C_q Bn), 128.8, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8 (H_{Ar} Bn), 114.3 (=CH_2 undecenyl), 87.0 (C-2), 84.9 (C-3), 73.5, 71.9, 71.8 (CH_2 Bn), 70.3 (C-1), 70.3 (C-4), 68.6 (C-5), 34.0 (CH_2-9 undecenyl), 30.0, 29.8, 29.7, 29.6, 29.3, 29.2, 26.8, 25.9 (8×CH_2 undecenyl). MS (ESI): found 572.4 $[M+H]^+$, calculated for $[C_{37}H_{49}NO_4+H]^+$ 572.4.



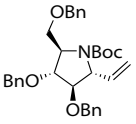
(1*R*)-2,3,5-Tri-*O*-benzyl-*N*-*t*-butyloxycarbonyl-1,4-dideoxy-1,4-imino-1-*C*-(undec-1-en-11-yl)-D-arabinitol (50). Zinc powder (553 mg, 8.46 mmol) was added to a mixture of **49** (1.61 g, 2.82 mmol) in EtOH (40 mL) and sat aq NH_4Cl (20 mL). The suspension was refluxed at 88 °C for 1h. The mixture was cooled to rt and filtered over celite. The filter cake was washed with EtOH (3×) and the combined filtrate was concentrated. The residue was divided between EtOAc (100 mL) and sat aq $NaHCO_3$ (200 mL). The aqueous phase was extracted with EtOAc (3×100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was dissolved in dioxane (20 mL) and aq 5% $NaHCO_3$ (10 mL) was added. Boc-anhydride (872 mg, 4 mmol) was added to the mixture and the resulting milk white mixture was stirred for 20h. The mixture was diluted with water (100 mL) and extracted with Et_2O (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 20% EtOAc in PE) to provide **50** (1.48 g, 2.26 mmol) in 80% yield over two steps as a colourless oil. R_F **50** = 0.71 (20% EtOAc in PE); R_F intermediate amine = 0.20 (20% EtOAc in PE + 5% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 7.35 – 7.10 (m, 30H, H_{Ar} Bn A/B), 5.79 (ddt, *J* = 6.7, 10.2, 16.9, 2H, =CH undecenyl A/B), 5.03 – 4.88 (m, 4H, =CH_2 undecenyl A/B), 4.66 – 4.28 (m, 12H, CH_2 Bn A/B), 4.23 (dd, *J* = 4.0, 10.4, 1H, H-4 B), 4.17 (s, 1H, H-3 B), 4.14 (s, 1H, H-3 A), 4.06 (dd, *J* = 3.9, 10.3, 1H, H-4 A), 4.04 (dd, *J* = 4.2, 8.7, 1H, H-5a B), 3.82 (dd, *J* = 2.8, 10.8, 1H, H-1 A/B), 3.80 (s, 1H, H-2 A/B), 3.80 – 3.75 (m, 2H, H-2 A/B, H-5a A), 3.68 (dd, *J* = 2.7, 11.0, 1H, H-1 A/B), 3.53 – 3.41 (m, 2H, H-5b A, H-5b B), 2.07 – 1.97 (m, 2H, CH_2-9 undecenyl A/B), 1.85 – 1.49 (m, 2H, CH_2-1 undecenyl A/B), 1.49 – 1.10 (m, 46H, 3×CH_3 Boc A/B, CH_2 undecenyl A/B). ^{13}C NMR (100 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 154.1, 153.7 (C=O Boc A/B), 139.1, 139.0 (=CH undecenyl A/B), 138.6, 138.3, 138.0, 137.8, 137.7 (C_q Bn A/B), 128.4, 128.3, 128.2, 127.7, 127.6, 127.5, 127.4 (CH_{Ar} Bn A/B), 114.2, 114.2 (=CH_2 undecenyl A/B), 84.6, 83.3, 83.2, 81.8, 79.5, 79.4 (C_q Boc A/B), 72.9, 72.9 (C-2 A/B), 71.1 (C-3 B), 70.9 (C-3 A), 70.8 (CH_2 Bn A/B), 68.7 (C-5 A), 68.0 (C-5 B), 64.7, 64.5 (C-1 A/B), 62.6 (C-4 A), 62.5 (C-4 B), 33.8 (CH_2-9 undecenyl A/B), 31.4, 30.2, 29.6, 29.5, 29.5, 29.3, 29.1, 28.9 (CH_2 undecenyl A/B), 28.5, 28.4 (CH_3 Boc A/B), 26.6 (CH_2 undecenyl A/B). MS (ESI): found 656.3 $[M+H]^+$, calculated for $[C_{42}H_{57}NO_5+H]^+$ 656.4.



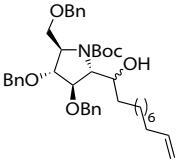
(1*R*)-2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-hydroxylimino-1-*C*-vinyl-D-arabinitol (51). Vinyl magnesiumbromide from a new bottle (3.2 mL, 3.2 mmol; 1M in THF) was added over a 1 min period to a dry and cooled (−50 °C) solution of **48** (334 mg, 0.8 mmol) in THF (8 mL). The reaction mixture was stirred at −50 °C until TLC analysis indicated complete consumption of **48**. The reaction mixture was poured into sat aq NH_4Cl (100 mL) and the mixture was extracted with EtOAc (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 30% EtOAc in PE) to afford **51** (295 mg, 0.66 mmol) in 83% yield as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 15H, H_{Ar} Bn), 6.09 – 5.98 (m, 1H, =CH vinyl), 5.33 – 5.24 (m, 1H, =CH_2 vinyl), 4.60 – 4.40 (m, 6H, CH_2 Bn), 4.05 – 3.95 (m, 1H, H-3), 3.95 – 3.86 (m, 1H, H-2), 3.82 – 368 (m, 2H, H-1, H-5a), 3.68 – 3.56 (m, 1H, H-5b), 3.55 – 3.46 (ddd, 1H, H-4). ^{13}C NMR (300 MHz, $CDCl_3$) δ 138.1, 138.0, 137.9 (C_q Bn), 135.5 (=CH vinyl), 128.3 – 127.4 (CH_{Ar} Bn), 119.1 (=CH_2 vinyl), 86.0 (C-2), 83.7 (C-3), 73.2, 71.8, 71.5 (CH_2 Bn), 72.7 (C-1), 69.5 (C-4), 67.7 (C-5). MS (ESI): found 446.2 $[M+H]^+$, calculated for $[C_{28}H_{31}NO_4+H]^+$ 446.2.



