Lead Optimization Studies on

E-Selectin Antagonists

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Daniel Schwizer

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Auf Antrag von:

Prof. Dr. B. Ernst, Institut für Molekulare Pharmazie, Universität Basel,

Prof. Dr. P. H. Seeberger, Laboratorium für Organische Chemie, ETH Zürich

Basel, den 26. Juni 2007

Prof. Dr. Hans-Peter Hauri

Dekan

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Institute of Molecular Pharmacy
Pharmacenter
University of Basel
Klingelbergstrasse 50
CH-4056 Basel
Switzerland

Declaration

I declare, that I wrote this thesis *"Lead Optimization Studies on E-Selectin Antagonists"* with the help indicated and only handed it in to the faculty of science of the University of Basel and to no other faculty and no other university.

Daniel Schwizer, Basel, the 8th of June 2007

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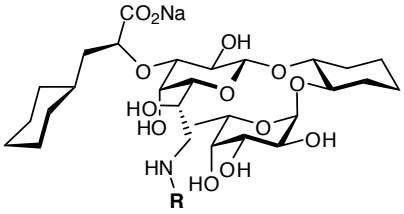
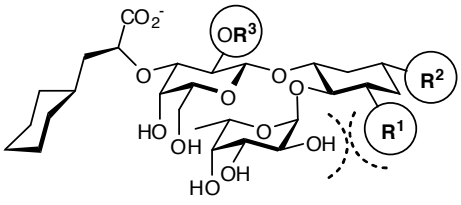
Daniel Schwizer

Abstract

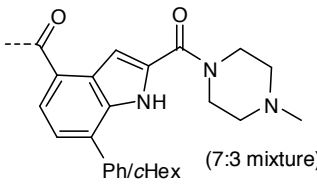
The interaction of E-, P- and L-selectin with their natural carbohydrate ligands has been shown to mediate the initial step of the recruitment of leukocytes and to play a crucial role in many physiological processes and disease states. Therefore, control of the leukocyte-endothelial cell adhesion process may be useful in cases where excessive recruitment of leukocytes can contribute to acute or chronic diseases such as stroke, reperfusion injury, psoriasis or rheumatoid arthritis.

The tetrasaccharide mimetic CGP69669 (**41**) was early recognized as a lead structure for the inhibition of E-selectin. In order to improve the lead compound's pharmacodynamic profile, two different optimization strategies were envisaged. On the one hand, an unoccupied hydrophobic patch on the lectin's surface was targeted with hydrophobic fragments, attached to the galactose moiety of the lead compound (**193**, **194**, **195**/**196**, **197**/**198**). On the other hand, the ligand's entropic costs upon binding were minimized by modifying the cyclohexane moiety (**226a**-**c**, **226e**-**h**, **244**, **255**).





193: R = biphenyl-4-carbonyl
194: R = 5-benzoyl-1H-indole-3-carbonyl
195/196: R = Bz/*c*-hexanecarbonyl (2:1 mixture)
197/198: R =



(7:3 mixture)

41:	R^1 = H,	R^2 = H,	R^3 = H
226a:	R^1 = Me,	R^2 = H,	R^3 = Bz
226e:	R^1 = Et,	R^2 = H,	R^3 = Bz
226c:	R^1 = *c*Pr,	R^2 = H,	R^3 = Bz
226b:	R^1 = *n*Bu,	R^2 = H,	R^3 = Bz
226f:	R^1 = $(CH_2)_2CO_2Me$,	R^2 = H,	R^3 = Bz
226g:	R^1 = Me,	R^2 = H,	R^3 = H
226h:	R^1 = Et,	R^2 = H,	R^3 = H
244:	R^1 = Me,	R^2 = CO_2Me,	R^3 = Bz
255:	R^1 = H,	R^2 = *t*Bu,	R^3 = Bz

Whereas the first strategy led to inactive compounds, the second resulted in potent antagonists, by supporting the pre-organization of the pseudotrisaccharide core in the bioactive conformation. The pre-organization and conformational flexibility of the antagonists were evaluated by NMR studies.

Abbreviations

Ac	Acetyl
AcOH	Acetic acid
AcOOH	Peracetic acid
AIBN	Azodiisobutyrodinitrile
aq.	Aqueous
Ar	Aryl
ax	Axial
bb	Backbone
BDEA	Borane *N,N*-diethylaniline complex
BMS	Borane dimethylsulfide complex
Bn	Benzyl
BnBr	Benzylbromide
BSA	Bovine serum albumine
Bz	Benzoyl
cat.	catalyst/catalytic amount
CD34	Cell differentiation antigen 34, sialomucin
CDI	Carbonyl diimidazole
CR	Complement regulatory-like domains
CRD	Carbohydrate recognition domain
Cy	Cyclohexyl
d	Days
dba	1,5-Diphenyl-1,4-pentadien-3-one
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DMTST	Dimethyl(methylthio)sulfonium triflate
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
DTBP	2,6-Di-*tert*-butylpyridine
e.g.	For example
ee	Enantiomeric excess
EGF	Epidermal growth factor
eq	Equivalent
ESL-1	E-selectin ligand 1
Fuc	Fucose
Gal	Galactose
GC	Gas chromatography
Glc*N*Ac	*N*-Acetylglucosamine
Glc	Glucose
Gly-CAM-1	Glycosylated cell adhesion molecule-1
GvHD	Graft *vs* host disease
h	Hour(s)
H	Hydrogen
Hep	Heptose
IC_{50}	Inhibitory concentration 50%
ICAM-1	Intercellular cell adhesion molecule 1
IL-1	Interleukine-1
IL-8	Interleukine-8
Ind	Indole
IR	Infrared spectroscopy
JBW	Jumping between wells
kDa	Kilo Dalton
Lac	Lactic acid
LAD	Leukocyte adhesion deficiency
Le^a	$Lewis^a$
Le^x	$Lewis^x$
LPS	Lipopolysaccharide
mAb	Monoclonal antibody
MadCAM-1	Mucosal vascular addressin cell adhesion molecule
Man	Mannose
MBP	Mannose binding protein
MC	Monte-Carlo
MD	Molecular dynamics
Me	Methyl
min	Minute(s)
MPLC	Medium pressure liquid chromatography
MS	Molecular sieves
MTPA	α-Methoxy-α-(trifluoromethyl)-phenylacetyl
MTPA-Cl	α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride
NaOMe	Sodium methoxide
Neu	Neuraminic acid
Neu5Ac	*N*-Acetyl neuraminic acid, sialic acid
NMM	*N*-Methylmorpholine
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
ODI	Oxalyl diimidazole
OH	Hydroxyl
Ph	Phenyl
Pip	Piperazine

PLE	Pig liver esterase
PMB	*p*-Methoxybenzyl
PSGL-1	P-selectin glycoprotein ligand 1
p-TsOH	*p*-Toluenesulfonic acid
pyr	Pyridine
rac	Racemic
RCM	Ring-closing metathesis
rIC_{50}	Relative IC_{50}
rot	Optical rotation
r.t.	Room temperature
SAR	Structure-activity relationship
satd.	Saturated
SCR	Short consensus repeats
SD	Stochastic dynamics
Seph	Sephadex
Sia	Sialic acid
sLe^a	Sialyl Lewis^a
sLe^x	Sialyl Lewis^X
S-Phos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
ss	Sidechain
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldiphenylsilyl
TBDPS	*tert*-Butyldimethylsilyl
TBME	*tert*-Butyl methyl ether
TBS	*tert*-Butyldimethylsilyl
TEAB	Tetraethylammonium bromide
Temp	Temperature
TES	Triethylsilane
Tf	Triflate, (triflouromethanesulfonate)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIS	Triisopropylsilane
TLC	Thin-layer chromatography
TMSOTf	Trimethylsilyl triflate
TMSSEt	(Ethylthio)trimethylsilane
TNF−α	Tissue necrosis factor α
Tr	Triphenylmethyl
Ts	Tosyl
TsCl	Tosyl chloride
VCAM-1	Endothelial vascular cell-adhesion molecule-1

Table of Contents

1. Introduction

The interaction of E-, P- and L-selectins with their natural carbohydrate ligands has been shown to mediate the initial step of the recruitment of leukocytes and to play a crucial role in many physiological processes and disease states. More specifically, selectins are a family of carbohydrate-binding proteins expressed at the site of inflammation in response to inflammatory stimuli liberated by the injured tissue. Their key role, early in the inflammatory cascade, is to promote the tethering and the rolling of leukocytes along the endothelial surface. These steps are then followed by the integrin-mediated firm adhesion and the final transendothelial migration.[1-4]

Therefore, control of the leukocyte-endothelial cell adhesion process may be useful in cases where excessive recruitment of leukocytes is contributing to acute or chronic diseases such as stroke, reperfusion injury, psoriasis or rheumatoid arthritis.[5, 6] In addition, it has been suggested that cancer may exploit the selectin-mediated adhesion process to metastasize after entering the bloodstream.[7, 8]

These therapeutic opportunities let the development of selectin antagonists become an attractive pharmacological target for the pharmaceutical industry as well as for academic research.

1.1. The selectins and their natural ligands

1.1.1. The selectin family

Lectins are proteins that recognize and bind to specific carbohydrate structures of glycoconjugates and are usually divided into four groups:[9]

- C-type lectins — Ca^{2+}-dependent lectins[10]
- P-type lectins — recognize phosphorylated mannose residues[11]
- Galectins — contain free thiol groups, former S-type lectins[9]
- other lectins not fitting in one of the above mentioned categories

The selectins as a Ca^{2+}-dependent C-type lectin family include the three members E-, P- and L-selectin. They are transmembrane glycoproteins and share common structural motifs like a N-terminal lectin domain (CRD), an epidermal growth factor (EGF)-like domain, a variable number of complement regulatory-like repeats (CR domains), a transmembrane segment and a short C-

terminal cytoplasmic tail (*figure* 1).[12] The overall homology within the three members of the selectin family is approximately 50% at the nucleic acid as well as at the protein level, with the lectin and the EGF-like domains showing the highest degree of conservation. The N-terminal, 120-130 amino acid long lectin domain (CRD) shows typical features of C-type animal lectins.[13] It bears the carbohydrate binding-site which is conformationally stabilized by a calcium ion.[12] The following sequence of 35-40 amino acids, the so-called EGF-like domain contains six conserved cystein residues forming three intramolecular disulfide bonds. Unlike the lectin domain, the EGF-like domain is less understood in its functional role. Although the carbohydrate binding-site is localized on the CRD for all three selectins, the EGF-like domain is also involved in ligand binding, either by stabilizing the conformation of CRD or by directly interacting with the ligand.[14, 15]

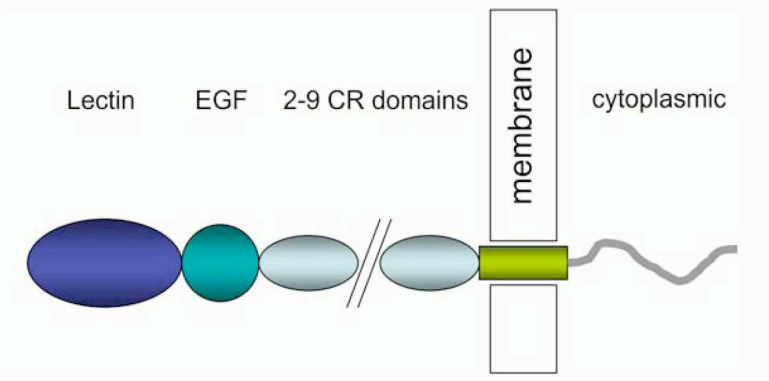


Figure 1: Common domains of the selectin family.[16]

The EGF-like domain is followed by a series of short consensus repeats (SCR), also named complement binding proteins (CB). The SCR are sixty amino acids long and contain each 3 disulfide bridges. The number of SCR differs throughout the selectin family and different species. In human, E-selectin contains six, P-selectin contains nine, and L-selectin two SCR. Among other species the number of SCR for E-selectin varies from four to six, for P-selectin from six to eight, whereas for L-selectin the same number of SCR are found in mouse and rat as in humans. Deleting various numbers of SCR in a membrane-anchored P-selectin construct resulted in impairment of P-selectin to contribute to leukocyte rolling. These findings suggest that the SCR facilitate the interaction of P-selectin with leukocyte and increase the intermembrane distance, minimizing the contact with the glycocalyx.[17-19] After the transmembrane domain, a rather small cytoplasmic tail follows, consisting of 17 amino acids in L-selectin, 32 amino acids in E-selectin and 35 amino acids in P-selectin. It probably plays a functional role in the signal transduction which is not yet fully understood.[20]

The prefixes of the three members of the selectin family were chosen according to the cell type where the molecules were first identified.[14] E-selectin, previously known as ELAM-1, was originally discovered on the surface of activated endothelial cells, P-selectin on activated platelets and activated endothelial cells and L-selectin is constitutively expressed on most types of leukocytes.

1.1.2. Natural glycoprotein ligands of the selectins

As selectins are carbohydrate binding proteins, their natural ligands are glycoproteins and glycolipids presenting oligosaccharide or sulfopolysaccharide structures as binding motifs. The common carbohydrate epitopes recognized by all three members of the selectin family were found to be the trisaccharides Lewis^x (Le^x, **1**) and Lewis^a (Le^a, **2**) and their sialylated derivatives sialyl Lewis^x (sLe^x, **3**) and sialyl Lewis^a (sLe^a, **4**) (*figure* 2).[21-23]

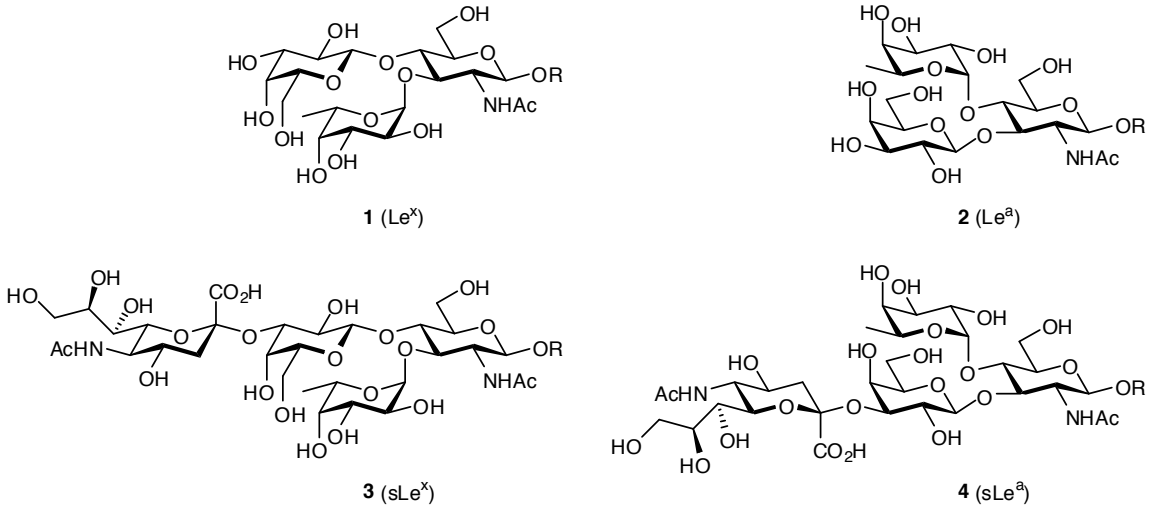


Figure 2: The common carbohydrate epitopes recognized by all three selectins.

Soluble recombinant forms of the selectins and selectin-IgG fusion proteins have been used for affinity isolation and identification of natural glycoprotein ligands for selectin.

For **L-selectin** seven glycoproteins were identified as ligands so far:[24] Gly-CAM-1,[25] CD34,[26] MAdCAM-1,[27, 28] podocalyxin-like protein,[29] endomucin,[30] endoglycan[31] and PSGL-1.[32] Glycosylation-dependent cell adhesion molecule-1 (Gly-CAM-1), a secreted glycoprotein usually stored in cytoplasmic granula, is the best characterized L-selectin ligand so far.[25, 33-37] Its functional role is supposed to be a secreted regulator, participating in the recruitment of lymphocytes into peripheral lymphnodes.[38, 39] Sialic acid, fucose and oligosaccharide sulfation

were found to be critical for the binding of Gly-CAM-1 to L-selectin. CD34 is a transmembrane type I sialomucin, presenting large clusters of *O*- and *N*-glycans with 6-sulfo sLe^x as capping structure.[40] Both proteins, Gly-CAM-1 and CD34 are also expressed in other tissues than the lymph nodes, but there they lack the correct carbohydrate modifications essential for binding.[26] MAdCAM-1 belongs to the Ig superfamily but also contains a short mucin domain. It serves as counter-receptor for $\alpha 4\beta 7$ in the integrin-mediated adhesion and arrest of lymphocytes, but one of its subpopulation also serves in the selectin mediated rolling. The podocalyxin-like protein (PCLP) is a transmembrane sialomucin similar in structure to CD34, and it is able to support the tethering and rolling of lymphocytes under physiological flow conditions *in vitro*.[29] Endoglycan (EG) belongs to the CD34 family like CD34 and podocalyxin, but shows a different binding mechanism as other L-selectin ligands. Instead of sulfopolysaccharides, endoglycan interacts with sulfation on two tyrosine residues and sLe^x structures similar to PSGL-1.

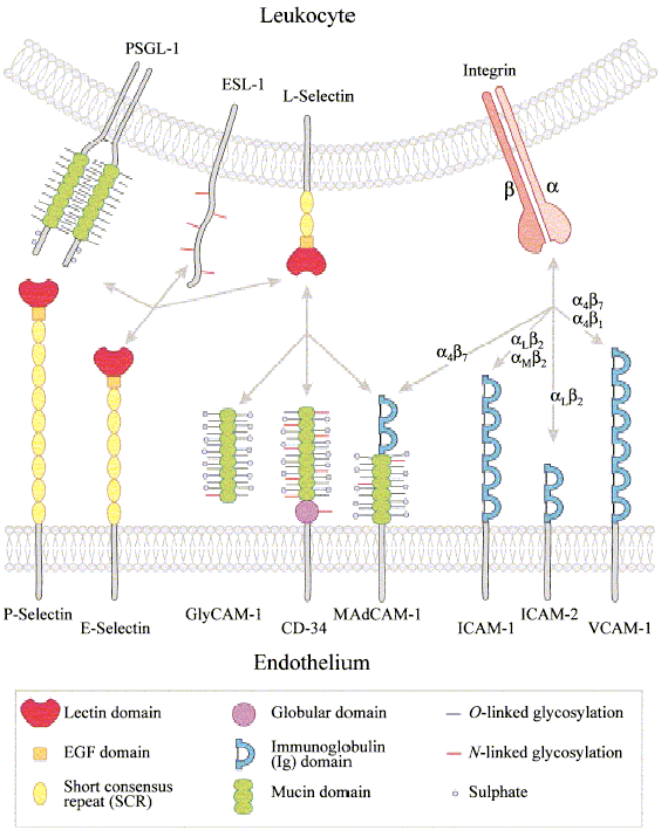


Figure 3: Major selectin and integrin ligands that have been identified so far by affinity isolation with the respective selectin as affinity probe.[38]

PSGL-1 has been identified as the major natural occurring **P-selectin** ligand, as well as ligand for L- and E-selectin.[41-43] It is a 250 kDa homodimeric type-I transmembrane protein linked by

two disulfide bridges.[44] The binding to the selectins takes place at the N-terminal region of PSGL-1 for P- and L-selectin, whereas E-selectin binds to one or more additional sites on the highly *O*-glycosylated PSGL-1. Beside a single *O*-glycan capped with sLe^x (Thr57), additional sulfation at two of the three *N*-terminal tyrosin residues (Tyr46, Tyr48 or Tyr51) is required for the binding of P- and L-selectin. Both sialidation and fucosylation of the *O*-glycan is essential for binding.[41, 45-56]

Compared to L- and P-selectin, **E-selectin** has different structural requirements for its ligands. Sulfation of the ligands was found to be dispensable for E-selectin, whereas it is essential for ligands binding to L- and P-selectin.[23, 50, 57] Two glycoprotein ligands were identified by affinity-isolation with E-selectin-Ig fusion proteins so far.[50, 57-60] E-selectin ligand-1 (ESL-1) is a 150 kDa glycoprotein containing five putative *N*-glycosylation sites and 16 cystein rich sites.[61] ESL-1 binds selectively to E-selectin, but not to P-selectin. By comparative analysis of cell lines binding to E-selectin and by the use of recombinant soluble E-selectin-agarose affinity chromatography, three unusual carbohydrate structures binding selectively to E-selectin were identified.[62] All of these structures bear a 3-sialyl di-$Lewis^x$ extension on one arm of an *N*-linked tetraantennary glycan. These carbohydrate structures are only present on leukocytic cell lines binding to E-selectin and may alone be responsible for the specificity of E-selectin-dependent adhesion. In addition to ESL-1, E-selectin binds also independently from tyrosin sulfation to PSGL-1 and to carbohydrates present on L-selectin of human neutrophiles.[50, 57, 60, 63, 64]

1.2. The role of selectins during inflammation and human diseases

The inflammatory response is an important mechanism of the body to defend itself against various pathogens like viruses, bacteria, fungi, protozoan and metazoan parasites, as well as to respond to the damage caused to cells and vascularised tissues. Main actors in this defense mechanism are leukocytes, migrating from circulation into tissues and responding to the damage by releasing cytotoxic and proinflammatory mediators, like chemokines or platelet-activating factors, and by phagocytosis. Selectins and their receptors play a predominant role among a multitude of signaling and adhesion molecules that control the directed migration of leukocytes from the circulation to the site of inflammation.[65]

1.2.1. The inflammatory cascade and its cellular mechanisms

During acute inflammation leukocytes migrate mainly in post-capillary venules in a highly regulated adhesion cascade into the inflamed tissues. This adhesion cascade is usually referred to as the inflammatory cascade and can be divided into five major steps: Inflammatory stimulus, tethering and rolling, integrin activation, firm adhesion and transendothelial migration as exemplified in *figure* 4.

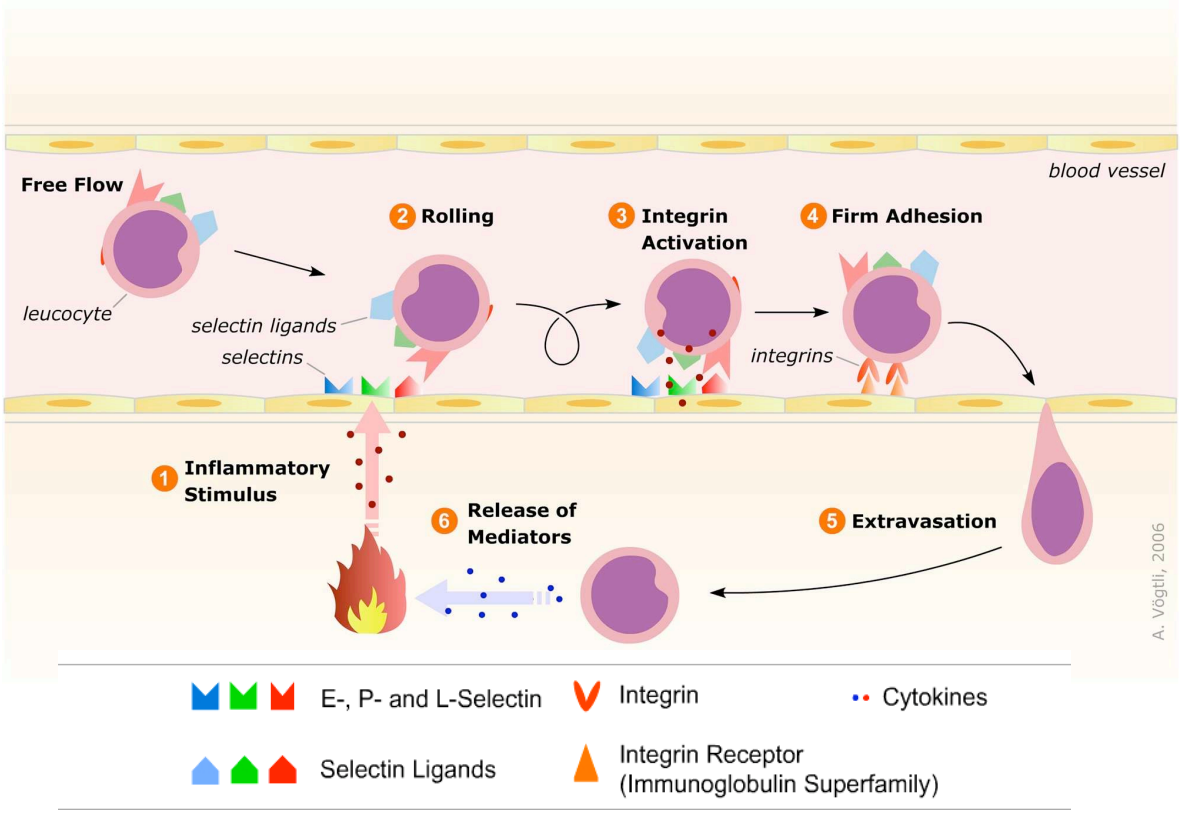


Figure 4: Schematic representation of the inflammatory cascade.[66]

The cascade is initiated by the release of proinflammatory mediators like chemokines or platelet activating factors.[67, 68] These stimuli cause the expression of E- and P-selectin on vascular endothelial cells, which are now in a pro-adhesive state. P-selectin is stored in α-granules of platelets and Waibel-Palade bodies of endothelial cells. After stimulation by endocytosis of proinflammatory mediators such as thrombin or histamine it can be transported to the cell surface within minutes.[69, 70] Within 30-60 minutes P-selectin is subsequently removed again from the endothelial surface by endocytosis. Beside the transport from storage granules to the

plasma membrane, the synthesis of P-selectin can be transiently induced by TNF-α in mouse and bovine endothelial cells, with slightly slower kinetics than found for E-selectin.[70-72]

In contrast to P-selectin, E-selectin has to be synthesized *de-novo.* Its transcription is induced by TNF-α, Interleukin-1 (IL-1) or lipopolysaccharide (LPS).[73, 74] Highest level of E-selectin expression at cell surfaces is reached within 3-4 h after stimulation and decreases to basal levels again after 16-24 h.[75] In the next step, endogenous ligands for E- and P-selectin like PSGL-1 and ESL-1 bind to the selectins in a fast association/dissociation process which leads to the well known tethering and rolling of leukocytes onto the endothelial surface (*figure* 5).[76, 77] L-selectin, which is constitutively expressed at the tips of leukocytes, serves not only as a ligand for E-selectin,[78] but additionally plays an important role in the so-called “secondary tethering” process. This process describes the tethering of leukocytes on other leukocytes, which are already associated on the endothelium by the interaction of PSGL-1.[79, 80] The “secondary tethering” expands the pool of leukocytes attracted to sites of inflammation. After cell activation, induced by a variety of chemo-attractants and activating factors, L-selectin gets rapidly cleaved at an extracellular cleavage site close to the cell membrane by metalloproteases.[81, 82] This proteolytic cleavage of L-selectin happens within minutes and is supposed to facilitate the detachment of leukocytes from endothelial cells prior to the migration through the endothelium.[38, 83-87]

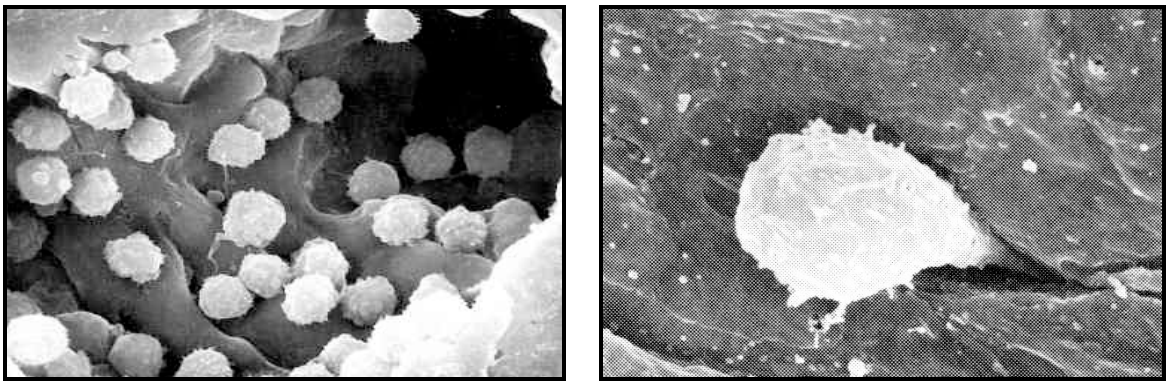


Figure 5: Leukocytes adhering on the endothelium (left) and leukocyte migrating through the endothelium (right).[88]

During the tethering and rolling phase, leukocytes are slowed from the microvascular free-stream blood flow velocity of 1-10 mm/s down to 5 μm/s before becoming fully stationary. It was shown that mainly E-selectin is responsible for the slow rolling of leukocytes (5 μm/s), since leukocytes roll significantly faster (12 to 20 μm/s) in E-selectin-deficient mice. Hence, the E-selectin-dependent slow-rolling drastically increases the transit time through the inflamed tissue

and enables the activation of leukocytes by chemo-attractants.[89, 90] The exposure of leukocytes to chemo-attractants (*e.g.* fMLP, PAF, C5a, IL-8, eotaxin) progressively triggers the activation and upregulation of β_2-integrins (CD18) on the cellular surface.[91, 92] These β_2-integrins (Mac-1, LFA-1 and $\alpha_x\beta_2$) interact in their activated state with endothelial ligands from the immunoglobulin (IgG)-superfamily like ICAM-1 and VCAM-1, enabling the firm adhesion of leukocytes on the endothelium and leading to a flattening which further increases the contact area of leukocytes to endothelium.[81, 92-94] Endothelial transmigration of leukocytes is finally achieved by the interaction of integrins located on leukocytes with endothelial PECAM-1 of the IgG superfamily.[95, 96]

1.2.2. The pathophysiological role of selectin-ligand interactions

Abnormal or excessive recruitment and influx of leukocytes into inflamed tissues is a central component of a variety of acute or chronic inflammatory diseases. Therefore, blocking of the selectin-ligand interactions has a dramatic impact on the progression of these diseases, as shown in a number of animal models.[97, 5, 98]

Studies on selectin-deficient mice gave first insights into the physiological and pathophysiological roles of these receptors. Selectin-deficient mice show no developmental defects nor suffer from multifocal infections.[99-101]

P-selectin-deficient mice show two- to threefold higher numbers of circulating neutrophils due to a prolonged circulation half-life by a decreased clearance of neutrophils.[99, 102] Whereas wild-type mice show an increase of rolling leukocytes after cremaster muscle surgery from initially 13% to 26% within 40 to 60 minutes, the initial rolling is absent in P-selectin-deficient mice and does not exceed 5% later.[103] In the thioglycolat-induced peritonitis model P-selectin-deficient mice have reduced peritoneal accumulation of neutrophils at the early stage of inflammation, but show normal levels later. In contrast to neutrophils, P-selectin seems to play an important role in the long-term recruitment for monocytes, as P-selectin-deficient mice show impaired monocyte influx 48 h after peritoneal thioglycolat injection.[102] L-selectin-deficient mice show a pronounced decline of rolling leukocytes during surgical dissection of the mesentery and in the thioglycolat-induced peritonitis model a reduced peritoneal accumulation for monocytes, neutrophils as well as lymphocytes.[100, 103, 104] This indicates that L-selectin is necessary for the recruitment of all types of leukocytes, whereas P-selectin is important for the long-term recruitment of monocytes. In contrast to P- and L-selectin, E-selectin-deficient mice displayed no significant change in the trafficking of neutrophils in several models of inflammation.[101]

In 1992, a rare autosomal recessive genetic disorder called “type 2 leukocyte adhesion deficiency” (LAD-2) was described in two patients.[105] The affected individuals suffer from recurrent infections, persistent leukocytosis, severe mental and growth retardation and numerous facial and skeletal abnormalities.[106, 107] Both patients exhibit the rare Bombay (hh) blood phenotype, show no expression of the Lewis blood group antigens, nor do they secret soluble blood group antigens in their saliva, which implies a global defect in fucose metabolism. Later it could be shown that LAD-2 results from a point mutation in the gene of a highly conserved GDP-fucose transporter on chromosome 11.[108, 109] The deficiency in fucosylated glycoconjugates like sLe^x leads to reduced rolling of leukocytes in postcapillary venules and the inability of neutrophils to bind to immobilized E-selectin. Recently, it was found in one patient that treatment with orally administrated fucose was able to induce the expression of fucosylated selectin ligands on neutrophils and core fucosylation of serum glycoproteins, resulting in a general improvement of the patient condition.[110, 111] The lack of appropriate inflammatory responses to external pathogens of LAD-2 patients clearly demonstrates the importance of selectin-ligand interactions to the inflammatory response.

The tissue and organ damage resulting from ischemia and reperfusion is an important example of inflammatory conditions, where selectins play a key role.[112, 113] Reperfusion injury occurs in a variety of clinical disorders like stroke, myocardial infarction and organ transplantation, leading to further damage to the vessel walls and surrounding tissues apart from the damage caused by the ischemia itself. Reperfusion of ischemic tissues results in a strong accumulation of neutrophils, mainly mediated by P- and E-selectin, followed by plugging of the microvasculature, infiltration of neutrophils into tissue and release of cell-activating and cytotoxic mediators. Preventing the neutrophil accumulation by antagonists is therefore an effective strategy to attenuate reperfusion injury. A variety of approaches to block selectins have been studied extensively and showed protective effects in reperfusion injury models, including monoclonal antibodies,[114-119] carbohydrates,[116, 120, 121] soluble forms of PSGL-1[122] and small molecular antagonists.[123, 124]

Sepsis, a state of severe systemic bacterial infection, results in peripheral hypoperfusion and frequently to life-threatening multiorgan dysfunction. Abnormal leukocyte activation and adhesion has been implicated in the pathogenesis of tissue damage and multiorgan failure observed under septic shock. The uncontrolled leukocyte activation results in a release of toxic products and leads to the hemodynamic and inflammatory derangement of the patients. Since selectins are involved in leukocyte adhesion, their blocking may be able to reduce vascular and

tissue injury during sepsis. However, the benefit of the tested anti-adhesion therapies on the clinical outcome is controversially discussed up to now.[125-128]

Selectins play also a predominant role in asthma, especially E-selectin together with the integrin receptors ICAM-1 and VCAM-1.[129-132] The increased serum concentrations of E-selectin observed during asthma attack probably result from an increased endothelial expression. Hence, E-selectin antagonism may helps to prevent the cellular infiltration during an asthma attack. In a primate model of allergic asthma, anti-E-selectin antibodies have been shown to reduce the neutrophil influx into the lung and to block the late-phase airway obstruction.[133] In a sheep asthma model, an anti-L-selectin antibody and a small molecular selectin antagonist successfully prevented antigen-induced late bronchial response and airway hyperresponsiveness.[134]

Rheumatoid arthritis represents one of the most prominent inflammatory rheumatic disorders and leads to a high percentage of disability and a significantly reduced life expectancy. Although the exact molecular mechanisms of rheumatoid arthritis are not yet fully elucidated, soluble E-selectin and ICAM-1 in serum and synovial fluid were recognized as important markers for the severity of the disease state, allowing early differentiation between mild and severe courses of the disease and providing essential information for therapeutic decisions.[135-138] In the adjuvant induced arthritis (AIA) model of Lewis rats, early treatment with mAb against E-selectin resulted in inhibition of antigen-dependent T cell-mediated inflammation, whereas treatment with mAb against P-selectin had no significant effect.[139] However, recently, a small molecular antagonist of P-selectin showed efficacy in the same model of rheumatoid arthritis.[140]

During the rejection of human renal,[141] cardiac[142, 143] and liver transplants[144] increased levels of endothelial adhesion molecules like E-selectin, ICAM-1 and VCAM-1 have been observed, which imply that selectins could play an important role in the pathophysiology of organ rejection. Indeed, the treatment of heart-transplanted mice with either anti-E- or P-selectin mAbs, or both, showed significant prolongation of graft survival, which suggests that P- and E-selectins are involved in development of acute heart rejection.[145] A recent study in a rat model revealed that a small molecular selectin antagonist blocked intragraft production of cyto- and chemokines and consequently inhibited kidney allograft rejection.[146] In addition synergistic effects of the antagonist in combination with cyclosporine, sirolimus and FTY720 were found. The “graft vs. host disease” (GvHD) is a multiorgan disease caused by the immune response of donor leukocytes against host tissue in recipients of bone marrow transplantation. In cutaneous and

intestinal lesions of such patients increased E-selectin expression on the venular endothelium close to site of leukocyte infiltration was found.[5, 147, 148]

Metastasis is defined as the spreading of a malignant tumor to a site different from its origin. A large pool of data suggests that during the tumor metastasis the malignant cells follow the pathway of leukocytes.[149-166] The expression of selectins on the endothelium could therefore initiate or even be a prerequisite for the development of metastases. Colon cancer was one of the first where the expression of selectin ligands was correlated with its metastatic behaviour and received most attention in selectin studies.[167-178] There is strong evidence that E-selectin mediates the initial rolling of colon tumor cells on the endothelium, followed by the subsequent firm adhesion involving other, yet unknown, adhesion molecules. However, also other cancer cell lines might be influenced by E-selectin-mediated adhesion as observed for several breast cancer cell lines.[179, 180] Numerous clinical studies additionally suggest that elevated serum levels of E-selectin in patients with various types of cancer reflect the tumor-progression.[181-185, 156, 186] The role of P-selectin in the metastasis of tumor cells received less attention as E-selectin and is therefore more speculative. Generally, it is supposed that P-selectin can display an identical mode of action to the one of E-selectin. Additionally, it is speculated that the stimulation of the P-selectin expression on platelets facilitates the interaction between platelets and tumor cells in the haematogenous metastasis.[187-189] This leads to the formation of aggregates of platelets and tumor cells which either could embolise small vessels or facilitate the adherence to the endothelium, initiating the metastasis. Although the physiological role of L-selectin is well understood, its role in cancer metastasis still remains uncertain. It is thought that L-selectin may be involved in the metastasis of malignant lymphoma to distant nodes which is supported by the strong expression of L-selectin in T-cell hybridoma cells which metastasize extensively to peripheral lymph nodes.[190] Yet, there is no evidence that L-selectin is a prerequisite for this process.

In summary, a strong deregulation of the selectins has been observed in many diseases such as cancer metastasis and angiogenesis, atherosclerosis, asthma, COPD, organ rejection, hemorrhagic shock, thrombosis, rheumatoid arthritis, atopic dermatitis, psoriasis,[191] diabetes-caused microangiopathy, or myocardial and cerebral ischemia. In these diseases patients may benefit from the blocking of the selectin-ligand interactions by small molecular antagonists or antibodies.

1.3. Structure activity relationship of Selectins binding to their ligands

Since the tetrasaccharide sialyl Lewis^x (**3**) (*figure* 2) is the carbohydrate epitope recognized by all three selectins,[192, 193, 21] it serves as a lead structure for the design of selectin antagonists.[194-197] In order to develop small molecular antagonists from this lead structure, a profound understanding of the ligand-protein complex is mandatory. In recent decades numerous experimental investigations by NMR-spectroscopy, X-ray crystallography, as well as derivatization- and *in-silico* studies provided growing insight into the complex interaction between selectins and their ligands. Despite the collected information, many aspects of this specific carbohydrate-protein interaction are still controversially discussed and numerous obscurities yet have to be clarified.

1.3.1. Pharmacophores

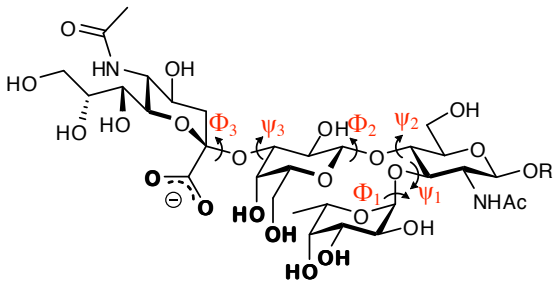
Preliminary insights into the interactions between selectins and sialyl Lewis^x was gained by systematic functional group derivatization studies. By altering individual functional groups, the essential ones for binding could be identified, which are commonly referred to as the pharmacophores of sLe^x and are highlighted in *figure* 6.

The fucose moiety of sLe^x was correctly assumed to bind to the Ca^{2+}. This was deduced from the earlier solved crystal structure of an oligosaccharide bound to the C-type lectin domain of the mannose-binding protein A (MBP-A).[198] Gaeta *et al.* and Hasegawa *et al.* observed that replacement of any of the fucose hydroxyls by hydrogen was completely deleterious to the binding to E-selectin.[199, 200] However, in the case of P-selectin only the 3-hydroxyl was found to be necessary for binding. Replacement of the fucose by arabinose led to a 5-fold decrease in potency towards E-selectin binding.

The importance of the galactose hydroxyls was probed by synthesizing deoxy- and fluoro-analogues of sLe^x.[201] The findings were that only the 4- and the 6-hydroxyl contribute to the binding, not the 2-hydroxyl. Yet, the replacement of any of the galactose hydroxyls is not as deleterious as in the case of fucose. Bänteli *et al.* closer investigated hypothetical interactions to E-selectin in the surroundings of the 6-position of galactose by synthesizing numerous ligands modified at this specific position. They concluded that the 6-hydroxyl is optimally suited for the binding to E-selectin, considering that all modified compounds were inactive.[202]

Of the functional groups of the Neu*N*Ac moiety, only the carboxyl group was found to be crucial for binding to E-selectin.[200, 203, 204] However, in the case of P-selectin, the crystal structure later revealed that the 4-hydroxyl and hydrophobic interactions additionally contribute to the binding.[46]

The Glc*N*Ac moiety rather serves as a spacer to optimally position the pharmacophores of fucose and galactose than directly contributing to the binding, as discussed in several studies.[205-207]



3 (sLe^x)

Figure 6: Structure of sialyl Lewis^x. Pharmacophores involved in binding to E-selectin and assignment of torsions angles are highlighted.

1.3.2. Conformational aspects

The conformational preferences of sLe^x in solution and bound to the selectins were elucidated primarily with the aid of molecular dynamics calculations and NMR spectroscopy with the labeled and unlabeled compound.