(1*R*)-2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-1-*C*-vinyl-D-arabinitol (52). Zinc powder (559 mg, 8.55 mmol) was added to a mixture of **51** (1.270 g, 2.85 mmol) in EtOH (20 mL) and sat aq NH_4Cl (10 mL). The suspension was refluxed at 88 °C for 1h. The mixture was cooled to rt and filtered over celite. The filter cake was washed with EtOH (3×) and the combined filtrate was concentrated. The residue was divided between EtOAc (50 mL) and sat aq $NaHCO_3$ (100 mL). The aqueous phase was extracted with EtOAc (3×100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was used crude in the next reaction. A small sample was purified by silica gel chromatography (15% » 20% EtOAc in PE) for characterization. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 15H, H_{Ar} Bn), 5.95 – 5.75 (m, 1H, =CH vinyl), 5.33 – 5.15 (m, 2H, $=CH_2$ vinyl), 4.60 – 4.40 (m, 6H, CH_2 Bn), 3.97-3.75 (m, 2H, H-2, H-3), 3.68 – 3.24 (m, 4H, H-1, H-4, CH_2-5). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0 (=CH vinyl), 128.1 – 127.0 (CH_{Ar} Bn), 117.7 ($=CH_2$ vinyl), 87.9, 85.5 (C-2, C-3), 73.0, 71.3, 71.1 (CH_2 Bn), 70.0 (C-1), 68.5 (C-5), 64.7 (C-4). MS (ESI): found 429.5 $[M+H]^+$, calculated for $[C_{28}H_{31}NO_3+H]^+$ 430.2.

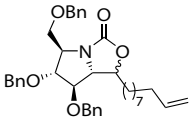


(1*R*)-2,3,5-Tri-*O*-benzyl-*N*-*t*-butyloxycarbonyl-1,4-dideoxy-1,4-imino-1-*C*-vinyl-D-arabinitol (53). Crude **52** (~2.85 mmol) was dissolved in dioxane (20 mL) and aq 5% $NaHCO_3$ (10 mL) was added. Boc-anhydride (1.27 g, 5.81 mmol) was added to the mixture and the resulting milk white mixture was stirred for 20h. The mixture was diluted with water (100 mL) and extracted with Et_2O (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 20% EtOAc in PE) to provide **53** (1.393 g, 2.63 mmol) in 92% yield over two steps as a colourless oil. R_F = 0.79 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of (A/B; 2/1) rotamers δ 7.39 – 7.10 (m, 30H, H_{Ar} Bn A/B), 5.92 – 5.78 (m, 2H, =CH vinyl A/B), 5.28 – 5.00 (m, 4H, $=CH_2$ vinyl A/B), 4.69 – 4.38 (m, 13H, CH_2 Bn A/B, H-1 B), 4.30 – 4.23 (m, 2H, H-1 A, H-4 A), 4.17 (s, 1H, H-3 B), 4.16 (s, 1H, H-3 A), 4.10 (dd, *J* = 3.7, 10.2, 1H, H-4 B), 3.98 (dd, *J* = 4.2, 8.9, 1H, H-5a A), 3.84 (s, 1H, H-2 B), 3.83 (s, 1H, H-2 A), 3.78 (dd, *J* = 4.0, 8.7, 1H, H-5a B), 3.57 – 3.47 (m, 2H, H-5b A/B), 1.40 (s, 18H, 3×CH_3 Boc A/B). ^{13}C NMR (100 MHz, $CDCl_3$) mixture of (A/B; 2/1) rotamers δ 154.6 (C=O Boc A/B), 138.1, 137.7 (C_q Bn A/B), 137.4, 137.0 (=CH vinyl A/B), 128.7, 128.6, 128.5, 128.5, 128.4, 127.9, 127.9, 127.8, 127.7, 127.6 (CH_{Ar} Bn A/B), 116.3, 116.0 ($=CH_2$ vinyl A/B), 87.1, 86.0 (C-2 A/B), 83.1, 81.6 (C-3 A/B), 80.1, 79.9 (C_q Boc A/B), 73.1, 71.5, 71.2, 71.0 (CH_2 Bn A/B), 68.9, 68.3 (C-5 A/B), 67.5, 66.6 (C-1 A/B), 63.1, 62.7 (C-4 A/B), 28.6, 28.5 (CH_3 Boc A/B). MS (ESI): found 530.3 $[M+H]^+$, calculated for $[C_{33}H_{40}NO_5+H]^+$ 530.3.

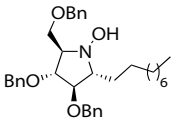


Mixture of 3,4,6-tri-*O*-benzyl-*N*-*t*-butyloxycarbonyl-1-*C*-(dec-1-en-10-yl)-2,5-dideoxy-2,5-imino-D-mannitol and 3,4,6-tri-*O*-benzyl-*N*-*t*-butyloxycarbonyl-1-*C*-(dec-1-en-10-yl)-2,5-dideoxy-2,5-imino-D-glucitol (54). A solution of **53** (530 mg, 1 mmol) in DCM (5 mL; EtOH stabilized) was cooled to −80 °C. Ozone gas was generated and bubbled through the reaction mixture (reaction gas outlet was passed over silica gel blue for detection of ozone generation). After the reaction mixture had turned blue, ozone flow was continued for a further 15 min. Ozone generation was stopped and oxygen was bubbled through the reaction mixture for ~15 min or until blue coloration had completely disappeared. Dimethylsulfide (0.2 mL, 2.7 mmol) was added and the mixture was stirred and allowed to warm to rt (~1h). The mixture was diluted with Et_2O (100 mL). and washed with water (100 mL). The organic phase was dried ($MgSO_4$), concentrated at ~30°C and the resulting crude aldehyde (colourless oil) was used crude in the next reaction. Next, a solution of dec-1-en-10-ylmagnesium bromide was prepared by combining 'dry stirred'[26] magnesium (146 mg, 6 mmol), 10-bromodec-1-ene (1.81 mL, 5 mmol) and two drops of ethylenedibromide in THF (5 mL). The reaction was stirred for 1h with optional heating if the reaction stalled and cooled to rt when finished. The solution of the undec-1-en-11-ylmagnesium bromide was added over a period of 1 min to a dry and cooled (−70 °C) solution of the crude aldehyde (~1 mmol) in THF