Early work suggested sLe^x to adopt a single conformation in solution.[208-210] However, subsequent NMR- and molecular dynamics studies revealed a certain degree of flexibility of the glycosidic linkages.[211-217] A compilation of the suggested conformations is displayed in *table* 1. It is noteworthy to say, that a general agreement is found in the torsion angles (*figure* 6) of the Gal-β(1-4)-Glc*N*Ac and Fuc-α(1-3)-Glc*N*Ac linkages of the Le^x moiety, commonly referred to as the core-structure. Substantial divergence is found in the torsion angles between Neu5Ac and Gal, depending on whether the NOE between Gal H-3 and Sia H-3$_{ax}$ was included into the considerations. However, the high flexibility of the Neu5Ac(2-3)Gal linkage suggests multiple conformations to be present in solution.[212, 213]

Table 1: Torsion angles of the solution conformation

References	Φ_3/Ψ_3 Neu5Ac(2-3)Gal	Φ_2/Ψ_2 Gal(1-4)Glc*N*Ac	Φ_1/Ψ_1 Fuc(1-3)Glc*N*Ac
NMR/GESA/MM2 (Ichikawa *et al.*, **1992**)[218, 219]	-170°/- 8°	+54°/+ 9°	+48°/+24°
NMR	--- / ---	+46°/+18°	+48°/+24°
(Poppe *et al.*, **1997**)[214]	--- / ---	+46°/+18°	-23°/+15°
NMR/MD (Rutherford *et al.*, **1993**)[213]	- 70°/+ 5°	+50°/+15°	+48°/+22°
MD (Veluraja *et al.*, **2005**)[220]	- 95°/-60° - 70°/ 0° -160°/-25°	+65°/+15°	+65°/+40°

Table 2: Torsion angles of the bioactive conformation.[211, 221]

References	**Selectin**	Φ_3/Ψ_3 Neu5Ac(2-3)Gal	Φ_2/Ψ_2 Gal(1-4)Glc*N*Ac	Φ_1/Ψ_1 Fuc(1-3)Glc*N*Ac
NMR (Scheffler *et al.*, **1995**)[222]	E	-76°/+ 6°	+39°/+12°	+38°/+26°
NMR	E	-58°/-22°	+24°/+34°	+71°/+14°
(Poppe *et al.*, **1997**)[214]	P	-85°/- 4°	+45°/+18°	+61°/+26°
NMR (Harris *et al.*, **1999**)[215]	E	-43°/-12°	+45°/+19°	+29°/+41°
X-ray	E	-65°/-12°	+34°/+16°	+41°/+22°
(Somers *et al.*, **2000**)[46]	P	-65°/- 8°	+40°/+ 8°	+40°/+16°
	P[a]	-55°/-11°	+40°/+16°	+70°/+20°

[a] Dihedral angles measured on the sLe^x moiety of PSGL-1 bound to P-selectin.

The bioactive conformation of sLe^x bound to E-selectin was determined in various studies based on a careful analysis of its NOE signals in solution and its transfer-NOE signals when bound to the selectins (*table* 2).[19, 46, 212, 214, 215, 220, 223, 222] The absence of the NOE between Gal H-3 and Sia H-3_{ax} in the bound state and the additional tr-NOE between Sia H-8 and Gal H-3 suggest a change in conformation for the Neu5Ac(2-3)Gal linkage during the binding to the selectins. In contrast, the core conformation seems to be rather rigid and shows only minor conformational changes upon binding. For the core-conformation a general agreement was found for the bound conformation as displayed in *table* 2, except for Poppe *et al.* who proposed a slightly modified conformation.[214] The recently published crystal structure of E-selectin co-crystallized with sLe^x was in good agreement with the findings of Scheffler *et al*. (*figure* 7)[46, 222 224]

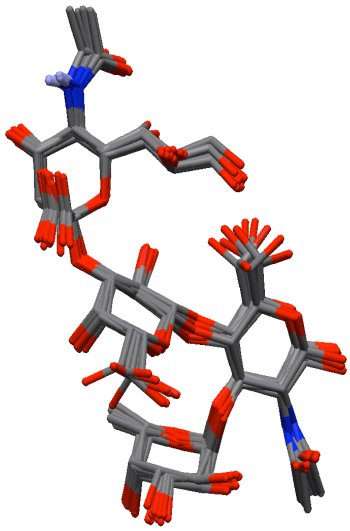


Figure 7: The bioactive conformation of sLe^x determined by Scheffler *et al.*[223, 222]

Kolb and Ernst made further use of Scheffler's conformational data to define a bioactive window for selectin antagonists, a powerful tool to preliminarily evaluate potential antagonists by MC(JBW)/SD-simulations.[216, 217] In this protocol, the hundred most favorable minima conformations of the compound of interest are searched by a systematic pseudo-Monte-Carlo method.[225] These conformations are then subjected to a "Jumping between Wells" stochastic-dynamics simulation (JBW-SD). For the calculations, a carbohydrate-adjusted AMBER force field in conjunction with the GB/SA continuum-water model is utilized.[216, 217, 226, 227] The results are usually displayed in a 2D internal coordinate system with the "core-conformation" and the "acid-orientation" as parameters, instead of the three **Φ/Ψ**–plots. The definition of the two parameters is exemplified in *figure* 8.

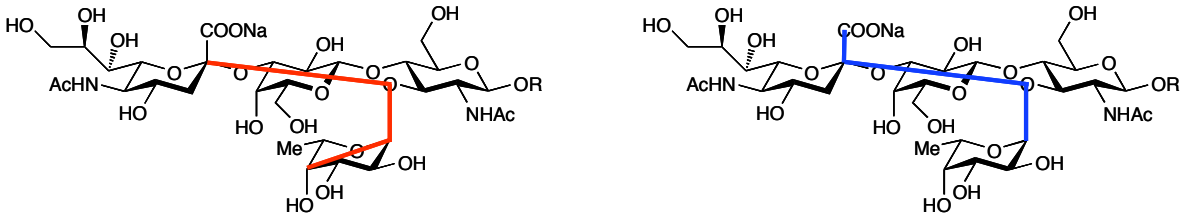


Figure 8: Definition of the core- and the acid-conformation

This protocol allows comparing the solution conformation of sLe^x, as well as the conformation of new antagonists with the bioactive conformation of sLe^x determined by NMR (*figure* 9).[216] Compounds having a high probability for conformations in the bioactive window were shown to usually have higher affinity to E-selectin, due to their increased pre-organization in the bioactive conformation.[216, 217]

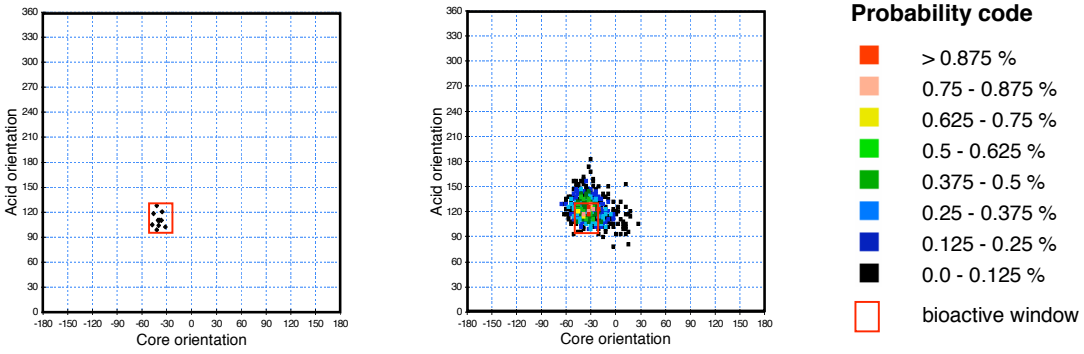


Figure 9: Bioactive conformation (left) determined by NMR by Scheffler *et al.* and solution conformation (right) of sLe^x calculated by MC(JBW)/SD-simulation.

1.3.3. Hypothetical models for the binding of sLe^x to E-selectin

Before the crystal structure of E-selectin/sLe^x was elucidated, several groups proposed various binding models for the binding of sLe^x to E-selectin. In a retrospective view each of the models was able to predict some of the interactions correctly, but none of them predicted exactly the binding as observed in the crystal structure. The largest discrepancy was found in the binding of the fucose to the Ca^{2+}. The fucose was generally thought to bind with the equatorial 2- and the 3-hydroxyl as observed in the crystal structure of the mannose-binding protein A (MBP-A). The

crystal structure of MBP-A was the only available crystal structure with a saccharide bound to a C-type lectin at that time and was solved in 1992 by Drickamer *et al.*[228, 198] It shows D-mannose binding to the Ca^{2+} by its equatorial 3- and 4-hydroxyls. This led to the hypothesis that the fucose binds in a similar fashion with its equatorial 2- and 3-hydroxyls to the Ca^{2+} of E-selectin, whereas the axial 4-hydroxyl of fucose is interacting with protein side-chains. This hypothesis had great impact on all later proposed models, until the year 2000, when the crystal structure of E-selectin proved the binding mode to be wrong.[46]

The critical region for carbohydrates binding to the lectin domain of E-selectin was firstly determined by mutagenesis studies of a lectin/EGF construct of E-selectin. In 1992, Erbe *et al.* hypothesized that E-selectin binds in a small shallow pocked formed by the residues Arg97, Lys111, Lys113, Ser47 and Tyr48.[12] The three closely situated, positively charged residues Arg97, Lys111 and Lys113 were proposed to be involved in the binding to the carboxylate of Neu5Ac since substitution of any of them led to a profound loss in binding. Erbe *et al.* further superimposed these critical residues on the crystal structure of MBP-A, which was published at the same time. This superimposition led to the first three-dimensional model of the E-selectin lectin domain.

Graves *et al.* were the first to solve the crystal structure of a soluble form of E-selectin containing the lectin/EGF domain.[229] Although the overall fold was found to be similar to MBP-A, significant differences were found in the coordination sphere of the Ca^{2+} to other C-type lectins. In the crystal structure, Ca^{2+} was coordinated by the side chains of Glu80, Asn82, Asn105, Asp106, as well as by the backbone carbonyl of Asp106 and by two water molecules. Further mutagenesis studies revealed Tyr48, Asn82, Asn83, Gluc92, Tyr94, Lys111, Lys113 as critical amino acids for neutrophil adhesion. Additionally, Asn82 was identified to not only coordinate to the Ca^{2+}, but also to bind to a ligand hydroxyl as observed from the N82D mutant.

The first published crystal structure complexed with sLe^x was a selectin-like triple mutant of the MBP-A.[230] In this mutant the residues 211-213 were replaced by the Lys111-Lys112-Lys113 sequence found in E-selectin. To clarify the carbohydrate-binding properties, the mutant was crystallized as complex with sLe^x, 3'-sulfo-Le^x and 4'-sulfo-Le^x. All the structures confirmed the binding of the two equatorial 2- and 3-hydroxyls of fucose to the Ca^{2+}, as expected from the binding of the natural MBP-A to mannose. However, the most surprising aspect in this structure was that the carboxylate moiety showed no direct interaction with the protein, which is in contrast to earlier studies with modified Neu5Ac moieties. The lack of this important interaction was thought to indicate that the orientation of the ligand differs from the selectin-bound one.

Based on the bioactive conformation of sLe^x and the crystal structure of E-selectin solved by Graves *et al.*,[229] two models for the binding of sLe^x to E-selectin were proposed. The first model

was presented by Kogan *et al.*[231] and used the NMR-determined E-selectin bound solution conformation of sLe^x [232] together with the crystal structure of E-selectin.[229] The fucose was first coordinated to the Ca^{2+} in an identical manner as mannose binds to the Ca^{2+} in the crystal structure of the MBP-A.[228, 198] The E-selectin-ligand interactions of this model are summarized in *table* 3. The second model was presented by Ernst *et al.* and was based on the docking of sLe^x in the bioactive conformation on the crystal structure solved by Graves *et al.*[233] The bioactive conformation of this model was determined by own NMR experiments. In both models the fucose is proposed to bind with the two equatorial 2- and 3-hydroxyls to the Ca^{2+} as observed for mannose with MBP-A.

Table 3: Proposed interactions between sLe^x and E-selectin by two models, and interactions found in the crystal structure of Camphausen *et al.*

Functional group	**Kogan *et al.*[231]**	**Ernst *et al.*[233]**	**Camphausen *et al.*[46]**
Fuc O-2	Ca^{2+} Asn105	Ca^{2+} Asn105	H_2O
Fuc O-3	Ca^{2+} Glu80 Asn82	Ca^{2+} Glu80	Ca^{2+} Asn105 H_2O
Fuc O-4		Asn82	Ca^{2+} Glu80 Asn82
Gal O-4		Asn105	Tyr94
Gal O-6	Tyr94	Tyr94	Glu92
Neu5Ac COOH	Arg97	Arg97	Arg97 Tyr48
Coordination sphere of the calcium	Glu80 Asn82 Asn105 Asp106 Fuc O-2 Fuc O-3	Glu80 Asn82 Asn105 Asp106 Fuc O-2 Fuc O-3	Glu80 Asn82 Asn83 Asn105 Asp106 Fuc O-3 Fuc O-4

In 2000, Camphausen *et al.* solved the crystal structure of the lectin/EGF domains of E- and P-selectin co-crystallized with sLe^x and the lectin/EGF domains of P-selectin with the N-terminal domain of human PSGL-1.[46] Surprisingly, the fucose complexes to the Ca^{2+} by the 3- and 4-hydroxyls, which is in contrast to all previously proposed models (*figure* 10). The 2-hydroxyl of fucose binds to Glu107 and Asn83 over water-mediated hydrogen-bonds. Other differences to earlier proposed models were the binding of the 4-hydroxyl of galactose to Tyr94 instead of the 6-hydroxyl and the additional interaction of the Neu5Ac carboxylate to Tyr48. The detailed binding pattern of sLe^x in the crystal structure of E-selectin is shown in *figure* 11.

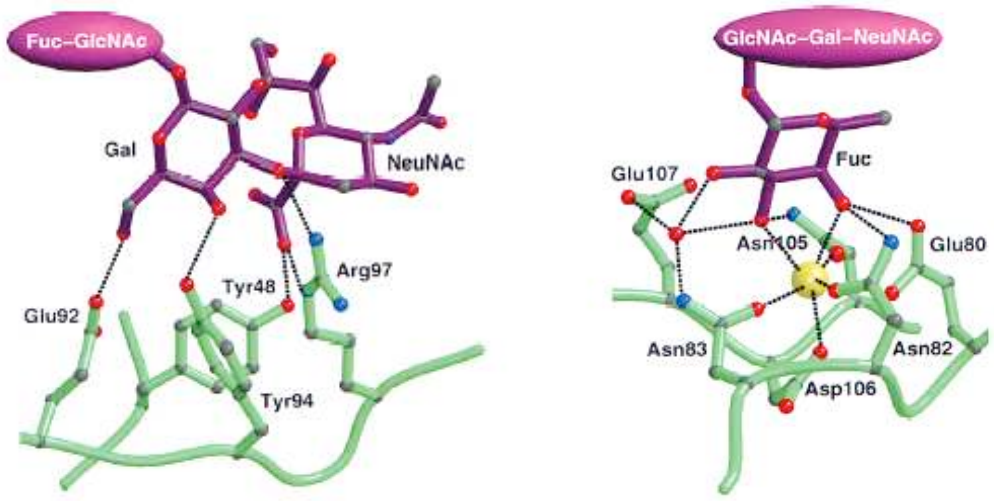


Figure 10: Interactions between sialyl Lewis^x and E-selectin in the crystal structure with focus on Neu5Ac-Gal (left) and coordination of Ca^{2+} by the fucose (right). Coordination of Glu80 and backbone-carbonyl of Asp106 are not shown.[46]

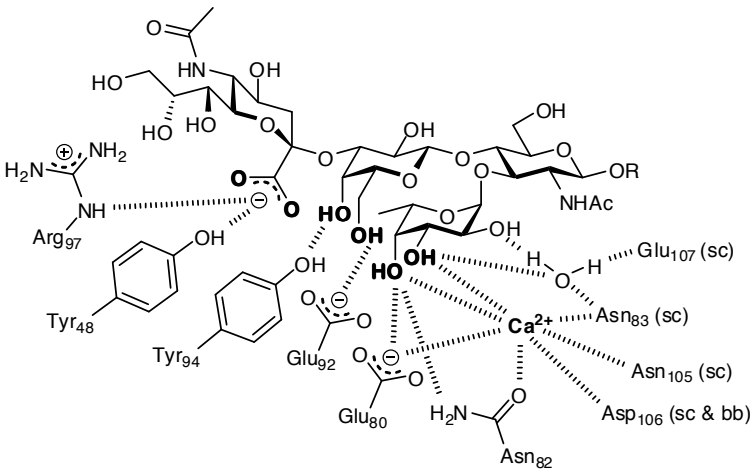


Figure 11: Binding pattern found in the crystal structure of E-selectin co-crystallized with sLe^x.

1.4. Development of sLe^x mimetics and small molecular weight selectin antagonists

The observation that E-selectin plays a key role early in the inflammatory cascade and promotes the tethering and rolling of leukocytes along the endothelial surface made of E-selectin a highly interesting pharmaceutical target. Therefore, blocking of the E-selectin-ligand interaction may be useful in cases, where excess recruitment of leukocytes can contribute to acute or chronic diseases such as stroke, reperfusion injury, psoriasis, rheumatoid arthritis or metastasis of cancer cells.

So far, all drug discovery approaches have been focused on blocking the lectin domain, since the role of the EGF and CR domains in ligand binding is still unclear.[15, 18, 211, 234-238]
Early approaches utilized carbohydrate fragments of the physiological ligands as potential anti-inflammatory therapeutics. This strategy led to the development of *Cylexin*, a sialyl Lewis^x pentasaccharide, which initially showed promising biological results,[239-242] but later turned out to be unsuccessful as a drug candidate, probably due to its low biological affinity[243] and limited bioavailability.[244] Because of its complex structure, the availability of *Cylexin* was initially very limited, as chemical synthesis provided only gram quantities.[245-247] This problem, however, was elegantly solved by Wong *et al.*,[209] who developed a multi-enzyme system for the large-scale production of sLe^x.[211]
Despite their ultimate failure, these early studies did provide the proof-of-principle, which prompted intense efforts towards finding more 'drug-like' selectin antagonists.[211] In the search of new E-selectin antagonists, the terminal carbohydrate epitope sialyl Lewis^x was commonly taken as a lead structure, apart from some recent studies that were using lead structures found by modern HTS techniques. Main objective in the drug development process was to address and overcome the following problems of the lead structure sialyl Lewis^x:

- low binding affinity
- low hydrolytical and metabolic stability
- low bioavailability due to its high polarity and molecular weight
- synthetical complexity and high production costs

In numerous studies it was tried to achieve this aim by substituting or omitting unnecessary structural elements while retaining the important pharmacophores or even finding new protein-ligand interactions. One of the most important and generally underestimated aspect in this lead

optimization process is the conformational pre-organization of the rather rigid sLe^x structure. Many of the described approaches resulted in low inhibition potencies or even failed due to an increase in flexibility by the replacement of sugar moieties with more flexible linkers.

The following overview of different approaches is structured in a reductionist fashion, starting with mimics where only one carbohydrate moiety of sLe^x was replaced, followed by mimics with two carbohydrate moieties replaced and so on. In each chapter further studies addressing secondary binding sites or conformational pre-organization will be discussed. At the end of the overview the *de-novo* design of antagonists will be discussed either based on the spatial orientation of the pharmacophores or on high throughput screening.

The IC_{50} values that are reported in the literature are difficult to compare directly, since they were obtained with conceptually different *in vitro* assays.[248] Therefore, whenever available, the relative affinities of the test compounds compared to sLe^x will be quoted, which has an IC_{50} value for E-selectin of approximately 1 mM. For example, a relative IC_{50} value (rIC_{50}) of 0.1 corresponds to an IC_{50} value of approximately 100 μM.

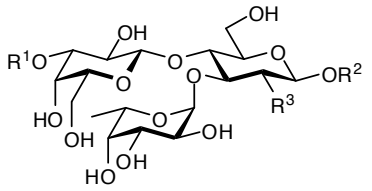
1.4.1. Antagonists with three sugar moieties

1.4.1.1. Replacements for sialic acid

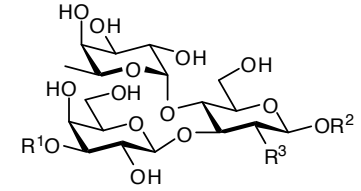
From early pharmacophore studies it is known that, in contrast to P-selectin, only the carboxylate of sialic acid is important for the interaction between E-selectin and sLe^x. Therefore, replacement of sialic acid by a negatively charged functionality was the first logical step, especially in respect to the tremendous costs of sialic acid. Several research groups reported the synthesis of ligands where the Neu5Ac is successfully replaced either by sulphate,[200, 243, 249] phosphate[250] or glycolate (*figure* 12).[251] Replacement of Neu5Ac by sulphate leads to the known natural '3-sulfo-analogues of sLe^x and sLe^a (**5**, **6**). Martin-Lomas *et al.* reported a more practical synthesis of similar ligands, where the Gal(1-4)Glc*N*Ac moiety was replaced by the more readily available lactose (**7**).[249] A phosphated lactose derivative of Le^a (**8**) was synthesized by Kiessling *et al.*[250] and was reported to show similar inhibition potency as '3-sulfo-Le^a, which itself was found to be 20-fold more potent than '3-sulfo-Le^x.

Most commonly the sialic acid was replaced by glycolic acid as in ligand **9**, which shows comparable affinity for E-selectin as sLe^x.[251] Thoma *et al.* fixed the carboxylate in equatorial position of a six-membered cyclic acetal to pre-organize the acid functionality.[252] However, from

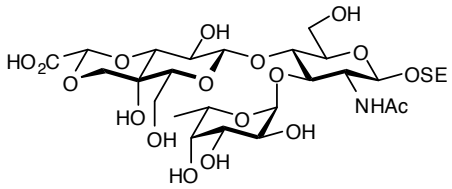
the inactivity of the compound (**10**), it could be concluded that the compound was pre-organized in a conformation different from the bioactive one. Other more rigid sialic acid mimics like lactic acid and derivatives thereof were found to be highly active, as described later in combination with replacements for Glc*N*Ac .



5: $R^1 = SO_3H$, $R^2 = H$, $R^3 = NHAc$
7: $R^1 = SO_3H$, $R^2 = H$, $R^3 = OH$
9: $R^1 = CH_2CO_2H$, $R^2 = H$, $R^3 = NHAc$



6: $R^1 = SO_3Na$, $R^2 = H$, $R^3 = NHAc$
8: $R^1 = PO_3Na_2$, $R^2 = Pr$, $R^3 = OH$



10

Figure 12: Ligands with replacement of Neu5Ac.

1.4.1.2. Replacements for Glc*N*Ac

SAR-studies and the crystal structure revealed that the Glc*N*Ac moiety rather serves as a spacer to optimally position the pharmacophores of fucose and galactose than directly contributes to the binding. Therefore, the Glc*N*Ac moiety is optimally suited for the replacement by spacers with improved pharmacodynamic or -kinetic properties, increased pre-organization or reduced synthetic complexity. [46, 205-207]

Hanessian *et al.* presented ligands where Glc*N*Ac was replaced by a (-)-quinic acid-derived carbocycle (**11**) and by an indolizidinone-type unit, as a β-turn-like scaffold (**12**).[253, 254] Whereas **11** was as active as sLe^x, **12** was found to be inactive due to the absence of any low energy conformer near the bioactive conformation of sLe^x. Töpfer *et al.* introduced (1*R*,2*R*)-trans-cyclohexanediol as Glc*N*Ac mimetic which resulted in a threefold more active compound than sLe^x.[255] This Glc*N*Ac mimetic is particularly interesting since it combines higher activity, lower synthetic complexity and higher lipophilicity in the same molecule, and hence found widespread application in the further synthesis of sLe^x antagonists (**13**, *figure* 13).

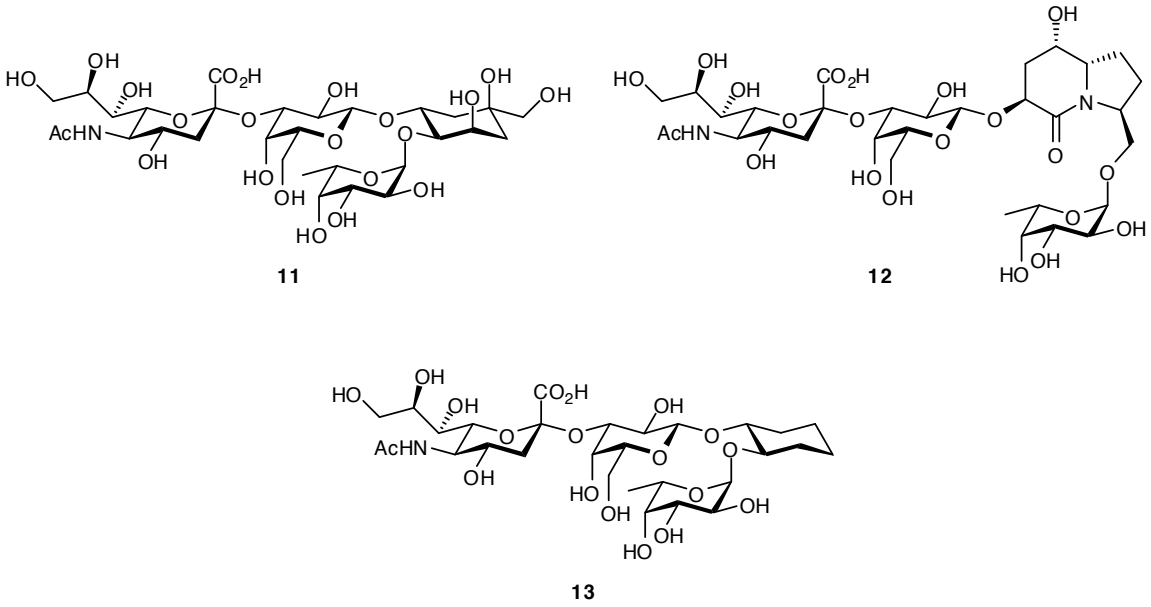


Figure 13: Ligands with replacement of Glc*N*Ac.

1.4.2. Antagonists with two sugar moieties

1.4.2.1. Replacements for the *N*-acetyl-lactosamine disaccharide

Several groups have been exploring suitable replacements for the central *N*-acetyl-lactosamine moiety (*figure* 14). However, the loss or inadequate replacement of the pharmacophores of galactose and the commonly increased flexibility of the linkers resulted in disappointing binding affinities. Töpfer *et al.* combined his successful Glc*N*Ac mimetic (1*R*,2*R*)-trans-cyclohexanediol with various aliphatic spacers for galactose. The compounds showed only moderate or no affinity and good results were surprisingly only achieved by switching from α- to the β-sialosides (**14**-**18**). Attempts to mimic the galactose pharmacophores by using polyols were unsuccessful.[255] Similar disappointing results were obtained from replacing the whole *N*-acetyl-lactosamine part by aliphatic spacers as in compounds **21**-**24**.[256] Also, the less flexible phenylenedimethanol spacers proposed by Kaila *et al.*[257] or the spiroketal spacer of Birkbeck *et al.*[258] led to less potent antagonists.

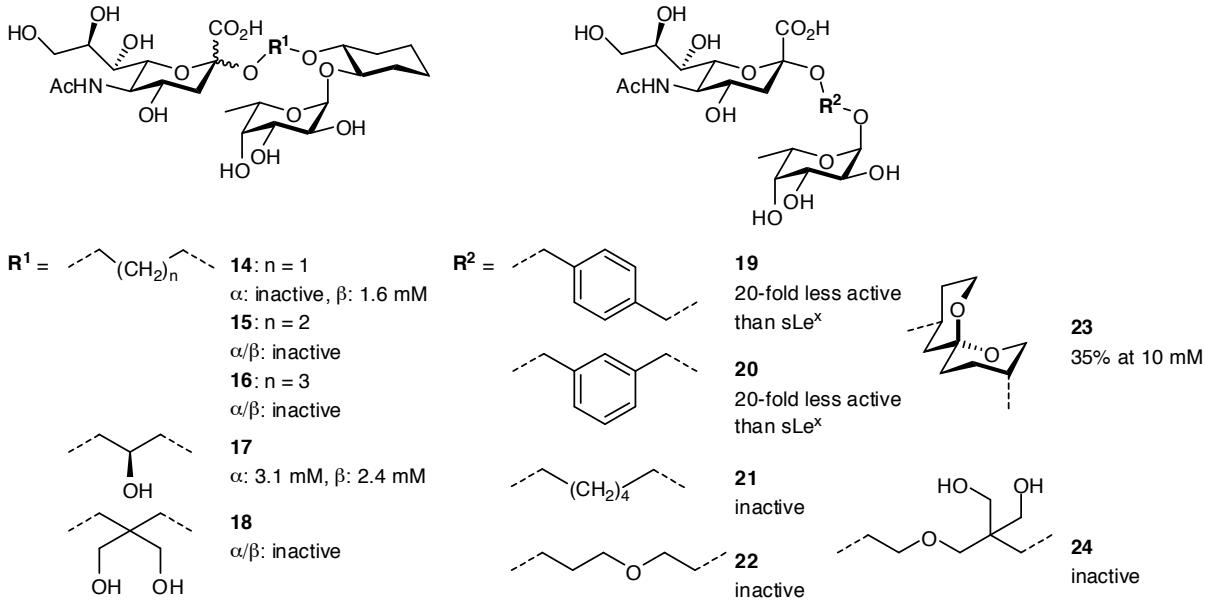


Figure 14: Ligands with replacements for *N*-acetyl-lactosamine.

Allanson *et al.* explored the possibility to link the sialic acid and the fucose by elongation from the fucose C-4 with suitable alkyl-chains and polyols (*figure* 15).[259, 260] However, these compounds were less active than sLe^x or were not active at all.

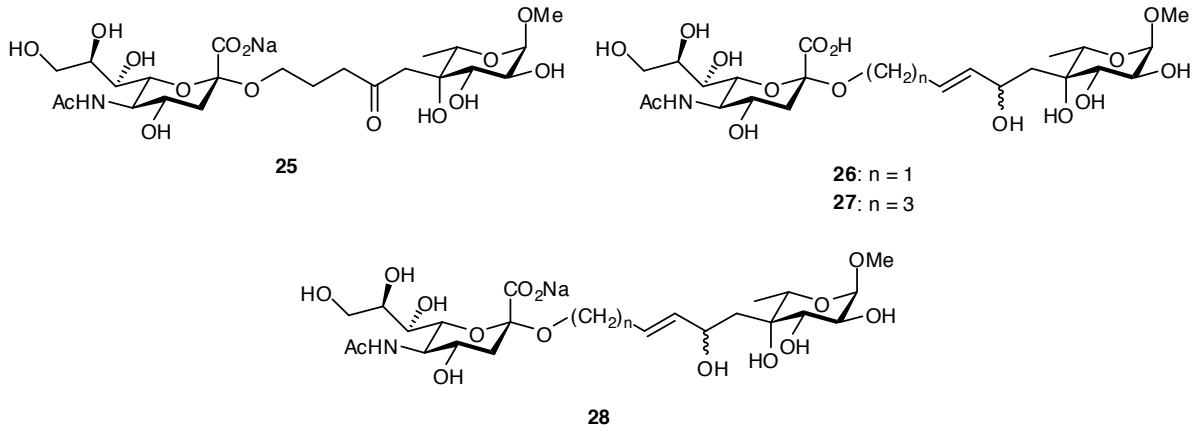


Figure 15: Ligands with replacements for *N*-acetyl-lactosamine proposed by Allanson *et al.*

1.4.2.2. Simultaneous replacement of Neu5Ac and Glc*N*Ac

Replacing both the sialic acid and Glc*N*Ac at the same time by simpler mimetics is a self-evident approach since both of them hardly bear any pharmacophores. Sialic acid was thereby commonly replaced by glycolic acid or aryl- and alkyl lactic acids, whereas the range of explored Glc*N*Ac mimetics was less narrow. A variety of Glc*N*Ac mimetics in combination with glycolic acid as Neu5Ac replacement is shown in *figure* 16.[261-266, 194]

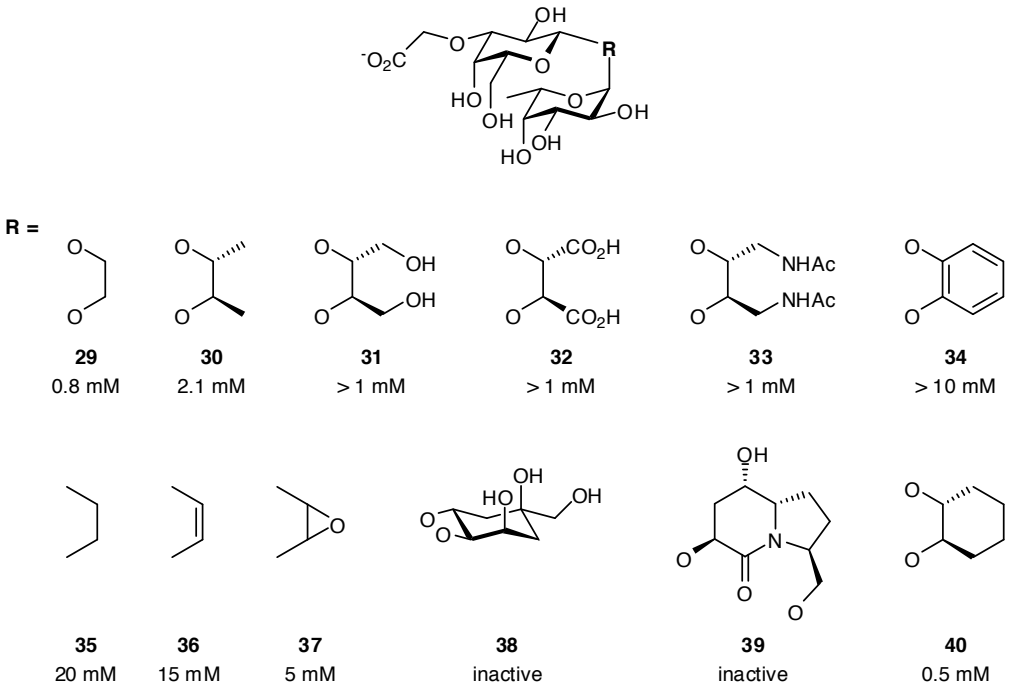


Figure 16: Ligands with glycolic acid as replacement for sialic acid.

Of all the Glc*N*Ac mimetics tested in combination with glycolic acid so far, the (1*R*,2*R*)-trans-cyclohexanediol (**40**) was the most promising one, providing an optimal spatial arrangement of the pharmacophores, compared to the similar but inactive ortho-catechol (**34**).[261] More flexible mimetics (**30**-**33**) or *C*-glycosides (**35**-**37**) led to a significant decrease in binding affinity due to the loss of pre-organization in the bioactive conformation.[261-266] Surprisingly, a simple ethanediol linker (**29**) was found to be almost as effective as (1*R*,2*R*)-trans-cyclohexanediol.[262] The previously mentioned quinic acid derivative (**38**) of Hanessian *et al.* lost in combination with glycolic acid its binding affinity to E-selectin.[254]

With the help of a molecular modelling tool Ernst *et al.* closer investigated replacements of Neu5Ac by lactic acid derivatives, in combination with cyclohexanediol as Glc*N*Ac mimetic.[216, 217]

The (*S*)-cyclohexyl lactic acid (**41**) was thereby found as the most potent replacement, optimally positioning the carboxylate in the bioactive conformation (*figure* 17). (*S*)-phenyl lactic acid (**42**) and the recently investigated (*S*)-adamantyl lactic acid (**43**) were found to be less potent.[267] The corresponding (*R*)-alkyl or aryl lactic acid derivatives were all inactive due to pre-organization of the carboxylate in the wrong conformation. In a combinatorial approach starting from (*S*)-isoserin the binding site was further explored (*e.g.* **44**-**48**), however without finding any more potent mimetics than cyclohexyl lactic acid, which was about 10-12 times more active than sLe^x.[268]

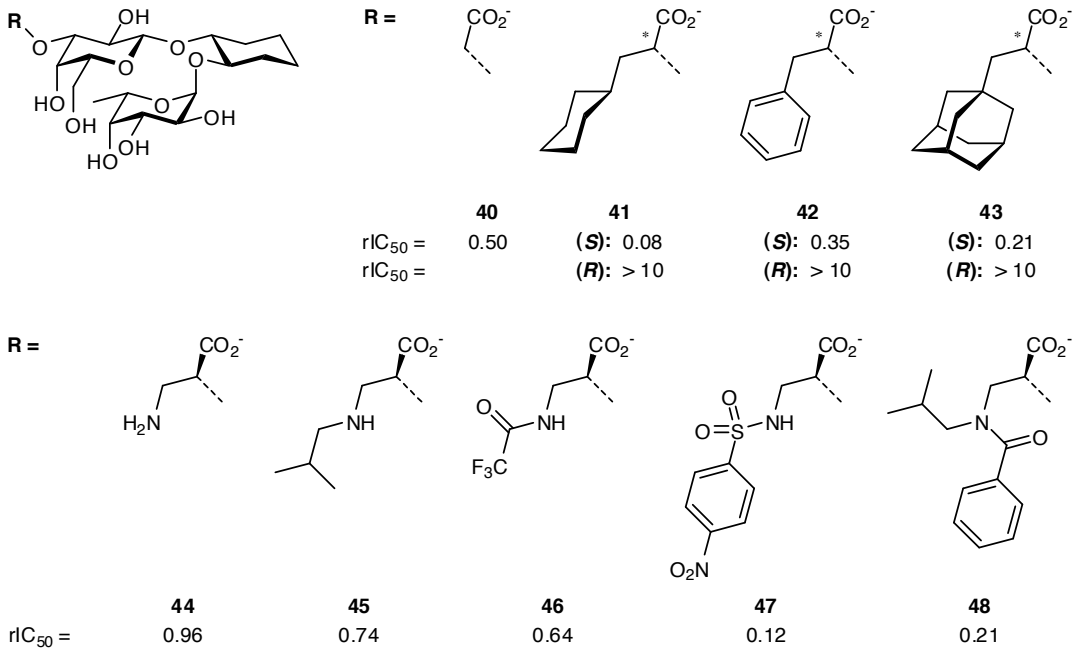


Figure 17: Ligands with lactic acid derivatives in combination with cyclohexanediol as Glc*N*Ac replacement.

Starting from compound **41** the role of the cyclohexanediol as Glc*N*Ac mimetic was further investigated (*figure* 18). Introducing more flexible linkers like ethanediol (**49**) or a xylal derivative (**50**) led to less active compounds.[269] However, introducing equatorial substituents in **50** at the position close to the fucose dramatically increased potency, leading to compounds (**51**-**55**) that are 25-fold more active than sLe^x.[269, 270] These findings were rationalized by the increased steric constrain applied to the fucose moiety, which leads to an improved pre-organization of the pharmacophores in the bioactive conformation. Finally, the 2-monobenzoylated antagonists **56**-**58**, resulting from incomplete deprotection, were up to three times more active than the corresponding fully deprotected antagonists.[270, 271]

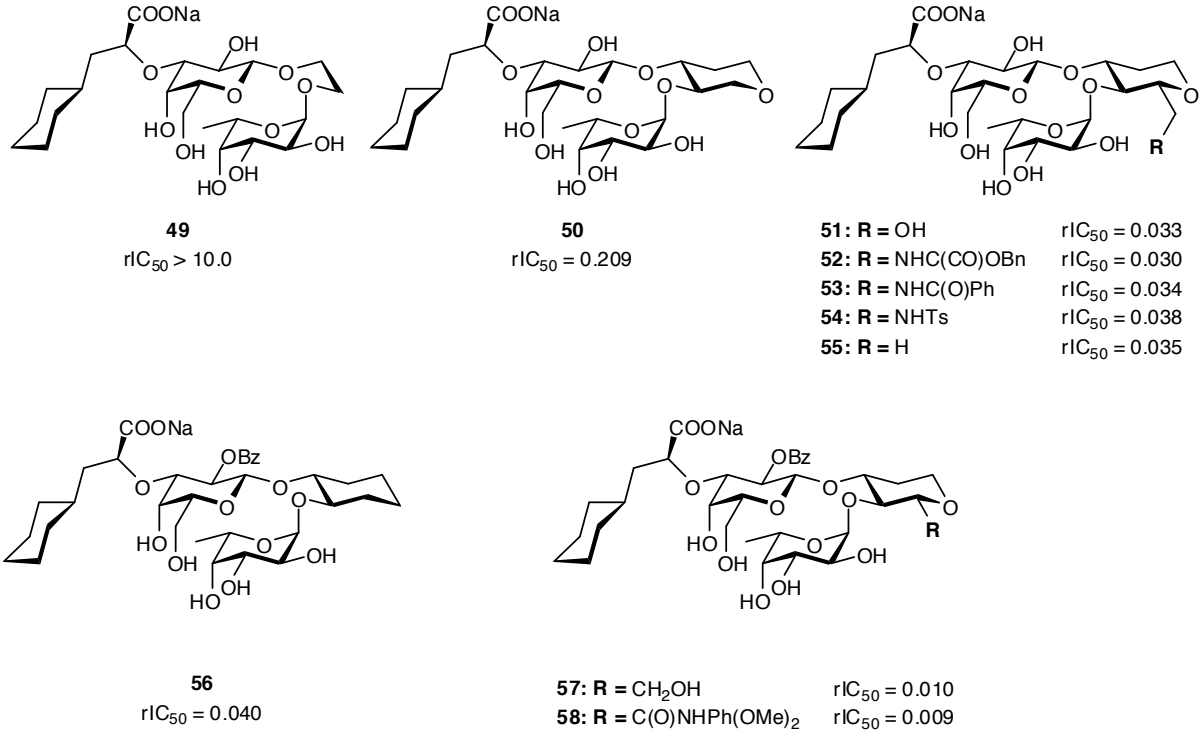
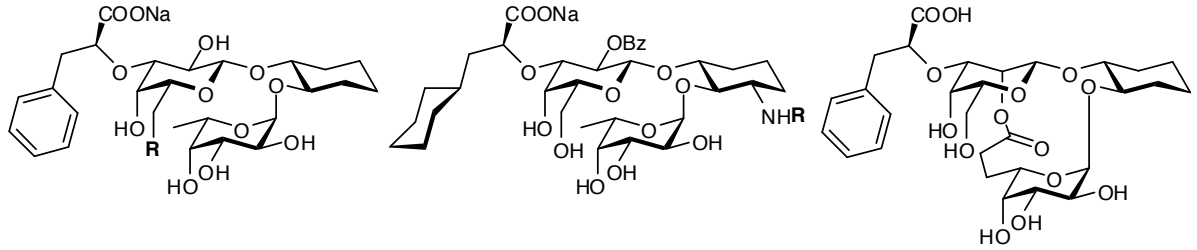


Figure 18: Ligands with different Glc*N*Ac mimetics in combination with cyclohexyl lactic acid.

Various attempts were undertaken to increase the potency of antagonists either by exploring further binding sites or by increasing the ligands pre-organization (*figure* 19). Bänteli *et al.* reported a library of compounds (*e.g.* **59**-**62**) with modifications at the 6-position of galactose.[202] However, the modifications were deleterious to the binding affinity and the 6-hydroxyl was suggested to be optimally suited for binding to E-selectin. Ernst *et al.* explored a hypothetical second binding site close to Glc*N*Ac by using a D-(-)-quinic acid-derived Glc*N*Ac mimetic, which was further acylated with numerous substituents (*e.g.* **63**-**65**).[233, 272] Similar work was performed earlier by Hayashi[273] and DeFrees[274] on sLe^x derivatives. In order to pre-organize the pharmacophores of the fucose, Kolb synthesized a macrocyclic sLe^x mimic, linking the fucose and the galactose directly.[275] However, the macrocyclic antagonist **66** turned out to be three times less active than sLe^x. A possible reason may be that the macrocycle locks a conformation slightly different from the bioactive one.