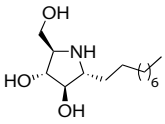
(10 mL). The reaction mixture was stirred for 30 min at −70 °C after which sat aq NH_4Cl was added carefully. The mixture was poured into sat aq NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (10% » 15% EtOAc in PE) to produce **54** (521 mg, 0.78 mmol) in 78% over two steps as a colourless oil. R_F = 0.52 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of diastereoisomers and rotamers δ 7.29 – 7.17 (m, 15H, H_{Ar} Bn), 5.83 – 5.75 (m, 1H, =CH decenyl), 5.10 – 4.85 (m, 2H, =CH_2 decenyl), 4.60 – 3.40 (m, 13H, 3×CH_2 Bn, H-1, H-2, H-3, H-4, H-5, CH_2-6), 2.03 – 1.94 (m, 2H, CH_2-8 decenyl), 1.43 (s, 9H, 3×CH_3 Boc), 1.70 – 1.10 (m, 14H, 7×CH_2 decenyl). ^{13}C NMR (400 MHz, $CDCl_3$) mixture diastereoisomers and rotamers δ 155.5, 154.7 (C=O Boc), 139.8 (=CH decenyl), 139.3 – 137.8 (C_q Bn), 128.2 – 127.9 CH_{Ar} Bn), 115.1 (=CH_2 decenyl), 85.6, 84.2 (C-3), 82.3, 80.8 (C-4), 74.0 (C_q Boc), 72.6 – 71.8 (CH_2 Bn), 71.5, 71.4 (C-1, C-2), 69.3, 68.7 (C-6, rotamers), 64.1, 63.9 (C-5), 34.7 – 29.8 (CH_2 decenyl), 29.0, 28.8 (CH_3 Boc), 27.1, 26.5 (CH_2 decenyl). MS (ESI): found 671.7 $[M+H]^+$, calculated for $[C_{42}H_{57}NO_6+H]^+$ 672.4.



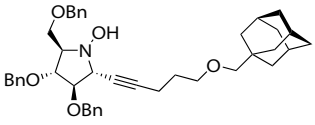
Mixture of 3,4,6-tri-*O*-benzyl-*N*,1-*O*-carbonyl-1-*C*-(dec-1-en-10-yl)-2,5-dideoxy-2,5-imino-D-mannitol and 3,4,6-tri-*O*-benzyl-*N*,1-*O*-carbonyl-1-*C*-(dec-1-en-10-yl)-2,5-dideoxy-2,5-imino-D-glucitol (55). Sodium hydride (10 mg, 0.26 mmol; 10% in mineral oil) was added to a dry and cooled (0 °C) solution of **54** (92 mg, 130 µmol) in DMF (10 mL). The reaction mixture was stirred at 0 °C for 2h. The reaction was quenched with H_2O, concentrated and the resulting residue was diluted with Et_2O (50 mL) and washed with H_2O (50 mL). The organic phase was dried ($MgSO_4$), concentrated and the resulting residue was purified by silica gel chromatography (10% » 13% EtOAc in PE) to yield **55** (52 mg, 87 µmol) as a 1:6 mixture of diastereoisomers in 67%. R_F = 0.71 (1:4; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) major isomer δ 7.41 – 7.18 (m, 15H, H_{Ar} Bn), 5.81 (ddt, *J* = 6.6, 10.1, 16.9, 1H, =CH decenyl), 5.09 – 4.93 (m, 2H, =CH_2 decenyl), 4.93 – 4.89 (m, 1H, H-1), 4.68 – 4.35 (m, 6H, 3×CH_2 Bn), 4.29 – 3.48 (m, 6H, H-2, H-3, H-4, H-5, CH_2-6), 2.11 – 1.95 (m, 2H, CH_2-8 decenyl), 1.84 – 1.48 (m, 2H, CH_2-1 decenyl), 1.48 – 1.14 (m, 20H, 6×CH_2 decenyl). ^{13}C NMR (50 MHz, $CDCl_3$) major isomer δ 154.1 (C=O), 139.3 (=CH decenyl), 137.0, 136.5 (C_q Bn), 128.6, 128.4, 128.3, 128.1, 127.9, 127.8 (CH_{Ar} Bn), 114.4 (=CH_2 decenyl), 88.2, 85.9 (C-3, C-4), 80.4 (C-1), 73.5, 72.7, 72.2 (CH_2 Bn), 69.9 (C-6), 67.6 (C-2), 62.5 (C-5), 34.1 (CH_2-8 decenyl), 29.8 – 24.8 (CH_2 decenyl). MS (ESI): found 598.3 $[M+H]^+$, calculated for $[C_{38}H_{47}NO_5+H]^+$ 598.3.



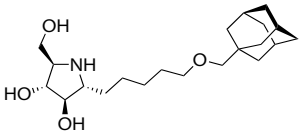
(1*R*)-2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-hydroxylimino-1-*C*-nonyl-D-arabinitol (56). A solution of nonyl magnesiumbromide was prepared by combining 'dry stirred'[26] magnesium (58 mg, 2.4 mmol), 1-bromononane (0.38 mL, 2.0 mmol) and a drop of ethylenedibromide in THF (2 mL). The reaction was stirred for 1h with optional heating if the reaction stalled and cooled to rt when finished. A portion of the nonyl magnesiumbromide solution (0.5 mL, ~0.5 mmol) was added drop wise to a dry and cooled (−50 °C) solution of **48** (70 mg, 0.17 mmol) in THF (2 mL). The reaction mixture was stirred for 1h at −50 °C after which sat aq NH_4Cl was added carefully. The mixture was poured into sat aq NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 30% EtOAc in PE) to afford **56** (75 mg, 0.14 mmol) in 82% as an off-white solid. R_F = 0.30 (20% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 15H, H_{Ar} Bn), 6.59 (s, 1H, N-OH), 4.62 – 4.41 (m, 6H, 3×CH_2 Bn), 3.94 (dd, *J* = 2.7, 4.0, 1H, H-3), 3.82 – 3.76 (m, 2H, H-2, H-5a), 3.58 (dd, *J* = 6.9, 9.3, 1H, H-5b), 3.54 – 3.49 (m, 1H, H-4), 3.16 (dt, *J* = 5.4, 8.1, 1H, H-1), 1.95 – 1.80 (m, 1H, C*H*H-1 nonyl), 1.56 – 1.40 (m, 1H, CH*H*-1 nonyl), 1.40 – 1.17 (m, 14H, 7×CH_2 nonyl), 0.88 (t, *J* = 6.9, 3H, CH_3 nonyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.4, 138.3 (C_q Bn), 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8 (CH_{Ar} Bn), 86.9, 84.8 (C-2, C-3), 73.5, 71.9, 71.8 (CH_2 Bn), 70.3 (C-1, C-4), 68.5 (C-5), 32.1, 30.0, 29.8, 29.6, 28.9, 26.8, 22.9 (CH_2 nonyl), 14.3 (CH_3 nonyl). MS (ESI): found 546.3 $[M+H]^+$, calculated for $[C_{35}H_{47}NO_4+H]^+$ 546.4.



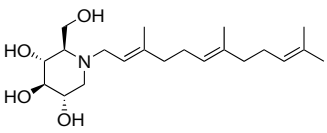
(1*R*)-1,4-dideoxy-1,4-imino-1-*C*-nonyl-D-arabinitol (57). Compound **56** (69 µmol) was subjected to general procedure A to provide **57** (15 mg, 58 µmol) after silica gel column chromatography (5% » 15% MeOH in $CHCl_3$ +5% NH_4OH) in 84% yield as a colourless oil. R_F = 0.25 (20% MeOH in $CHCl_3$ +5% NH_4OH). ^1H NMR (300 MHz, MeOD) δ 3.85 (dd, *J* = 5.9, 6.5, 1H, H-3), 3.76 (dd, *J* = 4.2, 11.5, 1H, H-5a), 3.71 (dd, *J* = 5.9, 7.0, 1H, H-2), 3.68 (dd, *J* = 6.2, 11.5, 1H, H-5b), 3.22 – 3.16 (m, 1H, H-4), 3.07 (ddd, *J* = 5.7, 7.0, 8.2, 1H, H-1), 1.86 – 1.68 (m, 1H, C*H*H-1 nonyl), 1.65 – 1.48 (m, 1H, CH*H*-1 nonyl), 1.48 – 1.23 (m, 14H, 7×CH_2 nonyl), 0.90 (t, *J* = 6.9, 3H, CH_3 nonyl). ^{13}C NMR (100 MHz, MeOD) δ 80.8 (C-2), 77.1 (C-3), 65.8 (C-4), 64.6 (C-1), 59.9 (C-5), 32.4 (CH_2-1 nonyl), 33.2, 30.8, 30.6, 30.6, 30.6, 27.4, 23.9 (7×CH_2 nonyl), 14.6 (CH_3 nonyl). MS (ESI): found 260.1 $[M+H]^+$, calculated for $[C_{14}H_{29}NO_3+H]^+$ 260.1.



(1*R*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pent-1-ynyl]-2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-hydroxylimino-D-arabinitol (58). A dry solution of 5-(adamantane-1-yl-methoxy)-pent-1-yne (46 mg, 0.2 mmol; see Chapter 5 for synthesis) in THF (2 mL) was cooled to –50 °C and BuLi (0.13 mL, 0.2 mmol, 1.6M in toluene) was added slowly to the solution. After stirring for 1 h at –50 °C, a dry solution of **48** (83 mg, 0.2 mmol) in THF (1 mL) was slowly added and the reaction was stirred at –50 °C for 1 h. The reaction mixture was quenched (sat aq NH_4Cl), warmed to rt and poured into sat aq NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 30% EtOAc in PE) to provide **58** (92 mg, 0.14 mmol) in70% yield as a colourless oil. R_F = 0.49 (25% EtOAc in PE). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 15H, H_{Ar} Bn), 5.68 (s, 1H, N-OH), 4.63 (d, *J* = 11.9, 1H, C*H*H Bn), 4.58 (d, *J* = 12.1, 1H, C*H*H Bn), 4.51 – 4.42 (m, 4H, 2×CH*H* Bn, CH_2 Bn), 4.22 (d, *J* = 2.1, 1H, H-1), 4.04 (dd, *J* = 2.4, 1H, H-2), 3.92 (dd, *J* = 2.5, 6.6, 1H, H-3), 3.71 (dd, *J* = 3.6, 9.4, 1H, H-5a), 3.68 (dd, *J* = 3.4, 9.4, 1H, H-5b), 3.43 (t, *J* = 6.1, 2H, CH_2-5 pentyn), 3.35 (dt, *J* = 4.3, 6.5, 1H, H-4), 2.92 (s, 2H, OCH_2-Ada), 2.33 (td, *J* = 2.0, 7.2, 2H, CH_2-3 pentyn), 1.93 (s, 3H, 3×CH Ada), 1.80 – 1.72 (m, 2H, CH_2-4 pentyn), 1.66 (dd, *J* = 12.1, 28.5, 6H, 3×CH_2 Ada), 1.50 (d, *J* = 2.6, 6H, 3×CH_2 Ada). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 138.2, 137.7 (C_q Bn), 128.5, 128.4, 128.1, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 88.4 (C_q pentyn), 86.6, 82.8 (C2. C-3), 82.1 (OCH_2-Ada), 75.0 (C_q pentyn), 73.5, 72.0, 71.9, 70.0 (3×CH_2 Bn, CH_2-5 pentyn), 69.3 (C-1), 68.1 (C-5), 62.2 (C-4), 39.8 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 29.0 (CH_2-4 pentyn), 28.4 (CH Ada), 15.9 (CH_2-3 pentyn). MS (ESI): found 650.3 $[M+H]^+$, calculated for $[C_{42}H_{52}NO_5+H]^+$ 650.4.