59: R = NH_3^+ inactive
60: R = NHAc inactive
61: R = NHBz inactive
62: R = OSO_3Na inactive

63: R = Ac $rIC_{50} = 0.110$
64: R = p-phenylbenzoyl $rIC_{50} = 0.095$
65: R = orotoyl $rIC_{50} = 0.022$

66: $rIC_{50} = 2.8$

Figure 19: Ligands addressing second binding sites or with pre-organized core-structures.

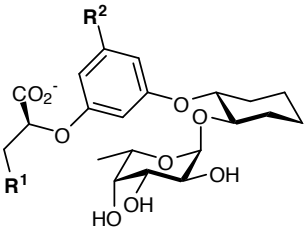
1.4.3. Antagonists with one sugar moiety

The L-fucose moiety contains two out of five pharmacophores binding to E-selectin and is probably the hardest residue to substitute with a non-carbohydrate moiety. Therefore, most of the monosaccharide antagonists were conserving the binding to the Ca^{2+} either by fucose or a monosaccharide with the same spatial orientation of the pharmacophores, such as galactose or mannose. The monosaccharide moiety was linked either to established mimetics, polyaryls, peptides or other suitable groups for mimicking the remaining pharmacophores (*figure* 20).

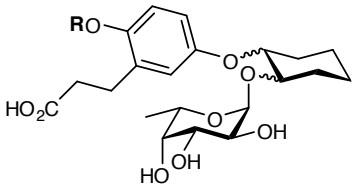
The group of Ernst *et al.* tried to further simplify their mimics **41** and **42** by replacing the galactose by aromatic spacers, whereas Neu5Ac and Glc*N*Ac were substituted by the already well established lactic acid derivatives and cyclohexanediol.[276] The compounds **67**-**72** were all inactive, probably due to the increased flexibility of the ether-linkage or wrong spatial orientation of the pharmacophores. A very similar approach was performed by Liu *et al.* for the compounds **73**-**76**.[277] Interestingly, the benzyl protected compounds were found to be active, rather than the one with a free phenolic group. Toepfer *et al.* reported mimics containing piperidine carboxylic acid (**77**-**80**) and malonic acid derivatives (**81**-**92**).[278, 279] However, none of these compounds was more active than sLe^x. Other unsuccessful approaches (**93**-**96**) were reported by other groups.[253, 263]

Kogan *et al.* designed a library of sLe^x mimetics by replacing L-fucose with D-mannose.[280-282] The carboxylic acid function, which replaces Neu5Ac was linked with the D-mannose by a biphenyl spacer, mimicking the Gal-β(1-4)-Glc*N*Ac disaccharide. Although these compounds lack the important pharmacophores of the galactose, they turned out to be slightly more potent than sLe^x

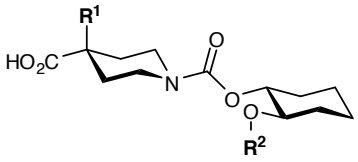
(**97**). The activity could further be improved by optimizing the biphenyl linker between the pharmacophores, leading to the compounds **98** and **99**. A breakthrough was achieved with the dimer of **97**, which was inspired by previous reports on the improved E-selectin binding of extended dimeric sialyl Lewis^x derivatives.[62, 283]



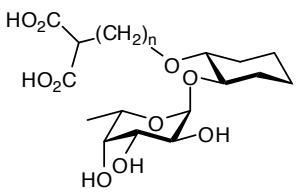
67: R^1 = Ph, R^2 = H
68: R^1 = Ph, R^2 = Ph
69: R^1 = Ph, R^2 = *i*-Pr
70: R^1 = Ph, R^2 = CO_2H
71: R^1 = Ph, R^2 = CH_2OH
72: R^1 = *c*-Hex, R^2 = CH_2OH
all inactive



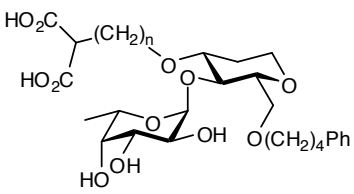
73: R = H (1*R*,2*R*), inactive
74: R = Bn (1*R*,2*R*), 3.3 mM
75: R = H (1*S*,2*S*), inactive
76: R = Bn (1*S*,2*S*), 0.87 mM



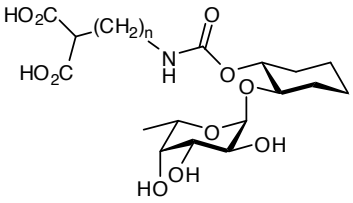
77: R^1 = CO_2H, R^2 = α-L-Fuc, 1.6 mM
78: R^1 = H, R^2 = α-L-Fuc, > 5 mM
79: R^1 = H, R^2 = α-L-Man, 5 mM
80: R^1 = H, R^2 = α-D-Man, > 10 mM



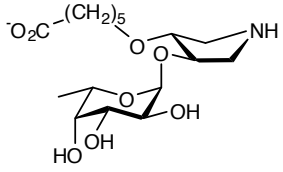
81-87: n = 3 - 8, 10
all > 5 mM



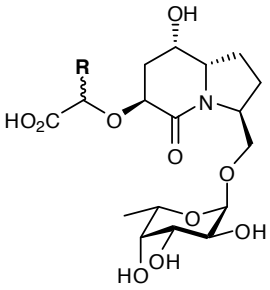
88: n = 4 4.8 mM
89: n = 5 2.6 mM



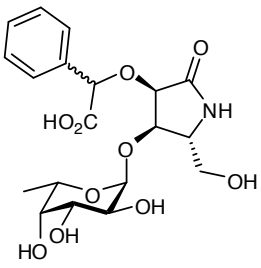
90: n = 2 3.4 mM
91: n = 3 1.0 mM
92: n = 4 4.0 mM



93: inactive

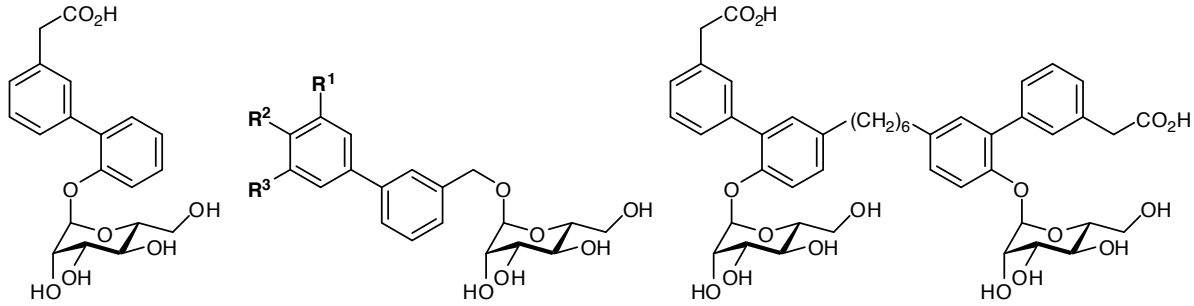


94: R = Ph, inactive
95: R = H, inactive



96: inactive

Figure 20: Antagonists with one sugar moiety.



97: rIC_{50} = 0.7

98: R^1, R^2 = H, R^3 = CH_2CO_2H, rIC_{50} = 0.4
99: R^1, R^3 = Me, R^2 = OCH_2CO_2H, rIC_{50} = 0.3

100: rIC_{50} = 0.15

Figure 21: Biphenyl-based antagonists by Kogan *et al.*

Wong *et al.* created a large library of fucose-, mannose-, or galactose-based glycopeptides.[194, 266, 284-291] Two variable design elements (*figure* 22) were used for replacing Glc*N*Ac and Gal, whereas the Neu5Ac was commonly replaced by glutaric or a related acid. In this series some of the most potent compounds against E- and P-selectin were found as displayed in *figure* 23 (**101**-**108**). However, the gain in affinity is commonly much more pronounced for P-selectin and rationalization of the source of the compounds' activity is difficult. In addition, Wong *et al.* took advantage of the increased metabolic stability of C-glycosides compared to O-glycosides. Recently, the macrocyclic glycopeptide **108** was found to be approximately 1000-fold more active than sLe^x against P-selectin.[291]

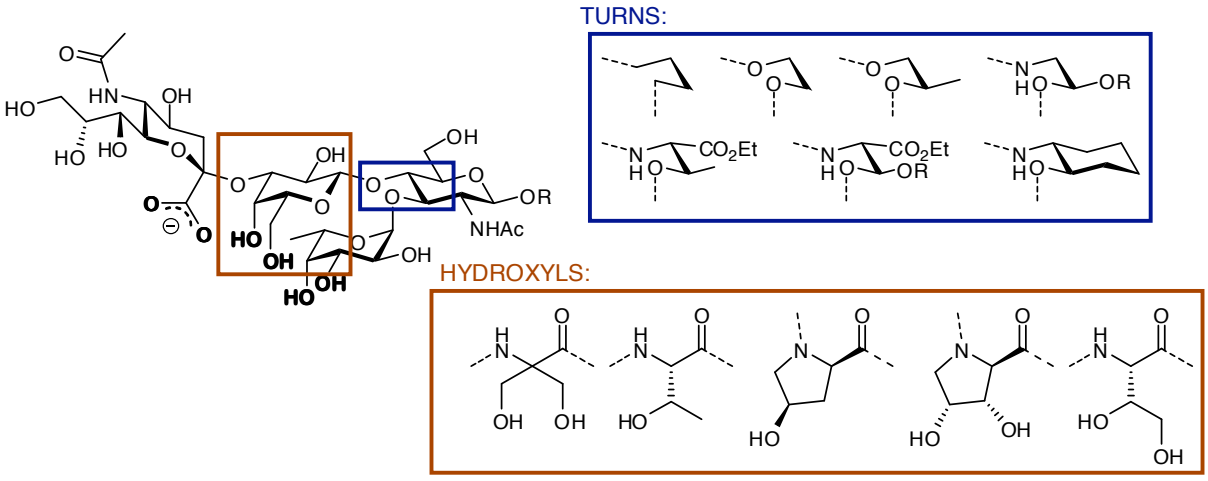
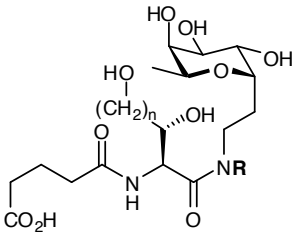
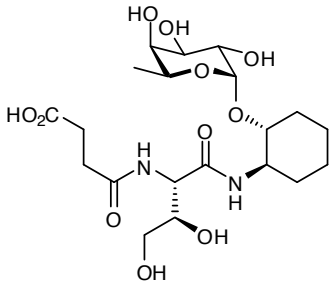


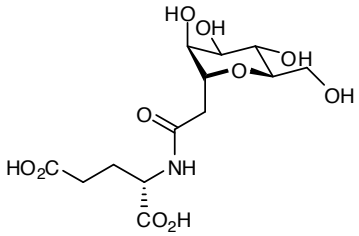
Figure 22: Design elements for replacing galactose and Glc*N*Ac.



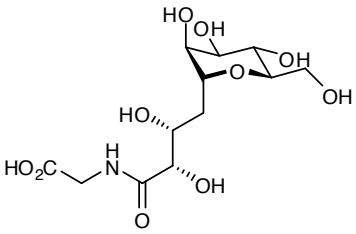
101: n = 1, R = H, 0.3 mM
102: n = 2, R = H, 0.5 mM
103: n = 1, R = $CH_2CONH(CH_2)_{13}CH_3$, 0.069 mM



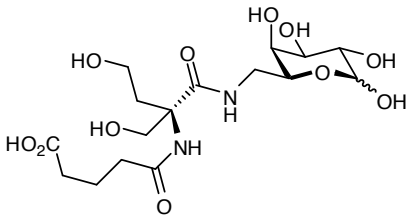
104: 0.2 mM



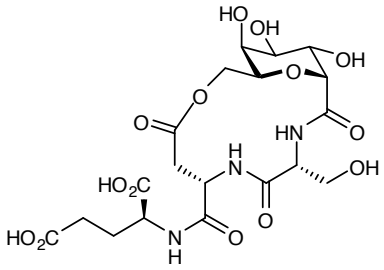
105: 0.1 mM



106: 0.16 mM



107: 0.2 mM



108: 1 μM
against P-selectin

Figure 23: Glycopeptide-based antagonists by Wong *et al.*

1.4.5 Non-carbohydrate based mimetics

Due to the unfavorable pharmacokinetic properties of carbohydrates numerous *de-novo* design approaches were undertaken, based on different means such as pharmacophore models and high throughput screening. Some of the discovered compounds are displayed in *figure* 24 and should illustrate the recent efforts made in order to find a small molecular weight selectin antagonists by *de-novo* design.

Kondo *et al.* has used a 3D pharmacophore model to screen a commercially available database for lead compounds. A preliminary lead optimization resulted in compound **109** with a micro-molar IC_{50} for E-selectin.[248]

With a similar pharmacophore model and by structure-based design the group of Ulbrich *et al.* found the micromolar lead compound **110**. The lead was evaluated in a flow-chamber assay, where it inhibited the rolling and adherence of cells. Its efficacy was further proofed in a *in vivo* peritonitis model of acute inflammation in mice.[292]

In a ligand-based approach starting from the earlier reported biphenyl-based antagonists **97**-**100**,[280-282] new non-glycosidic antagonists were discovered (**111**, **112**). The novel small

molecules were bearing a trihydroxybenzene motif, which probably replaces the pharmacophores of the former fucose. The compounds showed micro- to nanomolar *in vitro* activity against E-selectin in a static assay as well as significant inhibition under dynamic conditions.[293]

High-throughput-screening of the Wyeth chemical library led to the discovery of quinoline salicylic acids as lead structure for P-selectin antagonists. Iterative medicinal chemistry resulted in more potent compounds like *e.g.* **113**, which was efficacious in the rat AIA model of rheumatoid arthritis. However, no data about E-selectin inhibition of these compounds have been published up to now.[294]

Recently, two research groups independently reported quinic acid derivatives (**114**-**116**) as selectin antagonists.[295, 296] In soaking experiments, the quinic acid was surprisingly found to bind the Ca^{2+} with its two equatorial 4- and 5-hydroxyls, which is in contrast to the binding of the fucose to the Ca^{2+}. In addition, quinic acid was found to bind with its ring parallel to the protein's surface, which leads to a significant change in the directional vectors of substituents attached to the 1-position of quinic acid.[296]

A further group of E-selectin antagonists is formed by peptidic antagonists. However, this class of antagonists will not be discussed in this thesis.[211]

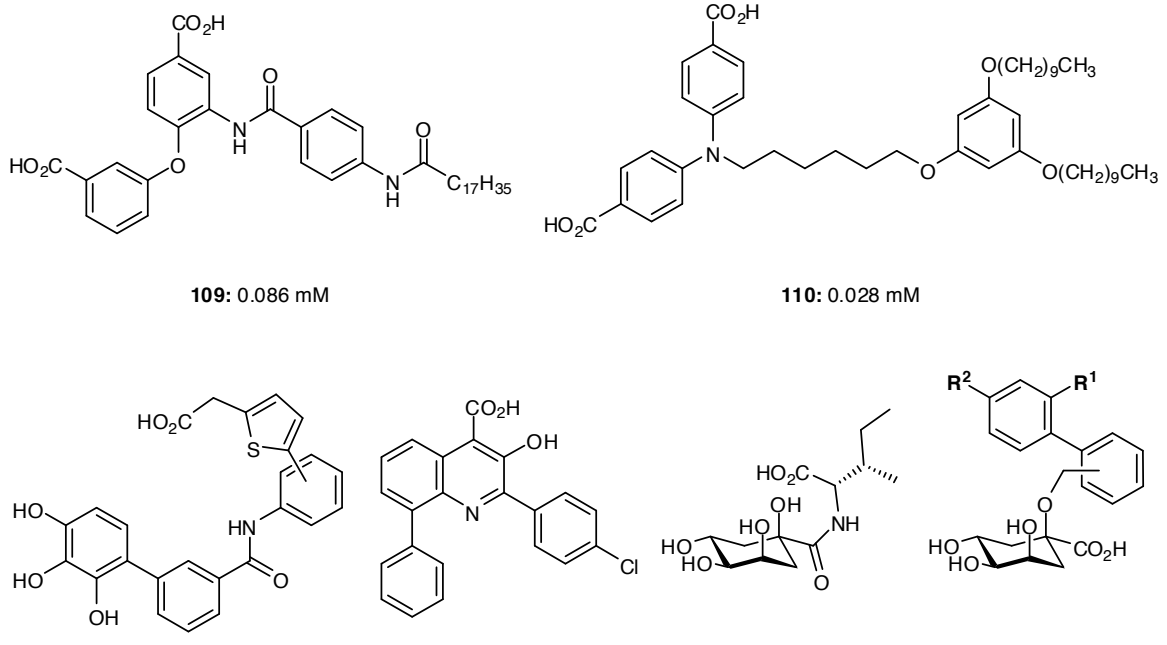


Figure 24: Non-carbohydrate based mimetics.

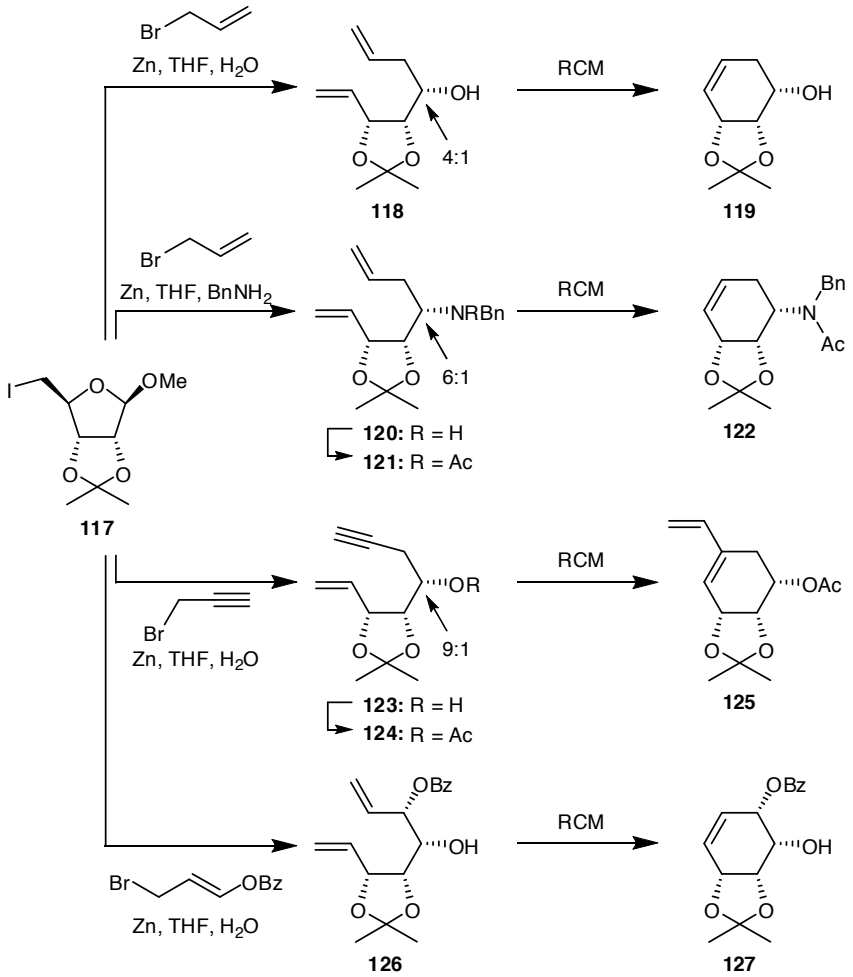
1.5. Polyhydroxylated carbocycles and carbasugars as carbohydrate mimetics in drug discovery – Some modern synthetic approaches to carbocycles

Carbohydrates play an important role in numerous biologically and clinically relevant events like intercellular adhesion, signal transduction, malignant transformation and viral and bacterial cell-surface recognition.[297-302] As more and more carbohydrate-related drug-discovery targets get discovered and validated, carbohydrates are emerging as potential therapeutic agents and are just at the very beginning of their exploitation by the pharmaceutical industry. However, the use of carbohydrates in drug discovery is hampered by their poor pharmacokinetic and pharmacodynamic properties, such as dense content of polar groups, low membrane permeability, low binding affinities and fast acidic and metabolic degradation after oral application. Numerous strategies were pursued to circumvent these carbohydrate-specific problems for drug discovery. One of the strategies is the replacement of the tetrahydropyran ring by functionalized carbocycles or carbasugars, while retaining essential pharmacophores for the binding. Beside the increased metabolic and chemical stability of these carbasugars, higher affinities can often be expected due to additional hydrophobic interactions by deletion of unnecessary polar groups. The loss of the anomeric center in carbasugars however, may have a dramatic effect on the conformational stability of the ring, and as a consequence thereof, on the entropic costs upon binding, and requires careful consideration in the design of antagonists. The following section highlights just a few of the numerous modern synthetic strategies for creating densely functionalized carbocycles.

1.5.1. Conversion of carbohydrates into carbocycles by the use of olefin metathesis

Carbohydrates are not obvious substrates for olefin metathesis. However, introducing two terminal olefins in a carbohydrate allows ring closing metathesis which results in an unsaturated polyhydroxylated carbocycle. The installation of the terminal olefins is usually done in two separate steps. The first one is the zinc-mediated fragmentation of primary iodo-glycosides, originally developed by Bernet and Vasella.[303] The installation of the second olefin is then usually performed by Wittig methylenation or organometallic reactions. A major breakthrough in this field was achieved by Hyldtoft and Madson who described the zinc-mediated domino elimination-alkylation reaction, where both steps are performed at the same time.[304-306] In a typical reaction of this type, the zinc mediates both, the fragmentation of the iodoglycoside and the subsequent Barbier-type alkylation of the intermediate aldehyde. The most promising

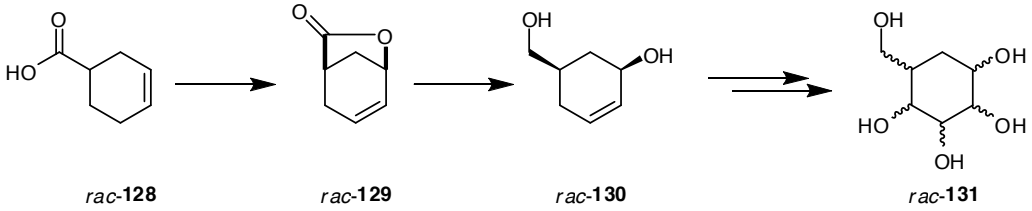
applications of this domino reaction have come from the use of allyl bromide or even functionalized allyl bromides like ethyl 4-bromocrotonate or 3-benzoyloxyallyl bromide. The stereochemical outcome of the reaction is determined by the proper choice of the iodoglycoside, except for the newly formed stereocenter, which is strongly influenced by the choice of the metal, *e.g.* indium *versus* zinc, and by the protecting groups.[304] The ring-closing metathesis (RCM) easily proceeds in good yields in dichloromethane with commercial catalysts. Sometimes, however, protection of the hydroxyl or amine at the newly formed stereocenter is necessary prior to the metathesis reaction. The unsaturated bond allows further modifications like hydrogenation, dihydroxylation and epoxidation, enabling the synthesis of a large variety of functionalized carbocycles with a minimum of chemical steps. The high diversity of this synthetic approach for carbocycles is exemplified in *scheme* 1.[306]



Scheme 1: Carbohydrate carbocyclization by zinc-mediated domino reaction and ring-closing metathesis (RCM).

1.5.2. 3-Cyclohexene-1-carboxylic acid based approaches

3-Cyclohexene-1-carboxylic acid (**128**) is a versatile starting material for the synthesis of a variety of carbasugars and functionalized carbocycles. Its importance for synthetic chemistry is reflected by the numerous publications dealing with its stereoselective synthesis or deracemization.[307-316] Typically, the synthesis starts with iodolactonization and dehydroiodination affording the lactone **129**, followed by reduction of the lactone. From the diol **130** further functional groups may be inserted *via* dihydroxylation, epoxidation or elimination of transient bromohydrins. An intelligent choice of protecting groups and reaction conditions allows to steer the *syn*-/*anti*-selectivities of the above mentioned reactions. Inversion of stereocenters under Mitsunobu conditions or by oxidation and subsequent reduction even broadens the range of synthetically possible carbocycles. The versatility of this approach was recently demonstrated by a practical synthesis of sixteen enantiopure carbasugars by Chung *et al.*[317, 318]



rac-**128** *rac*-**129** *rac*-**130** *rac*-**131**

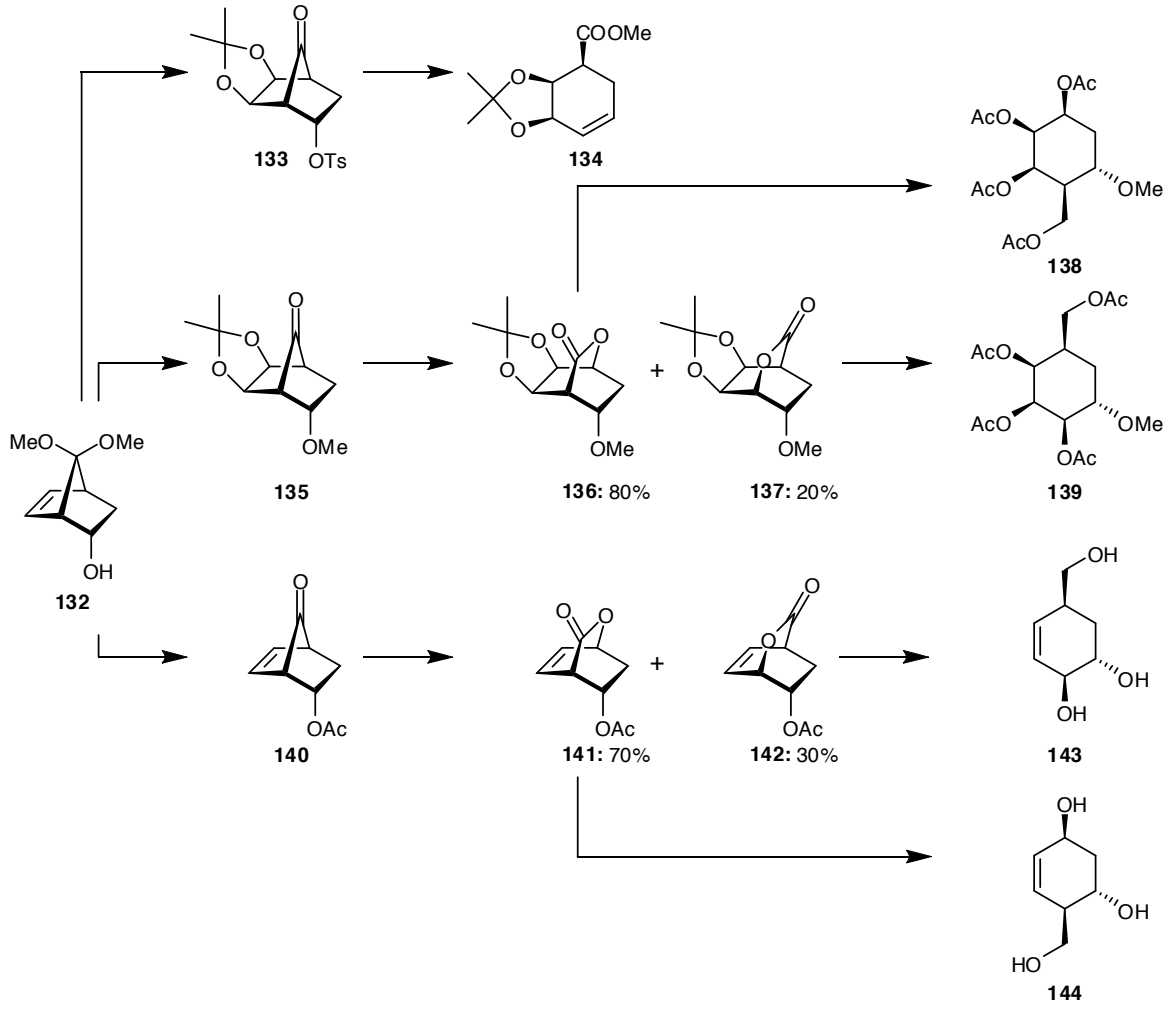
Scheme 2: General synthesis of carbasugars from 3-cyclohexene-1-carboxylic acid.

1.5.3. Norbornyl based synthetic approaches

A simple synthetic pathway to carbasugars and so-called “confused” carbasugars starts from 7-norbornenone derivatives. The term “confused” carbasugar refers to functionalized carbocycles, where the hydroxymethyl and the “para”-hydroxyl of the corresponding carbasugar are interchanged. The 7-norbornenone derivatives and their precursor ketals are readily available through Diels-Alder reaction between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and various vinyl alcohols, followed by reductive dehalogenation.

Basically, 7-norbonenone derivatives like **135** and **140** are locked carbasugars, from which the six-membered carbasugar skeleton can be easily retrieved through *m*-CPBA mediated C1-C7 or C4-C7 bond scission. The C1-C7 bond scission leads to carbasugars, whereas the C4-C7 bond scission leads to the corresponding “confused” carbasugars. Further refinement by dihydroxylation, epoxidation or hydrogenation gives access to a variety of interesting carbocycles, as depicted in *scheme* 3. A slightly altered fragmentation process can be achieved

by converting the 2-hydroxyl into a leaving group, which results in functionalized 3-cyclohexene-1-carboxylates.[319-321]

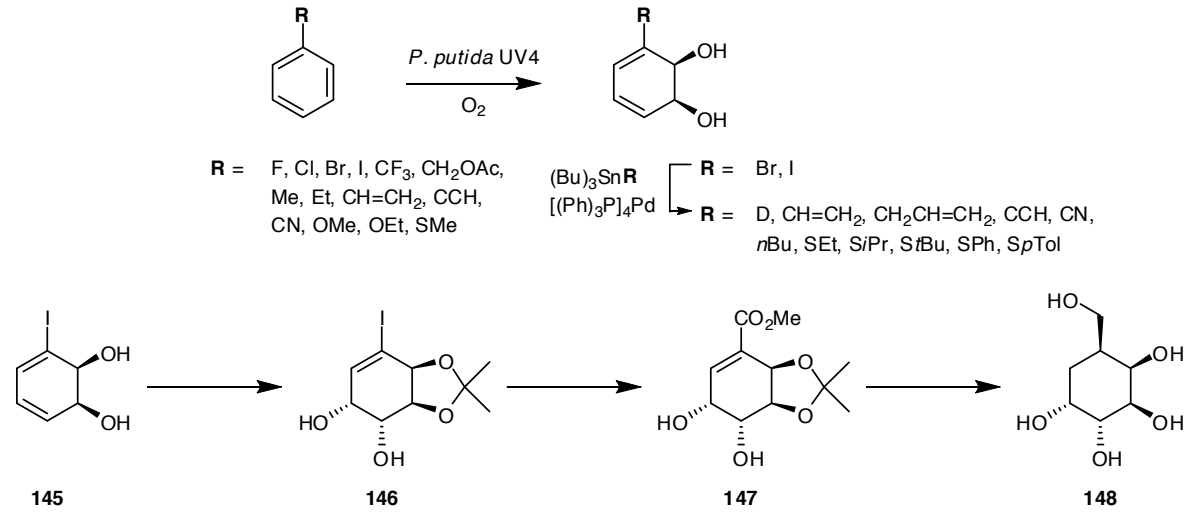


Scheme 3: Norbornyl-based approach to functionalized carbocycles.

1.5.4. Approaches from substituted cyclohexadienediols

The toluene dioxygenase of the constitutive mutant strain *Pseudomonas putida* UV catalyzes the asymmetric dihydroxylation of a wide range of monocyclic arenes. Up to date more than 50 enantiopure cis-dihydrodiol metabolites of mono-substituted benzene substrates have been reported, with fluorobenzene as the only member with exceptionally low enantiomeric excess.[322-325] Despite the broad substrate tolerance, the majority of the reports are focused on metabolites of toluene, chloro-, bromo- and iodobenzene. Especially, the metabolite of iodobenzene found

particular interest due to the facile substitution of the iodine atom either by reductive dehalogenation or Stille coupling and due to the directing effect of the bulky iodine atom on other reactions.[324-326] These *cis*-dihydrodiol metabolites found widespread application in the stereoselectiv synthesis of carbasugars[326] (*scheme* 4) as well as natural products like conduritol C,[327, 328] shikimic acid[329] and many others.[330, 331]



Scheme 4: Toluene dioxygenase catalyzed reaction of substituted arenes and chemoenzymatic synthesis of carbasugars from iodobenzene.

2. Aim of the Thesis

The compound CGP69669 (**41**) was early recognized as lead for inhibiting E-selectin. However, this lead shows insufficient binding affinity, high synthetic complexity and is supposed to have a poor pharmacokinetic profile due to its susceptible *O*-glycosidic bonds and the high density of polar groups. In order to reach the profile of a development candidate, the optimization of the lead's pharmacodynamic and pharmacokinetic properties is inevitable. The compound's potency can be increased by different means such as installing additional interactions with the protein or reducing the ligands flexibility and thereby reducing the entropic costs upon binding.

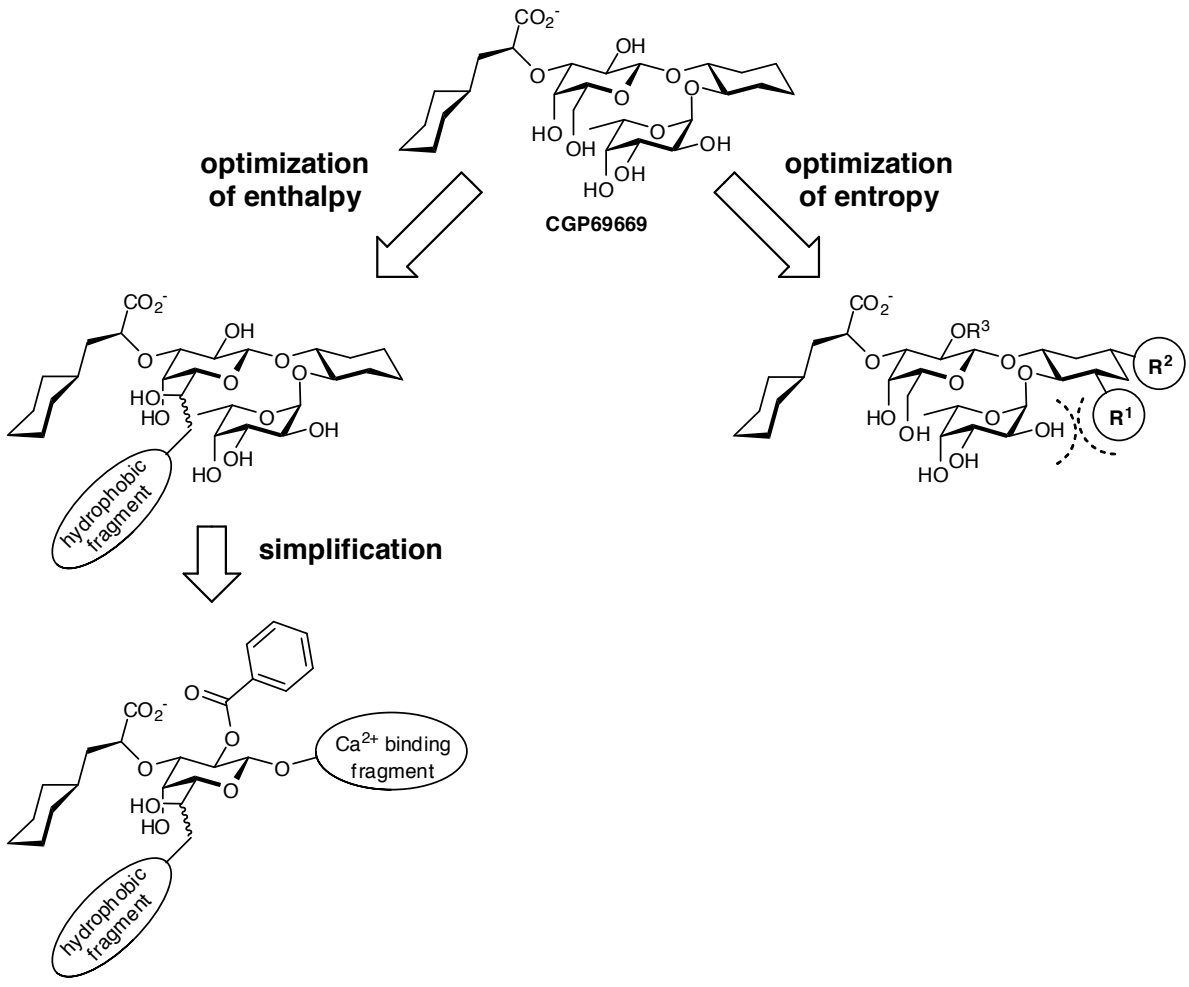


Figure 25: Lead compound CGP69669 (**41**) and general target structures of the two projects.

In the first part of this thesis, it was planned to occupy a hydrophobic pocket close to the 6-position of the galactose moiety, which was identified in the recently published crystal structure

of E-selectin. Since the 6-hydroxyl is crucial for binding to E-selectin, it will remain untouched, and the hypothetical fragments for binding to the hydrophobic pocket will alternatively be attached to the C-6 of the galactose. The *de-novo* design of the hydrophobic fragment, as well as its linker, will be assisted by molecular modeling tools, enabling a fragment-based design of novel ligands with their subsequent iterative scoring and optimization. The increase of potency, gained by an optimal occupation of the hydrophobic pocket, may allow drastically simplifying or even omitting original pharmacophores (*e.g.* fucose) of the ligand. This strategy would finally result in more drug-like E-selectin antagonists with only minor carbohydrate character.

The second part of this thesis is dedicated to the optimization of the pre-organization of the antagonist in its bioactive conformation. Although the Glc*N*Ac moiety of sLe^x displays no pharmacophores and mainly serves as a spacer between the fucose and the galactose, it makes an important contribution to the spatial pre-organization of the pharmacophores in the binding conformation. Replacing Glc*N*Ac by suitable mimetics not only increases the drug-likeness of antagonists, but additionally helps to increase the extent of pre-organization. The aim of the current work is to develop novel potent antagonists by reducing the ligand's entropic costs upon binding through Glc*N*Ac mimetics that allow an optimized pre-organization. This is planned to be realized by different means like steric compression or conformational stabilization, while preserving the ligand's drug-likeness and synthetic accessibility. The degree of pre-organization may be further evaluated by NMR-investigations.

3. Results and Discussion

3.1. E-selectin antagonists containing substituted L-*glycero*-β-D-*galacto*-hepto-pyranoses as replacement for galactose (optimization of enthalpy)

3.1.1. *De-novo* design of E-selectin antagonists

The goal of the *de-novo* design of E-selectin antagonists was to identify hydrophobic pockets on the surface of E-selectin and target them with appropriately modified ligands. This should lead to antagonists with improved affinity.

The crystal structure of E-selectin reveals several hydrophobic patches close to the galactose moiety.[46] The first hydrophobic patch is found close to the Neu5Ac binding site (sidechains of Asp98 and Lys99), the second one close to the 2-hydroxyl of galactose (Pro78) and the last one close to the 6-hydroxyl of galactose. The accumulation of hydrophobic patches around the galactose moiety suggests the role of galactose to act as the scaffold to position novel hydrophobic substituents into these areas. Another point which argues for galactose as central scaffold is that the Neu5Ac and the galactose moieties make a great contribution to the binding affinity, whereas the fucose contributes only with the 3- and 4-hydroxyl directly to the binding, and the Glc*N*Ac moiety serves mainly as spacer to optimally position the fucose. The so potentially gained increase in binding affinity may allow to omit the fucose and the Glc*N*Ac moieties completely or to replace them by more simple Ca^{2+}-binding fragments. This strategy would finally result in more drug-like E-selectin antagonists with only minor carbohydrate character.

For the *de-novo* design of novel E-selectin antagonists we focused on a shallow hydrophobic pocket close to the 6-hydroxyl of the galactose moiety of sLe^x (*figure* 26). The pocket is formed by the residues Lys111, Lys112, Lys113, Pro46, Tyr48 and Ser47. It was previously shown by Bänteli and Ernst that straight derivatization of the 6-hydroxyl of the lead compound CGP69669 (**41**) leads to inactive compounds, probably due to the loss of the hydrogen bond between 6-OH and Glu92 (*figure* 11).[202] In addition, the region close to the 6-hydroxyl shows steric restriction caused by the residues Lys 111 and Tyr48 which could lead to steric clashes for hydrophobic extensions of the hydroxyl group in the 6-position. For our approach, we therefore decided to introduce substituents at the position of one of the hydrogens at C-6 of galactose in CGP69669 (**41**), conserving the 6-hydroxyl for hydrogen bonding and avoiding the steric problem. Replacement of the hydrogen should be realized with a short linker, which passes the constriction and enters into the spacious binding pocket (*figure* 26).