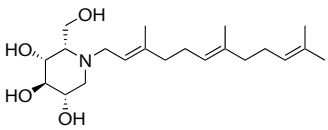


(1*R*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pent-1-ynyl]-1,4-dideoxy-1,4-imino-D-arabinitol (59). Compound **58** (80 µmol) was subjected to general procedure A to provide **59** (26 mg, 71 µmol) after silica gel column chromatography (5% » 15% MeOH in $CHCl_3$ +5% NH_4OH) in 89% yield as a colourless oil. R_F = 0.25 (20% MeOH in $CHCl_3$ +5% NH_4OH). ^1H NMR (400 MHz, MeOD) δ 3.98 (dd, *J* = 5.6, 6.3, 1H, H-3), 3.88 (dd, *J* = 4.1, 12.1, 1H, H-5a), 3.86 (dd, *J* = 5.6, 6.6, 1H, H-2), 3.82 (dd, *J* = 6.4, 12.1, 1H, H-5b), 3.49 (td, *J* = 3.8, 6.3, 1H, H-4), 3.40 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.36 – 3.33 (m, 1H, H-1), 2.97 (s, 2H, OCH_2-Ada), 1.94 (s, 3H, 3×CH Ada), 1.92 – 1.83 (m, 1H, C*H*H-1 pentyl), 1.82 – 1.41 (m, 19H, 6×CH_2 Ada, CH*H*-1 pentyl, 3×CH_2 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 80.5 (C-2), 76.8 (C-3), 72.6 (CH_2-5 pentyl), 65.8 (C-4), 64.6 (C-1), 59.7 (C-5), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.2 (CH_2-2 pentyl), 30.5 (CH_2-4 pentyl), 29.9 (CH Ada), 27.2, 27.1 (2×CH_2 pentyl). MS (ESI): found 368.3 $[M+H]^+$, calculated for $[C_{21}H_{37}NO_4+H]^+$ 368.3.



***N*-[1-(*trans*,*trans*-3,7,11-trimethyl-2,6,10-dodecatriene)]-1-deoxynojirimycin (60).** Potassium carbonate (34 mg, 0.25 mmol) was added to a dry solution of 1-deoxynojirmycin (24 mg, 0.15 mmol; synthesis described in Chapter 3) and *trans*,*trans*-farnesyl bromide (43 µL,

0.16 mmol) in DMF (0.5 mL). The reaction mixture was heated at 105 °C for 5h after which the mixture was filtered over a glass fibre filter and concentrated. The residue was purified by silica gel column chromatography (10% » 20% MeOH in DCM + 1% NH_4OH) to afford **60** (45 mg, 0.12 mmol) in 80% yield as a colourless oil. R_F = 0.17 (20% MeOH in DCM + 1% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 5.48 – 5.29 (m, 1H, =CH-2 farnesyl), 5.27 – 5.02 (m, 2H, =CH-6, =CH-10 farnesyl), 4.23 – 4.05 (m, 1H, H-6a), 4.04 – 3.85 (m, 2H, H-6b, NC*H*H-1 farnesyl), 3.83 – 3.73 (m, 1H, NCH*H*-1 farnesyl), 3.73 – 3.62 (m, 1H, H-2), 3.62 – 3.51 (m, 1H, H-4), 3.46 – 3.33 (m, 2H, H-3, H-1a), 3.05 – 2.88 (m, 1H, H-5), 2.86 – 2.66 (m, 1H, H-1b), 2.40 – 1.91 (m, 8H, CH_2-4,5,8,9 farnesyl), 1.91 – 1.46 (m, 12H, 4×CH_3 farnesyl). ^{13}C NMR (50 MHz, MeOD) δ 149.1, 137.0, 132.3 (=C_q-3,7,11 farnesyl), 125.5, 124.8, 114.0 (=CH-2,6,10 farnesyl), 78.6, 69.3, 68.2, 67.3 (C-2, C-3, C-4, C-5), 55.7, 54.6, 51.7 (C-1, C-6, NCH_2-1 farnesyl), 41.0, 40.9, 27.9, 27.3 (4×CH_2 farnesyl), 26.0, 17.9, 17.2, 16.3 (4×CH_3 farnesyl). IR ν_{max}(thin film)/ cm^{-1}: 3333, 2962, 2924, 1643, 1443, 1381, 1080, 1026. $[\alpha]^{20}_D$: −1.3 (*c* 0.9, MeOH). HRMS: found 368.2820 $[M+H]^+$, calculated for $[C_{21}H_{37}O_4N+H]^+$ 368.2795.



***N*-[1-(*trans*,*trans*-3,7,11-trimethyl-2,6,10-dodecatriene)]-L-*ido*-1-deoxynojirimycin (61).** Potassium carbonate (648 mg, 4.69 mmol) was added to a dry solution of L-*ido*-1-deoxynojirmycin (521 mg, 3.19 mmol; synthesis described in Chapter 3) and *trans*,*trans*-farnesyl bromide (924 µL, 3.44 mmol) in DMF (16 mL). The reaction mixture was heated at 90 °C for 4h after which the mixture was filtered over a glass fibre filter and concentrated. The residue was purified by silica gel column chromatography (10% » 20% MeOH in DCM + 1% NH_4OH) to afford **61** (905 mg, 2.36 mmol) in 77% yield as an off-white hygroscopic foam. R_F = 0.19 (20% MeOH in DCM + 1% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 5.32 (t, *J* = 6.9, 1H, =CH-2 farnesyl), 5.17 – 5.01 (m, 2H, =CH-6, =CH-10 farnesyl), 3.91 (d, *J* = 5.2, 2H, CH_2-6), 3.87 – 3.78 (m, 1H, H-4), 3.73 – 3.63 (m, 1H, H-2), 3.63 – 3.46 (m, 3H, H-3, NCH_2-1 farnesyl), 3.26 – 3.12 (m, 1H, H-5), 3.07 – 2.93 (m, 1H, H-1a), 2.92 – 2.71 (m, 1H, H-1b), 2.22 – 1.95 (m, 8H, CH_2-4,5,8,9 farnesyl), 1.73, 1.67, 1.61, 1.60 (4×s, 4×3H, 4×CH_3 farnesyl). ^{13}C NMR (100 MHz, MeOD) δ 136.7, 132.3 (=C_q-3,7,11 farnesyl), 125.6, 125.1 (=CH-2,6,10 farnesyl), 72.7, 70.6, 64.1 (C-2, C-3, C-4, C-5), 59.1, 53.1, 53.0 (C-1, C-6, NCH_2-1 farnesyl), 41.1, 41.0, 27.9, 27.5 (4×CH_2 farnesyl), 26.0, 17.9, 16.9, 16.3 (4×CH_3 farnesyl). IR ν_{max}(thin film)/ cm^{-1}: 3317, 2962, 2916, 2862, 1666, 1443, 1381, 1242, 1072, 1042, 980, 833. MS (ESI): found 368.5 $[M+H]^+$, calculated for $[C_{21}H_{37}O_4N+H]^+$ 368.3.

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Samenvatting | Summary in Dutch

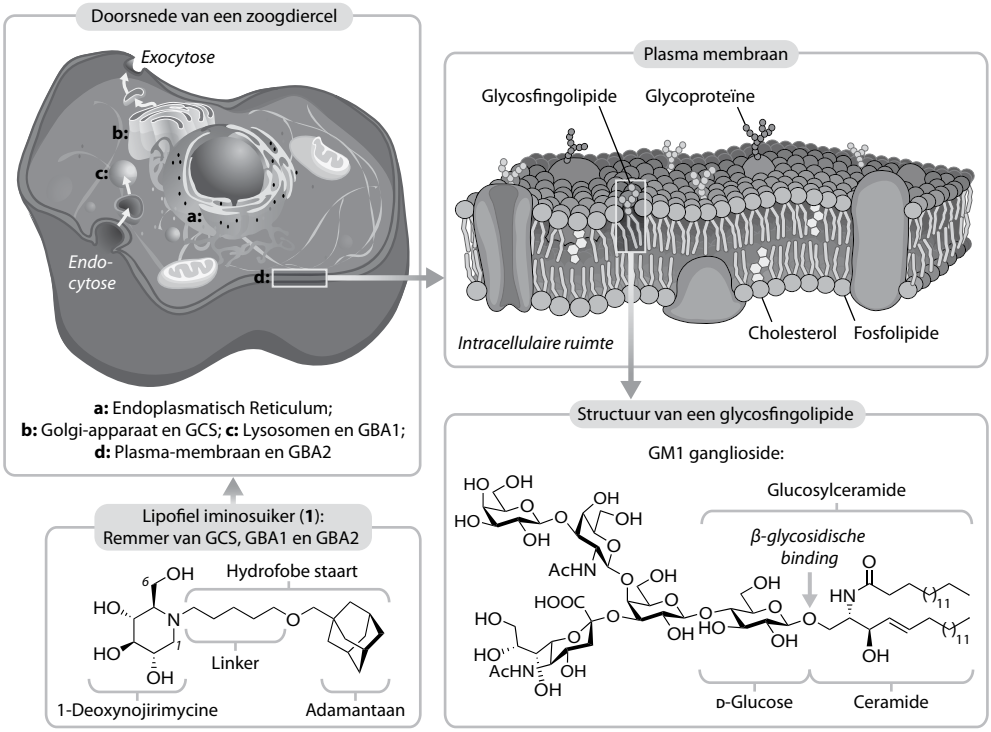
Lipofiele Iminosuikers

Synthese en Evaluatie als Remmers van Glucosylceramide Metabolisme

Alle menselijke cellen zijn aan de buitenkant bekleed met een glycocalyx, een dikke laag van diverse soorten suikerstructuren (koolhydraten). Het merendeel van deze suikers is verankerd in het plasma-membraan door conjugatie met een lipide (glycolipiden) of een eiwit (glycoproteïnen; zie figuur op pagina 312). Een fysiologisch belangrijke en omvangrijke klasse van glycolipiden is die van de glycosfingolipiden, waarvan de structuur bestaat uit een oligosaccharide, een variabele hoeveelheid van aaneengeschakelde monosaccharides, die aan het lipide ceramide gebonden is. Onderzoek heeft uitgewezen dat glycosfingolipiden niet willekeurig verspreid zijn tussen de fosfolipiden van het plasma-membraan, maar zich tezamen met cholesterol groeperen in microdomeinen, de zogenoemde lipide 'rafts'. Glycosfingolipiden zijn betrokken bij vele biologische processen zoals communicatie tussen cellen en signaaloverdracht via membraan gebonden receptoren. Ze spelen ook een rol in diverse ziektes. De exacte rol die glycosfingolipiden in zowel ziekte als gezondheid vervullen is echter vaak niet volledig bekend.

Het manipuleren van de hoeveelheid glycosfingolipiden is een van de mogelijkheden om hun functies te onderzoeken. Controle kan worden bereikt door invloed uit te oefenen op de enzymen die hun aanmaak en afbraak bewerkstelligen, oftewel die betrokken zijn bij hun metabolisme. Glycosfingolipide metabolisme begint met de biosynthese van ceramide in de membranen van het endoplasmatisch reticulum. Hierna wordt ceramide gekoppeld aan de suiker D-glucose op de buitenkant van het Golgi-apparaat door het membraan gebonden glycosyltransferase enzym, glucosylceramide synthase (GCS). Binnen in het Golgi-apparaat worden vervolgens stapsgewijs andere suikers aan het product glucosylceramide gekoppeld door diverse glycosyltransferases. Dit resulteert uiteindelijk in het uitgebreide palet van complexe glycosfingolipiden die door de cel gebruikt wordt (bv. GM1 ganglioside; zie figuur). Deze glycosfingolipiden worden daarna in membraanblaasjes naar het cel-oppervlak getransporteerd (exocytose). Afbraak van glycosfingolipiden (katabolisme) gebeurt door het afsnoeren van plasma-membraanblaasjes en het transport daarvan (endocytose) naar de lysosomen van de cel. Hier verwijderen glycosidases één voor één de suikerresiduen. In de laatste stap van de afbraak wordt met glucosylceramide als substraat door glucocerebrosidase (GBA1) en assistentie van het activator eiwit saposin C de laatste suiker verwijderd. Een derde enzym, β-glucosidase 2 (GBA2), is daarnaast ook in staat de β-glycosidische band in

glucosylceramide te hydrolyseren. Dit membraan-gebonden enzym bevindt zich nabij het plasma-membraan. Zijn functie is vooralsnog onbekend. Glucosylceramide neemt een unieke positie in omdat het de meest simpele glycosfingolipide is waaruit bijna alle complexere varianten worden vervaardigd. Het vertegenwoordigt tevens het substraat in de laatste stap van het katabolisme. De drie enzymen die betrokken zijn bij het metabolisme van glucosylceramide zijn dus de ideale kandidaten om de hoeveelheid glycosfingolipiden te kunnen beïnvloeden.