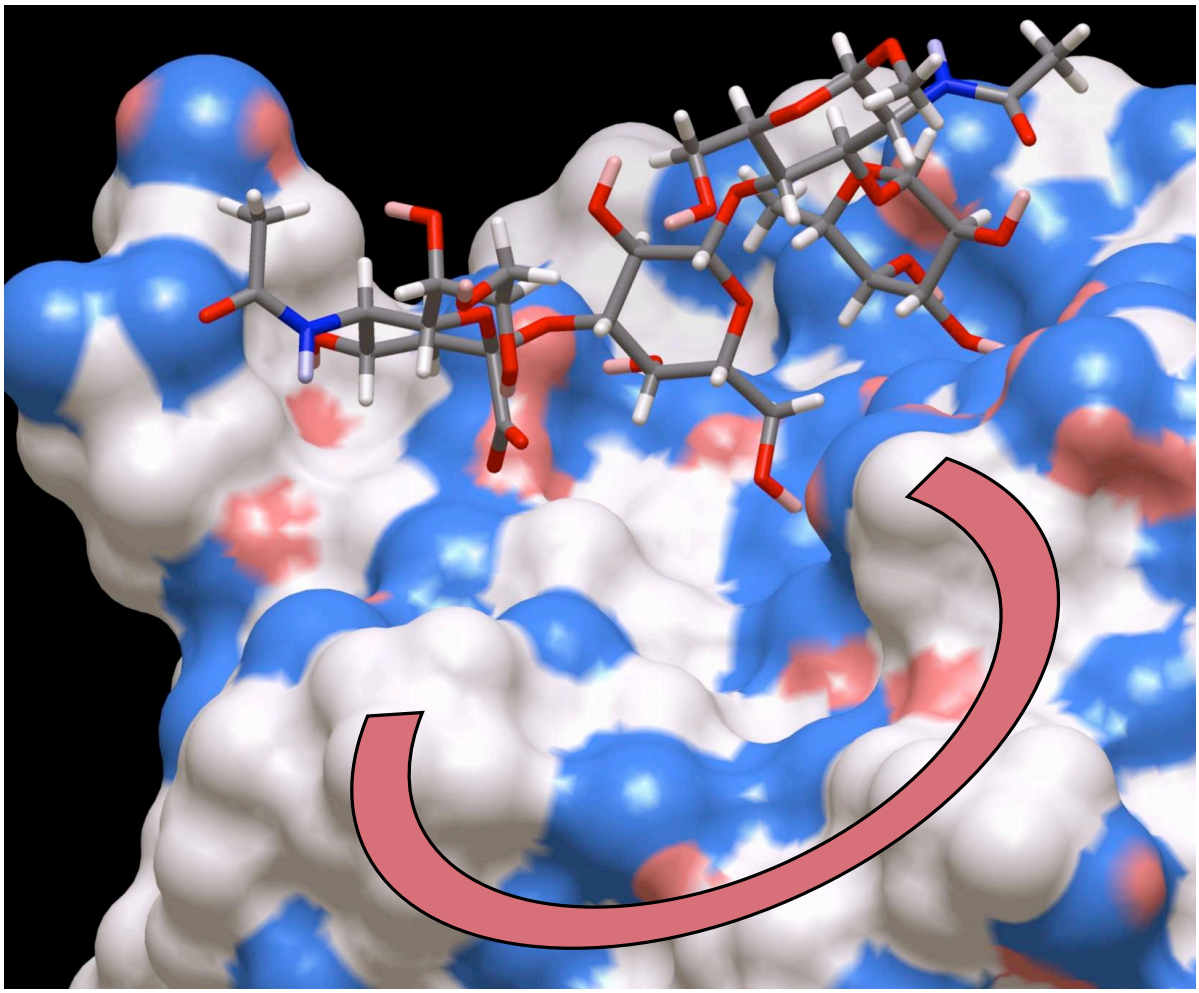


Figure 26: sLe^x docked onto E-selectin. The hydrophobic pocked is highlighted.

Suitable replacements for the hydrogen were investigated by using *Allegrow*.[332, 333] CGP69669 (**41**), docked on the surface of E-selectin was taken as lead. The lead and the protein were prepared as discussed in the thesis of Michele Porro.[334] One of the hydrogens at a time was marked with X, indicating where the fragment-based grow-routine should start. Several thousands newly generated hypothetical ligands were minimized with the QXP force field and evaluated by a post-grow scoring function. The most potent ligands were then visually analyzed for hydrogen-bonding patterns and hydrophobic interactions.[332, 333] Recurrent motifs were used for a second grow-routine and the resulting data analyzed as before. The new ligands were optimized by combining recurrent motifs and taking drug-likeness and feasibility of the chemical synthesis into consideration. As recurrent functional groups, two carbonyls were found, one hydrogen-bonding to Lys111 and Lys113 and the second one as H-bond acceptor of the

backbone NH of Lys112. The second carbonyl could also be replaced by an optimally oriented *N*-heterocycle or an ether moiety like morpholine (for examples see *figure* 27).

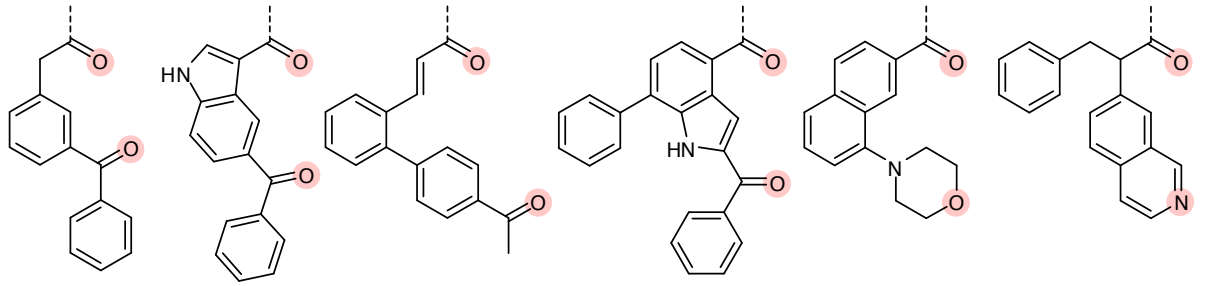
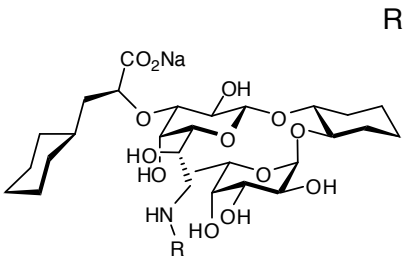
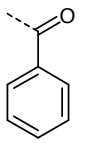
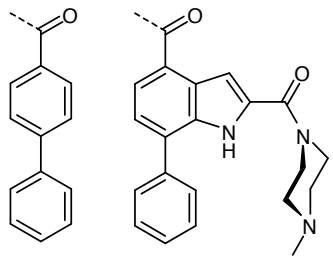
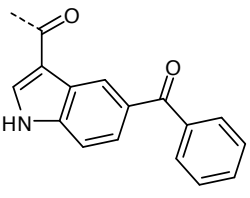


Figure 27: Promising fragments with optimized orientation of H-bond acceptors and hydrophobic regions. The H-bond acceptors are highlighted in red.

A 5-membered heterocyclic ring annealed to a six membered ring was found as optimal spacer in terms of distance and "exiting vector" for the two carbonyls. Hydrophobic interactions were supposed to be formed with the following residues: Pro46, Lys111, Lys112, Lys113 and Tyr48. As linker between the C-6 of the galactose moiety and the new carbonyl a CH_2NH unit was found to be optimal, so that the carbonyl is part of an amide bond. The amide bond implies chemical and biological stability and simplifies the chemical diversification. The stereochemistry at the newly formed stereocenter (C-6) seems to play only a minor role as both epimers showed similar results in the *in-silico* affinity prediction. Due to easier synthetic accessibility the (6*S*)-epimer was chosen as the starting point. For preliminary probing of the hydrophobic pocket a small library of *N*-acylating agents was selected (*table* 4). The preference was set according to calculated dissociation constants, drug-likeness, water solubility (piperazin-, indole moiety) and commercial availability or ease of synthetic access.

Table 4: Calculated pK_D of antagonists with different substituents

compound:	**195**	**193**	**197**	**194**
R:				
calc. pK_D:	5.7	6.0 - 7.3	8.0 - 9.0	7.6 - 8.7

The optimal fit of the substituents onto the hydrophobic patch and the hydrogen-bonding pattern is exemplified in *figure* 28 for compound **197**, which was docked onto the surface of E-selectin by using the QXP force field.

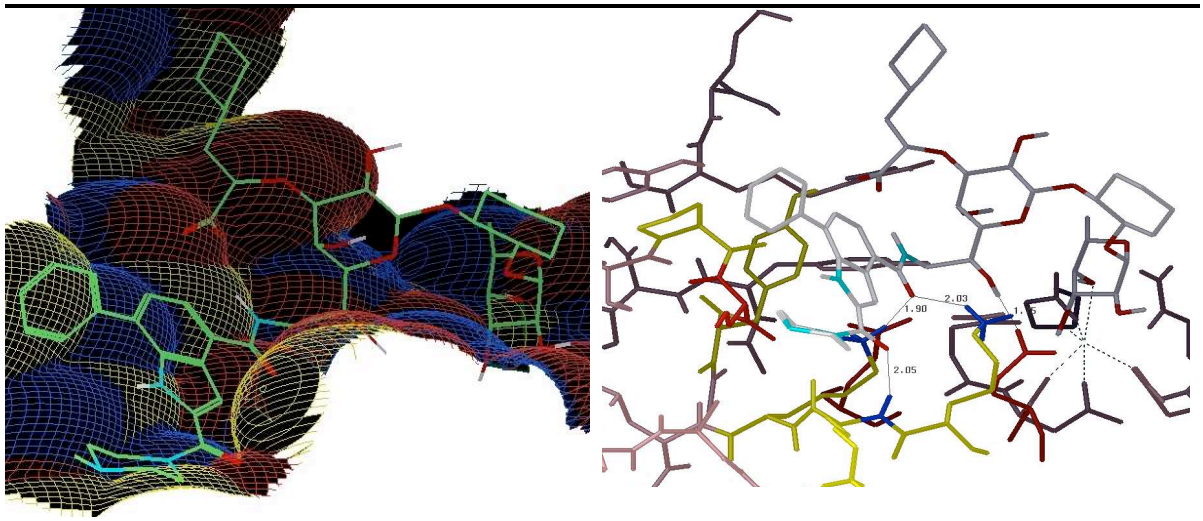
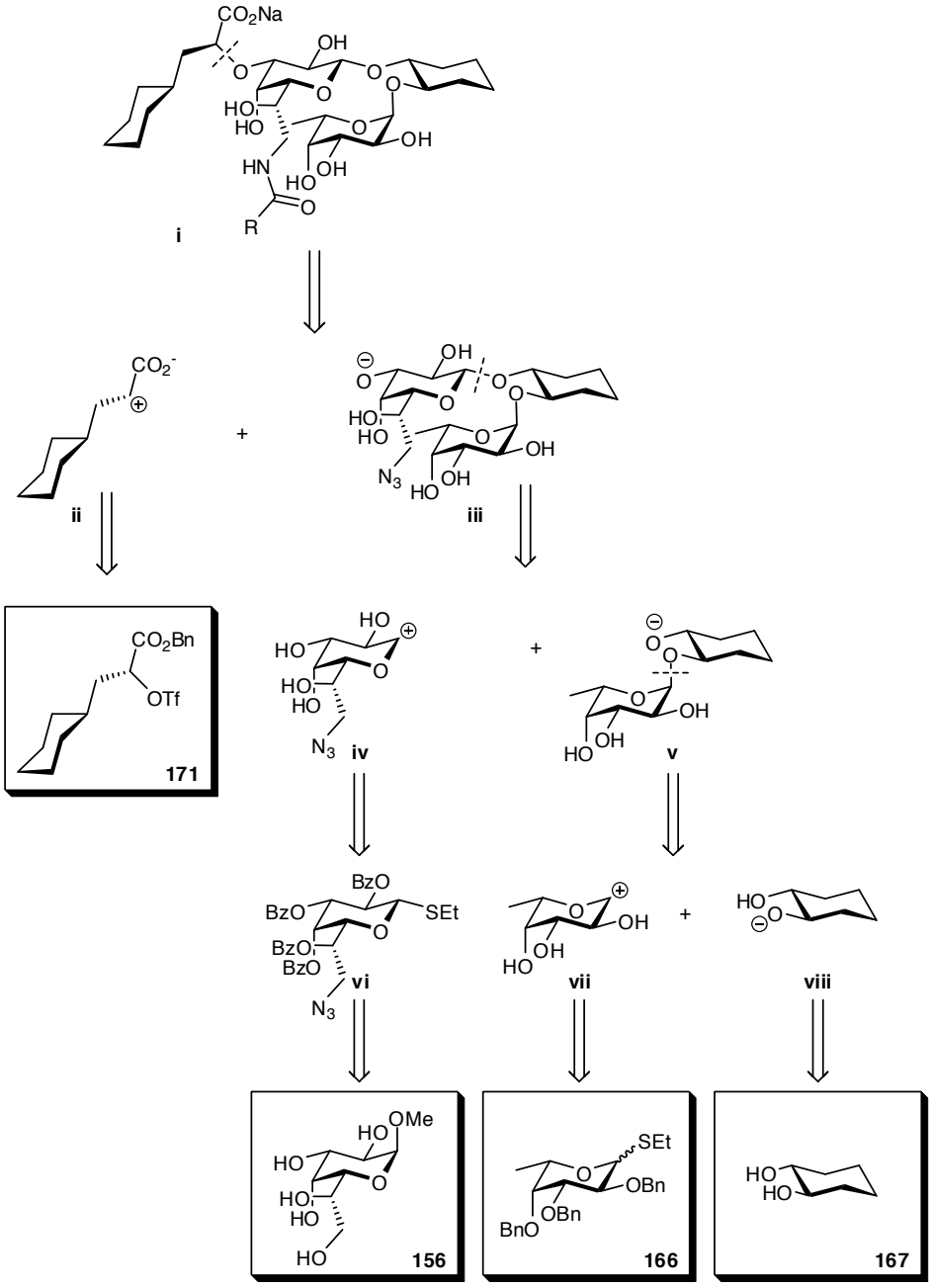


Figure 28: Antagonist **197** docked onto the surface of E-selectin (left side) and H-bond pattern of **197** (right side).

3.1.2. Retro-synthetic considerations

For the synthetic approach to this new class of E-selectin antagonists, a 7-amino-7-deoxy-tetrasaccharide mimetic was chosen as scaffold allowing the subsequent derivatization and diversification by acylation of the primary amine. This tetrasaccharide mimic (**i**) was first dissected into a cyclohexyllactic acid electrophile (**ii**) and a trisaccharide mimic (**iii**). The trisaccharide mimic (**iii**) was further dissected into the known building block (**v**) and the L-*glycero*-β-D-*galacto*-heptopyranoside (**iv**).[335] The former is readily available by α-selective glycosylation from a suitable fucosyl donor (**166**) with non-participating benzyl groups and cyclohexanediol (**167**).[255] For the selective deprotection of the heptopyranoside moiety (**156**) and for the β-selective glycosylation, benzoyl groups were chosen.

From a retro-synthetic point of view, the target molecule can be synthesized from the three partially protected building blocks **156**, **166**, **171** and commercial (1*R*,2*R*)-trans-1,2-cyclohexanediol (**167**), as depicted in *scheme* 5.

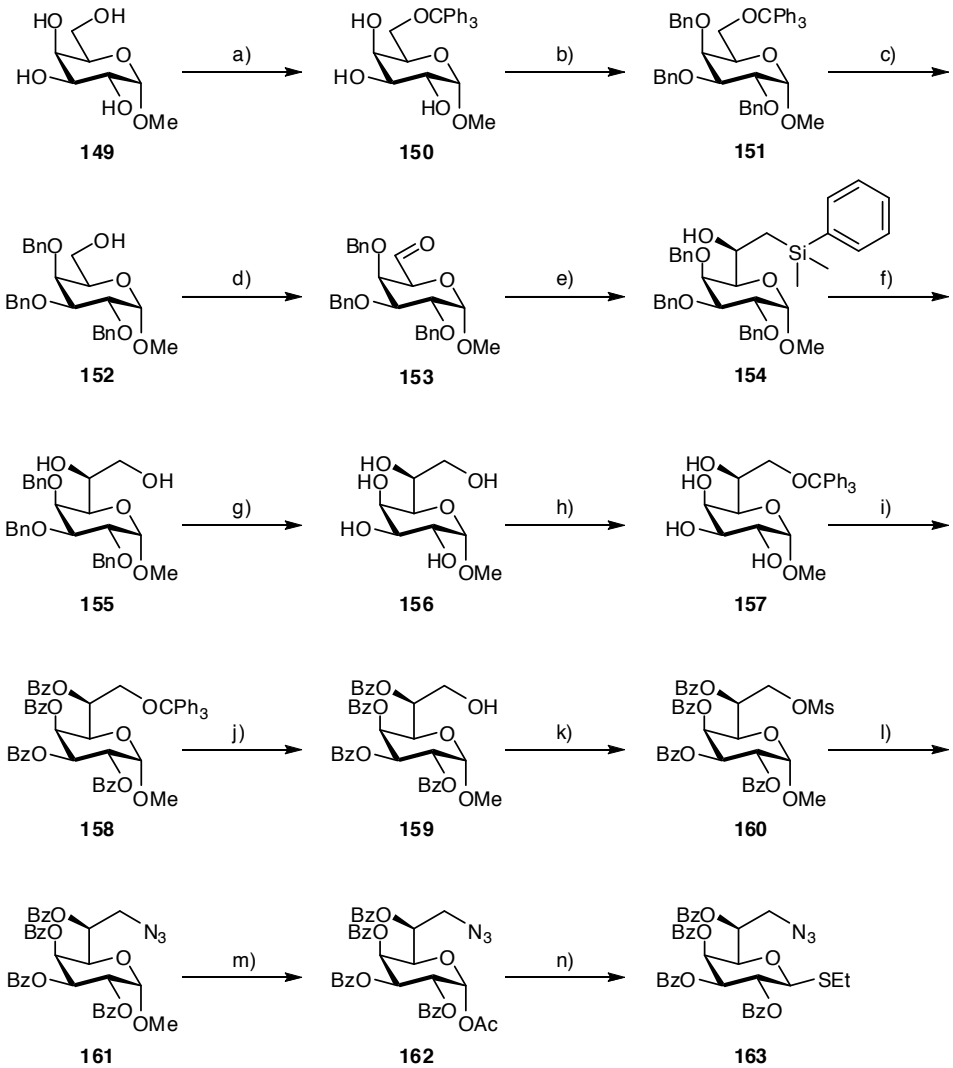


Scheme 5: Retro-synthesis for E-selectin antagonist which contains L-glycero-β-D-galacto-heptopyranose as galactose replacement.

3.1.3. Synthesis of the scaffold

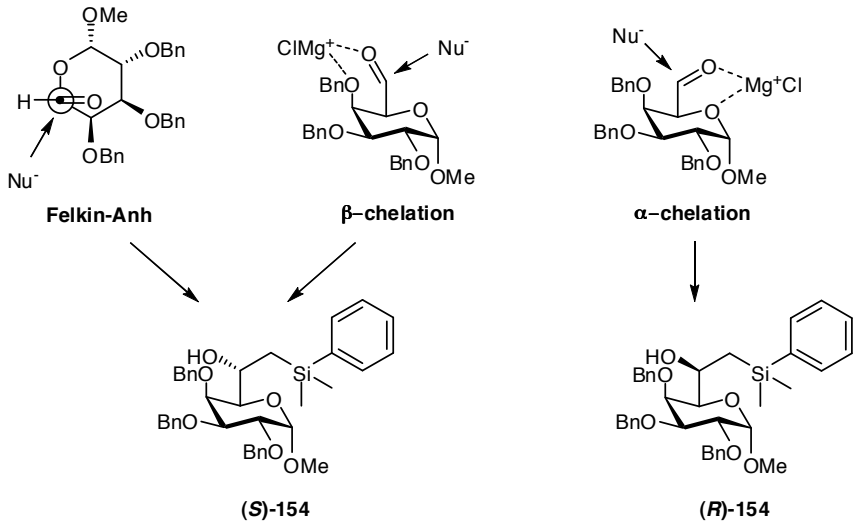
3.1.3.1. Synthesis of ethyl 7-azido-2,3,4,6-tetra-*O*-benzoyl-7-deoxy-1-thio-L-glycero-β-D-galacto-heptopyranoside (163)

The ethyl thioglycoside **163** was chosen as suitable glycosyl donor for the synthesis of the trisaccharide mimic and was easily prepared from commercial methyl galactopyranoside in 14 steps as depicted in *scheme* 6.



Scheme 6: a) Ph_3CCl, cat. DMAP, pyr, r.t., 50 h (85%); b) NaH, BnBr, DMF, 30℃, 19 h (91%); c) i. TES, cat. TMSOTf, CH_2Cl_2, r.t., 4.5 h, ii. 80% aq. AcOH, THF, r.t., 1 h (89%); d) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78℃, 2 h (92%); e) Mg, $(CH_3)_2Si(Ph)CH_2Cl$, THF, -78℃-r.t., 17 h (75%); f) AcOH, AcO_2H, KBr, AcONa, 0℃, 2.5 h (76%); g) Pd/C, 4 bar H_2, EtOH, cat. AcOH, r.t., 19 h (98%); h) Ph_3CCl, cat. DMAP, pyr, r.t., 36 h (79%); i) BzCl, cat. DMAP, pyr, r.t., 22 h (93%); j) i. TES, TMSOTf, CH_2Cl_2, r.t., 1 h, ii. 80% aq. AcOH, THF, r.t., 1 h (94%); k) MsCl, cat. DMAP, Et_3N, CH_2Cl_2, r.t., 26 h (97%); l) NaN_3, DMF, 100℃, 48 h (88%); m) AcOH, Ac_2O, H_2SO_4, r.t., 24 h (92%); n) ZnI_2, TMSSEt, CH_2Cl_2, MS 4Å, µW 50℃, 1.5 h (82%).

For selective protection at the 6-OH, triphenylmethyl was found to be superior to TBDPS, due to its increased selectivity for the 6-OH and its increased stability under the basic conditions of the subsequent benzylation. In case the benzylation was performed with the 6-*O*-TBDPS galactopyranoside, up to 25% of the undesired tetrabenzylated galactopyranoside were formed, whereas benzylation of the 6-*O*-triphenylmethyl galactopyranoside (**150**) gave **151** with a yield up to 91%. Detritylation of **151** was performed with cat. amounts of TMSOTf and in the presence of triethylsilane for quenching the trityl cation. The resulting triethylsilyl derivative of the product was then treated with aqueous acetic acid in THF.[336] Oxidation of the primary alcohol was performed under Swern conditions to yield aldehyde **153** in 92% yield.[337, 338] For the elongation of the hexose, the Grignard reagent of (phenyldimethylsilyl)methyl chloride was used, due to its strong preference for the L-configuration at C-6. It is assumed that for silyl Grignard reagents α-chelation (*scheme* 7) plays the decisive role in the stereoselective attack of the nucleophile. However, the outcome of the reaction also strongly depends on the protecting groups present. For the corresponding aldehyde protected as acetonide, the formation of a mixture of stereoisomers is reported. The reason is a competition of the Felkin-Anh pathway with α-chelation. The benzyl protected aldehyde **153** was in analogy to literature procedures stereoselectively transformed into the (*R*)-isomer of **154** in 75% yield. Initial starting problems of the reaction were easily overcome by using fresh magnesia turnings, fresh magnesia powder or a mixture thereof.[339-341]

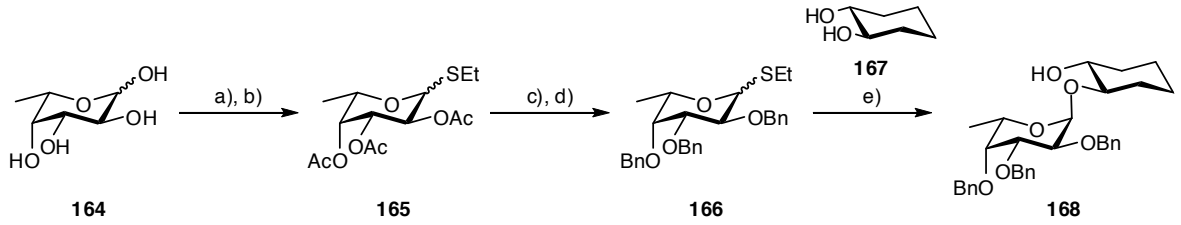


Scheme 7: Effects influencing the stereoselective outcome of carbonyl reactions.

In the following step, the phenyldimethyl silyl group was oxidatively removed in a one-pot procedure by Fleming-Tamao-Oxidation yielding **155**.[342] Since the later β-selective glycosylation requires participating protecting groups, the benzyl groups were removed by hydrogenation to yield methyl L-*glycero*-α-D-*galacto*-heptopyranoside **156**. For the selective activation of the primary alcohol, various literature procedures were investigated using methyl α-D-galactopyranoside as model compound.[343-345] None of the tested conditions showed sufficient selectivity for the primary alcohol. Therefore, the problem of regioselective activation of the 7-position was circumvented by tritylation of the primary alcohol, benzoylation and subsequent detritylation of the heptopyranose (→**159**). The primary alcohol could then easily be activated with mesyl chloride, Et_3N and cat. DMAP. The azide functionality was introduced with sodium azide in DMF, followed by acetolysis to yield **162**.[346] The ethyl thioglycoside **163** was prepared according to a modified procedure of Hanessian *et al*. to give predominantly the β-anomer as indicated by NMR ($J_{1,2}$ = 10.0 Hz).[347, 348]

3.1.3.2. Synthesis of the (1*R*,2*R*)-trans-1,2-cyclohexanediol derivative 168

Synthesis of the ethyl thiofucoside **166** was done by a co-worker according to procedures reported in literature (*scheme* 8).[349] The ethyl thiofucoside was transformed into the α-fucosyl bromide by treatment with bromine in CH_2Cl_2 at 0℃. *In situ* anomerization with TEAB creates the more reactive β-fucosyl bromide which reacts smoothly with (1*R*,2*R*)-trans-1,2-cyclohexanediol (**167**) to yield the α-anomer of **168** in 42% yield as observed by NMR ($J_{1,2}$ = 3.6 Hz).[350, 351]

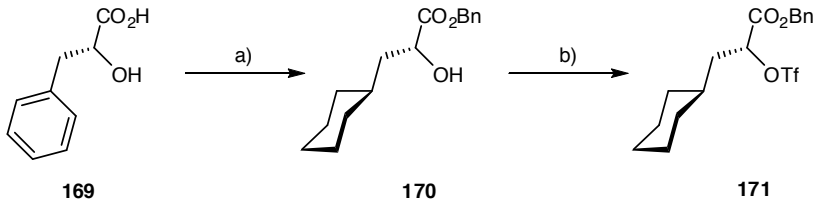


Scheme 8: a) Ac_2O, pyr, 0℃-r.t., 17 h (100%); b) EtSH, $SnCl_4$, DCE, 0℃, 4 h (78%); c) K_2CO_3, aq. MeOH, r.t., 19 h (86%); d) BnBr, NaH, DMF, 0℃-r.t., 16 h (80%); e) i. Br_2, CH_2Cl_2, 0℃, 1 h, ii. TEAB, MS 4Å, DMF, CH_2Cl_2, r.t., 3 h (42%).

3.1.3.3. Synthesis of benzyl (*R*)-3-cyclohexyl-2-trifluoromethanesulfonyloxypropionate (171)

The alkylating agent benzyl (*R*)-3-cyclohexyl-2-(trifluoromethanesulfonyloxy)propionate (**171**) was prepared from commercial (*R*)-phenyllactic acid.[352, 353] Reduction of (*R*)-phenyllactic acid in

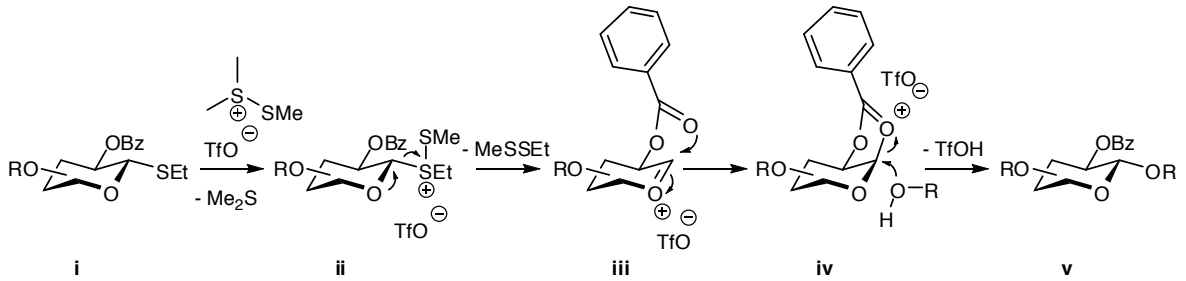
presence of 4 bar of H_2 and rhodium on activated alumina yielded the corresponding (*R*)-cyclohexyllactic acid, which was used for esterification with benzyl bromide without further purification. The leaving group for the later nucleophilic attack was introduced by treating the secondary alcohol in **170** with Tf_2O in presence of a sterically hindered base (*scheme* 9).



Scheme 9: a) i. Rh/Al_2O_3, 4 bar H_2, THF, H_2O, r.t., 4 d ii. aq. Cs_2CO_3, MeOH, H_2O, iii. BnBr, DMF, r.t., 24 h (80%); b) Tf_2O, 2,6-DTBP, CH_2Cl_2, -20°C, 3 h (95%).

3.1.3.4. Completion of the scaffold 175

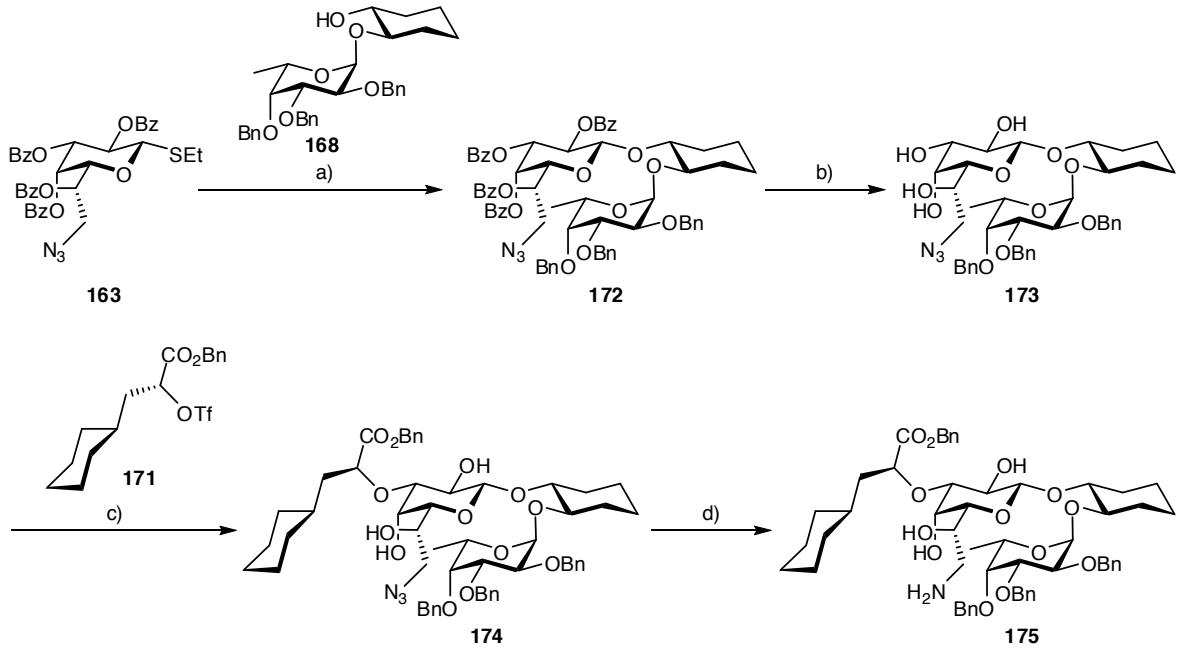
Thioglycosides show a wide variability in their application, can be used under mild reaction conditions and show improved stability compared to glycosyl halides and trichloroacetimidates.[354-356] Their activation by DMTST is initiated by the attachement of the soft electrophile MeS^+ to the sulfur of the donor (**i**) (*scheme* 10).[357, 358] By breaking the anomeric carbon-sulfur bond the oxycarbenium ion (**iii**) is formed, which is then attacked by the acceptor nucleophile to form the *O*-glycoside. One of the most reliable ways to control stereoselectivity in glycosylations is achieved by neighboring group participation. Participating protecting groups like acetates and benzoate stabilize the oxycarbenium ion by forming the cyclic dioxolenium cation (**iv**), which is opened by nucleophilic S_N2 attack. This finally leads to the 1,2-*trans* glycoside (**v**).



Scheme 10: DMTST-promoted β-selective glycosylation with neighboring group participation.

Starting from thioglycoside **163**, the trisaccharide mimetic **172** was obtained by DMTST-promoted glycosylation in 89% yield and high β-selectivity due to the participating benzoate (*scheme* 11).

Deprotection of the trisaccharide **172** was performed under standard Zemplén conditions to afford **173** in 98% yield.[359] In the next step, the 3-position was regioselectively alkylated. Regioselectivity was achieved by forming an *O*-stannylene acetal with dibutyltin oxide in refluxing methanol. In presence of the triflate **171** and CsF as nucleophile to accelerate the reaction, **173** was regioselectively aklylated in 54% yield.[360, 361] Although TLC control indicated that triflate **171** was still present, the alkylation did not go to completion and 29% starting material could be recovered.



Scheme 11: a) DMTST, MS 4Å, CH_2Cl_2, r.t., 67 h (89%); b) NaOMe, MeOH, r.t., 23 h (97%); c) i. Bu_2SnO, MeOH, reflux, 3 h, ii. CsF, DME, r.t., 24 h (54%); d) i. PPh_3, THF, r.t., 24 h, ii. H_2O, r.t., 4h (98%).

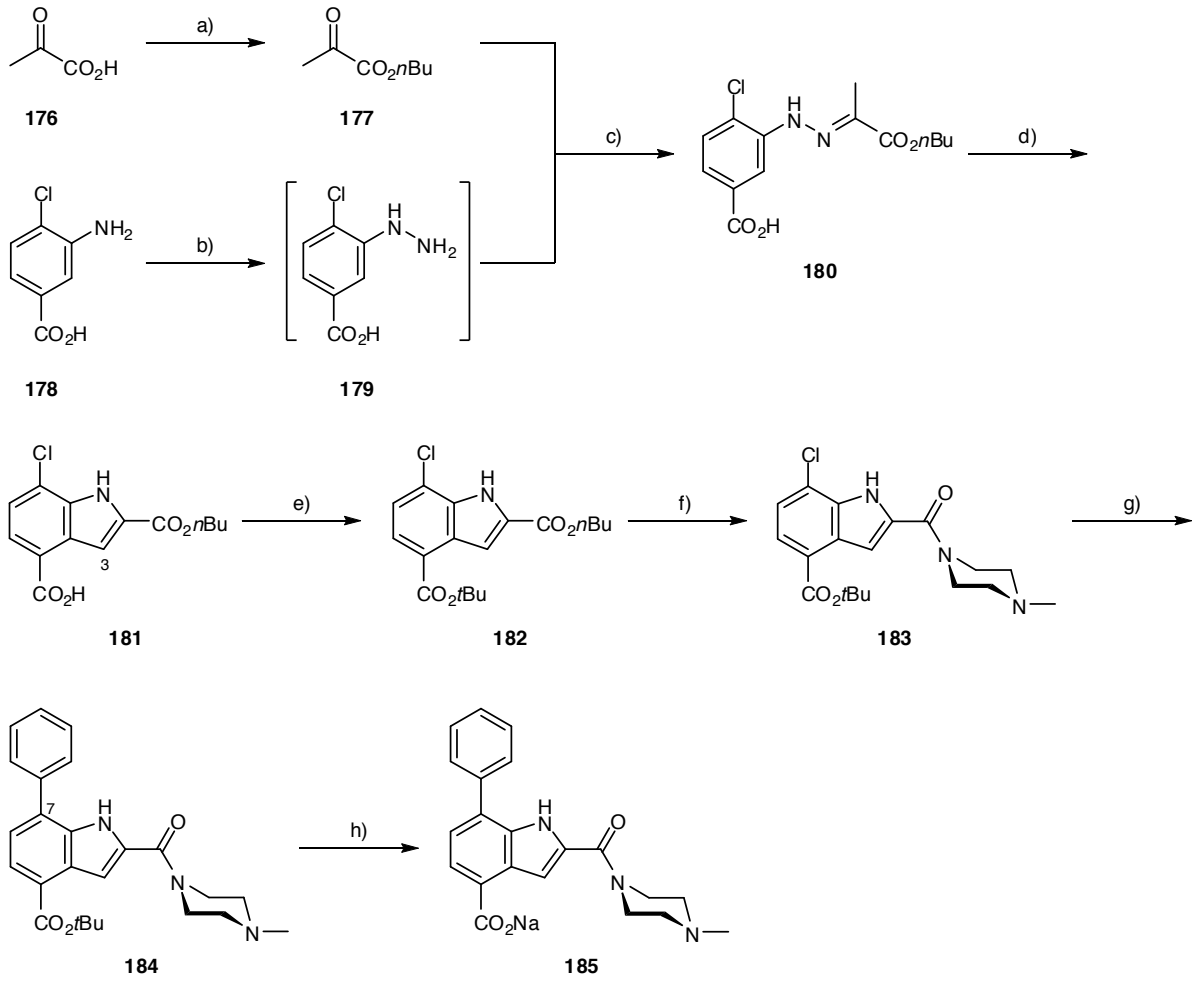
Finally, the azide was reduced to the corresponding amine under Staudinger conditions.[362, 363] It should be noted that longer reaction times led to formation of a lactone between the acid moiety and the 2-position of the heptopyranoside. Prolonged storage in $CDCl_3$ even led to full conversion to the lactone.

3.1.4. Synthesis of indole substituents

3.1.4.1. Synthesis of sodium 2-[(4-methyl-1-piperazinyl)carbonyl]-7-phenyl-indole-4-carboxylate (185)

Among the vast possibilities of building the desired indole scaffold, the Fischer indole synthesis promised the shortest synthetic approach and had the advantage that all starting materials were

commercially available.[364, 365] However, *n*-butyl pyruvate was preferred to the commercial methyl or ethyl pyruvate esters due to the higher lipophilicity of the resulting hydrazone, which facilitates work-up and purification. Esterification of pyruvic acid with *n*-butanol proceeded smoothly without addition of any catalyst by azeotropic removal of water in refluxing benzene.[366] The ketoester **177** was condensed with hydrazine **179**, which is *in situ* generated from 3-amino-4-chlorobenzoic acid, to yield the hydrazone **180** in 86% (*scheme* 12).



Scheme 12: a) *n*BuOH, benzene, reflux, 18 h (79%); b) i. $NaNO_2$, conc. HCl, H_2O, -10°C, 10 min, ii. $SnCl_2$, conc. HCl, -10°C, 30 min; c) *n*-butyl pyruvate, 90°C, 2.5 h (86% over two steps); d) AcOH, $BF_3{\cdot}Et_2O$, µW 90°C, 5 h (16%); e) CDI, THF, *t*BuOH, DBU, reflux, 76 h (54%); f) i. aq. NaOH, acetone, r.t., 69 h, ii. imidazole, $(COCl)_2$, MeCN, 45°C, 1 h, iii. *N*-methylpiperazine, 55°C, 3 h (89%); g) $PhB(OH)_2$, $Pd_2(dba)_3$, S-Phos, Cs_2CO_3, toluene, µW 90°C, 3 h (100%); h) i. TFA, TIS, CH_2Cl_2, H_2O, r.t., 70 min, ii. Na_2CO_3, CH_2Cl_2, MeOH, H_2O, r.t., 15 min (73%).

The first attempts of the Fischer cyclization of **180** were performed with polyphosphoric acid in acetic acid, as described in the literature for similarly substituted hydrazones.[367] However, under these conditions no product could be isolated. Therefore, the cyclization was closer investigated

by testing numerous Lewis or Brønsted acids and solvent systems in small scale reactions, which were analyzed only by TLC. However, under all tested conditions, the cyclization was accompanied by the fast formation of various side products. $BF_3 \cdot Et_2O$ in AcOH under mild microwave irradiation was the final choice not only due to the favorable product/side-product ratio, but also due to the ease of work-up and purification.[365] The low yield of the cyclization (16%) can be explained by the unsubstituted, nucleophilic 3-position of the indole. Under the strongly acidic conditions, the carboxylic acid forms an activated carbocation which is attacked by the nucleophilic 3-position of the indole. This could be the reason for the oligo- and polymerization instead of the formation of the desired product.

For the orthogonal protection of the second carboxylic acid, the *t*-butyl ester was formed by activating the acid with carbonyl diimidazole in presence of *t*-butanol and DBU. Despite the mild conditions, polymerization was observed due to the reasons mentioned above. The *t*-butyl ester was therefore obtained only in low 54% yield. In the next step, the *N*-methylpiperazine moiety was introduced by basic hydrolysis of the *n*-butyl ester and activation with oxalyl diimidazole.[368]

The new C-C bond at the 7 position of the indole **183** was formed by Suzuki-Miyaura coupling. The optimization of the reaction conditions is summarized in *table* 5. The coupling reaction with S-Phos as Pd-ligand succeeded quantitatively manner using Cs_2CO_3 as base and toluene as solvent (entry 5). Reducing the reaction temperature to 90°C turned out to be crucial for the stability of the catalyst.[369-372] Final deprotection of the carboxylic acid was performed according to standard procedures to yield the sodium salt **185** in 73%.

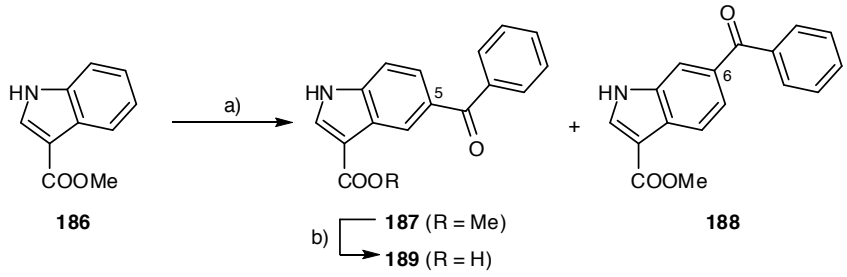
Table 5: Studies on Suzuki-coupling of arylchloride **183** with $Pd_2(dba)_3$ as pre-catalyst and S-Phos as ligand

Entry	$PhB(OH)_2$[a)]	Solvent	Base[b)]	Temp	Time	Yield[c)]
1	1.2 eq.	THF	K_3PO_4	µW, 100°C	20 h	12.5% (66%)[d)]
2	1.2 eq.	THF	Cs_2CO_3	µW, 120°C	3 h	0% (96%)[d), e)]
3	1.5 eq.	THF/H_2O	K_3PO_4	80°C	3 h	[f), g)]
4	1.5 eq.	Toluene	Ag_2CO_3	µW, 90°C	6 h	[h), i)]
5	1.5 eq.	Toluene	Cs_2CO_3	µW, 90°C	3 h	100%[h)]

a) equivalent to aryl chloride; b) 3 equivalents were used; c) isolated yield, number in brackets represents recovered starting material; d) 1 mol% $Pd_2(dba)_3$ and 3 mol% S-Phos were used; e) Pd-black formation observed; f) 3 mol% $Pd_2(dba)_3$ and 3 mol% S-Phos were used; g) no isolated yield, TLC-monitoring showed deactivation of catalyst before full conversion; h) 1 mol% $Pd_2(dba)_3$ and 5 mol% S-Phos were used; i) no isolated yield, decomposition of Ag_2CO_3 before full conversion.

3.1.4.2. Synthesis of 5-benzoyl-indole-3-carboxylic acid (189)

Friedel-Crafts acylation of indole-3-carboxylic acid was achieved in presence of benzoyl chloride and $AlCl_3$ as catalyst. As expected from the electron distribution in the indole ring-system, acylation occurred predominantly at C-5 (71%). The C-6 acylation product was only formed in minor amounts (27%) and from the acylation product at C-7, only traces were detectable.[373, 374] Saponification of **187**, followed by acidification yielded the 5-benzoyl-indole-3-carboxylic acid (**189**) in quantitative yield (*scheme* 13).