Het onderzoek dat beschreven wordt in dit proefschrift heeft de ontwikkeling van selectieve remmers te ontwikkelen voor GCS, GBA1 en GBA2 ten doel. De structuur van deze remmers is gebaseerd op lipofiel iminosuiker **1** (zie figuur). Iminosuikers zijn natuurlijk voorkomende derivaten van suikers waarbij het zuurstof atoom in de ring is vervangen door een stikstof atoom. Het synthetische iminosuiker **1** is een sterke remmer van zowel GCS, GBA1 als GBA2, maar ook van diverse andere niet aan glucosylceramide gerelateerde glycosidases. Meer selectievere remmers voor elk van de drie doel enzymen zijn nodig omdat hierdoor het glucosylceramide metabolisme nauwkeuriger gemanipuleerd kan worden. Bovendien zullen de hieruit resulterende effecten op biologische processen door verminderde aanwezigheid van bijwerkingen beter te interpreteren zijn. De selectievere remmers werden ontwikkeld door analoga van **1** te ontwerpen, te synthetiseren en te evalueren op hun capaciteit de diverse enzymen te remmen.

De algemene inleiding van dit proefschrift (**Hoofdstuk 1**) behandelt de biologische basis van het uitgevoerde onderzoek vanuit een historisch perspectief gezien. Het metabolisme van glycosfingolipiden wordt besproken met de nadruk op de beschikbare kennis over de werking van GCS, GBA1 en GBA2. Vervolgens wordt de huidige kennis over de rol die glycosfingolipiden in (patho)fysiologische processen vervullen uiteengezet, alsmede de therapeutische rol die remmers van glucosylceramide metabolisme kunnen vervullen in de behandeling van verscheidene ziektes zoals de ziekte van Gaucher en type 2 diabetes. Het hoofdstuk eindigt met een overzicht van de tot nu toe ontwikkelde en gepubliceerde remmers van GCS, GBA1 en GBA2.

Bij aanvang van het hier beschreven onderzoek was een grote hoeveelheid van iminosuiker **1** nodig voor evaluatie in diverse biologische studies. **Hoofdstuk 2** beschrijft de ontwikkeling en optimalisatie van een synthetische route die geschikt is voor het verkrijgen van kilogram hoeveelheden van **1**. Door middel van tien reacties met 2,3,4,6-tetra-*O*-benzyl-D-glucose, 1,5-pentanediol en 1-adamantanemethanol als grondstoffen kon onder cGMP omstandigheden iminosuiker **1** gemaakt worden in twee batches van ieder 1.38 kg. Met behulp van dit materiaal kon de verbetering van glycemisch controle (op bv. de bloedsuikerspiegel) in diermodellen van type 2 diabetes onder invloed van **1** worden bestudeerd. Hoewel deze verbetering aan de remming van GCS wordt toegeschreven was dit vanwege de remming van meerdere andere enzymen door **1** niet met zekerheid vast te stellen.

Het onderzoek van **Hoofdstuk 3** poogt de verbeterde controle eenduidig te verklaren door het ontwikkelen van een meer selectieve remmer voor GCS. Hiervoor werden analoga van **1** met andere stereochemie op de C-4 en C-5 posities van het 1-deoxynojirimycine iminosuiker ontwikkeld. Een analoog van **1** met L-*ido* stereochemie (C-5 epimeer) bleek een even sterke en bovendien selectievere remmer van GCS te zijn. Vergelijking van deze remmer met **1** in twee diermodellen van type 2 diabetes liet zien dat de verbeterde glycemische controle m.b.v. **1** wordt verkregen door een combinatie van twee effecten: de verlaging van de cellulaire glycosfingolipide concentratie door GCS remming en de hieruit resulterende verbeterde gevoeligheid van de insuline receptor alsmede de gereduceerde opname van suikers uit voedsel door remming van darm glycosidases.

Hoofdstuk 4 behandelt de synthese van dimeer variaties van **1** en het L-*ido* analoog uit hoofdstuk 3. Bij dit ontwerp werd het iminosuiker pentyl-linker gedeelte van de remmers verdubbeld en werden deze twee elementen op twee verschillende manieren aan één adamantaan bevestigd. Evaluatie van de vier dimeer variaties voor remming van GCS, GBA1 en GBA2 liet een vergelijkbare selectiviteit maar een verminderde activiteit zien in vergelijking met hun monovalente tegenhangers. Een mogelijk 'bivalent' effect veroorzaakt door dimerisatie van het iminosuiker, dient dus voorlopig te worden uitgesloten.

Het onderwerp van **Hoofdstuk 5** is het bestuderen van het effect op de remming wanneer de hydrofobe staart van de ring stikstof in **1** wordt verplaatst naar de C-1, O-2,

O-3, O-4 of O-6 positie. Het aldus vrijgekomen secundaire amine werd gealkyleerd tot een tertiair amine (als in **1**) met een methyl of butyl groep. Onder de O-2 en O-6 variaties van deze serie analoga bevonden zich drie selectieve GBA1 remmers. Met uitzondering van de C-1 modificatie resulteerde alle verplaatsingen van de hydrofobe staart tot verlies van de capaciteit om GCS te remmen.

Hoofdstuk 6 behandelt het vervolgonderzoek naar de structuur–activiteit relatie van de C-1 analoga, aza-*C*-glycosiden genaamd. β-Aza-*C*-glucosiden, zoals besproken in hoofdstuk 5, werden gesynthetiseerd door additie van een acetyleen anion derivaat van de hydrofobe staart op gluconolacton. Na een reductie/oxidatie/dubbele reductieve aminerings sequentie werden na ontscherming de eindproducten verkregen. Hierbij werd gevarieerd in de linker lengte en de alkylering van het stikstof atoom. Een serie van α-aza-*C*-glycosiden met een D-*gluco* (als in **1**), L-*ido* of D-*xylo*-iminosuiker werd bereid met behulp van een 'Grubbs' gekatalyseerde cross-metathese reactie. Deze serie bevatte tevens variërende linker lengtes en hydrofobe staarten. Geen van de gesynthetiseerde verbindingen vertoonde een sterkere remming van GCS dan **1** of de C-1 analoga uit hoofdstuk 5. Eén β-aza-*C*-glucoside met een acetyleen in de linker lengte bleek een selectieve remmer van GBA2 te zijn. Onder de α-aza-*C*-D-xylosiden bevonden zich meerdere zeer sterke en selectieve GBA1 remmers.