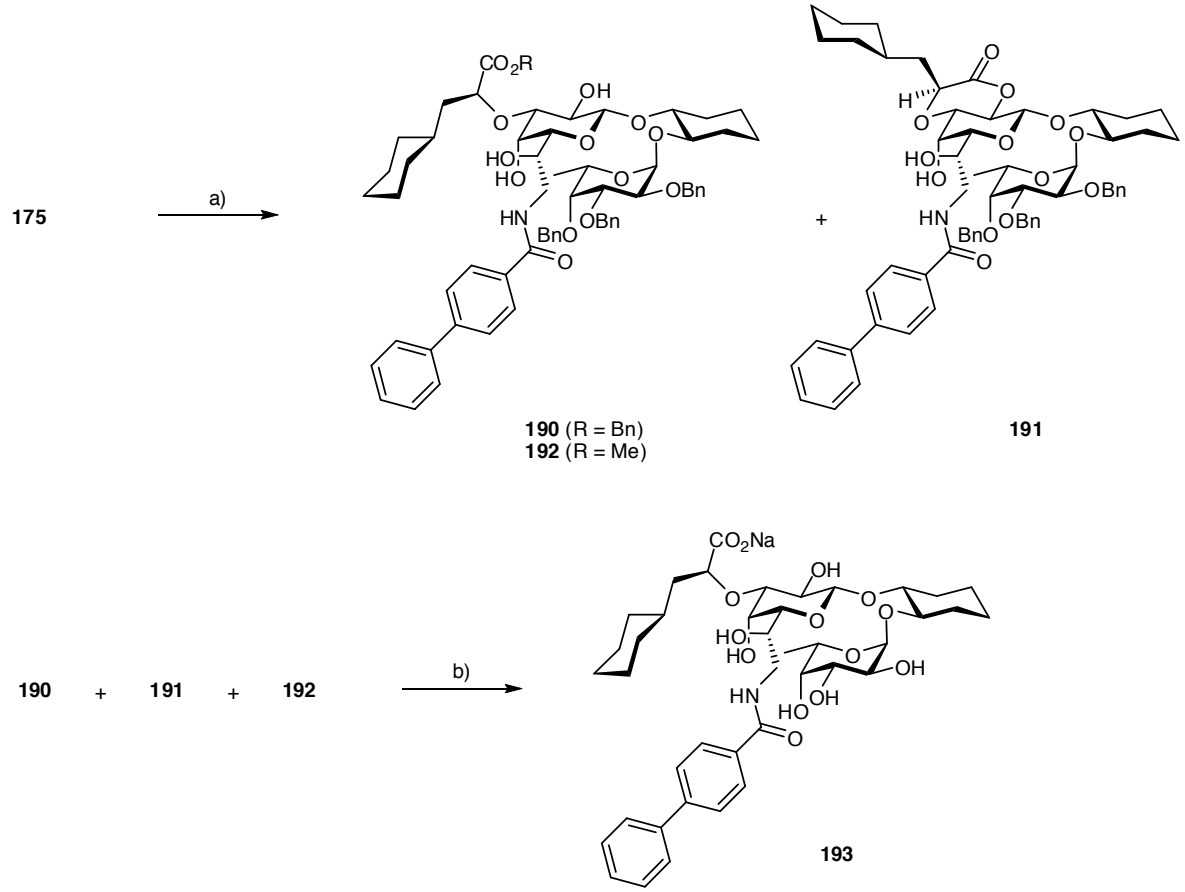


Scheme 13: a) BzCl, $AlCl_3$, $MeNO_2$, r.t., 2.5 h (**187**: 71%, **188**: 27%); b) MeCN, aq. NaOH, r.t., 10 days (100%).

3.1.5. Synthesis of the acyl-antagonists

3.1.5.1. Synthesis of the 4-phenylbenzoyl antagonist (193)

Acylation of a primary amino group in presence of secondary alcohols usually proceeds selectively due to the stronger *N*-nucleophilicity. Therefore, the amine **175** was reacted with excess of biphenyl-4-carbonyl chloride and triethyl amine as base without prior protection of the hydroxyls. TLC showed fast consumption of the starting material and formation of two main products. The more lipophilic one was identified as the desired product **190**, whereas the second product was identified as lactone **191**. During work-up, lactone **191** was partly opened by methanol leading to an inseperable mixture of lactone **191** and methylester **192**. For the subsequent deprotection, a mixture of **190**, **191** and **192** was subjected to hydrogenation and saponification with sodium hydroxide to give the final E-selectin antagonist **193** in 38% yield over two steps (*scheme* 14).

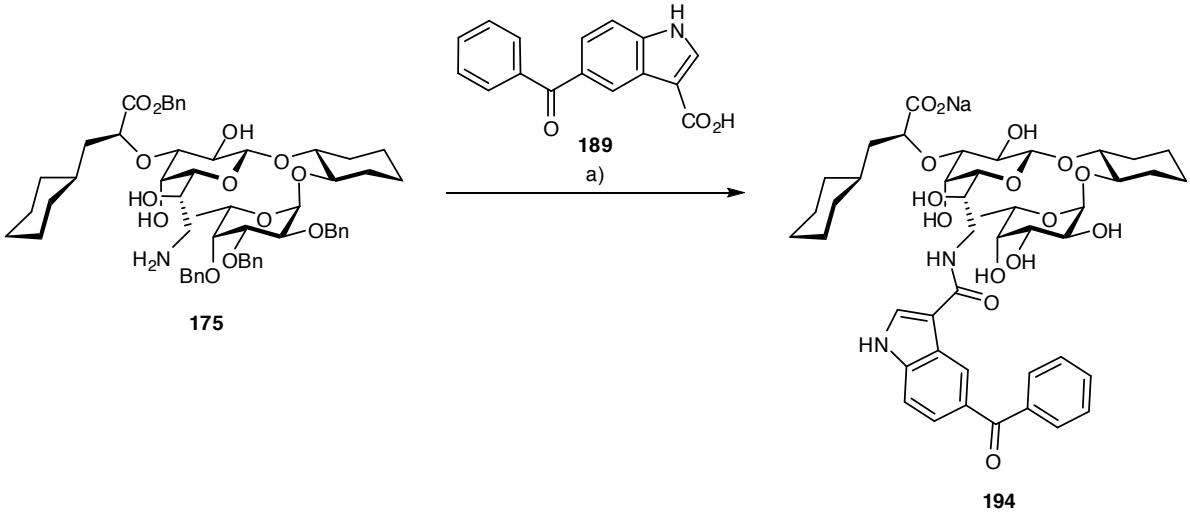


Scheme 14: a) biphenyl-4-carbonyl chloride, Et_3N, CH_2Cl_2, MeCN, r.t., 30 min (**190**: 31%); b) i. Pd/C, H_2, dioxane, H_2O, r.t., 40 h, ii. aq. NaOH, MeOH, r.t., 50 min (38% over two steps).

3.1.5.2. Synthesis of the 5-benzoyl-indole-3-carboxyl antagonist (194)

For the coupling of non-activated carboxylic acids to the amine **175** various coupling reagents were tested in small-scale, starting from indole-3-carboxylic acid and methyl 6-amino-2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-galactopyranoside as a testing model. PyBoP® showed superior results compared to other coupling reagents (*e.g.* EDC, DCC, HBTU) by means of conversion rate, side-product formation and ease of purification of the reaction mixture.[375] However, applying these conditions to amine **175** and indole **189** resulted in incomplete reaction and the product's isolation from the remaining amine and tris-(1-pyrrolidinyl)-phosphine oxide could not be achieved. In order to avoid the separation problem, the use of a polymer-bound coupling reagent with similar or higher efficiency was considered. The monomeric reagents PyBroP® and PyCloP® were reported to be superior reagents to PyBoP® in coupling reaction with sterically hindered amino acids.[376] However, these reagents are not yet commercially available in a polymer-bound form. Hence, a combination of polymer-bound PPh_3 and CCl_4 was considered to show similar efficiency than PyCloP®, but easier separation by simply filtering off the resin.[377] Indeed, the use

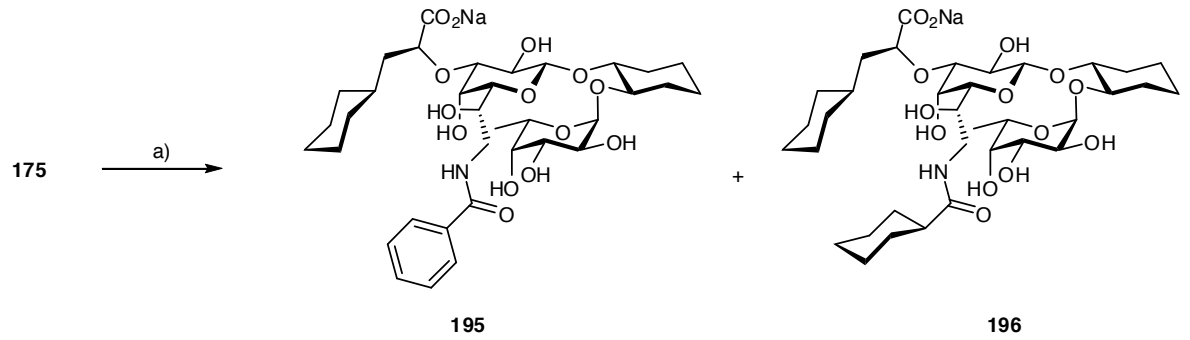
of this system showed clean and full conversion of the amine to a mixture of the corresponding derivatized benzylester and 2-*O*-lactone. After preliminary purification, the mixture was subjected to hydrogenation and saponification with sodium hydroxide to give the final E-selectin antagonist **194** in 27% yield over three steps (*scheme* 15).



Scheme 15: a) i. PPh_3-polymer, NMM, CCl_4, CH_2Cl_2, reflux, 5.5 h, ii. Pd/C, H_2, dioxane, H_2O, r.t., 4 d, iii. aq. NaOH, MeOH, r.t., 4 h (27%).

3.1.5.3. Synthesis of the benzoyl antagonist (195)

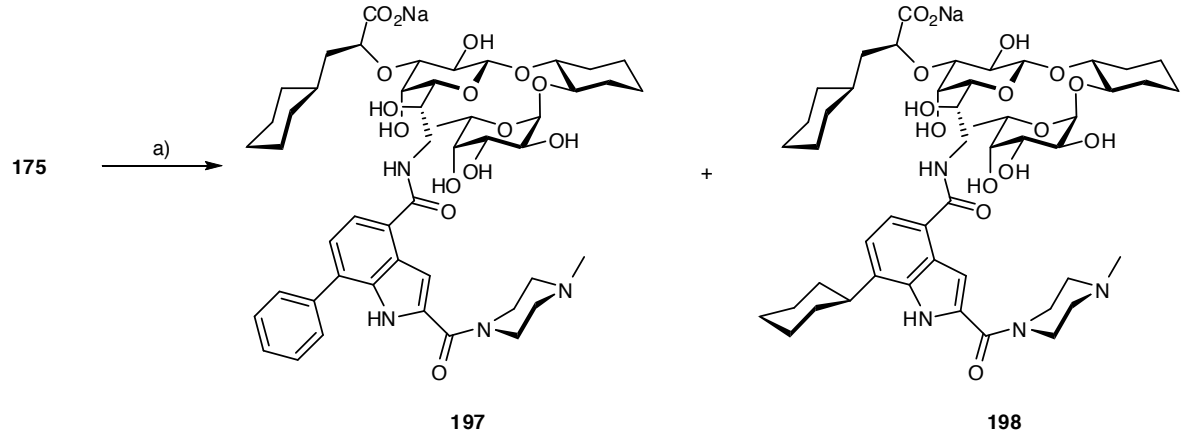
Benzoylation of the amine **175** was performed with benzoic acid in presence of PPh_3/CCl_4 instead of benzoyl chloride in order to avoid the use of an excess of the acylating agent. Hydrogenation of the resulting lactone/benzylester mixture led to partial ring hydrogenation of the benzoyl moiety. Saponification yielded a 2:1 mixture (36%) of the benzoylated (**195**) and cyclohexanecarboxylated (**196**) E-selectine antagonists, which were not separable on LC-MS (*scheme* 16).



Scheme 16: a) i. BzOH, PPh_3-polymer, NMM, CCl_4, CH_2Cl_2, reflux, 4 h, ii. $Pd(OH)_2/C$, H_2, dioxane, H_2O, r.t., 6 d, iii. aq. NaOH, MeOH, r.t., 3 h (**195**:**196** = 2:1, 36%).

3.1.5.4. Synthesis of the 2-[(4-methyl-1-piperazinyl)carbonyl]-7-phenyl-indole-4-carboxyl antagonist (197)

Acylation of **175** with **185** was again carried out in presence of PPh_3 and CCl_4. Subsequent deprotection and saponification resulted in a 7:3 mixture of **197** and **198** (29%) due to partial hydrogenation of the biphenyl moiety (*scheme* 17). For analytical investigations **197** was isolated from the mixture by preparative LC-MS.



Scheme 17: a) i. **185**, PPh_3-polymer, NMM, CCl_4, CH_2Cl_2, reflux, 3.25 h, ii. Pd/C, H_2, dioxane, H_2O, r.t., 9 d, iii. aq. NaOH, MeOH, r.t., 6 h (**197**:**198** = 7:3, 29%).

3.1.6. Biological evaluation of E-selectin antagonists containing substituted L-*glycero*-β-D-*galacto*-hepto-pyranoses as replacement for galactose

(in collaboration with Dr. John L. Magnani, Glycomimetics Inc., Rockville, USA)

The synthesized antagonists containing the L-*glycero*-β-D-*galacto*-hepto-pyranose moiety were analyzed in a static cell free ligand binding assay that measures E-selectin inhibition under equilibrium conditions.[378, 379] All of the synthesized antagonists were found to be inactive (rIC_{50} > 10mM). The reason for this is not clear. Most probably the inactivity is caused by either an inappropriate linker, insufficient binding of the fragments or interference with the bioactive conformation. However, NMR analysis gave no clear evidence about interference with the bioactive conformation, which should result in a shift of the relevant protons (*figure* 29) or carbons. The suitability of the linker is more difficult to judge. To address this question, the biological equality of the two epimers at the 6-position should be confirmed by also synthesizing the (*R*)-epimer *e.g.* under Mitsunobu conditions. Besides, the rotatable bonds of the linker moiety result in an entropic penalty for the antagonists, which may abolish any enthalpic gain. For elucidating the binding properties of the fragments, they could be tested for their

independent binding to E-selectin in a second binding site screening with a TEMPO labelled E-selectin antagonist.[380]

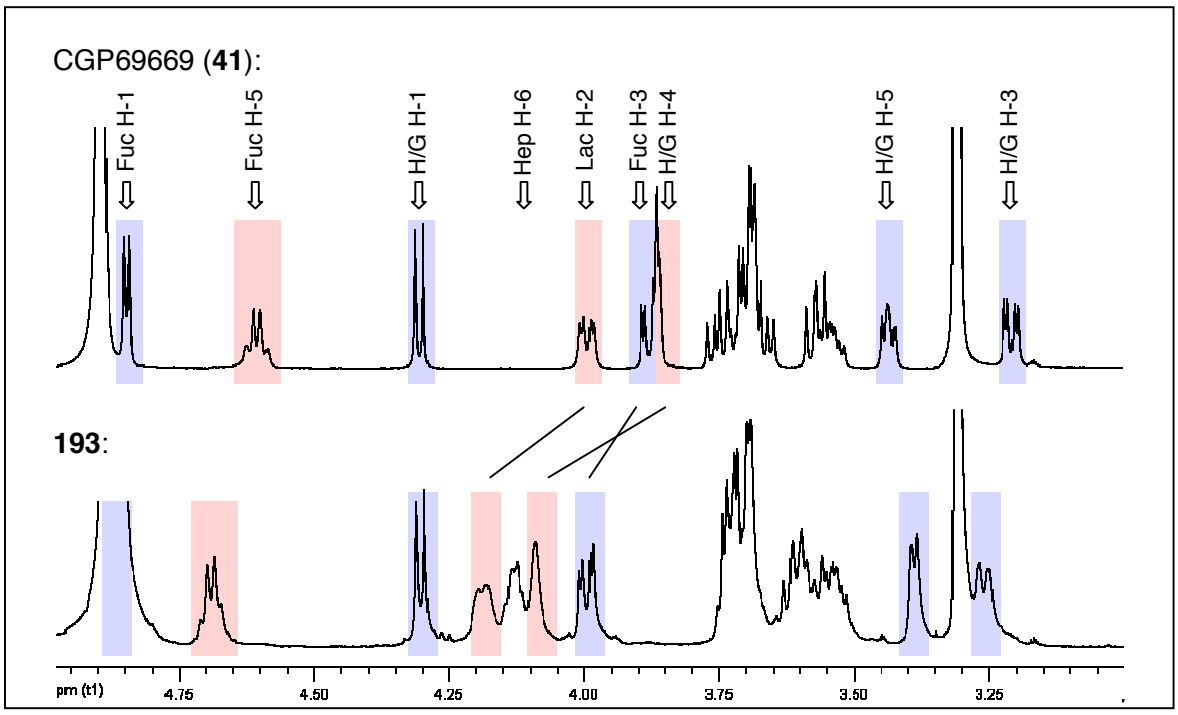
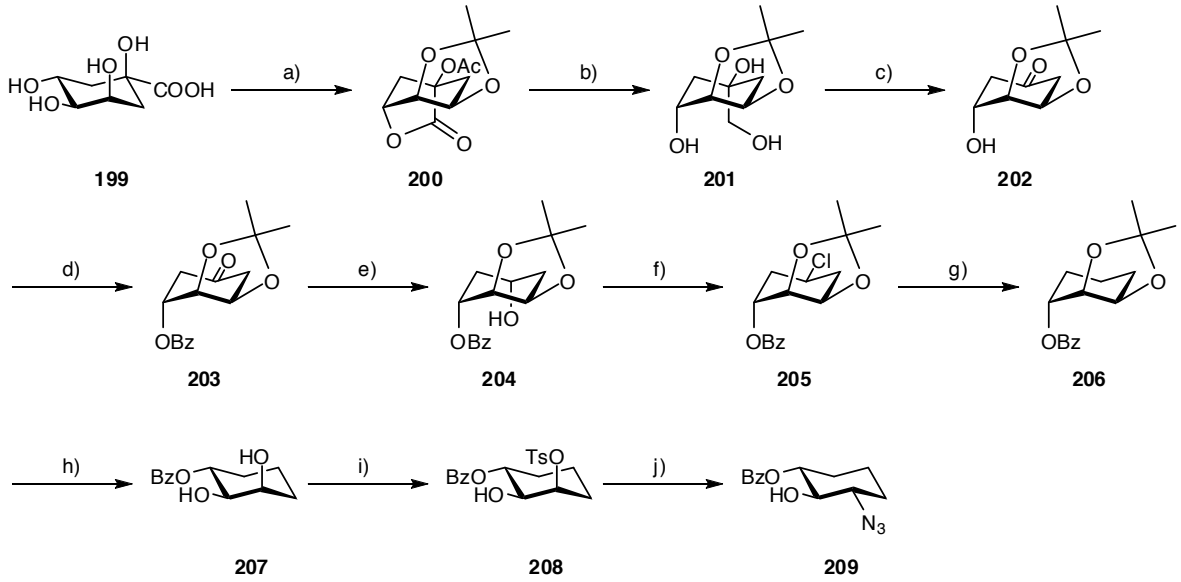


Figure 29: Superposition of ^{1}H-NMRs of CGP69669 (**41**) and **193**.

3.2. Design and synthesis of Glc*N*Ac mimetics for E-selectin antagonists (optimization of entropy)

3.2.1. Optimization of the synthesis of (1*R*,2*R*,3*S*)-3-azidocyclohexane-1,2-diols as Glc*N*Ac mimetics

Several highly active E-selectin antagonists containing (1*R*,2*R*,3*S*)-3-aminocyclohexane-1,2-diols as replacement for Glc*N*Ac have been synthesized in our group.[272] As key precursor in the synthesis of these ligands (1*R*,2*R*,3*S*)-3-azido-2-hydroxycyclohexyl benzoate was used, which was obtained from the natural product D-(-)-quinic acid (*scheme* 18).



Scheme 18: a) i. *p*-TsOH, 2,2-dimethoxypropane, acetone, reflux, 5 h, ii. Ac_2O, DMAP, pyr, r.t., 20 h (82%); b) $LiAlH_4$, Et_2O, 0°C-r.t., 24 h (81%); c) phosphate buffer pH 7, $NaIO_4$, 0°C-r.t., 0.5 h (68%); d) BzCl, DMAP, pyr, CH_2Cl_2, r.t., 18 h (93%); e) $NaBH_4$, MeOH, 0°C, 0.5 h (91%); f) 1-chloro-*N*,*N*,2-trimethylpropenylamine, $CHCl_3$, reflux, 0.5 h (92%); g) Bu_3SnH, AIBN, toluene, 90°C, 1.5 h (72%); h) 80% aq. AcOH, 80°C, 0.5 h (80%); i) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, r.t., 18 h (68%); j) NaN_3, DMF, 80°C, 1 h (81%).

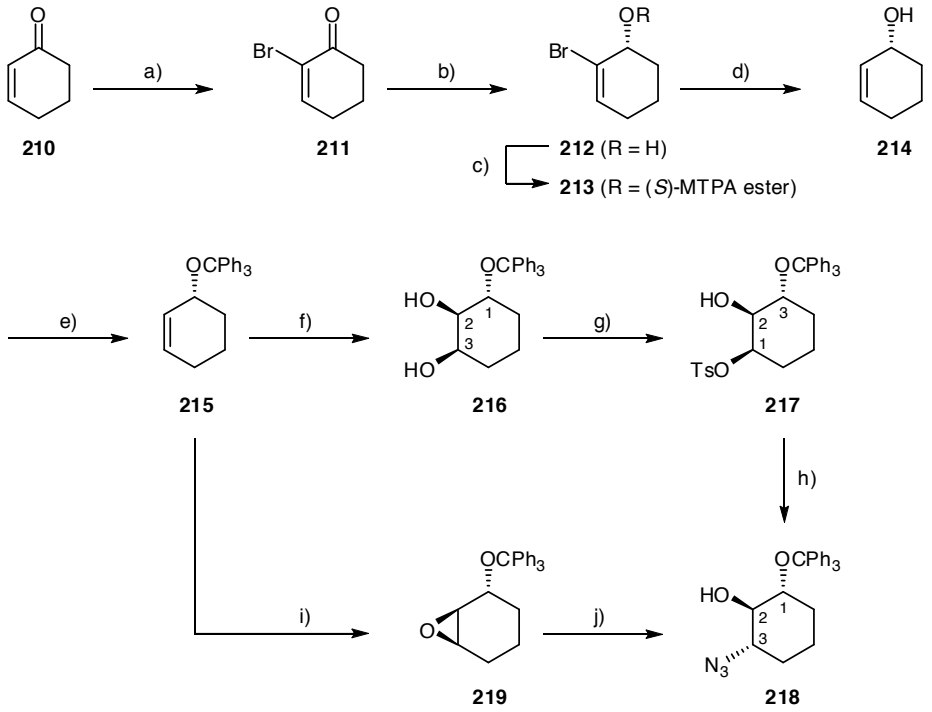
Although the synthesis proceeds smoothly and the desired product is obtained stereoselectively, benefiting from preset stereocenters of the natural product, the synthesis was not to our entire satisfaction in terms of number of steps and overall yield (11%). Retrosynthetic consideration revealed (*R*)-cyclohex-2-en-1-ol (**214**) as key intermediate, which would allow the regio- and stereoselective introduction of the remaining functionalities.

3.2.1.1. Synthesis of (1*R*,2*R*,3*S*)-3-azido-1-*O*-triphenylmethyl-cyclohexane-1,2-diol as Glc*N*Ac mimetic (218)

Numerous preparative methods have been reported over the last decades for the synthesis of enantiopure (*R*)-cyclohex-2-en-1-ol.[381-386]

In a first approach, a direct enantioselective reduction of cyclohex-2-en-1-on to (*R*)-cyclohex-2-en-1-ol (**214**) with chirally modified $LiAlH_4$ was applied.[384] The reducing agent with the hypothetical formula $LiAlH(NEtPy)_2(OCH(Ph)CH(Me)NMe_2)$ was formed by treating $LiAlH_4$ with 2-(ethylamino)pyridine and (1*R*,2*S*)-(-)-*N*-methylephedrine as carrier of the stereochemical information. However, the low chemical and optical yields (55%, 23% ee) obtained by this method, made a change of strategy necessary to a less direct approach.

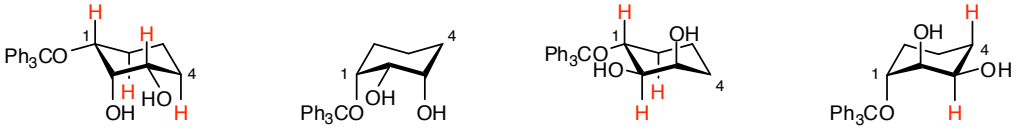
Introducing a bromide in α-position to the ketone as sterically demanding group followed by an asymmetric Corey-Bakshi-Shibata (CBS) reduction of the bromoketenone, published first by Corey *et al.*,[386] was considered as most promising indirect approach (*scheme* 19).



Scheme 19: a) i. 2-cyclohexenone, Br_2, CH_2Cl_2, 0°C, 2.5 h, ii. Et_3N, CH_2Cl_2, r.t., 2 h (62%); b) (*S*)-α,α-diphenylprolinol, $B(OMe)_3$, BH_3·*N*,*N*-diethylaniline, THF, -10°C-0°C, 3.75 h (93%, 96% e e); c) (1*R*)-(-)-MTPA-Cl, DMAP, pyr, r.t., 60 h (100%); d) i. *t*-BuLi, Et_2O, -78°C to -20°C, 4.75 h, ii. aq. $NaHCO_3$, -20°C-r.t., 1 h (85%); e) Ph_3CCl, CH_2Cl_2, DBU, r.t., 45 h (71%); f) NMO, OsO_4, acetone, H_2O, r.t., 19 h (87%); g) TsCl, *n*-Bu_2SnO, Et_3N, CH_2Cl_2, r.t., 19 h (92%); h) DMF, NaN_3, 65°C, 50 h (88%); i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0°C-r.t., 5 h (72%); j) CsF, NaN_3, 15-crown-5, DMF, 65°C, 48 h then 100°C, 43 h (87%).

Bromoketenone **211** was obtained by bromination of commercial cyclohexenone.[387] The CBS-reduction was performed with two different catalytic systems, in order to investigate the enantio-selectivity of the reaction. The original procedure published by Corey *et al.*[388-390] yielded alcohol **212** with 89-90% ee, whereas the improved method recently published by Blechert *et al.*[391] gave 93% of **212** with an enantiomeric excess of 96%. Both enantiomeric excesses were determined by optical rotation and by calculations based on the ^{13}C-satellites of the methyl signal of the (*S*)-mosher ester **213**. After halogen-metal exchange with *tert*-BuLi and subsequent hydrolysis, the secondary alcohol **(*R*)-214** was tritylated to give tritylether **215** in 71% yield. The triphenylmethyl group was found to be a suitable protection for various reasons: (i) sterical control of the later dihydroxylation, epoxidation or tosylation, (ii) ease of cleavage under almost neutral conditions and (iii) increase of boiling point.[392, 393]

For the regio- and stereoselective introduction of the hydroxyl-group at C-2 and the azide at C-3 two synthetic pathways were envisaged. The first pathway leads over dihydroxylation of the double bond, regioselective conversion of 3-OH into a leaving group and its substitution with azide by a S_N2 mechanism. The dihydroxylation was carried out under standard Upjohn conditions.[394] The diastereomeric outcome was examined by ^{1}H-NMR. The sharp peaks of H-1 (4.04 ppm) and H-2 (3.49 ppm) and the slightly broader multiplet of H-3 suggest a distorted $^4C_1$ conformation of *anti*-**216** (*figure* 30), but the $^4C_1$ conformation of *syn*-**216** could not be clearly excluded. However, according to the well studied reaction mechanism, the *anti* product should preferably be formed because of the sterically demanding trityl group.[395] The $^1C_4$ conformations of *syn*-**216** and *anti*-**216** could be clearly excluded due to the observed coupling constants.



syn-**216** $^1C_4$-configuration | *syn*-**216** $^4C_1$-configuration | *anti*-**216** $^1C_4$-configuration | *anti*-**216** $^4C_1$-configuration

Figure 30: Possible configurations of *syn*- and *anti*-**216**. Relevant protons showing axial-axial coupling are highlighted in red.

The *cis*-diol was selectively monotosylated in presence of dibutyltin oxide to afford **217** in 92% yield.[345, 396] The downfield shift of the H-1 (4.80 ppm, former H-3) of **217** compared to H-3 (3.58 ppm) of **216** confirmed the correct regioselectivity. The large coupling constant between H-1 (former H-3) and H-6$_{ax}$ suggests a $^4C_1$ chair conformation with an axial trityloxy group. Nucleophilic displacement of the tosylate with sodium azide gave **218** in 88% yield. The coupling

constants observed in the ^{1}H-NMR indicate axial positions for H-1, H-2 and H-3, which confirms the expected $^1C_4$ chair conformation for **218**.

In a second approach, **218** was obtained by *anti*-epoxidation of the cycloalkene, followed by a regioselective, nucleophilic attack of an azide ion. Epoxidation with *m*-CPBA yielded epoxide **219** in an *anti*:*syn* ratio of 76:24 and a yield of 72% for the *anti*-epoxide. The *anti* preference is the consequence of a directive effect of the sterically demanding triphenylmethyl group, as reported earlier for the TBDMS protected cyclohex-2-enol.[392, 393] For the opening of epoxide **219** by an azide ion several conditions were tested (*table* 6). Although, the successful formation of the product could be observed (entries 1 and 3), the tedious separation from the remaining starting material made the reaction impracticable. Finally, addition of cesium fluoride and 15-crown-5 resulted in complete conversion under elevated temperature to afford **218** in 87% yield.[397, 398] Analytical data confirmed the identical regio- and stereochemical properties compared to **218** obtained *via* dihydroxylation.

Table 6: Studies on the nucleophilic attack on *anti*-epoxide **219**

Entry	Solvent	Additives	Temperature	Time	Yield [a)]
1	MeOH	NH_4Cl	50°C	32.75 h	43% [b), c)]
2	THF	15-crown-5	60°C	6 ½ d	0% [d)]
3	DMF	CsF	65-100°C	11 d	[e)]
4	DMF	15-crown-5, CsF	65-100°C	91 h	87% [f)]

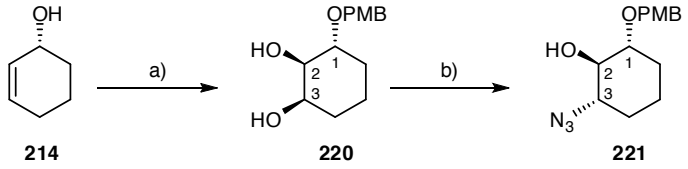
a) isolated yield; b) in addition 39% of an inseparable epoxide/product mixture (1:2.2) was recovered; c) TLC-monitoring showed partial detritylation; d) TLC-monitoring showed decomposition; e) no isolated yield, but TLC-monitoring showed almost full conversion; f) TLC-monitoring showed full conversion.

In conclusion, the desired Glc*N*Ac mimic **218** was regio- and stereoselectively synthesized in 6 and 7 steps, respectively, with an overall yield of 22-25% from inexpensive cyclohex-2-enon. Compared to the original synthesis with 11 synthetic steps and an overall yield of 11%, a clear improvement was achieved. In addition, it could be shown that the new synthesis can easily be performed on a multigram-scale.

3.2.1.2. Synthesis of (1*R*,2*R*,3*S*)-3-azido-1-*O*-(4-methoxybenzyl)-cyclohexane-1,2-diol (221) as Glc*N*Ac mimetic

For certain reactions it would be desirable to have a Glc*N*Ac mimic protected with a sterically less demanding protecting group than triphenylmethyl. Therefore, the feasibility of a *p*-methoxybenzyl (PMB)-protected Glc*N*Ac mimic was tested. *p*-Methoxybenzyl was chosen due to its adequate stability under glycosylation conditions and to the numerous cleavage procedures, which are orthogonal to various protecting groups applied in carbohydrate chemistry. The epoxidiation of the PMB-protected allylalcohol was expected to give a low *anti*/*syn* ratio due to the low sterical influence of the PMB-protecting group. Therefore, the previously explored dihydroxylation pathway (chapter 3.2.1.1.) was applied.[393]

Alkylation of **214** with PMB chloride was carried out under standard conditions, yielding the PMB-ether polluted with traces of an inseparable side-product. However, after the subsequent dihydroxylation the pure *anti*-**220** could be easily isolated in a yield of 48% over two steps. Considering the long coupling constants of H-1 ($^3J_{1,2}$ = 8.9 Hz, $^3J_{1,6ax}$ = 10.4 Hz), a $^1C_4$ conformation can be assumed, which is in contrast to the triphenylmethyl protected compound **216**. The *cis*-diol was converted into the monotosylate by treatment with tosyl chloride in presence of Et_3N and *n*-Bu_2SnO. The monotosylate was obtained as an inseparable mixture of 3-Ts-**220** and 2-Ts-**220** (9:1). The lower regioselectivity can be explained by a decrease in sterical restriction at the 2-position compared to **216** and by the increased reactivity of the 2-hydroxyl, which is now in equatorial position, compared to the axial 2-hydroxyl of **216**. The mixture of tosylates was transformed into the corresponding azides, which could be smoothly separated to yield the desired PMB protected Glc*N*Ac mimic **221** in an overall yield of 19% from cyclohexenone (*scheme* 20).



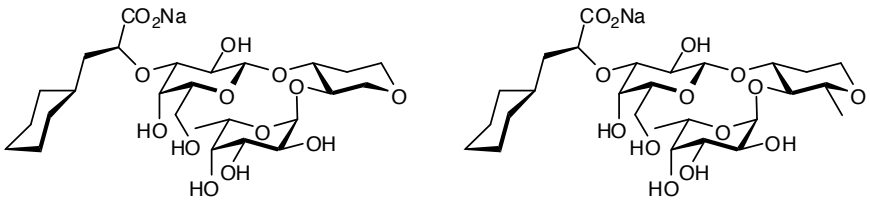
Scheme 20: a) i. NaH, TBAB, THF, PMBCl, r.t., 7 h, ii. NMO, OsO_4, acetone, H_2O, r.t., 47 h (48% over two steps); b) i. TsCl, *n*-Bu_2SnO, Et_3N, CH_2Cl_2, r.t., 15.5 h, ii. DMF, NaN_3, 65°C, 72 h (82% over two steps).

3.2.2. Synthesis of E-selectin antagonists with novel alkylated Glc*N*Ac mimics

3.2.2.1. Synthesis of E-selectin antagonists with (1*R*,2*R*,3*S*)-3-alkyl-cyclohexane-1,2-diols as Glc*N*Ac mimics

In the past decade, numerous sLe^x analogues and related compounds were synthesized by various groups.[221] Within the class of sLe^x analogues, the *N*-acetylglucosamine moiety is commonly replaced by xylal- or glucal-derived structures[269, 270] or by (*R*,*R*)-cyclohexane-1,2-diol.[255]

Earlier synthetic studies revealed that in sLe^x analogues the 2-position of the former *N*-acetylglucosamine moiety is crucial for the pre-organization of the Le^x core. The glucal-derived antagonist **55** was reported to be five-fold more potent than its xylal-derived counterpart **50** (*figure* 31).[269] This increase in activity is probably due to the steric compression exercised by the equatorial methyl group, which leads to the pre-organization of the core structure in the biologically active conformation. In addition it was shown, that carbocyles show better binding properties than pyrans. Hence, an *N*-acetylglucosamine mimic without a ring-oxygen, but bearing a sterically demanding substituent at the 2-position should result in a compound with increased affinity towards the target protein. Therefore, we designed a synthesis allowing to stereoselectively introduce alkyl substituents at the 3-position of (*R*,*R*)-cyclohexane-1,2-diol.

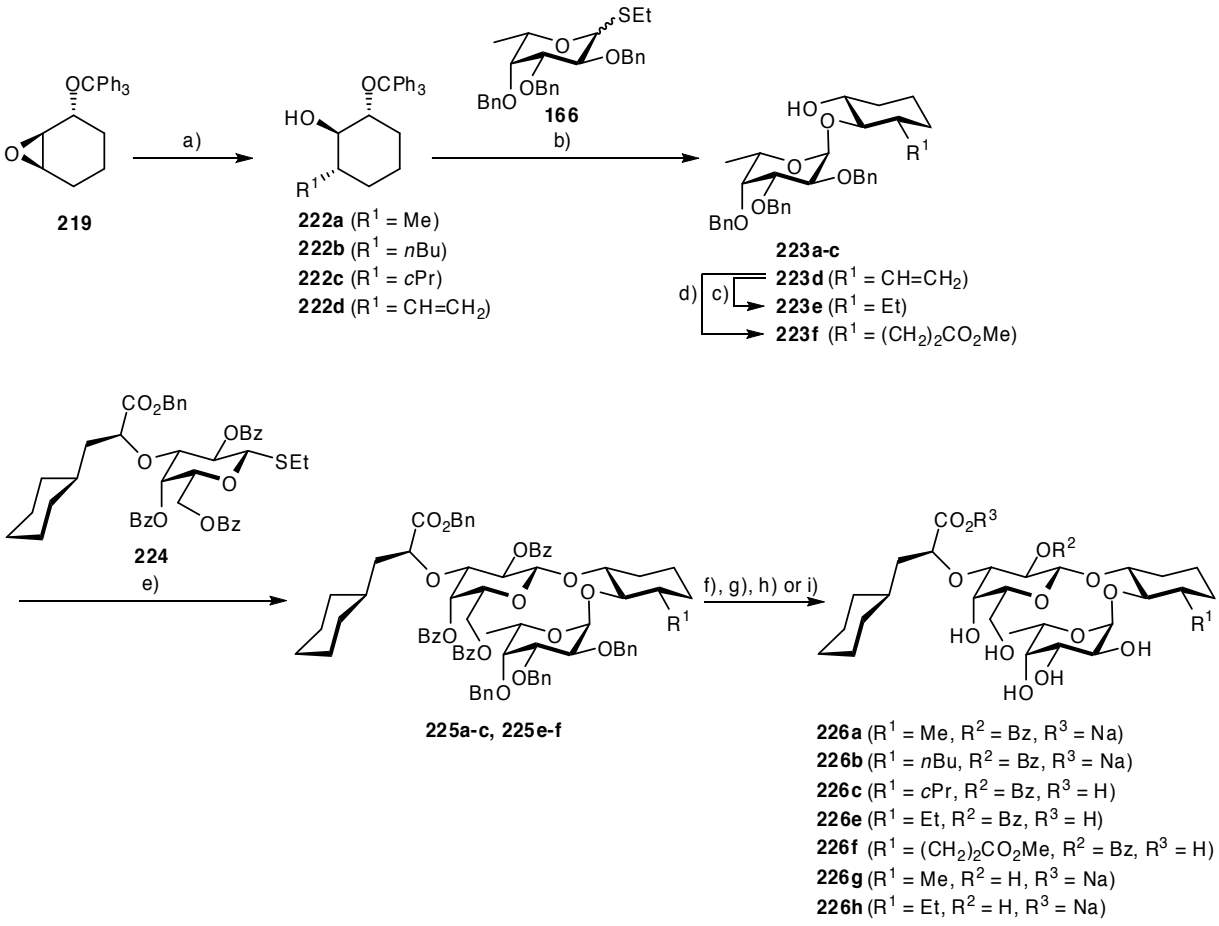


50 **55**

Figure 31: E-selectin antagonist with xylal-derived Glc*N*Ac mimic (left) and its glucal-derived counterpart (right).

The synthesis for (1*R*,2*R*,3*S*)-3-alkyl-cyclohexane-1,2-diols **222a-d** started with the nucleophilic opening of epoxide *anti*-**219** (chapter 3.2.1.1.) by organocopper reagents. A preliminary experiment with the homocuprate $Me_2CuLi{\cdot}LiI$ showed low, but sufficient reactivity and the desired compound **222a** was stereo- and regioselectively obtained after 1 week in 61% yield, with 2-triphenylmethoxy-cyclohexanone as minor side-product. It was supposed that taking advantage of the enhanced reactivity of the higher-order cyanocuprate $Me_2Cu(CN)Li_2$ in presence of $BF_3{\cdot}Et_2O$ would lead to higher yields in a shorter reaction time.[399, 400] Indeed, under optimized conditions, the nucleophilic opening took place even at low temperature and **222a** was cleanly formed with 84% yield.

Under these optimized conditions, epoxide **219** was reacted with a variety of organocopper reagents to yield **222a-d**. However, the reactions failed with the less reactive diphenylcuprate[401] and the sterically demanding and instable *t*-butyl cyano copper reagent (chapter 3.2.2.2.1.).[399] Fucosylation of the Glc*N*Ac mimics **222a-d** was performed under *in situ* anomerization conditions to yield predominantly the α-glycoside as indicated by NMR ($^3J_{F1,F2}$ = 3.6 Hz).[349-351] The tedious separation of the α-glycoside from traces of β-glycoside was circumvented by detritylating the pre-purified cyclohexane derivatives in presence of $ZnBr_2$ as mild Lewis acid and triethylsilane as trityl cation scavenger.[402, 403] The resulting α-fucosides **223a-d** could then be readily separated from its β-anomers and other side-products.



Scheme 21: a) R^1Li, CuCN, $BF_3{\cdot}Et_2O$, THF, -78℃ to -30℃, 22 h-51 h (**222a**: 85%, **222b**: 70%, **222c**: 82%, **222d**: 81%); b) i. Br_2, CH_2Cl_2, 0℃, 30-50 min, ii. TEAB, MS 3Å, DMF, CH_2Cl_2, r.t., 1-4 d, iii. $ZnBr_2$, TES, CH_2Cl_2, r.t., 45 min-8 h, (**223a**: 49%, **223b**: 55%, **223c**: 67%, **223d**: 60%, yields are over two steps); c) Pd/C, H_2, THF, r.t., 30 min (77%); d) i. methyl acrylate, Grubbs cat. 2nd gen., CH_2Cl_2, reflux, 9d, ii. Pd/C, H_2, THF, r.t., 30 min (25% over two steps); e) DMTST, MS 3Å, CH_2Cl_2, r.t., 43 h to 65.5 h (**225a**: 59%, **225b**: 80%, **225c**: 87%, **225e**: 78%, **225f**: 79%); f) i. Pd/C, H_2, EtOH, cat. AcOH, r.t., 8 d, ii. NaOMe, MeOH, r.t., 18 h, iii. Dowex (Na^+), Seph.-G15 (**226a**: 79%); g) i. $Pd(OH)_2$/C, H_2, dioxane/H_2O, r.t., 49 h, ii. NaOMe, MeOH, r.t., 17 h, iii. Dowex (Na^+), Seph.-G15 (**226b**: 56%); h) i. $Pd(OH)_2$/C, H_2, dioxane/H_2O, r.t., 24 h to 72 h, ii. NaOMe, MeOH, r.t., 16 h (**226c**: 72%, **226e**: 77%, **226f**: 73%); i) i. Pd/C, H_2, EtOH, cat. AcOH, r.t., 6 d to 60 d, ii. LiOH, MeOH/H_2O, r.t., 2 d, iii. Dowex (Na^+), Seph.-G15 (**226g**: 74%, **226h**: 30%).

The disaccharide mimic **223d** was further transformed into the disaccharide mimics **223e** and **223f**. For the synthesis of the ethyl-substituted antagonist, **223d** was selectively hydrogenated in presence of Pd/C to yield **223e**. This step was necessary prior to galactosylation since DMTST-promoted glycosylation in presence of the vinyl group of **223d** failed.

Cross-metathesis of **223d** with methyl acrylate in presence of Grubbs' 2nd generation catalyst proceeded only slow- and incompletely and resulted in a remarkably low *trans*/*cis* ratio of the product.[404] Both the slow reaction and the low *trans*/*cis* ratio are supposed to result from the huge sterical hindrance by the benzylated fucose. Hydrogenation of the inseparable *cis*/*trans* mixture yielded the 2-methoxycarbonyl-ethyl substituted disaccharide mimic **223f** in a low yield of 25% over two steps.

Subsequent β-glycosylation with donor **224**[405] and dimethyl(methylthio)sulfonium triflate (DMTST) as promoter afforded the tetrasaccharide mimics **225a-c** and **225e-f** in a β-selective manner. For the debenzylation $Pd(OH)_2/C$ was found to be a superior hydrogenation catalyst compared to Pd/C and markedly reduced the reaction time. The frequently observed catalyst's poisoning presumably by disulfides was overcome by exchanging the catalyst after one day of hydrogenation. Saponification was either carried out with catalytic amounts of sodium methoxide in methanol to yield the 2-monobenzoylated antagonists **226a-c** and **226e-f**, or with lithium hydroxide to yield the fully deprotected antagonists **226g-h**.

3.2.2.2. Synthetic challenges in the synthesis of alkylated Glc*N*Ac mimics

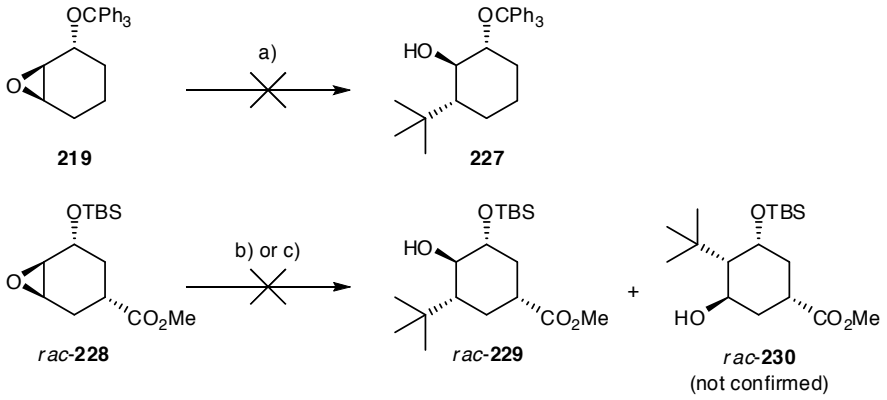
3.2.2.2.1. *tert*-Butyl Glc*N*Ac mimics 227 and 229

Steric compression of the fucose moiety by a bulky equatorial substituent could improve the pre-organization of the core structure in the biologically active conformation and lead to increased biological activity. To closer investigate the influence of bulky substituents at the former 2-position of Glc*N*Ac, the synthesis of a *t*-butyl substituted Glc*N*Ac mimic was envisaged (*scheme* 22).

The di-*t*-butyl cuprate reagent ($tBu_2CuCNLi_2$) is known to be instable and to decompose even at low temperature to isobutylene and a hydrido-copper species. This hydride species preferentially leads to the reduction product.[399] By using the *t*-butyl cyano copper reagent (*t*BuCuCNLi) instead of the di-*t*-butyl cuprate reagent, smooth opening of epoxides by the *t*-butyl group can normally be achieved. However, in case of the triphenylmethyl protected epoxide **219**, the stability of the *t*-butyl cyano copper reagent was found to be insufficient and the reagent rapidly decomposed when slowly warming the reaction from -78° to -30°C . Work-up of the reaction confirmed the absence of product formation and led to the recovery of the starting material **219**.

To test further reaction conditions, the sterically less hindered epoxide **228** (see chapter 3.2.2.3.) was chosen as starting material. To avoid decomposition of the copper reagent, the reaction was this time kept constantly at -78°C, even during the formation of the reagent. Addition of **228**, followed by $BF_3 \cdot Et_2O$ resulted in a mixture of alcohols with a partially or fully alkylated ester moiety, as observed by MS. Obviously, the formation of the copper reagent at -78°C was incomplete, and the remaining *t*-BuLi preferentially attacked the methylester. However, the reduction of the epoxide cannot be explained, since depletion of *t*-BuLi renders the formation of a di-*tert*-butyl cuprate species unlikely.

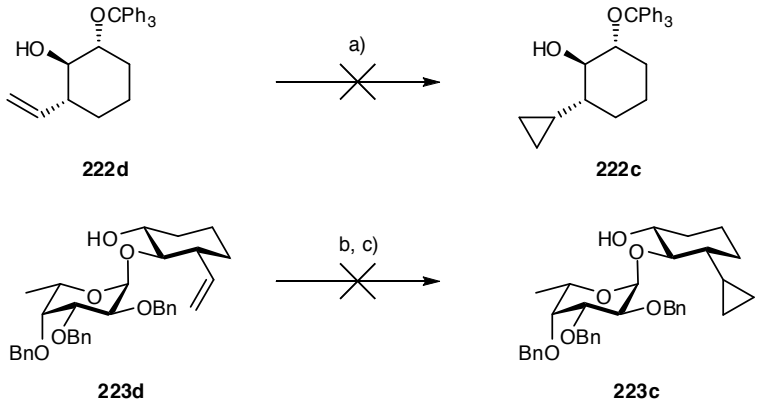
In order to favor the epoxide opening over the reduction, a reaction was started at -30°C. It was assumed, that the less sterically demanding epoxide **228** would react fast enough at this temperature, before the copper reagent is fully decomposed. However, most of the starting material was recovered unreacted, together with a significant amount of a compound, which probably is the 4-*tert*-butyl derivative **230** and only traces of the desired 3-*tert*-butyl derivative **229**. These results led to the conclusion that the preparative synthesis of a 3-*tert*-butyl derivative can not be achieved by the current synthetic strategy, due to the low reactivity of the reactants and the instability of the *t*-butyl copper reagent.



Scheme 22: a) *t*-BuLi, CuCN, $BF_3 \cdot Et_2O$, THF, -78°C to -30°C, 24 h (0%), b) *t*-BuLi, CuCN, $BF_3 \cdot Et_2O$, Et_2O, -78°C, 4 h (0%), c) *t*-BuLi, CuCN, $BF_3 \cdot Et_2O$, Et_2O, -30°C, 4 h (traces).

3.2.2.2.2. Cyclopropyl Glc*N*Ac mimic 222c

A cyclopropyl Glc*N*Ac mimic is supposed to exert increased steric compression on the fucose compared to unbranched alkyl chains, and therefore may enhance the pre-organization of the core structure. In addition, compared to the isopropyl functionality, cyclopropyls show enhanced metabolic stability and therefore attracted increasing attention in medicinal chemistry in recent years.[406] Since the di-cyclopropyl cuprate reagent was considered as too sterically hindered to react with epoxide **219**, an alternative route to **222c** was explored. Simmons-Smith reaction is a simple and powerful method to generate cyclopropanes from olefins.[407] Reacting one of the vinyl intermediates with the corresponding zinc reagent would therefore lead to a terminal cyclopropane in a single step. Recently, cyclopropanation reagents generated by reacting $Zn(CH_2I)_2$ with halogen-substituted carboxylic acids such as TFA were found to have increased reactivity and dramatically shorten the usually long reaction times.[408] First attempts with the triphenylmethyl protected compound **222d** failed due to the susceptibility of the triphenylmethyl group towards acids (*scheme* 23).



Scheme 23: a) Et_2Zn, CH_2I_2, CF_3COOH, CH_2Cl_2, 0°C to r.t. (0%), b) Et_2Zn, CH_2I_2, CH_2Cl_2, 0°C to r.t. (0%), c) Et_2Zn, CH_2I_2, CF_3COOH, CH_2Cl_2, -20°C to r.t. (0%).

To circumvent this problem, **222d** was first fucosylated and deprotected prior to cyclopropanation (→**223d**). However, the disaccharide mimic showed to be completely inert to various cyclopropanation conditions, probably due to steric shielding by the benzylgroups. Cyclopropanation with dichlorocarbene to form the geminal dichlorocyclopropane and subsequent reduction to the cyclopropane under various conditions resulted in low yields of inseparable mixtures. Finally, the cyclopropyl derivative **222c** was obtained by treatment of **219** with the dicyclopropyl cuprate reagent (see chapter 3.2.2.1.).

3.2.2.3. Synthesis of E-selectin antagonists (244) with methyl (1*R*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-methyl-cyclohexane-1-carboxylate as Glc*N*Ac mimic

Several highly active E-selectin antagonists contain differently acylated (1*R*,2*R*,3*S*)-3-amino-cyclohexane-1,2-diols as replacements for Glc*N*Ac.[272] Closer investigations on this particular type of Glc*N*Ac mimetic revealed that attaching an additional methyl ester at the former ring-oxygen position of Glc*N*Ac leads to even superior antagonists. Ligands containing methyl (1*R*,3*S*,4*R*,5*R*)-*N*-acyl-3-amino-4,5-dihydroxy-cyclohexane carboxylates as Glc*N*Ac mimics were found to be usually four- to six-fold more potent compared to the corresponding antagonists without the methyl ester (*table* 7). Since the crystal structure of E-selectin co-crystallized with sLe^x shows no close contact between the ring-oxygen position of Glc*N*Ac and E-selectin (chapter 3.1.1., *figure* 26), the increase in binding affinity is probably due to a stabilization of the chair conformation. This stabilizing effect was supposed to be also present in antagonists containing (1*R*,2*R*,3*S*)-3-methyl-cyclohexane-1,2-diol as Glc*N*Ac mimic and an additional methyl ester functionality in the 5-position.

Table 7: Improvement of binding affinity by introducing a methylester

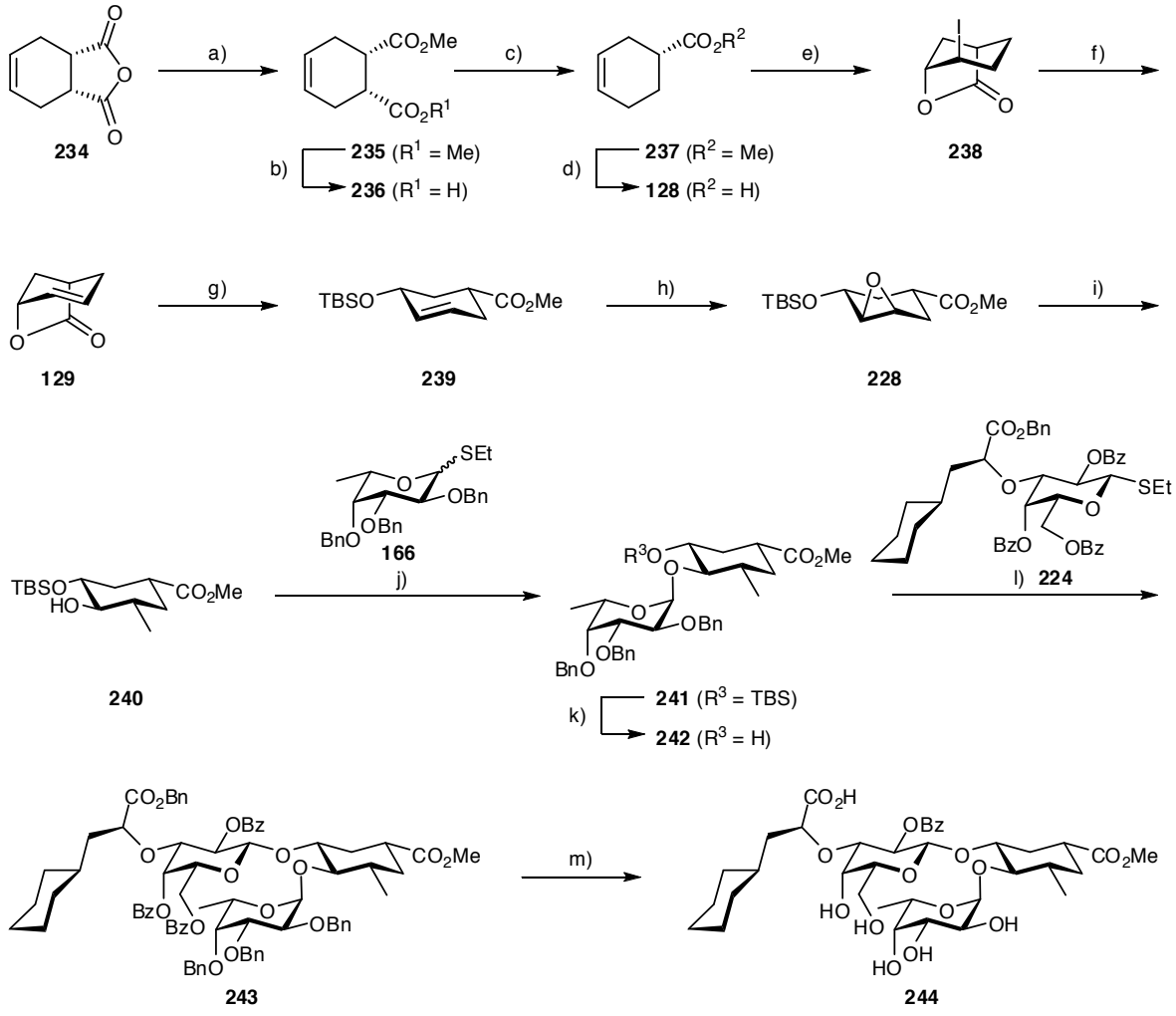
Entry	Structure:		R^2 = H rIC_{50} [a), 272]		$R_2 = CO_2Me$ rIC_{50} [a), 272]		factor
1	R^1 = acetyl		**63**:	0.110	**231**:	0.018	6.1
2	R^1 = *p*-phenylbenzoyl		**64**:	0.095	**232**:	0.014	6.8
3	R^1 = orotoyl		**65**:	0.022	**233**:	0.005	4.4

a) Sialyl Lewis^x (sLe^x) was taken as reference compound (IC_{50} = 1 mM, rIC_{50} = 1.0).

Since the methyl ester in **244** is positioned in a non-binding region without any sterical restriction, it can easily be used for the synthesis of multivalent E-selectin antagonists, for linking to biosensor chips or for labeling of the antagonist.

The synthesis of the novel Glc*N*Ac mimic **240** started from commercial *cis*-1,2,3,6-tetrahydrophthalic anhydride, which was transformed into the dimethyl ester **235** by acid catalysis in methanol (*scheme* 24). Deracemization was accomplished by enantioselective hydrolysis of the symmetrical diester by pig liver esterase (PLE).[316] The optical purity of the resulting half-ester **236** was analyzed by optical rotation (96.4% ee) and by chiral GC (96.0%

ee). Subsequent Barton decarboxylation and enzymatic hydrolysis of the methyl ester yielded (*R*)-cyclohex-3-ene carboxylic acid (**128**) with an enantiomeric excess of 96.3% ee, determined by chiral GC.[409, 410] Iodolactonization and DBU induced dehydroiodination afforded lactone **129**, followed by transesterification with methanol in presence of sodium bicarbonate and protection of the secondary alcohol with *tert*-butyl-dimethylsilyl chloride (→**239**). Epoxidation with *m*-CPBA yielded preferentially *anti*-epoxide **228** due to the directing effect of the sterically demanding TBDMS group.[392, 393]



Scheme 24: a) amberlyste 15, MeOH, $CH(OCH_3)_3$, r.t., 9d (88%); b) PLE, pH 7 buffer, aq. NaOH, 20°C, 56.5 h (90%, 96% ee); c) i. $(COCl)_2$, CH_2Cl_2, cat. DMF, r.t., 3 h, ii. 2-mercaptopyridine-1-oxide sodium salt, *t*-BuSH, cat. DMAP, THF, reflux, 3 h (83%); d) PLE, pH 7 buffer, aq. NaOH, r.t., 11 h (84%, 96% ee); e) KI, I_2, $NaHCO_3$, H_2O, r.t., 24 h (95%); f) DBU, THF, reflux, 20 h (94%); g) i. $NaHCO_3$, MeOH, r.t., 12 h, ii. TBSCl, DBU, CH_2Cl_2, r.t., 12 h (100%); h) *m*-CPBA, CH_2Cl_2, 10°C to r.t., 17 h (78%); i) MeLi, CuCN, $BF_3{\cdot}Et_2O$, THF, -78°C, 5 h (78%); j) TBAB, 2,6-di- *t*-butyl-4-methylpyridine, MS 4Å, $CuBr_2$, DMF, CH_2Cl_2, r.t., 20 h (76%); k) TBAF, THF, r.t., 13 h (78%); l) DMTST, MS 4Å, CH_2Cl_2, r.t., 63 h (66%); m) i. $Pd(OH)_2/C$, H_2, dioxane/H_2O, r.t., 46 h, ii. NaOMe, MeOH, r.t., 16 h (76%).

Regioselective opening of epoxide **228** with $Me_2Cu(CN)Li_2$ in presence of $BF_3 \cdot Et_2O$ provided the new semi-protected Glc*N*Ac mimic methyl (1*R*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-methyl-cyclohexane-1-carboxylate (**240**).[399, 400]

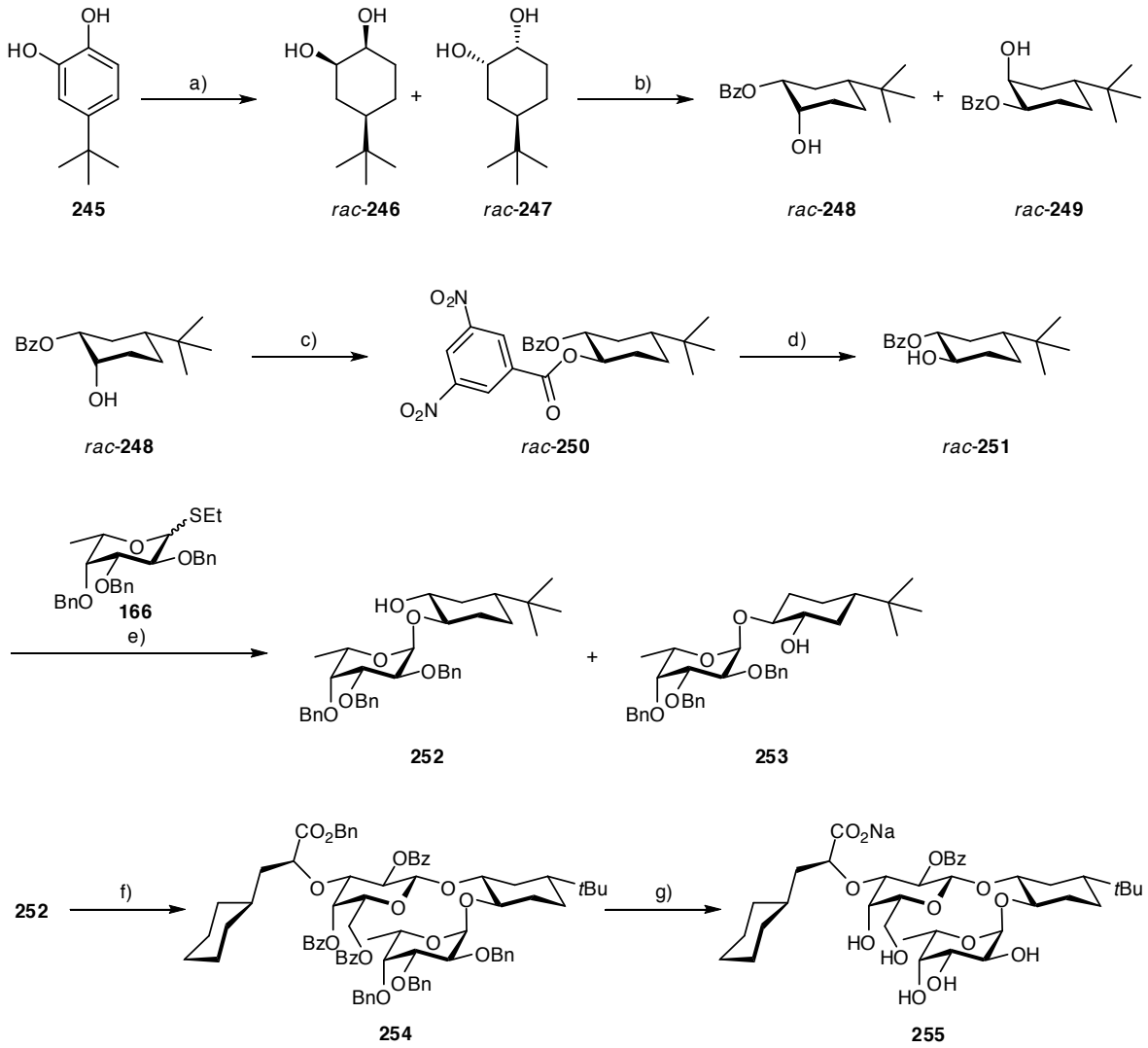
Selective α-fucosylation of **240** was performed under the previously used *in situ* anomerization conditions (chapter 3.1.3.2.) in presence of tetraethylammonium bromide.[349-351] Unlike earlier experiments with similar Glc*N*Ac mimics, the desired disaccharide mimic was only isolated as minor product (20%). Closer investigation of the side-products revealed a significant amount of the difucosylated Glc*N*Ac-mimic. Obviously, under the reaction conditions the TBDMS group, which is known to be sensitive to halides and acidic conditions, was cleaved. Fucosylation under Ogawa conditions in presence of 2,6-di-*t*-butyl-4-methylpyridine successfully prevented desilylation and yielded selectively the disaccharide mimic **241**, which was then further deprotected according to standard procedures to yield **242**.[411] Subsequent glycosylation with donor **224**[405] and dimethyl(methylthio)sulfonium triflate (DMTST) as promoter afforded the tetrasaccharide mimic **243** in β-selective manner. Debenzylation according to the previously described procedure (chapter 3.2.2.1) and saponification with catalytic amounts of sodium methoxide in methanol yielded the 2-monobenzoylated antagonist **244**.

3.2.2.4. Synthesis of E-selectin antagonist (255) with (1*R*,2*R*,4*R*)-4-*tert*-butyl-cyclohexane-1,2-diol as Glc*N*Ac mimic

The conformational stability of Glc*N*Ac mimics is supposed to play a crucial role in the biological activity of E-selectin antagonists (see chapter 3.2.3.). Large substituents on a cyclohexane ring prefer to occupy equatorial positions due to unfavorable 1,3-diaxial interactions. Large substituents can therefore be used to lock the cyclohexane ring in one of the chair conformations, which may pre-organizes the antagonists and leads to higher binding affinities. Commonly, *tert*-butyl substituents are used to completely lock the chair conformation of cyclohexane due to the high free energy difference between the equatorial and axial orientation of more than 4.5 kcal/mol.[412] To closer investigate the influence of the ring-stability of Glc*N*Ac mimics, a novel mimic with an additional *tert*-butyl substituent at the former ring-oxygen position of Glc*N*Ac was synthesized (*scheme* 25).

The synthesis started from commercial 4-*tert*-butylcatechol (**245**) which was hydrogenated in a Parr-shaker under 5 bar pressure at r.t. with an alumina oxide supported rhodium catalyst. Test reactions with different solvent mixtures indicated that apolar solvents like cyclohexane give preferentially the *syn*-*syn* diol (3:1 ratio), as reported for similar *tert*-butylphenols.[413] However, because of the higher catalytic activity observed with THF as co-solvent and the later possibility

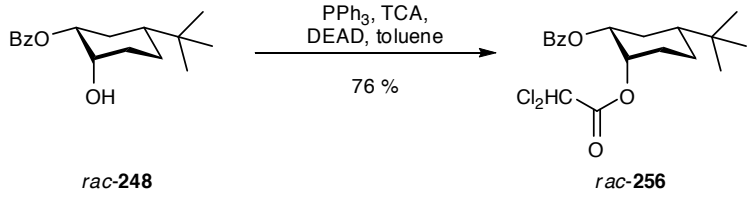
of epimer-separation, a THF/cyclohexane mixture was chosen for the final hydrogenation (1.4:1 ratio). The equatorial hydroxyls of the mixture of *rac*-**246** and *rac*-**247** were selectively mono-benzoylated in the presence of dibutyltin oxide. Subsequently, the two diastereomers were separated to yield 44% of the *syn-syn* epimer *rac*-**248** and 26% of the *syn-anti* epimer *rac*-**249**.



Scheme 25: a) Rh/Al_2O_3, H_2, *c*-hexane/THF (8:1), 5 bar, r.t., 24 h (78%, *rac*-**246**:*rac*-**247** = 1.4:1); b) nBu_2SnO, BzCl, Et_3N, CH_2Cl_2, 0℃-r.t., 3 h, (*rac*-**248**: 44%, *rac*-**249**: 26%); c) PPh_3, DEAD, 3,5-dinitrobenzoic acid, toluene, 50℃, 22. 5 h (63%); d) MeOH, Et_3N, r.t., 1 h (80%); e) i. TBAB, MS 4Å, $CuBr_2$, DMF, CH_2Cl_2, r.t., 11 h, ii. $MeOH/H_2O$, LiOH, 50℃, 4 h (α/β-**252**: 44%, α-**253**: 38%); f) **224**, DMTST, MS 4Å, CH_2Cl_2, r.t., 45 h (68%); g) i. $Pd(OH)_2/C$, H_2, dioxane/H_2O, r.t., 37 h, ii. NaOMe, MeOH, r.t., 14 h (88%).

The axial hydroxyl of *rac*-**248** was inverted under Mitsunobu conditions, using 3,5-dinitrobenzoic acid in 63% yield.[414] 3,5-dinitrobenzoic acid was preferred over *p*-nitrobenzoic acid because the subsequent hydrolysis of the *p*-nitrobenzoyl ester required more drastic conditions which led to partial cleavage of the benzoylgroup. Trichloroacetic acid (TCA) was considered as an

alternative to the nitrobenzoic acids by reason of its high reactivity and ease of cleavage under almost neutral conditions. However, treatment of rac-**248** with TCA under Mitsunobu conditions yielded the 2,2-dichloroacetylated starting material **256** (76%) instead of the inverted 2,2,2-trichloroacetylated diol as unexpected major product (*scheme* 26). Presence of the dichloroacetoxy group was confirmed by MS and NMR analysis ($Cl_2HC(O)O$: δ = 6.02 ppm), and its axial position can be deduced from the two axial-equatorial couplings ($^3J_{ax,eq}$ = 2.7, 4.7 Hz) and the axial-axial coupling ($^3J_{1ax,6ax}$ = 12.0 Hz) of the proton adjacent to the benzoyloxy group. As possible reaction mechanism, the formation of a mixed phosphinic anhydride as acylating reagent can be considered. Thereby, trichloroacetic acid forms the phosphonium salt similar to the commonly used carbon tetrahalogenides, resulting in the dichloroacetate which nucleophilically displaces the chloride on the phosphor.



rac-**248** *rac*-**256**

Scheme 26: Unexpected reaction pathway of Mitsunobu reaction with TCA.

Selective deprotection of the 3,5-dinitrobenzoyl group was carried out with triethylamine in methanol, resulting in the corresponding alcohol with 80% yield. Sodium azide in methanol showed similar efficiency but increased formation of a side-product, which was later identified as (1*R*,2*R*,4*R*)-4-*tert*-butyl-2-hydroxy-cyclohexyl benzoate.[415] This implies that the benzoyl group tends to slowly migrate in solution.

The racemic mixture of equatorial alcohols was reacted with ethyl thiofucoside under Ogawa conditions to yield a scarcely separable mixture of the two diastereomers.[411] However, after subsequent debenzoylation with lithium hydroxide, the two diastereomers could easily be separated on silica to give **252** as an α/β-mixture (1:0.12) and **253** as pure α-anomere. Assignment of the diastereomers was accomplished by comparing their NMR spectra with the reference compound **168** (*figure* 32 *and figure* 33).

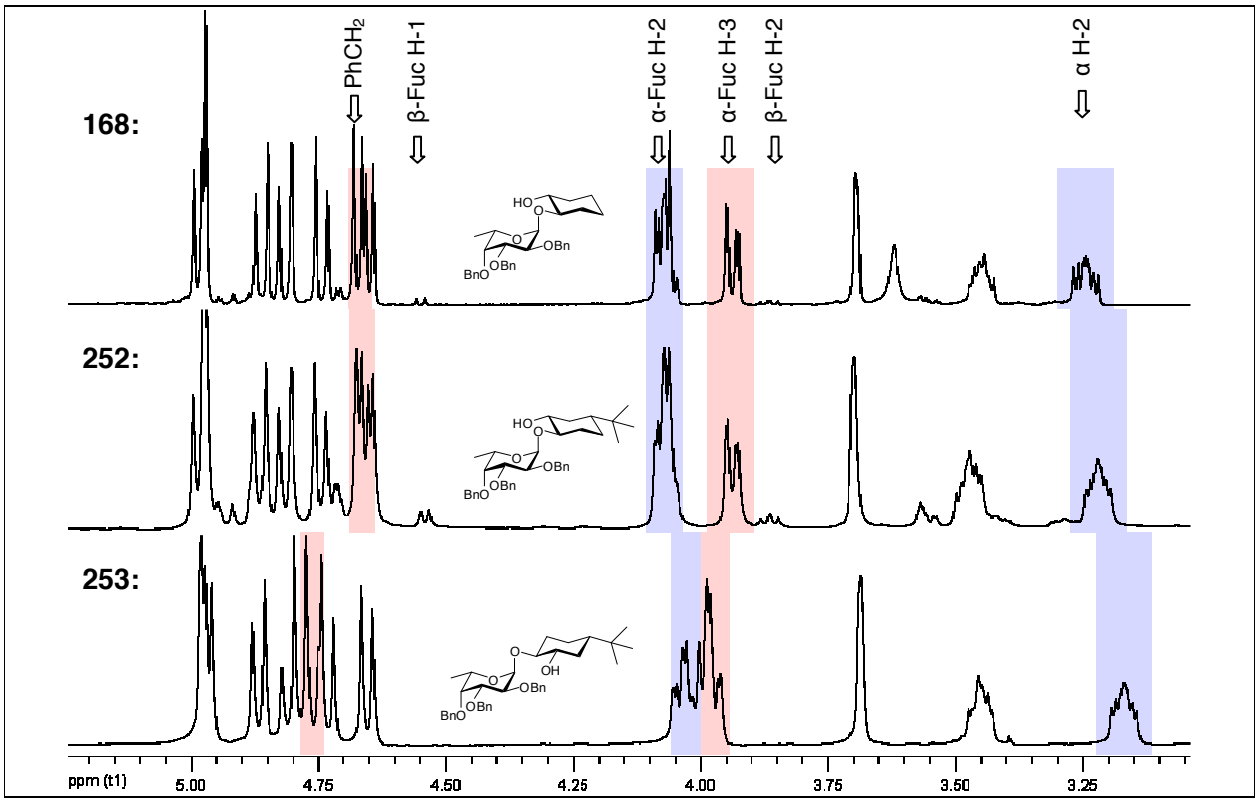


Figure 32: Superposition of ^{1}H-NMRs of **168** and the two diastereomers **252** & **253**.

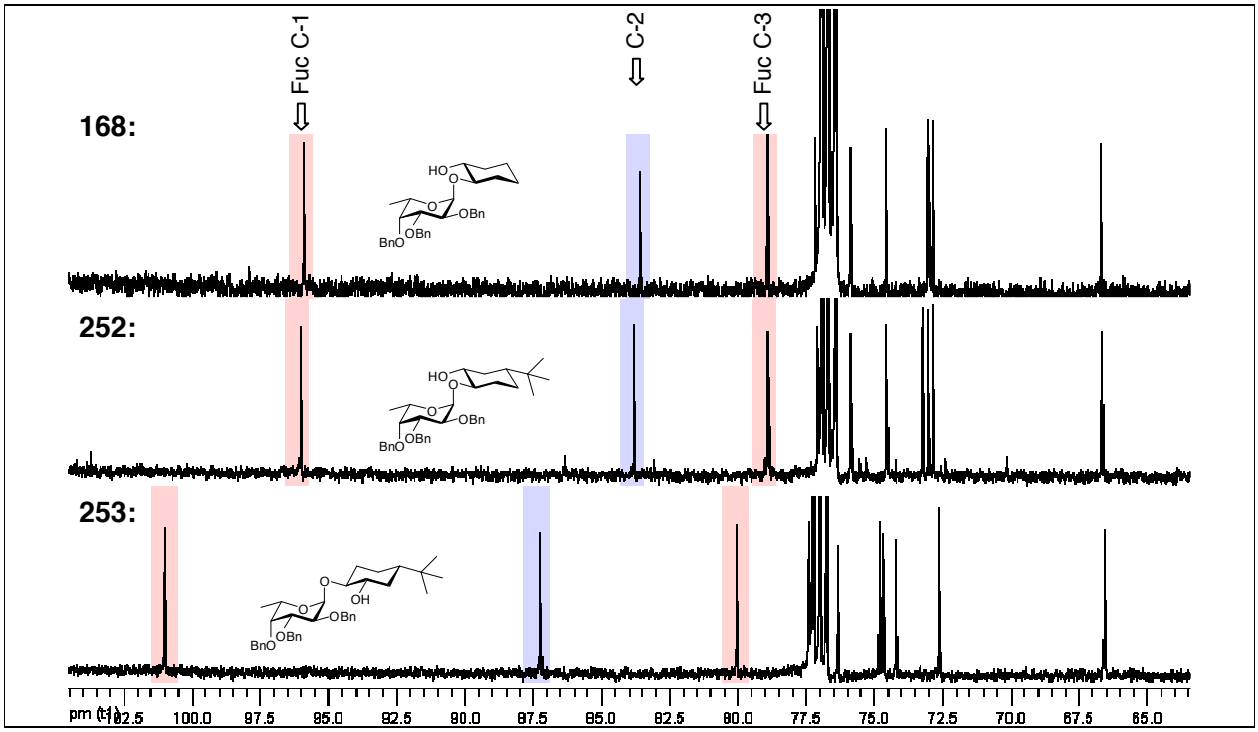


Figure 33: Superposition of ^{13}C-NMRs of **168** and the two diastereomers **252** & **253**.

Subsequent glycosylation of **252** with donor **224**[405] and DMTST as promoter afforded the tetrasaccharide mimic **254** in a β-selective manner. At this stage, remaining traces of the β-fucosylated mimic could be separated from the desired α-fucosylated mimic. Debenzylation with $Pd(OH)_2/C$ and saponification with catalytic amounts of sodium methoxide in methanol yielded the 2-monobenzoylated antagonist **255**.

3.2.3. Biological evaluation of antagonists with novel alkylated Glc*N*Ac mimics

(in collaboration with Dr. John L. Magnani, Glycomimetics Inc., Rockville, USA)

All the synthesized antagonists with modified Glc*N*Ac mimics were analyzed in a static cell free ligand binding assay that measures E-selectin inhibition under equilibrium conditions.[378, 379] Since IC_{50}s may vary depending on the conditions from assay to assay, relative inhibitory concentrations (rIC_{50}) were calculated by standardizing the values on CGP69669 (**41**), which is measured on the same plate and known to have a rIC_{50} of 0.080. All the values are expressed as relative IC_{50} to sialyl Lewis^x (sLe^x, **3**) which was taken as a reference compound with an IC_{50} of 1 mM (rIC_{50} = 1.0). The rIC_{50}s of the new antagonists bearing modifications on the Glc*N*Ac moiety (general structure is shown in *figure* 34) are summarized in *table* 8.

The antagonists **226g** and **226h**, bearing an alkyl modification at the former 2-position of Glc*N*Ac, show increased biological activity in the ligand binding assay compared to the unsubstituted antagonist CGP69669 (**41**).[216] This can be rationalized by the steric compression exercised by the equatorial alkyl group, which supports the pre-organization of the core pseudotrisaccharide in the biologically active conformation. This result is in good agreement with observations from glucal-derived antagonists earlier reported in literature.[269]

Similar results were obtained for antagonists bearing an additional benzoate at the 2'-position of galactose. From earlier publications, it is known that an additional benzoate increases binding affinity approximately 3-fold.[269, 416] The reason for this increase in potency is not yet fully elucidated. Either hydrophobic interactions with the protein, CH-π interactions to the cyclohexyllactic acid moiety or the influence on the core conformation through the electron withdrawing and steric effect of the benzoate can be considered.

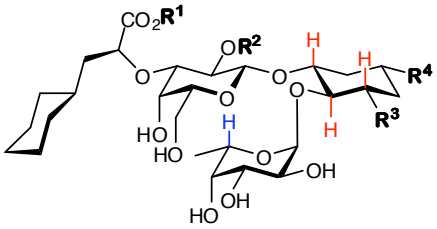


Figure 34: General structure of antagonists with novel Glc*N*Ac mimics.

Table 8: Biological and NMR data of antagonists with novel Glc*N*Ac mimics.

Compound	R^1	R^2	R^3	R^4	rIC_{50} [a]	δ of Fuc H-5 [b] [ppm]	$^3J_{1ax,2ax} + {}^3J_{2ax,3ax}$ [Hz]
CGP69669 (**41**)[202]	Na	H	H	H	0.080	4.61	17.8
BW408-0 (**257**)[417]	H	H	Me	H	0.013	4.89	18.6
226g	Na	H	Me	H	0.016	4.89	18.9
226h	Na	H	Et	H	0.009	4.84	---
56[417]	H	Bz	H	H	0.040	4.60	17.5
BW408-11 (**258**)[417]	H	Bz	Me	H	---	4.97	18.4
226a	Na	Bz	Me	H	0.004	4.96	18.5
226e	H	Bz	Et	H	0.007	4.90	17.8
226b (H)	H	Bz	*n*Bu	H	---	4.90	17.8
226b (Na)	Na	Bz	*n*Bu	H	0.009	4.85	17.7
226c	H	Bz	*c*Pr	H	0.032	4.88	17.0
226f	H	Bz	$(CH_2)_2CO_2Me$	H	0.008	4.83	16.9
244	H	Bz	Me	CO_2Me	0.002	4.99	19.2 [c]
255 (H)	H	Bz	H	*t*Bu	---	4.77	20.6
255 (Na)	Na	Bz	H	*t*Bu	> 10	4.75	---

a) Sialyl Lewis^x (sLe^x, **3**) was taken as reference compound (IC_{50} = 1 mM, rIC_{50} = 1.0); b) all ^{1}H-NMR were measured in MeOH; c) corresponds to $^3J_{3ax,4ax} + {}^3J_{4ax,5ax}$ in this compound.

Among the benzoylated antagonists (*table* 8), the 3-alkylated compounds show increased biological activity compared to the unsubstituted reference compound **56**.[269, 271] The most potent antagonist is obtained by methylation at the 3-position of the Glc*N*Ac mimic and benzoylation of the 2'-position of galactose (**226a**), while increasing the steric bulk leads again to a slight decrease in activity, as *e.g.* observed for the cyclopropyl modification (**226c**).

The distance between the fucose and the galactose in the antagonist's solution conformation can be estimated by NMR according to the chemical shift of the Fuc H-5 proton.[269] The closer the fucose H-5 proton is located to the galactose, the stronger it is shifted downfield. In our series of antagonists, the observed shifts of the fucose H-5s correlate well with the biological activity, resulting in a pronounced downfield shift for the most potent compounds **244** and **226a** (*table* 8). Therefore, these shifts can be used to preliminarily evaluate the potency of future antagonists.

The controversial results from the compounds with increased steric bulk led to the hypothesis that with increased bulkiness the conformational stability of the cyclohexane starts to play a decisive role for the biological activity. The huge steric constraint around the fucose may destabilize the all-equatorial conformation and lead to a partial distortion from the ideal all-equatorial chair conformation. However, even the all-axial conformation can not be fully excluded, as similar observations were made for trans-1,2-bis-silyloxycyclohexanes and all-trans-polyisopropylcyclohexanes.[418, 419] Despite the inherent preference of substituents for the equatorial conformation, the all-axial conformation gives relief from the 1,2-diequatorial steric repulsions and from the destabilizing interaction of carbon-oxygen bond dipoles. In addition, alkoxy groups have a rather small axial penalty as expressed in the the low A-value compared to other functional groups (*table* 9).

Table 9: Conformational energies (A-Values).[412]

Residue	A-Value [kcal/mol]	Residue	A-Value [kcal/mol]
-OMe	0.6	-*i*Pr	2.2
-Me	1.7	-*t*Bu	4.7
-Et	1.8	-CO_2Me	1.3

Our hypothesis is in agreement with the observation that an additional isolated methyl ester attached at the former ring oxygen position usually increases binding affinity as seen for antagonist **244**. Since the methyl ester shows no close interaction with the protein's surface (*figure* 35), the increased potency can only be rationalized by the additional stabilizing effect on the chair conformation due to the distinct equatorial preference of the isolated methyl ester.

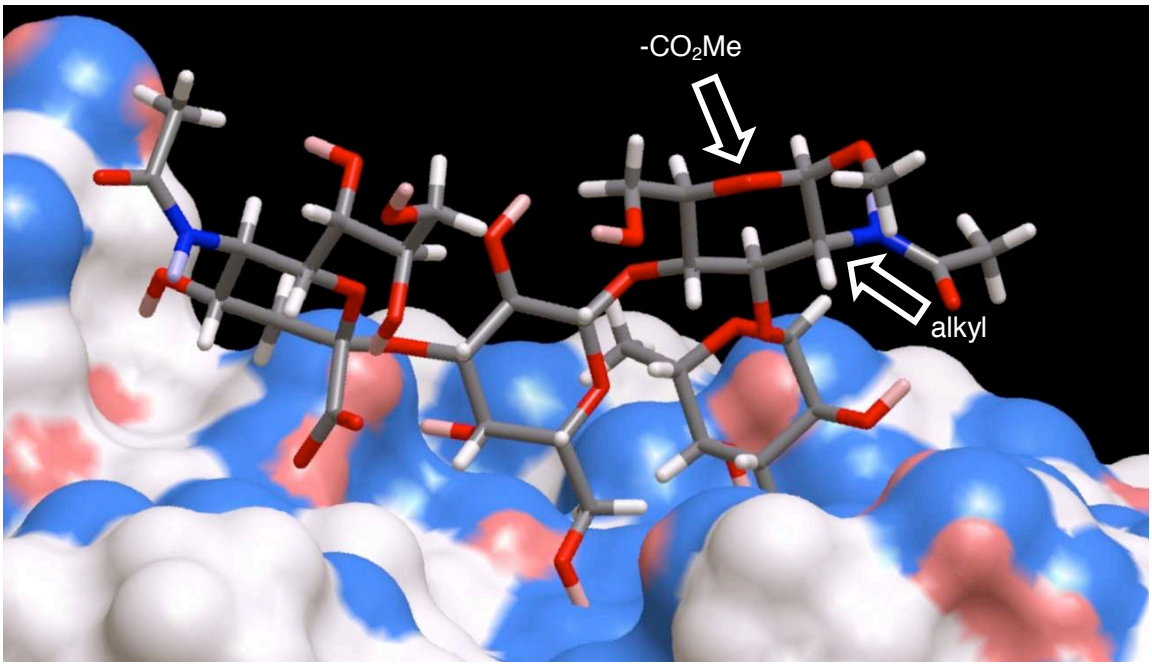


Figure 35: sLe^x docked onto E-selectin. Position of the 3-alkyl group and the methyl ester of the Glc*N*Ac mimetics are highlighted.