Hoofdstuk 7 bespreekt de synthese van diverse lipofiele piperidine en pyrrolidine iminosuikers met behulp van de Staudinger/aza-Wittig/Ugi drie-component reactie. Onder deze verbindingen die variëren in de stereochemie, substitutie van het iminosuiker op de C-1 positie en de substitutie van het stikstof atoom, bevonden zich een remmer van GCS en een aantal remmers van GBA1 en GBA2.

Tot slot bespreekt **Hoofdstuk 8** enkele voorlopige resultaten van nog lopende studies en presenteert het een aantal mogelijke nieuwe remmers en hun toepassingen voor toekomstig onderzoek.

Het in dit proefschrift beschreven onderzoek heeft diverse op lipofiel iminosuiker **1** gebaseerde selectieve remmers van GCS, GBA1 en GBA2 opgeleverd. Het succesvolle gebruik van lipofiele iminosuikers in diabetes type 2 modellen en de opheldering van hun duale actiemechanisme hierbinnen bieden uitzicht op de ontwikkeling van een therapie voor diabetes type 2. Doordat alle in dit proefschrift beschreven verbindingen zijn getest op zowel remming van GCS, GBA1, GBA2 en enkele andere glycosidases, is een hoeveelheid nieuwe informatie verkregen over de selectiviteit van remmers van het type lipofiel iminosuiker.

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Glycosylation of Cyclitols: Synthesis of Neamine-type Aminoglycosides
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Wennekes, T.; van den Berg, R.J.B.H.N.; Boltje T. J.; Donker-Koopman, W.E.; Kuijper, B.; van der Marel, G.A.; Strijland, A.; Verhagen, C.P.; Aerts, J.M.F.G.; Overkleeft, H.S.
Manuscript in preparation

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Human Glycosphingolipids – Their Metabolism and Functions in Health and Disease
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Manuscript in preparation

Synthesis of Lipophilic Iminosugars with a Tandem Staudinger/aza-Wittig/Ugi Multicomponent Reaction and Evaluation as Glucosylceramide Metabolism Inhibitors
Wennekes, T.; Bonger, K.M.; van den Berg, R.J.B.H.N.; Poolman, J.; Donker-Koopman, W.E.; van der Marel, G.A.; Strijland, A.; Vogel, K.; Aerts, J.M.F.G.; Overkleeft, H.S.
Manuscript in preparation

Curriculum Vitae

Tom Wennekes was born in Middelburg on the 19th of June 1979. After secondary HAVO education at the Maurick College in Vught, he started with a bachelor equivalent (HLO) education in chemistry at the Hogeschool in Eindhoven in 1997. As part of this study he conducted an internship at the bio-organic synthesis group of Prof. dr. J.H. van Boom from January to June 2000. During this internship he synthesized conjugates of peptide nucleic acids and artificial ribonucleases under the supervision of dr. B.E.A. Burm and dr. M.C. de Koning. After obtaining his ingenieurs degree in June 2000, he started his academic studies in chemistry at Leiden University in August of that same year. From August 2001 to September 2002 undergraduate research was conducted at the bio-organic synthesis group of Prof. dr. J.H. van Boom and Prof. dr. H.S. Overkleeft. This research under the supervision of dr. S.H.L. Verhelst resulted in the master thesis 'Synthesis of aminoglycoside analogs and conjugates'. In December 2002 Tom obtained his doctorandus (Master of Science) degree.

After a short period working as a research assistant in the bio-organic synthesis group, Tom was affiliated with Leiden University as a Ph.D. student from October 2003 until April 2008. The work described in this thesis was conducted under the supervision of Prof. dr. G.A. van der Marel and Prof. dr. H.S. Overkleeft in close cooperation with the group of Prof. dr. J.M.F.G. Aerts of the University of Amsterdam, and with financial support from Macrozyme B.V.

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January 2009, Tom will commence his post-doctoral studies as a NWO-Rubicon fellow at the University of British Columbia in Vancouver (Canada) at the research group of Prof. dr. S.G. Withers.

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'So it goes'
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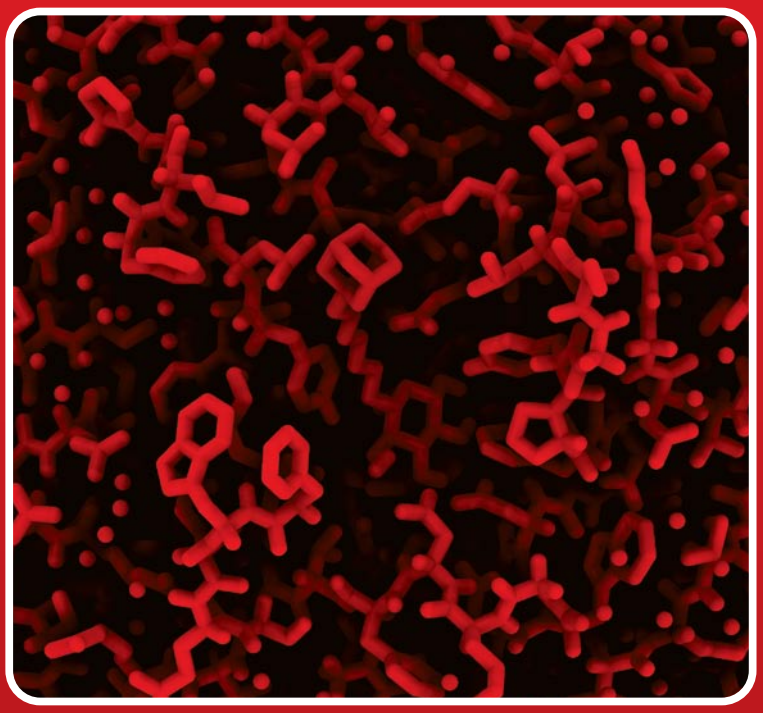

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