This theory is supported by the analysis of the chair conformation by NMR experiments. The sum of the two diaxial coupling constants of the axial proton (*figure* 34) attached to the fucose linkage ($^3J_{1ax,2ax}$ + $^3J_{2ax,3ax}$) can be used to estimate the portion of the ideal all-equatorial chair conformation. The values in *table* 8 show that a small substituent like methyl at the 3-position stabilizes the chair conformation due to its equatorial preference, whereas with larger substituents like cyclopropyl the 1,2-diequatorial repulsion plays a dominant role and the chair conformation gets destabilized. The addition of an isolated methyl ester in **244** leads to larger diaxial coupling constants, which implies stabilization of the all-equatorial chair-conformation and therefore improved potency.

The role of the chair-stabilizing effect in the biological activity of E-selectin antagonists can be dissociated from the fucose-stabilizing effect in compound **255**, where steric compression of the fucose is absent. In this compound the all-equatorial chair-conformation is completely locked by the isolated *t*-butyl functionality. This results indeed in distinctly large diaxial coupling constants. However, **255** was found to be inactive in a static cell free ligand binding assay. This result may be rationalized either by its unfavorable solvation properties like aggregate formation or by steric clashes of the *tert*-butyl group with the protein's surface. Assuming that the new antagonists bind to E-selectin in a similar fashion as sLe^x in the crystal structure of E-selectin, renders steric

clashes of **255** with the protein's surface unlikely. However, for this new class of antagonists we cannot fully exclude a binding mode different from the one observed with sLe^x.

This leads to the conclusion that the activity of E-selectin antagonists with diverse Glc*N*Ac mimics depends on a combination of the optimal pre-organization of the fucose by applying steric compression and the conformational stability of the cyclohexane ring. However, the latter still needs to be fully proven by further investigations.

3.2.4 ROESY studies on 3-methylated antagonist 226g

To investigate the hypothesis that the higher binding affintity of 3-alkylated antagonists is a consequence of the closer stacking of fucose and galactose, the solution conformations of **226g** and CGP69669 (**41**) were studied by NMR experiments. This has been performed through selective one-dimensional ROESY measurements, according to earlier published methods.[420-423] The interglycosidic ROEs between Fuc H-5 and Gal H-2 (*figure* 36) were used to determine the proximity of fucose to galactose in CGP69669 (**41**) and **226g**. Assuming a distance of 2.60 Å from Fuc H-5 to Fuc H-3, the mean distance between Fuc H-5 and Gal H-2, weighted by the populations of the different conformations, was quantified to be 2.98 Å for CGP69669 (**41**) and 2.73 Å for **226g**. The measured ROE values provide evidence for the closer stacking of the fucose to the galactose and therefore an increased extent of pre-organization of the core structure in the biologically active conformation.

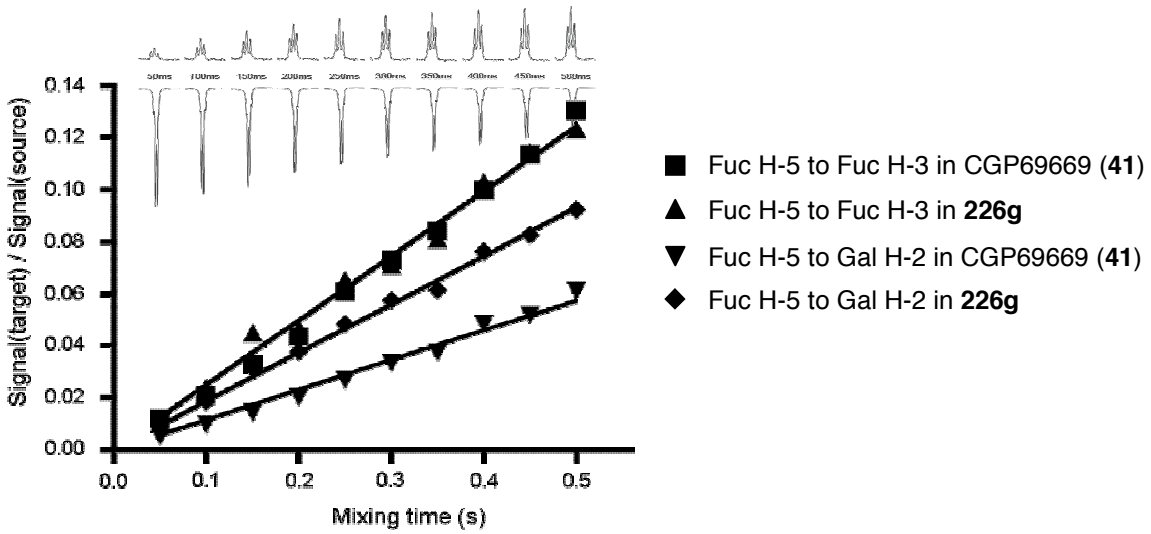


Figure 36: Cross-relaxation rate constants which are used to determine the internuclear distance.

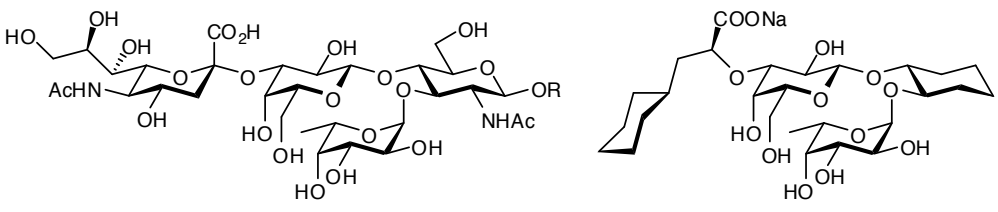
4. Conclusion and Outlook

4.1. Summary of the thesis

4.1.1. General background

The interaction of E-, P- and L-selectin with their natural carbohydrate ligands has been shown to mediate the initial step of the recruitment of leukocytes, and to play a crucial role in many physiological processes and disease states.[1-4] More specifically, selectins are a family of carbohydrate-binding proteins expressed at the site of inflammation in response to early precursors, liberated by the inflamed tissue. Their key role, early in the inflammatory cascade, is to promote the tethering and the rolling of leukocytes along the endothelial surface.[1-4] These steps are then followed by integrin-mediated firm adhesion and final transendothelial migration. Therefore, control of the leukocyte-endothelial cell adhesion process may be useful in cases where excessive recruitment of leukocytes contributes to acute or chronic diseases such as stroke, reperfusion injury, psoriasis or rheumatoid arthritis.[5, 6] In addition, it has been suggested that cancer may exploit this adhesion process after entering the bloodstream to metastasize.[7, 8]

Tetrasaccharide sialyl Lewis^x (sLe^x) (**3**, *figure* 37) was identified as the minimal carbohydrate epitope recognized by E-selectin.[21, 424, 425] Important pharmacophores of sLe^x are the three OH groups of the fucose moiety, the 4- and the 6-OH of the galactose moiety and the COOH group of the sialic acid residue.[426-429, 200, 204, 201, 252, 194-197] The *N*-acetylglucosamine portion of sLe^x (**3**) mainly serves as spacer between the fucose- and the galactose moiety, and forces the fucose ring to stack under the β-face of galactose. Due to the flat binding site of E-selectin[46] and to the considerable distances between the pharmacophores, their three-dimensional orientation and pre-organization becomes exceedingly important.



sialyl Lewis^x (sLe^x, **3**)
rIC_{50} = 1.0

CGP69669 (**41**)
rIC_{50} = 0.080

Figure 37: The carbohydrate epitope sLe^x (**3**) and its analogue CGP69669 (**41**) as a lead compound for inhibiting E-selectin.

In the past decade, numerous sLe^x analogues and related compounds were synthesized by various groups.[221] Within the class of sLe^x analogues, the *N*-acetylneuraminyl portion is commonly replaced by (*S*)-cyclohexyl lactic acid, whereas the *N*-acetylglucosamine moiety is substituted by xylal- or glucal-derived structures or by (*R*,*R*)-cyclohexane-1,2-diol as in CGP69669 (**41**).

4.1.2. Aim of the thesis

For this thesis, the compound CGP69669 (**41**) served as a lead compound for the design of E-selectin antagonists. In order to improve the lead compound's pharmacodynamic profile, two different optimization strategies were envisaged (*figure* 38).

The first part of the thesis aimed at probing an unoccupied hydrophobic patch close to the 6-position of galactose. Since the 6-hydroxyl is optimally suited for binding to E-selectin it was kept untouched, and the hypothetical fragments for binding to the hydrophobic pocket were alternatively attached to the C-6 of the galactose. The *de-novo* design of the hydrophobic fragments, as well as its linker, was supported by molecular modeling tools.

The second part of the thesis was dedicated to the optimization of the ligand's pre-organization in the bioactive conformation. Although the Glc*N*Ac moiety of sLe^x displays no pharmacophores and mainly serves as a spacer between the fucose and the galactose, it makes an important contribution to the spatial pre-organization of the pharmacophores to the receptor site. The aim was to develop novel potent antagonists by reducing the ligand's entropic costs upon binding through optimization of the Glc*N*Ac mimetics. The new mimetics should provide a maximal extent of pre-organization, realized by different means like steric compression or conformational stabilization, while preserving the ligands drug-likeness and synthetic accessibility.

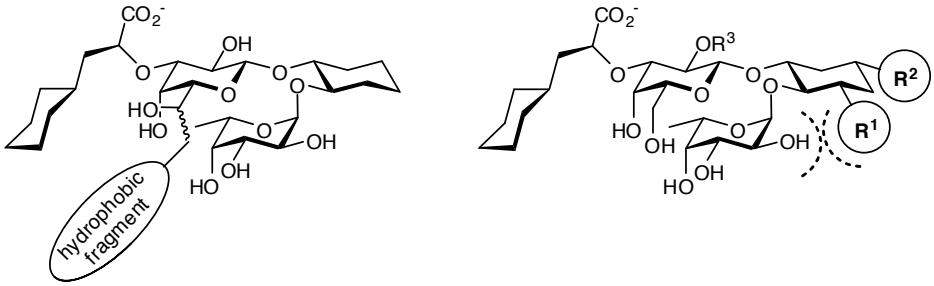


Figure 38: General structures for the two subprojects: Probing of a hydrophobic pocket (left) and optimization of the ligand's pre-organization (right).

4.1.3. E-selectin antagonists containing substituted L-*glycero*-β-D-*galacto*-hepto-pyranoses as replacement for galactose (optimization of enthalpy)

Supported by molecular modeling tools, a small library of fragments were chosen for probing the hydrophobic patch close to the 6-position of galactose moiety of sLe^x. The fragments were attached to the C-6 position of galactose by a $-CH_2NH-$ unit as linker, so that the galactose became a 7-amino-7-deoxy-L-*glycero*-β-D-*galacto*-hepto-pyranose. The synthesis of the ligands started with the donor heptopyranoside, which was obtained in 14 steps. The key reaction was the stereoselective chain elongation with a silyl Grignard reagent resulting in the desired (6*S*)-isomer of the heptopyranoside. The donor heptopyranoside was incorporated in a tetrasaccharide mimetic of sLe^x by DMTST-promoted glycosylation and regioselective alkylation with known building blocks. The fragments binding to the hydrophobic patch were either commercially available or synthesized by Friedel-Crafts acylation or by the Fischer indole synthesis. The fragments were then coupled to the amine group at the 7'-position of the scaffold by activation with PPh_3/CCl_4 or as acid chlorides. Subsequent deprotection yielded the new E-selectin ligands either in pure form (**193**, **194**) or as mixtures with the partly reduced form (**195**/**196**, **197**/**198**), due to ring hydrogenation during the deprotection step (*figure* 39).

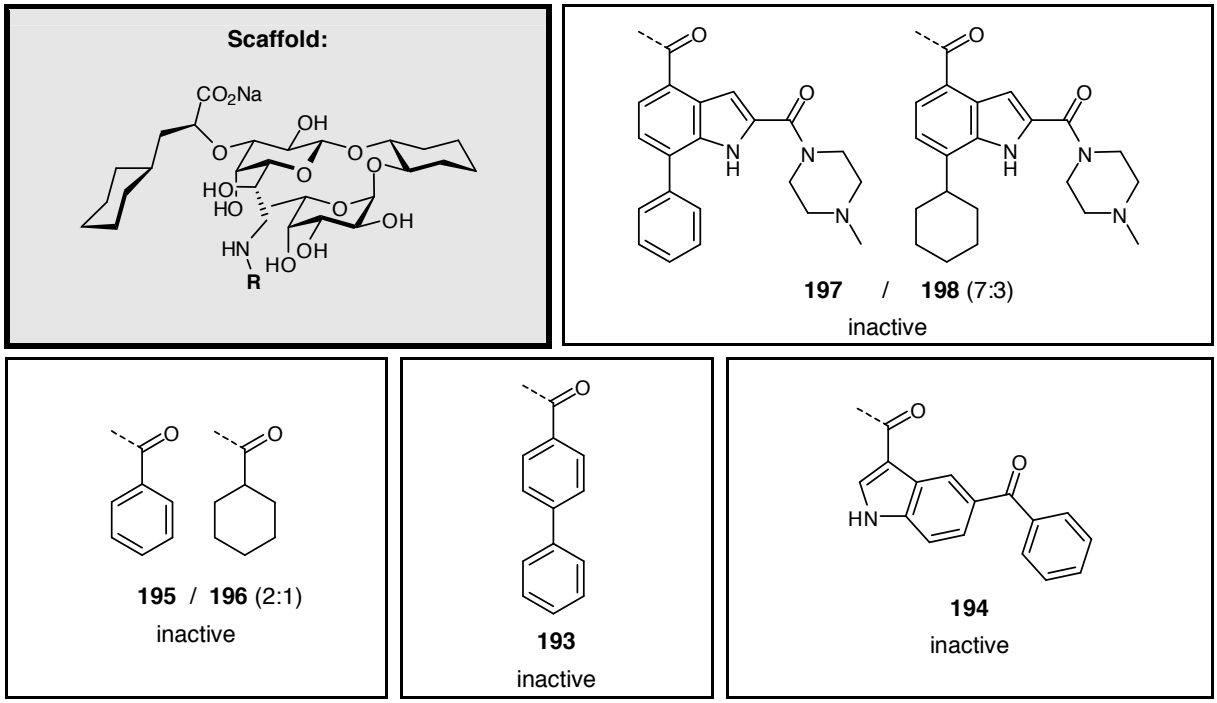
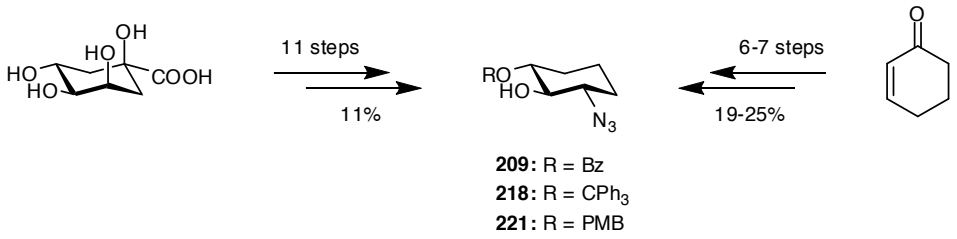


Figure 39: E-selectin ligands with fragments which are probing the hydrophobic patch close to the 6-position of galactose.

The synthesized ligands, analyzed in a static cell free ligand binding assay, were found to be inactive (rIC_{50} > 10mM).[378, 379] The inactivity of the ligands may be due to an inappropriate choice of the linker, insufficient binding of the fragments or interference with the bioactive conformation. For the full understanding of the negative results, further studies will be inevitable, like co-crystallization of E-selectin with the lead compound **41** or testing the binding of the fragments by NMR.

4.1.4. Design and synthesis of Glc*N*Ac mimetics for E-selectin antagonists (optimization of entropy)

The second project started with the optimization of the synthesis of the established Glc*N*Ac mimic **209**. The original synthesis from (D)-(-)-quinic acid yielded **209** with 11% in an 11 step synthesis. For the optimization, a bottom-up approach was chosen from the inexpensive cyclohex-2-en-1-on. The desired Glc*N*Ac mimic was stereo- and regioselectively synthesized on a multi-gram scale in 6-7 steps with an overall yield of 19% for the *p*-methoxybenzyl- and 25% for the trityl-protected Glc*N*Ac mimic (*scheme* 27).

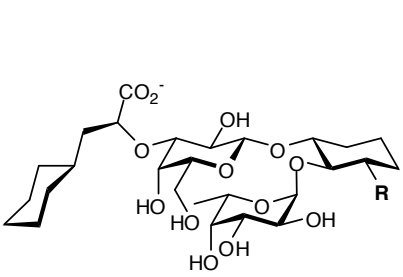


Scheme 27: Optimization of the synthesis of the Glc*N*Ac mimic **209**.

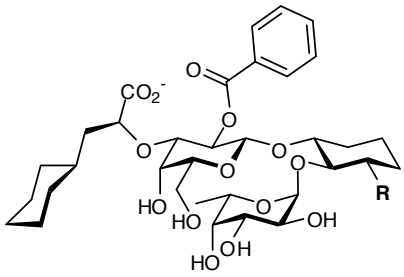
Earlier synthetic studies with glucal- and xylal-derived antagonists[269, 270] revealed that the 2-position of the *N*-acetylglucosamine part of sLe^x analogues is crucial for the pre-organization of the core in the bioactive conformation. Therefore, we designed a synthesis for the regioselective introduction of alkyl substituents at the 3-position of (*R*,*R*)-cyclohexane-1,2-diol to yield suitably protected (1*R*,2*R*,3*S*)-3-alkyl-cyclohexane-1,2-diols as novel Glc*N*Ac mimics. All of the synthesized antagonists bearing an alkyl substitutent in the 3-position (*figure* 40) showed increased potency compared to the unsubstituted cyclohexanediol.

The increased extent of pre-organization of the alkylated antagonists was confirmed by the pronounced downfield shift of the fucose H-5 proton and by selective one-dimensional ROESY experiments. Assuming a distance of 2.60 Å from fucose H-5 to fucose H-3, the mean distance between fucose H-5 and galactose H-2 was quantified to be 2.98 Å for the unsubstituted antagonist CGP69669 (**41**) and 2.73 Å for the methylated antagonist **226g**. The ROE values

provide evidence for the closer stacking of the fucose to the galactose and therefore increased extent of pre-organization of the core structure in the biologically active conformation.



41:	R = H	80 μM
226g:	R = Me	16 μM
226h:	R = Et	9 μM



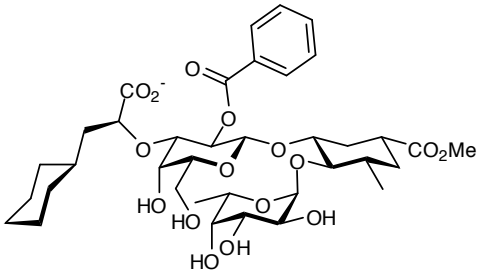
56:	R = H	40 μM
226a:	R = Me	4 μM
226e:	R = Et	7 μM
226c:	R = *c*Pr	32 μM
226b:	R = *n*Bu	9 μM
226f:	R = $(CH_2)_2CO_2Me$	8 μM

Figure 40: E-selectin antagonists with (1*R*,2*R*,3*S*)-3-alkyl-cyclohexane-1,2-diols as Glc*N*Ac mimics.

The most potent antagonist was obtained by simple methylation at the 3-position (**226a**), while increasing the steric bulk led to a slight decrease in activity, as *e.g.* observed for the cyclopropyl modification (**226c**). This surprising decrease may be rationalized by the conformational destabilization of the cyclohexane ring through 1,2-diequatorial steric repulsions. This explanation is supported by the slight tendency of the axial proton attached to the fucose linkage to lower coupling constants for compounds with increased steric bulk at the 3-position.

Starting from the methylated, most potent antagonist **226a**, further optimization of the pre-organization was envisaged. Earlier studies on a similar type of Glc*N*Ac mimetics revealed that attaching an additional methyl ester at the former ring-oxygen position of Glc*N*Ac leads to a further improvement of affinity. Based on the assumption that these findings could be transferred to the new antagonist **226a**, a stereoselective synthesis for antagonist **244** was designed. The new Glc*N*Ac mimetic was stereoselectively synthesized from commercial *cis*-1,2,3,6-tetrahydrophthalic anhydride with enzymatic deracemization as key step, and incorporated into the new antagonist **244** (*figure* 41). Biological evaluation of **244** confirmed our hypothesis, as the new antagonist showed a two-fold increase in potency compared to antagonist **226a**. Since the additional methyl ester is supposed to have no contact with the protein, the increased potency may be rationalized by the enhanced conformational stabilization of the cyclohexane moiety. This theory is supported by a slight increase of the above mentioned coupling constants for **244** compared to **226a**. Since the methyl ester of the new antagonist is supposed to be positioned in

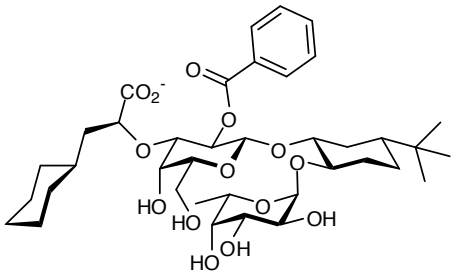
a non-binding region, without any sterical restriction, it can easily be used for the synthesis of multivalent E-selectin antagonists, for linking to biosensor chips or for labeling of the antagonist.



244: 2 μM

Figure 41: E-selectin antagonist with methyl (1*R*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-methyl-cyclohexane-1-carboxylate as Glc*N*Ac mimic.

The newly synthesized antagonists suggest that the conformational stability of the antagonists' cyclohexane moiety plays an important role for the biological activity. To closer investigate the influence of the conformational stability, a new antagonist was envisaged, where the Glc*N*Ac mimic's chair conformation is completely locked by an isolated equatorial *tert*-butyl substituent (*figure* 42). The conformational freeze would allow applying more steric compression on the fucose without simultaneously destabilizing the chair conformation by 1,2-diequatorial repulsions.



255: inactive

Figure 42: E-selectin antagonist with (1*R*,2*R*,4*R*)-4-*tert*-butyl-cyclohexane-1,2-diol as Glc*N*Ac mimic.

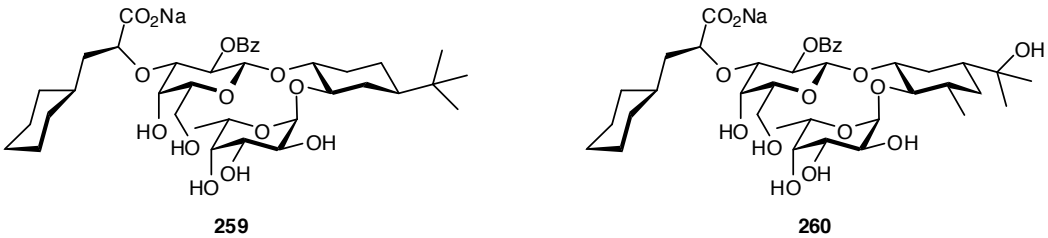
The position of the former ring-oxygen in Glc*N*Ac was chosen as the position for the bulky *tert*-butyl group, since earlier antagonists were already successfully substituted at this position. Deracemization of the *tert*-butyl-substituted cyclohexane moiety was performed on the level of diastereomers, obtained by α-fucosylation and subsequent deprotection. The final antagonist **255**, however, was found to be inactive in a static cell free ligand binding assay. This result may be rationalized either by the unfavorable solvation properties of the molecule, like aggregate formation, or by steric clashes of the *tert*-butyl group with the protein's surface. Assuming that the new antagonists bind to E-selectin in a similar fashion as sLe^x in the crystal structure of E-

selectin, renders steric clashes of **255** with the protein's surface unlikely. However, for this new class of antagonists, we cannot fully exclude a binding mode different from the one observed with sLe^x.

4.2. Outlook

In order to synthesize low nanomolar E-selectin antagonists with the lead compound CGP69669 (**41**) as molecular scaffold, the discovery of new hydrophobic interactions is inevitable. The failure of several molecular modeling-guided attempts to discover new hydrophobic interactions casts doubts on the predictive value of our model with CGP69669 docked on the crystal structure of E-selectin. Therefore, the project would immensely profit from an E-selectin crystal structure, co-crystallized with our lead compound CGP69669 (**41**). This may help to clarify the exact binding mode of the lead compound, as well as the inactivity of the new E-selectin antagonists containing substituted L-*glycero*-β-D-*galacto*-hepto-pyranoses as replacement for galactose (see *figure* 39) and the inactivity of the *tert*-butyl antagonist **255** (see *figure* 42).

Ongoing investigations in our group are focusing on the elucidation of the influence of the Glc*N*Ac mimetic's conformational flexibility on the antagonist's potency. For this purpose several new Glc*N*Ac mimetics are being synthesized and incorporated into E-selectin antagonists (*figure* 43). In order to explain the inactivity of **255**, compounds **259** and **260** are being synthesized. In antagonist **259** steric clashes with the protein are avoided by placing the *tert*-butyl group at a position different from **255**, whereas in **260** the solubility problem is addressed by using a 2-hydroxypropan group instead of a *tert*-butyl group. Finding a solution for locking the Glc*N*Ac mimic's chair conformation would allow to further pre-organize the other moieties of the antagonists without conformationally destabilize the cyclohexane ring.



259 **260**

Figure 43: E-selectin antagonists with conformational stabilized Glc*N*Ac mimetics.

Since the methyl group of **226a** simultaneously applies steric compression on the fucose and stabilizes the chair conformation, the synthesis of compound **261** was envisaged, where only the

latter effect is present. Compound **262** will finally combine the effects of the two methyl groups and is supposed to show a potency similar to **244**, but with an increased metabolic stability (*figure* 44).

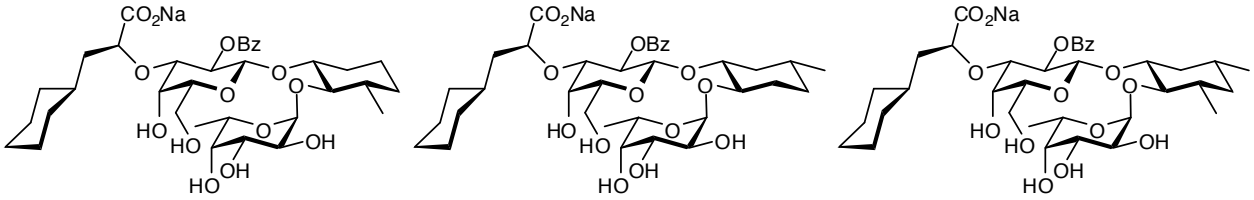


Figure 44: E-selectin antagonists with methyl substituents at different positions of the Glc*N*Ac mimetic.

5. Experimental Section

5.1. General methods

Nuclear magnetic resonance:

Nuclear magnetic resonance spectroscopy was performed on a Bruker Avance 500 Ultra Shield spectrometer at 500 MHz (^{1}H NMR) or 125 MHz (^{13}C NMR). Chemical shifts are given in ppm and were assigned in relation to the solvent signals on the δ-scale or to tetramethylsilane (0 ppm) as internal standard. ^{1}H: 7.26 ppm ($CDCl_3$), 5.32 ppm (CD_2Cl_2), 3.31 ppm (CD_3OD), 4.79 ppm (D_2O), 2.50 ppm ($(CD_3)_2SO$); ^{13}C: 77.00 ppm ($CDCl_3$), 53.50 ppm (CD_2Cl_2), 49.00 ppm (CD_3OD), 39.43 ppm ($(CD_3)_2SO$). Coupling constants *J* are given in Hertz (Hz). Multiplicities were specified as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), dq (double quartet), m (multiplet). Assignment of ^{1}H and ^{13}C NMR spectra was achieved using 2D methods (COSY, HSQC, HMQC, HMBC, APT).

For assignment of resonance signals to the appropriate nuclei the following abbreviations have been used: Ar (aryl), Cy (cyclohexyl), Fuc (fucose), Gal (galactose), Hep (heptose), Ind (indole), Lac (lactic acid), Pip (piperazine), PMB (*p*-methoxybenzyl).

Infrared spectroscopy:

IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer as KBr pellets or films on NaCl plates. Most characteristic absorption bands of the spectrum were given in cm^{-1} and specified as vs (very strong), s (strong), m (medium), w (weak), vw (very weak), b (broad).

Optical rotation:

Optical rotations were measured on a Perkin Elmer 341 polarimeter with a path length of 1 dm. The optical rotation for the Na-D-line (589 nm) can be extrapolated from the lines of a mercury lamp (546 nm and 579 nm) using the Drude equation:[430]

$$[\alpha]_D^T = \frac{[\alpha]_{578}^T \cdot 3.199}{4.199 - \frac{[\alpha]_{578}^T}{[\alpha]_{546}^T}} \qquad [\alpha]_\lambda^T = \frac{\alpha \cdot 100}{c \cdot d}$$

α = measured rotation
c = concentration in g/100 ml
d = cell length in dm
T = temperature in °C
λ = wavelength in nm

Microanalysis:

Microanalysis was performed at the Institute of Organic Chemistry at the University of Basel, Switzerland.

Mass spectroscopy:

Mass spectra were recorded on a Waters micromass ZQ and HR-MS spectra were obtained on an ESI Bruker Daltonics micrOTOF spectrometer equipped with a TOF hexapole detector.

Thin layer chromatography:

TLC was performed using silica gel 60 coated glass plates containing fluorescence indicator from Merck KGaA (Darmstadt, Germany) using either UV light (254 nm) or Mostain solution [0.8 g $Cer(SO_4)_2$, 40 g $(NH_4)_6(Mo_7O_{24}) \cdot 4\ H_2O$ dissolved in 300 ml of 10% aq. H_2SO_4] followed by heating to 140℃ for 5 minutes to visibilize the substances.

Chromatography:

Column chromatography was performed using silica gel 60 (40-63 μm) from Fluka. Reversed-phase column chromatography was carried out using LiChroprep RP-18 (40-63 μm) from Merck KGaA, Darmstadt, Germany.

Microwave reactions:

Microwave reactions were performed in a CEM Discover microwave apparatus.

Hydrogenations:

Hydrogenation reactions were performed in a shaking apparatus from Parr Instruments Company (Moline, Illinois, USA) in 250 ml or 500 ml bottles under a H_2 pressure of 4 bar.

Solvents:

Solvents and phosphate buffer solutions were purchased from Fluka. Solvents were dried prior to use. Diethylether, dioxane, toluene and tetrahydrofurane (THF) were dried by refluxing with sodium/benzophenone and distilled immediately before use. Pyridine was freshly distilled from CaH_2. Dichloromethane (CH_2Cl_2), acetonitrile and nitromethane were dried by filtration over Al_2O_3 (Fluka, type 5016 A basic). DMF, acetic acid and DMSO were dried by stirring over activated MS 4Å overnight, followed by microfiltration. Methanol was dried by distillation from sodium methoxide.

LC-MS:

LC-MS separations were carried out using sunfire C_{18} columns (analytical: 2.1 x 50 mm, 3.5 μm; preparative: 19 x 150 mm, 5.0 μm) on a Waters 2525 LC, equipped with Waters 2996 photodiode array and Waters micromass ZQ MS for detection.

GC:

Gas chromatography was carried out on a VARIAN 3600 or CEIntruments 8000Top using a chiral betacyclodextrine DEtTBuSil (SE54) column from Brechbühler.

MPLC:

MPLC separations were carried out on a CombiFlash Companion from Teledyne Isco equipped with RediSep normal-phase flash columns.

ROESY analysis:

The ROESY measurements were performed by Dr. Brian Cutting. The samples for the ROESY analysis consisted of approximately 5 mg of the compounds, solvated in 99.8% D_2O (Armar Chemicals). The samples had a pH of approximately 7.0, uncorrected for D_2O and were measured without the addition of a buffer. Shigemi NMR tubes were used to reduce the sample volume needed for measurement. Each tube was filled with 200 µl of the solution to be analyzed. Measurements were performed at 25°C using the same NMR spectrometer that was used to validate the compounds synthesized. Chemical shifts were referenced with respect to earlier work,[269] which assigned a chemical shift of 4.60 ppm to the $H5^F$ resonance of CGP69669 (**41**).

The doubly-selective homonuclear Hartmann-Hahn scheme[423] was used to selectively transfer magnetization from $H6^F$ to $H5^F$. This scheme allowed a highly selective transfer of magnetization from $H6^F$ to $H5^F$ through their scalar coupling. The selective excitation of $H5^F$ allowed an accurate quantitation of this resonance by avoiding the excitation of residual H_2O, which has a similar chemical shift. To remove any remaining magnetization from $H6^F$, a selective gradient echo at the frequency of $H5^F$ was applied. A 200 ms REBURP[224] 180° refocusing pulse was applied to the $H5^F$ resonance. The REBURP pulse was sandwiched by a pair of Gaussian shaped gradients of 1 ms each and an amplitude of 20 G/cm. This additional spectral filter ensured that the observed ROESY[421] peaks were due to magnetization that originated from the $H5^F$ resonance.[420]

The jump-symmetrized CW-ROESY variation of the ROESY sequence was used in all experiments to minimize TOCSY artifacts.[422] This sub-element of the pulse sequence was

inserted following the selective gradient echo. During the ROESY period, the transmitter frequency was shifted up or downfield during the first or second half of the mixing-time, respectively. The high-field spin lock was applied at 4.9 ppm and the low-field at 0.9 ppm. The spin lock was a rectangular pulse of 2 kHz amplitude. For both compounds measured, 10 experiments were measured to record a build-up curve of the ROE transfer. The 10 experiments were sampled with increasing durations of the spin lock, beginning after 50 ms, and repeated after each 50 ms increment, resulting in a 500 ms spin lock duration for the final experiment.

Following the application of the spin lock, the transmitter was returned to the center of the spectrum, at 2.9 ppm, and the fid measured using 4096 complex points to sample a bandwidth of 7 ppm. To achieve a high signal-to-noise, 1024 scans were measured for mixing time. Using a prescan delay of 3 s, on average the experiments lasted approximately 1.2 hours each. The NMR data were analyzed using XWINNMR version 3.0 operating on a Silicon Graphics O2. The spectra were apodized with an exponential decay function with 2 Hz line broadening. An additional advantage of the selective experiments was the lack of signal overlap which allowed the possibility of integrating the signals without interference from other resonances.

To determine the internuclear distances, the rotating-frame cross-relaxation rates were calculated from the build up curves. Traditionally, the cross-relaxation rate is determined from fitting the spectra to a bi-exponential function that depends upon both the cross- and auto-relaxation rates.[431-433] The extent to which accurate cross-relaxation rates can be determined by this manner depends upon how well the auto-relaxation rate can be defined. Alternatively, it is possible to remove the dependence on the auto-relaxation by dividing the target-peak by the source-peak for each value of the mixing time.[434-436] The resulting function is a hyperbolic tangent, the arguement of which is the product of the cross-relaxation rate and the mixing time. For the longest mixing times performed and highest rate of cross-relaxation expected for the compounds studied herein, the hyperbolic tangent function is indistinguishable from a linear function, hence offering the potential to apply linear regression to extract the cross-relaxation rate. The above procedure resulted in values that were well described by linear functions. Removal of auto-relaxation through the conversion of bi-exponential into hyperbolic tangent functions has as well been recently applied to determine accurate relaxation rates in cross-correlation measurements.[437-439]

Biological evaluation:

The binding assay was performed by Dr. J. L. Magnani (Glycomimetics, Rockville, USA). Wells in a microtiter plate (plate 1, Falcon probind™) were coated with E-selectin/hIg chimera by incubation of 100 μL of the purified chimeric protein at a concentration of 200 ng/well in 50 mM

Tris, 0.15 M NaCl, 2 mM $CaCl_2$, pH 7.4 (Tris-Ca^{2+}). After 2 h, 100 μL of a 1:1 mixture of 1% BSA in Tris-Ca^{2+} and Stabilcoat™ were added to each well and incubated at 22°C to block nonspecific binding. During this incubation, inhibitory test compounds (diluted in Tris-Ca^{2+}, 1% BSA) were titrated by a twofold serial dilution in a second U-shaped bottom low-bind microtiter plate (plate 2, Costar). An equal volume of a performed complex of a biotinylated sialyl Lewis^a polymer and horseradish peroxidase-labeled streptavidine (KPL, Gathersburg, MD) at 1 μg/mL in Tris-Ca^{2+}, 1% BSA was added to each well. After 2 h at 22°C, plate 1 was washed with Tris-Ca^{2+}, and 100 μL/well was transferred from plate 2 to plate 1. The binding reaction was allowed to proceed for 2 h at 22 °C while rocking. Plate 1 was then washed with Tris-Ca^{2+} and 100 μL of TMB substrate reagent (KPL, Gathersburg, MD) was added to each well. After 3 min, the colorimetric reaction was stopped by adding 100 μL/well of 1 M H_3PO_4, and the optical density was determined at 450 nm.[378, 379]

5.2. Experiments

Methyl 6-*O*-triphenylmethyl-α-D-galactopyranoside (**150**), (DS-03-13, DS-03-16).
Methyl α-D-galactopyranoside (15.0 g, 77.3 mmol), trityl chloride (43.2 g, 155 mmol) and DMAP (472 mg, 3.86 mmol) were stirred in pyridine (400 mL) at r.t. for 50 h under argon. The reaction was quenched with brine (200 mL) and extracted with CH_2Cl_2 (3 x 350 mL). The organic layer was each time washed with brine (200 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure and co-evaporated with toluene. The residue was purified by silica gel chromatography (CH_2Cl_2/methanol, 40:1 to 13:1) to afford **150** (28.6 g, 85%) as a yellowish foam, the NMR data of which were in accordance with Lit.[440]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**151**), (DS-03-11, DS-03-17, DS-03-26, DS-04-02, DS-04-58).
NaH (60% in oil, 6.95 g, 174 mmol) was suspended in DMF (20 mL) and washed several times with pentane under argon. After cooling to 0°C, a solution of **150** (11.4 g, 26.1 mmol) in DMF (55 mL) was slowly added and the suspension stirred for one hour at 0°C. The mixture was warmed to r.t. and benzyl bromide (18.6 mL, 156 mmol) was added. The reaction was stirred at 30°C for 19 h, then quenched with methanol (5 mL) and H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (150 mL) and H_2O (150 mL) and, after separation, the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with H_2O (100 mL) and the aqueous layer was again twice extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers

were dried over Na_2SO_4, filtered, concentrated under reduced pressure and co-evaporated with toluene. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 1:0 to 7:1) to afford **151** (16.9 g, 91%) as a white foam, the optical rotation of which was in accordance with Lit.[441]

Methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (**152**), (DS-03-15, DS-03-17, DS-03-26, DS-04-03, DS-04-06).

To a stirred solution of tritylether **151** (10.6 g, 15.0 mmol) in CH_2Cl_2 (50 mL) was added TES (2.86 mL, 18.0 mmol) and TMSOTf (60 µl, 0.311 mmol). After 1 h another 0.02 eq of TMSOTf (60 µl, 0.311 mmol) was added and after 3.5 h another 0.04 eq (120 µl, 0.621 mmol). After 4.5 h the reaction was quenched by adding H_2O (1 mL) and evaporated under reduced pressure. The resulting syrup was dissolved in THF (25 mL) and 80% AcOH (25 mL) and stirred for 1 h at r.t.. The reaction was then neutralised with $NaHCO_3$, transferred into a separation funnel with ethyl acetate (150 mL) and extracted with satd. aqueous $NaHCO_3$ (2 x 150 mL). The aqueous layers were each extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 3:1 to 1:1) to afford **152** (6.19 g, 89%) as a yellowish oil, the NMR data of which were in accordance with Lit.[442]

Methyl 2,3,4-tri-*O*-benzyl-α-D-*galacto*-hexodialdo-1,5-pyranoside (**153**), (DS-03-04, DS-03-18, DS-03-29, DS-04-05, DS-04-10).

CH_2Cl_2 (5 mL) was cooled to -78°C and oxalyl chloride (85 5 µl, 9.95 mmol) was added. Then DMSO (1.75 mL, 24.6 mmol) was slowly added and the solution stirred for 5 min. A solution of alcohol **152** (2.29 g, 4.92 mmol) in CH_2Cl_2 (35 mL) was slowly added and the reaction stirred at -78°C for 2 h, before Et_3N (3.42 mL, 24.6 mmol) was added. The reaction was warmed to r.t. and extracted with satd. aqueous $NaHCO_3$ (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 3:1 to 2:1) to afford **153** (2.10 g, 92%) as a yellowish oil, the NMR data of which were in accordance with Lit.[442]

Methyl 7-deoxy-2,3,4-tri-*O*-benzyl-7-(phenyldimethylsilyl)-L-*glycero*-α-D-*galacto*-heptopyranoside (**154**), (DS-03-06, DS-03-19, DS-03-33, DS-04-07, DS-04-13).

Dry magnesium turnings (329 mg, 13.6 mmol) were covered with THF (7 mL) and a small amount of (phenyldimethylsilyl)methyl chloride (2.44 mL, 13.6 mmol) was added. After initiating

the reaction either by the addition of I_2 in THF, crushing the turnings or local heating, the remaining (phenyldimethylsilyl)methyl chloride was added in such a rate as to maintain a gentle reflux. Upon completion of the Grignard reagent formation, the reaction was cooled to -78°C and the aldehyde **153** (2.09 g, 4.52 mmol) dissolved in THF (15 mL) was slowly added to the reaction. The mixture was then slowly brought to r.t. over 17 h. The reaction was quenched by addition of satd. aqueous NH_4Cl (15 mL). After extraction and separation the aqueous layer was extracted with TBME (2 x 15 mL). The combined organic layers were washed with H_2O (30 mL) and the aqueous layer was extracted with TBME (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 6:1 to 4:1) to afford **154** (2.07 g, 75%) as a colourless oil, the NMR data of which were in accordance with Lit.[335]

Methyl 2,3,4-tri-*O*-benzyl-L-*glycero*-α-D-*galacto*-heptopyranoside (**155**), (DS-03-12, DS-03-22, DS-03-23, DS-03-43, DS-04-09, DS-04-15).

To a solution of **154** (7.38 g, 12.1 mmol) in AcOH (107 mL) were added KBr (1.73 g, 14.5 mmol) and sodium acetate (12.3 g, 150 mmol). The solution was cooled to 0°C, stirred under argon and protected from light. AcOOH (50 mL, 39% solution in AcOH) was added to the mixture. After stirring for 2.5 h at 0°C the reaction was brought to r.t. and quenched by pouring into an ice-cold, aqueous solution of $Na_2S_2O_4$ (20%, 300 mL). CH_2Cl_2 (150 mL) was added and the mixture transferred into a separation funnel. After extraction and separation the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with H_2O (300 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure and co-evaporated with toluene. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 1:2) to afford **155** (4.54 g, 76%) as a yellowish resin, the NMR data of which were in accordance with Lit.[335]

Methyl L-*glycero*-α-D-*galacto*-heptopyranoside (**156**), (DS-03-20, DS-03-21, DS-03-25, DS-04-11, DS-04-16).

To Pd/C (310 mg, 10% Pd) under argon atmosphere was added a solution of **155** (930 mg, 1.88 mmol) in ethanol (10 mL) with a catalytic amount of acetic acid (100 µl). The resulting suspension was hydrogenated under 70 psi at r.t.. After 19 h the reaction was quenched with CH_2Cl_2, filtered over celite and washed with ethanol (30 mL). The filtrate was concentrated *in vacuo* to afford **156** (414 mg, 98%) as a white solid, the NMR data of which were in accordance with Lit.[335]

Methyl 7-*O*-triphenylmethyl-L-*glycero*-α-D-*galacto*-heptopyranoside (**157**), (DS-03-30, DS-04-12, DS-04-23).

Heptopyranoside **156** (376 mg, 1.68 mmol), trityl chloride (935 mg, 3.35 mmol) and DMAP (10.3 mg, 84.3 µmol) were stirred in pyridine (8 mL) at r.t. for 36 h under argon. The reaction was quenched with brine (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure and co-evaporated with toluene. The residue was purified by silica gel chromatography (CH_2Cl_2/methanol, 20:1 to 10:1) to afford **157** (618 mg, 79%) as a white solid.

$[\alpha]_D^{21}$ = + 67.7 (*c* = 0.64, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 2.12 (d, 1 H, OH), 2.72 (m, 1 H, OH), 3.08 (d, 1 H, OH), 3.22-3.25 (dd, $^3J_{6,7a}$ = 6.7 Hz, $^2J_{7a,7b}$ = 9.5 Hz, 1 H, H-7_a), 3.25 (s, 3 H, OCH_3), 3.33 (d, 1 H, OH), 3.38 (dd, $^3J_{6,7b}$ = 5.5 Hz, $^2J_{7a,7b}$ = 9.4 Hz, 1 H, H-7_b), 3.73 (m, 1 H, H-3), 3.80 (dd, $^3J_{1,2}$ = 3.6 Hz, $^3J_{2,3}$ = 9.2 Hz, 1 H, H-2), 3.87 (m, 1 H, H-5), 4.03 (m, 1 H, H-4), 4.10 (m, 1 H, H-6), 4.79 (d, $^3J_{1,2}$ = 3.8 Hz, 1 H, H-1), 7.31 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 55.47 (OCH_3), 64.04 (C-7), 68.27 (C-5), 69.60 (C-2), 71.14 (C-3), 71.62 (C-4), 72.27 (C-6), 87.06 (*C*Ph_3), 99.37 (C-1), 127.24, 127.93, 128.60, 143.63 (18 C, 3 C_6H_5); elemental analysis calcd (%) for $C_{27}H_{30}O_7$ (466.53) + ½ H_2O: C 68.20, H 6.57; found: C 68.47, H 6.77.

Methyl 2,3,4,6-tetra-*O*-benzoyl-7-*O*-triphenylmethyl-L-*glycero*-α-D-*galacto*-heptopyranoside (**158**), (DS-03-37, DS-04-14, DS-04-27).

To a stirred solution of **157** (4.21 g, 9.03 mmol) and DMAP (56.3 mg, 0.461 mmol) in pyridine (50 mL) was slowly added benzoyl chloride (8.3 ml, 72.0 mmol). The mixture was stirred at r.t. for 22 h under argon, and then carefully quenched by adding MeOH (3 mL). The mixture was diluted with CH_2Cl_2 (100 mL) and transferred into a separation funnel. The organic layer was washed with brine (2 x 150 mL) and the aqueous layers were extracted with CH_2Cl_2 (4 x 60 mL). The combined organic layers were dried with Na_2SO_4, filtered and co-evaporated with toluene. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 5:1 to 4:1) to yield **158** (7.41 g, 93%) as a white foam.

$[\alpha]_D^{21}$ = + 144.6 (*c* = 0.57, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 3.30 (dd, $^3J_{6,7a}$ = 5.4 Hz, $^2J_{7a,7b}$ = 10.7 Hz, 1 H, H-7_a), 3.42 (s, 3 H, OCH_3), 3.48 (dd, $^3J_{6,7b}$ = 2.9 Hz, $^2J_{7a,7b}$ = 10.8 Hz, 1 H, H-7_b), 4.73 (m, 1 H, H-5), 5.26 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, H-1), 5.60 (dd, $^3J_{1,2}$ = 3.5 Hz, $^3J_{2,3}$ = 10.6 Hz, 1 H, H-2), 5.64 (m, 1 H, H-6), 5.87 (m, 1 H, H-4), 5.94 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{2,3}$ = 10.6 Hz, 1 H, H-3), 7.14-8.06 (m, 35 H, 7 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 55.53 (OCH_3), 62.09 (C-7), 67.41 (C-5), 68.62 (C-3), 69.12 (C-4), 69.39 (C-2), 72.18 (C-6), 86.91 (*C*Ph_3), 97.32 (C-1), 127.05,

127.90, 128.20, 128.36, 128.40, 128.43, 128.52, 129.17, 129.22, 129.68, 129.78, 129.87, 129.91, 133.01, 133.06, 133.27, 133.32, 143.44 (42 C, 7 C_6H_5), 165.06, 165.33, 165.57, 166.01 (4 C=O); MS (ESI) *m/z*: calcd for $C_{55}H_{46}NaO_{11}$ $[M+Na]^+$: 905.3; found: 905.3; elemental analysis calcd (%) for $C_{55}H_{46}O_{11}$ (882.96): C 74.82, H 5.25; found: C 74.52, H 5.32.

Methyl 2,3,4,6-tetra-*O*-benzoyl-L-*glycero*-α-D-*galacto*-heptopyranoside (**159**), (DS-03-39, DS-04-17, DS-04-30).

To a stirred solution of tritylether **158** (5.20 g, 5.89 mmol) in CH_2Cl_2 (50 mL) was added TES (1.13 mL, 7.08 mmol) and TMSOTf (21.0 µl, 0.109 mmol). After 1 h of stirring at r.t. the reaction was quenched by adding a few drops of H_2O and evaporated under reduced pressure. The resulting syrup was dissolved in THF (20 mL) and 80% AcOH (20 mL) and stirred for 1 h at r.t.. The reaction was then neutralised with $NaHCO_3$, transferred into a separation funnel with ethyl acetate (100 mL) and successively washed with satd. aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The aqueous layers were each extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 4:1 to 2:1) to afford **159** (3.56 g, 94%) as a white foam.

$[\alpha]_D^{21}$ = + 209.2 (*c* = 0.57, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.93 (m, 1 H, OH), 3.44 (s, 3 H, OCH_3), 3.89 (m, 1 H, H-7_a), 4.01 (m, 1 H, H-7_b), 4.70 (m, 1 H, H-5), 5.30 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, H-1), 5.50 (m, 1 H, H-6), 5.66 (dd, $^3J_{1,2}$ = 3.6 Hz, $^3J_{2,3}$ = 10.6 Hz, 1 H, H-2), 5.99 (dd, $^3J_{3,4}$ = 3.3 Hz, $^3J_{2,3}$ = 10.7 Hz, 1 H, H-3), 6.09 (m, 1 H, H-4), 7.21-8.06 (m, 20 H, 4 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 55.60 (OCH_3), 61.62 (C-7), 67.50 (C-5), 68.58 (C-3), 69.30 (C-2, C-4), 73.75 (C-6), 97.45 (C-1), 128.24, 128.41, 128.44, 128.63, 129.05, 129.14, 129.70, 129.76, 129.87, 129.99, 133.14, 133.27, 133.35, 133.60 (24 C, 4 C_6H_5), 165.48, 165.74, 165.94, 166.03 (4 C=O); MS (ESI) *m/z*: calcd for $C_{36}H_{32}NaO_{11}$ $[M+Na]^+$: 663.2; found: 663.2; elemental analysis calcd (%) for $C_{36}H_{32}O_{11}$ (640.64): C 67.49, H 5.03; found: C 67.28, H 5.17.

Methyl 2,3,4,6-tetra-*O*-benzoyl-7-*O*-methanesulfonyl-L-*glycero*-α-D-*galacto*-heptopyranoside (**160**), (DS-03-42, DS-04-18, DS-04-43).

To a stirred solution of **159** (701 mg, 1.09 mmol) and DMAP (6.8 mg, 55.7 µmol) in CH_2Cl_2 (8 mL) and Et_3N (306 µL, 2.20 mmol) was slowly added mesyl chloride (171 µL, 2.20 mmol). The reaction was stirred at r.t. for 26 h under argon. The mixture was diluted with CH_2Cl_2 (20 mL) and transferred into a separation funnel. The organic layer was washed with brine (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified

by column chromatography (petroleum ether/ethyl acetate, 2:1) to yield **160** (761 mg, 97%) as a white foam.

$[\alpha]_D^{21}$ = + 162.3 (*c* = 0.65, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 3.06 (s, 3 H, SCH_3), 3.46 (s, 3 H, OCH_3), 4.42 (dd, $^3J_{6,7a}$ = 4.3 Hz, $^2J_{7a,7b}$ = 11.7 Hz, 1 H, H-7_a), 4.64-4.68 (m, 2 H, H-7_b, H-5), 5.30 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, H-1), 5.65 (m, 1 H, H-6), 5.67 (dd, $^3J_{1,2}$ = 3.5 Hz, $^3J_{2,3}$ = 10.7 Hz, 1 H, H-2), 5.94 (dd, $^3J_{3,4}$ = 3.3 Hz, $^3J_{2,3}$ = 10.7 Hz, 1 H, H-3), 6.05 (m, 1 H, H-4), 7.21-8.05 (m, 20 H, 4 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 37.61 (SCH_3), 55.84 (OCH_3), 67.04 (C-5), 67.57 (C-7), 68.48 (C-3), 68.92 (C-4), 69.01 (C-2), 70.13 (C-6), 97.55 (C-1), 128.27, 128.45, 128.52, 128.66, 128.75, 128.96, 129.05, 129.10, 129.68, 129.89, 130.02, 133.25, 133.43, 133.53, 133.89 (24 C, 4 C_6H_5), 165.47, 165.90, 166.00 (4 C=O); IR (KBr) ν: 3439 (w), 2939 (vw), 1729 (vs, C=O), 1602 (w), 1452 (m), 1364 (m), 1316 (m), 1268 (vs), 1179 (s), 1109 (vs), 1070 (s), 1027 (s), 937 (w), 828 (w), 710 (s) cm^{-1}; MS (ESI) *m*/*z*: calcd for $C_{37}H_{34}NaO_{13}S$ $[M+Na]^+$: 741.2; found: 741.2; elemental analysis calcd (%) for $C_{37}H_{34}O_{13}S$ (718.72): C 61.83, H 4.77; found: C 61.79, H 4.81.

Methyl 7-azido-2,3,4,6-tetra-*O*-benzoyl-7-deoxy-L-*glycero*-α-D-*galacto*-heptopyranoside (**161**), (DS-03-50, DS-03-54, DS-04-20, DS-04-45).

Mesylate **160** (257 mg, 0.358 mmol) was dissolved in DMF (3 mL) under argon. NaN_3 (69.4 mg, 1.07 mmol) was added with stirring and the mixture was heated at 100℃ for 2 d. The reaction was cooled to r.t., quenched with water (1 mL) and transferred into a separation funnel with ethyl acetate (20 mL). The organic layer was washed with H_2O (20 mL) and the aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were dried with Na_2SO_4, filtered and co-evaporated with toluene. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 8:1 to 5:1) to yield **161** (209 mg, 88%) as a yellowish foam.

$[\alpha]_D^{21}$ = + 109.6 (*c* = 0.72, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 3.44 (s, 3 H, OCH_3), 3.55 (dd, $^3J_{6,7a}$ = 4.4 Hz, $^2J_{7a,7b}$ = 13.8 Hz, 1 H, H-7_a), 3.76 (dd, $^3J_{6,7b}$ = 3.2 Hz, $^2J_{7a,7b}$ = 13.8 Hz, 1 H, H-7_b), 4.62 (m, 1 H, H-5), 5.29 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, H-1), 5.59 (m, 1 H, H-6), 5.65 (m, 1 H, H-2), 5.96-5.99 (m, 2 H, H-4, H-3), 7.21-8.07 (m, 20 H, 4 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 50.74 (C-7), 55.66 (OCH_3), 67.58 (C-5), 68.42, 68.95 (C-3, C-4), 69.18 (C-2), 71.45 (C-6), 97.45 (C-1), 128.26, 128.43, 128.52, 128.70, 128.81, 129.02, 129.13, 129.21, 129.69, 129.83, 129.87, 130.02, 133.20, 133.39, 133.46, 133.76 (24 C, 4 C_6H_5), 165.40, 165.44, 165.75, 166.00 (4 C=O); IR (KBr) ν: 3440 (vw), 2934 (vw), 2107 (m, N_3), 1728 (vs, C=O), 1602 (w), 1452 (m), 1315 (m), 1268 (vs), 1178 (m), 1108 (s), 1070 (s), 1027 (m), 929 (vw), 709 (s) cm^{-1}; MS (ESI) *m*/*z*: calcd for $C_{36}H_{31}N_3NaO_{10}$ $[M+Na]^+$: 688.2; found: 688.2; elemental analysis calcd (%) for $C_{36}H_{31}N_3O_{10}$ (665.65): C 64.96, H 4.69, N 6.31; found: C 64.81, H 4.72, N 6.09.

1-*O*-Acetyl-7-azido-2,3,4,6-tetra-*O*-benzoyl-7-deoxy-L-*glycero*-α-D-*galacto*-heptopyranoside (**162**), (DS-03-58, DS-03-97, DS-04-47).

A stirred solution of **161** (210 mg, 0.315 mmol) in AcOH (1.5 mL) and acetic anhydride (1.5 mL) was cooled to 0℃ under argon. Concentrated sulphuric acid (30 µL) was added dropwise to the stirred solution and the reaction warmed to r.t.. After 24 h the reaction was cooled to 0℃ and neutralized by adding satd. aqueous $NaHCO_3$ and pulverized $NaHCO_3$. The mixture was transferred into a separation funnel with CH_2Cl_2 and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 5:1 to 4:1) to afford **162** (201 mg, 92%) as a white foam.

$[\alpha]_D^{21}$ = + 111.5 (*c* = 0.54, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 2.23 (s, 3 H, C(O)CH_3), 3.56 (dd, $^3J_{6,7a}$ = 5.0 Hz, $^2J_{7a,7b}$ = 13.4 Hz, 1 H, H-7_a), 3.75 (dd, $^3J_{6,7b}$ = 4.4 Hz, $^2J_{7a,7b}$ = 13.4 Hz, 1 H, H-7_b), 4.73 (m, 1 H, H-5), 5.51 (m, 1 H, H-6), 5.87 (dd, $^3J_{1,2}$ = 3.7 Hz, $^3J_{2,3}$ = 10.7 Hz, 1 H, H-2), 5.97 (dd, $^3J_{3,4}$ = 3.3 Hz, $^3J_{2,3}$ = 10.8 Hz, 1 H, H-3), 6.06 (m, 1 H, H-4), 6.70 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, H-1), 7.23-7.99 (m, 20 H, 4 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 20.90 (C(O)*C*H_3), 50.43 (C-7), 67.43 (C-2), 68.44 (C-3), 68.63 (C-4), 69.56 (C-5), 71.16 (C-6), 89.80 (C-1), 128.34, 128.37, 128.51, 128.57, 128.65, 128.72, 128.73, 129.01, 129.72, 129.73, 129.77, 129.85, 129.94, 130.05, 133.42, 133.57, 133.77 (24 C, 4 C_6H_5), 165.52 (4 *C*(=O)Ph), 168.74 (*C*(=O)CH_3); IR (KBr) ν: 3440 (vw), 3065 (vw), 2108 (s, N_3), 1760 (s, C=O), 1730 (vs, C=O), 1602 (w), 1585 (vw), 1492 (vw), 1452 (m), 1370 (w), 1316 (m), 1267 (vs), 1218 (s), 1178 (m), 1108, (vs), 1070 (s), 1026 (m), 935 (w), 872 (vw), 709 (s) cm^{-1}; MS (ESI) *m*/*z*: calcd for $C_{37}H_{31}N_3NaO_{11}$ $[M+Na]^+$: 716.2; found: 716.2; elemental analysis calcd (%) for $C_{37}H_{31}N_3O_{11}$ (693.66): C 64.07, H 4.50, N 6.06; found: C 63.95, H 4.54, N 5.99.

Ethyl 7-azido-2,3,4,6-tetra-*O*-benzoyl-7-deoxy-1-thio-L-*glycero*-β-D-*galacto*-heptopyranoside (**163**), (DS-03-62, DS-03-98, DS-03-101, DS-04-59).

ZnI_2 (186 mg, 0.581 mmol) was mixed with activated 4Å molecular sieves (800 mg) in a microwave tube, which was then evacuated overnight. **162** (195 mg, 0.280 mmol) was dissolved in CH_2Cl_2 (4 mL) and added to the tube *via* a syringe. After stirring for 20 min under argon, (ethylthio)trimethylsilane (90%, 105 µL, 0.584 mmol) was added *via* a syringe and the tube was heated by microwave irradiation to 50℃ for 1.5 h. The reaction was filtered through celite and the celite washed with CH_2Cl_2 (30 mL). The filtrate was successively washed with satd. aqueous $NaHCO_3$ (30 ml) and water (30 ml). The aqueous layers were each time extracted with CH_2Cl_2 (3 x 30 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The

crude product was purified by column chromatography (petroleum ether/ethyl acetate, 5.5:1 to 5:1) to afford **163** (159 mg, 82%) as colourless foam.

$[\alpha]_D^{21}$ = + 80.4 (*c* = 0.61, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.16 (t, ^3J = 7.4 Hz, 3 H, SCH_2CH_3), 2.58-2.75 (m, 2 H, SCH_2CH_3), 3.55 (dd, $^3J_{6,7a}$ = 4.5 Hz, $^2J_{7a,7b}$ = 13.8 Hz, 1 H, H-7_a), 3.80 (dd, $^3J_{6,7b}$ = 3.3 Hz, $^2J_{7a,7b}$ = 13.8 Hz, 1 H, H-7_b), 4.37 (m, 1 H, H-5), 4.87 (d, $^3J_{1,2}$ = 10.0 Hz, 1 H, H-1), 5.56 (m, 1 H, H-6), 5.65 (dd, $^3J_{3,4}$ = 3.4 Hz, $^3J_{2,3}$ = 9.9 Hz, 1 H, H-3), 5.80 (m, 1 H, H-2), 5.99 (m, 1 H, H-4), 7.21-8.05 (m, 20 H, 4 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 14.89 (SCH_2CH_3), 24.42 (SCH_2CH_3), 50.59 (C-7), 68.12 (C-4), 68.30 (C-2), 71.57 (C-6), 72.73 (C-3), 75.96 (C-5), 84.22 (C-1), 128.27, 128.38, 128.42, 128.62, 128.65, 128.71, 129.13, 129.17, 129.72, 129.79, 129.84, 130.02, 133.31, 133.43, 133.80 (24 C, 4 C_6H_5), 165.30, 165.38, 165.62 (4 C, C=O); MS (ESI) *m*/*z*: calcd for $C_{37}H_{33}N_3NaO_9S$ $[M+Na]^+$: 718.2; found: 718.3; elemental analysis calcd (%) for $C_{37}H_{33}N_3O_9S$ (695.74): C 63.88, H 4.78, N 6.04; found: C 64.02, H 4.84, N 5.78.

(1*R*,2*R*)-2-Hydroxycyclohexyl-2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranoside (**168**), (DS-03-45, DS-03-51, DS-03-55).

A solution of Br_2 (380 µl, 7.49 mmol) in CH_2Cl_2 (12 mL) was slowly added at 0°C to a solution of ethyl 2,3,4-tri-*O*-benzyl-1-thio-L-fucopyranoside (**166**) (3.00 g, 6.27 mmol) in CH_2Cl_2 (6 mL). After stirring for 1 h at 0 °C, cyclohexene (1.5 mL) was added and the solution stirred for another 20 min. The mixture was added dropwise to a solution of (1*R*,2*R*)-trans-1,2-cyclohexanediol (**167**) (610 mg, 5.25 mmol) and Et_4NBr (1.31 g, 6.23 mmol) in DMF/CH_2Cl_2 (50 mL, 1:1) which has been stirred over activated 4Å molecular sieves (2.4 g) for 2 h. The mixture was stirred for 3 h at r.t.. The reaction was quenched with pyridine (6 mL) and filtered over celite with addition of CH_2Cl_2 (100 mL). The solution was washed with brine (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 70 mL). The combined organic phases were washed with brine (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 70 mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed azeotropically with toluene. The residue was purified by repeated flash chromatography (toluene/ethyl acetate, 10:1 to 9:1) to afford **168** (1.19 g, 42%) as yellowish resin, the NMR data of which were in accordance with Lit.[264]

Benzyl (*R*)-3-cyclohexyl-2-hydroxypropionate (**170**), (DS-03-49, DS-04-39, DS-04-100).

Rh/Al_2O_3 (101 mg, 5% Rh) was suspended under argon in THF/H_2O (10 mL, 1:1). D-(+)-3-Phenyllactic acid (1.99 g, 12.0 mmol) was added and the resulting mixture was hydrogenated under 70 psi at r.t. for 4 days. The reaction was quenched with CH_2Cl_2 and filtered over celite.

The filtrate was concentrated *in vacuo*, suspended in methanol/water (9:1, 10 mL) and the pH adjusted to 8.0 by addition of an aqueous solution of Cs_2CO_3. The solvent was removed azeotropically with toluene and the residue was dried *in vacuo* and redissolved in DMF (35 mL). Benzylbromide (1.43 mL, 12.0 mmol) was slowly added and the mixture was stirred at r.t. for 24 h. The mixture was diluted with CH_2Cl_2 (100 mL) and transferred into a separation funnel. The organic layer was washed with H_2O (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried with Na_2SO_4, filtered and co-evaporated with toluene. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 8:1 to 6:1) to yield **170** (2.51 g, 80%) as a white solid, the NMR data of which were in accordance with Lit.[443]

Benzyl (*R*)-3-cyclohexyl-2-trifluoromethanesulfonyloxypropionate (**171**), (DS-03-90, DS-03-108, DS-04-34, DS-04-85, DS-04-92, DS-04-96).

To a stirred solution of **170** (1.08 g, 4.12 mmol) and 2,6-di-*tert*-butylpyridine (1.20 mL, 5.34 mmol) in CH_2Cl_2 (10 mL) was slowly added Tf_2O (835 µL, 4.96 mmol) at -20°C. The mixture was stirred for 3 h at -20°C under argon. The mixture was diluted with CH_2Cl_2 (20 mL) and transferred into a separation funnel. The organic layer was washed with satd. aqueous KH_2PO_4 (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The organic phases were combined, washed with satd. aqueous KH_2PO_4 (50 mL) and the aqueous layer was reextracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 1:0 to 25:1) to yield **171** (1.54 g, 95%) as a colourless oil, the NMR data of which were in accordance with Lit.[443]

(1*R*,2*R*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 7-azido-2,3,4,6-tetra-*O*-benzoyl-7-deoxy-L-*glycero*-β-D-*galacto*-heptopyranoside (**172**), (DS-03-103, DS-03-105, DS-04-66).

Dry CH_2Cl_2 (10 mL) was added to a mixture of thioglycoside **163** (224 mg, 0.322 mmol), glycosyl acceptor **168** (208 mg, 0.390 mmol) and activated 4Å molecular sieves (4 g) under argon. A suspension of DMTST (258 mg, 0.333 mmol) and activated 4Å molecular sieves (1.5 g) in CH_2Cl_2 (3 mL) was prepared in a second flask. Both suspensions were stirred at r.t. for 4 h, then the DMTST suspension was added in two portions to the other suspension. The reaction was stopped after 67 h and filtered through celite. The celite was washed with CH_2Cl_2 (40 mL). The filtrate was successively washed with satd. aqueous $NaHCO_3$ (40 ml) and water (30 ml). The aqueous layers were each time extracted with DCM (3 x 40 ml). The combined organic layers

were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to afford **172** (333 mg, 89%) as a yellowish foam.

$[\alpha]_D^{21}$ = - 20.1 (*c* = 0.98, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.94 (m, 1 H, Cy), 1.00-1.10 (m, 2 H, Cy), 1.16 (m, 1 H, Cy), 1.23 (d, $^3J_{F5,F6}$ = 6.3 Hz, 3 H, Fuc H-6), 1.43, 1.51, 1.77, 1.92, 3.50 (5 m, 5 H, Cy), 3.56-3.59 (m, 2 H, Cy, Hep H-7_a), 3.70 (m, 1 H, Fuc H-4), 3.77 (dd, $^3J_{H6,H7b}$ = 2.4 Hz, $^2J_{H7a,H7b}$ = 13.8 Hz, 1 H, Hep H-7_b), 4.00 (dd, $^3J_{F1,F2}$ = 3.2 Hz, $^3J_{F2,F3}$ = 9.8 Hz, 1 H, Fuc H-2), 4.11 (m, 1 H, Fuc H-3), 4.28-4.29 (m, 2 H, Hep H-5, Fuc H-5), 4.60-4.74 (4 m, 4 H, 4 CH_2Ph), 4.86 (d, $^3J_{F1,F2}$ = 3.4 Hz, 1 H, Fuc H-1), 4.90 (d, 1 H, Hep H-1), 4.92, 5.00 (2 m, 2 H, 2 CH_2Ph), 5.53-5.56 (m, 2 H, Hep H-3, Hep H-6), 5.72 (m, 1 H, Hep H-2), 5.92 (m, 1 H, Hep H-4), 7.21-8.07 (m, 35 H, 7 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.86 (Fuc C-6), 22.35, 22.39, 28.04, 28.08 (4 C, Cy), 50.46 (Hep C-7), 66.36 (Fuc C-5), 68.00 (Hep C-4), 69.74 (Hep C-2), 71.34, 72.15 (3 C, Hep C-3, Hep C-5, Hep C-6), 72.85, 73.00, 74.76 (3 *C*H_2Ph), 75.12 (Cy), 76.62 (Fuc C-2), 77.54 (Cy), 78.65 (Hep C-4), 79.57 (Fuc C-3), 94.71 (Fuc C-1), 98.45 (Hep C-1), 127.18, 127.32, 127.39, 127.43, 127.78, 128.19, 128.26, 128.37, 128.61, 128.64, 128.86, 129.17, 129.34, 129.59, 129.73, 129.83, 130.04, 133.18, 133.22, 133.29, 133.82, 138.92, 139.07, 139.36 (42 C, 7 C_6H_5), 164.96, 165.31, 165.44, 165.62 (4 C=O); elemental analysis calcd (%) for $C_{68}H_{67}N_3O_{15}$ (1166.27): C 70.03, H 5.79, N 3.60; found: C 69.96, H 5.85, N 3.60.

(1*R*,2*R*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 7-azido-7-deoxy-L-*glycero*-β-D-*galacto*-heptopyranoside (**173**), (DS-03-106, DS-03-110, DS-04-72).

172 (333 mg, 0.286 mmol) was dissolved in methanol (8 ml) and sodium methanolate (0.029 mmol in 108 µl MeOH) was added. After stirring at r.t. under argon for 13 h additional sodium methanolate (0.029 mmol in 108 µl MeOH) was added. After stirring the reaction for totally 23 h the reaction was quenched by addition of acetic acid (15 µl). The mixture was concentrated *in vacuo* and the crude product was purified by column chromatography (CH_2Cl_2/methanol, 20:1) to afford **173** (207 mg, 97%) as a yellowish foam.

$[\alpha]_D^{21}$ = - 65.3 (*c* = 0.54, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.10 (d, $^3J_{F5,F6}$ = 6.5 Hz, 3 H, Fuc H-6), 1.12-1.38 (m, 4 H, Cy), 1.68-1.72 (m, 2 H, Cy), 1.89 (s, 1 H, OH), 2.02-2.07 (m, 2 H, Cy), 2.94, 2.97, 3.06 (3 s, 3 H, 3 OH), 3.29 (dd, $^3J_{H6,H7a}$ = 5.1 Hz, $^2J_{H7a,H7b}$ = 12.6 Hz, 1 H, Hep H-7_a), 3.40 (m, 1 H, Gal H-5), 3.45 (dd, $^3J_{H6,H7b}$ = 5.2 Hz, $^2J_{H7a,H7b}$ = 12.6 Hz, 1 H, Hep H-7_b), 3.51-3.58 (m, 3 H, Hep H-2, Hep H-3, Cy), 3.68-3.73 (m, 2 H, Fuc H-4, Cy), 3.91 (m, 1 H, Hep H-4), 3.99-4.05 (m, 3 H, Hep H-6, Fuc H-3, Fuc H-2), 4.31 (d, $^3J_{H1,H2}$ = 6.7 Hz, 1 H, Hep H-1), 4.35 (m, 1 H, Fuc H-5), 4.61, 4.68, 4.76, 4.78, 4.82, 4.95 (6 m, 6 H, 3 CH_2Ph), 4.97 (d, $^3J_{F1,F2}$ = 3.0 Hz, 1 H, Fuc H-1), 7.24-7.41 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.68 (Fuc C-6),

23.53, 23.57, 29.51, 29.67 (4 C, Cy), 52.19 (Hep C-7), 66.31 (Fuc C-5), 69.47 (Hep C-4), 71.01, 71.02 (Hep C-2, Hep C-6), 72.56 (*C*H_2Ph), 73.21, 73.27 (2 C, Hep C-3, *C*H_2Ph), 73.54 (Hep C-5), 74.85 (*C*H_2Ph), 76.18, 76.31 (2 C, Fuc C-3, Cy), 77.75, 78.13 (2 C, Fuc C-4, Cy), 79.52 (Fuc C-2), 94.38 (Fuc C-1), 100.22 (Hep C-1), 127.31, 127.47, 127.67, 128.00, 128.13, 128.28, 128.29, 128.30, 138.43, 138.74, 139.04 (18 C, 3 C_6H_5); elemental analysis calcd (%) for $C_{40}H_{51}N_3O_{11}$ (749.85): C 64.07, H 6.86, N 5.60; found: C 64.20, H 6.85, N 5.44.

(1*R*,2*R*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 7-azido-3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-7-deoxy-L-*glycero*-β-D-*galacto*-heptopyranoside (**174**), (DS-03-109, DS-03-112, DS-04-99).

A suspension of **173** (136 mg, 0.181 mmol) and Bu_2SnO (49.6 mg, 0.199 mmol) in dry MeOH (4 mL) was refluxed for 3 h. The solvent was removed and the resulting foam dried *in vacuo* overnight. CsF (55.0 mg, 0.362 mmol) was dried *in vacuo* at 200°C for 30 min and flushed with argon. Then the triflate **171** (144 mg, 0.365 mmol) and the tin acetal were added to the CsF in DME (5 mL) *via* syringe. The reaction was stirred for 24 h, transferred into a separation funnel with ethyl acetate and extracted with brine (2 x 25 mL). The aqueous layers were each extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 3:1) to afford **174** (97.3 mg, 54%) as yellowish foam.

$[\alpha]_D^{21}$ = - 63.8 (*c* = 0.85, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.86-2.04 (m, 21 H, CyCH_2, Cy), 1.10 (d, $^3J_{F5,F6}$ = 6.5 Hz, 3 H, Fuc H-6), 2.40 (s, 1 H, OH), 3.20 (dd, $^3J_{H6,H7a}$ = 4.9 Hz, $^2J_{H7a,H7b}$ = 12.6 Hz, 1 H, Hep H-7_a), 3.25 (dd, $^3J_{H3,H4}$ = 3.1 Hz, $^3J_{H2,H3}$ = 9.3 Hz, 1 H, Hep H-3), 3.32 (m, 1 H, Hep H-5), 3.39 (dd, $^3J_{H6,H7b}$ = 5.3 Hz, $^2J_{H7a,H7b}$ = 12.6 Hz, 1 H, Hep H-7_b), 3.50-3.55 (m, 2 H, OH, Cy), 3.65-3.70 (m, 2 H, Hep H-2, Cy), 3.72 (m, 1 H, Fuc H-4), 3.76 (m, 1 H, Hep H-4), 3.99-4.04 (m, 4 H, Fuc H-2, Fuc H-3, Hep H-6, OH), 4.26-4.27 (m, 2 H, Hep H-1, Lac H-2), 4.44 (m, 1 H, Fuc H-5), 4.62, 4.68, 4.77, 4.78, 4.84, 4.95 (6 m, 6 H, 3 C*H*$_2$Ph), 4.92 (d, $^3J_{F1,F2}$ = 2.7 Hz, 1 H, Fuc H-1), 5.15-5.21 (m, 2 H, C*H*$_2$Ph), 7.25-7.42 (m, 20 H, 4 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.66 (Fuc C-6), 23.45, 29.48, 29.67, 30.50 (4 C, Cy), 25.97, 26.18, 26.37, 32.08, 33.49, 33.84 (6C, Cy, CyCH_2), 40.92 (Cy*C*H_2), 52.10 (Hep C-7), 66.17 (Fuc C-5), 67.21 (*C*H_2Ph), 68.31 (Hep C-4), 70.68 (Hep C-2), 71.00 (Hep C-6), 72.61 (*C*H_2Ph), 72.96, 73.08 (2 C, Hep C-5, *C*H_2Ph), 74.85 (*C*H_2Ph), 76.14, 76.18 (2 C, Fuc C-2, Cy), 77.32 (Lac C-2), 77.94 (Fuc C-4), 78.47 (Cy), 79.72 (Fuc C-3), 82.61 (Hep C-3), 94.75 (Fuc C-1), 100.53 (Hep C-1), 127.19, 127.27, 127.37, 127.49, 127.91, 128.08, 128.23, 128.24, 128.29, 128.53, 128.71, 135.11,

138.74, 138.93, 139.31 (24 C, 4 C_6H_5), 174.90 (C=O); elemental analysis calcd (%) for $C_{56}H_{71}N_3O_{13}$ (994.18): C 67.65, H 7.20, N 4.23; found: C 67.58, H 7.32, N 4.18.

(1*R*,2*R*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 7-amino-3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-7-deoxy-L-*glycero*-β-D-*galacto*-heptopyranoside (**175**), (DS-03-111, DS-04-103).

174 (346 mg, 0.348 mmol) was dissolved in THF (8 mL) and PPh_3 (184 mg, 0.700 mmol) was added. After stirring under argon for 24 h, H_2O (200 μL) was added and the reaction stirred for another 4 h. The mixture was concentrated *in vacuo* and the crude product was purified by column chromatography (petroleum ether/CH_2Cl_2/methanol, 20:20:1 to 0:20:1, + 0.5% Et_3N) to afford **175** (332 mg, 98%) as a colourless foam.

^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.86-0.97, 1.21-1.32, 1.55-1.67, 1.87-1.89, 2.08 (m, 21 H, $CyCH_2$, Cy), 1.15 (m, 3 H, Fuc H-6), 2.53 (dd, $^3J_{H6,H7a}$ = 7.2 Hz, $^2J_{H7a,H7b}$ = 13.0 Hz, 1 H, Hep H-7_a), 2.71 (dd, $^3J_{H6,H7b}$ = 3.2 Hz, $^2J_{H7a,H7b}$ = 13.0 Hz, 1 H, Hep H-7_b), 3.16 (m, 1 H, Gal H-5), 3.23 (dd, $^3J_{H3,H4}$ = 2.9 Hz, $^3J_{H2,H3}$ = 9.3 Hz, 1 H, Hep H-3), 3.52 (m, 1 H, Cy), 3.57 (m, 1 H, Hep H-2), 3.70 (m, 1 H, Cy), 3.79-3.83 (m, 2 H, Hep H-4, Hep H-6), 3.90 (m, 1 H, Fuc H-4), 3.96 (m, 1 H, Fuc H-2), 4.07 (dd, $^3J_{F3,F4}$ = 2.6 Hz, $^3J_{F2,F3}$ = 10.1 Hz, 1 H, Fuc H-3), 4.23 (d, $^3J_{H1,H2}$ = 7.7 Hz, 1 H, Hep H-1), 4.49 (m, 1 H, Lac H-2), 4.59-4.62 (m, 2 H, C*H*$_2$Ph), 4.68-4.74 (m, 3 H, Fuc H-5, C*H*$_2$Ph), 4.82-4.91 (m, 2 H, C*H*$_2$Ph), 4.96 (d, $^3J_{F1,F2}$ = 2.9 Hz, 1 H, Fuc H-1), 5.15, 5.23 (2 m, 2 H, C*H*$_2$Ph), 7.25-7.45 (m, 20 H, 4 C_6H_5); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 16.95 (Fuc C-6), 24.76, 24.85, 27.19, 27.43, 27.65, 31.06, 31.34, 33.47, 34.65, 35.08, 42.30 84 (11 C, Cy, $CyCH_2$), 43.83 (Hep C-7), 65.21 (*C*H$_2$Ph), 67.75 (Fuc C-5), 68.88 (Hep C-4), 72.48, 72.95 (Hep C-2, Hep C-6), 73.85, 74.27, 76.34 (3 *C*H$_2$Ph), 76.88 (Hep C-5), 77.58 (Fuc C-2), 78.03 (1 C, Cy), 78.43 (Lac C-2), 78.89 (1 C, Cy), 79.79 (Fuc C-4), 80.94 (Fuc C-3), 83.58 (Hep C-3), 95.78 (Fuc C-1), 102.22 (Hep C-1), 127.97, 128.24, 128.42, 128.46, 128.58, 128.82, 129.18, 129.34, 129.37, 129.46, 139.80, 140.22, 140.67, 142.67 (24 C, 4 C_6H_5), 177.30 (C=O); HR-MS (ESI) *m*/*z*: calcd for $C_{56}H_{73}NNaO_{13}$ $[M+Na]^+$: 990.4974; found: 990.4971 (0.3 ppm).

***n*-Butyl pyruvate** (**177**), (DS-03-65).

Freshly destilled pyruvic acid (41.2 g, 468 mmol) was esterified with *n*-butanol (51.9 g, 700 mmol) in benzene (80 mL). After refluxing for 18 h with a water separator, the reaction mixture was concentrated and vacuum distilled to give *n*-butyl pyruvate (53.3 g, 79%) as a pale green-yellowish oil, the NMR data of which were in accordance with Lit.[444]

Butyl 2-oxopropanoate (5-carboxy-2-chlorophenyl) hydrazone (**180**), (DS-03-67, DS-03-74, DS-03-84).

3-Amino-4-chlorobenzoic acid (6.87 g, 40.1 mmol) was suspended in H_2O (30 mL) and dissolved with conc. HCl (32 mL). While stirring mechanically, the solution was cooled to -10°C. Sodium nitrite (3.31 g, 48.0 mmol) was dissolved in H_2O (16 mL) and carefully added to the reaction, not allowing the temperature to raise above 0°C. After stirring for 10 min at -10°C, tin(II) chloride dihydrate (27.1 g, 120 mmol) dissolved in conc. HCl (30 mL) was slowly added and the reaction stirred at -10°C for another 30 min. *n*-Butyl pyruvate (11.5 g, 80.1 mmol) was added to the white suspension and the mixture heated to 90°C for 2.5 h. The reaction mixture was allowed to cool to r.t. and the product was extracted into ethyl acetate (3 x 100 mL). The combined organic layers were successively washed with HCl (3 M, 3 x 100 mL), dilute HCl (0.1 M, 150 mL) and brine (100 mL). The organic layer was concentrated to a syrup under reduced pressure, then ice was added and, after melting, the yellow pellets were filtered off and dried *in vacuo* at 50°C to give hydrazone **180** (10.7 g, 86%).

^{1}H-NMR (DMSO, 500.1 MHz) δ: 0.86 (t, ^3J = 7.4 Hz, 3 H, *n*Bu), 1.34 (m, 2 H, *n*Bu), 1.59 (m, 2 H, *n*Bu), 2.10 (CH_3), 4.18 (m, ^3J = 6.5 Hz, 2 H, *n*Bu), 7.41 (m, 1 H, C_6H_3), 7.49 (m, 1 H, C_6H_3), 8.02 (m, 1 H, C_6H_3), 12.30 (s, 1 H, NH), 13.19 (br, s, 1 H, COOH); ^{13}C-NMR (DMSO, 125.8 MHz) δ: 13.91 (*n*Bu), 19.02 (*n*Bu), 19.93 (*C*H_3), 30.28 (*n*Bu), 65.23 (*n*Bu), 114.36, 121.77, 122.64, 130.10, 130.46, 131.26 (6 C, C_6H_3), 139.88 (C=N), 163.52 (C=O), 166.97 (COOH); MS (ESI) *m*/*z*: calcd for $C_{14}H_{16}ClN_2O_4$ $[M-H]^-$: 311.1; found: 311.1; elemental analysis calcd (%) for $C_{14}H_{17}ClN_2O_4$ (312.75): C 53.77, H 5.48, N 8.96; found: C 53.78, H 5.50, N 8.75.

2-Butoxycarbonyl-7-chloro-indole-4-carboxylic acid (**181**), (DS-03-77, DS-03-83, DS-03-85).

Hydrazone **180** (1.29 g, 4.13 mmol) was placed in a microwave tube and purged with argon. AcOH (5 mL) and BF_3 etherate (1.04 mL, 8.25 mmol) were added and the mixture heated in the microwave for 5 h to 90°C. The mixture was poured into ice-water, filtered and dried *in vacuo*. The crude product was purified by column chromatography (toluene/THF, 5:1 to 3:1) to afford **181** (196 mg, 16%) as a creamy solid. For the scaling-up, purification was performed by redissolving the crude product in THF and treatment with an equal amount of activated charcoal. Filtration, concentration *in vacuo* and recrystallization from acetone yielded the pure indole as a creamy solid.

^{1}H-NMR (DMSO, 500.1 MHz) δ: 0.89 (t, 3 H, *n*Bu), 1.37 (m, 2 H, *n*Bu), 1.67 (m, 2 H, *n*Bu), 4.27 (t, 2 H, *n*Bu), 7.41, 7.62, 7.71 (m, 3 H, Ind), 12.43 (s, 1 H, NH), 13.05 (br, s, 1 H, COOH); ^{13}C-NMR (DMSO, 125.8 MHz) δ: 13.65, 18.73, 30.29, 64.59 (4 C, *n*Bu), 109.77, 122.03, 122.48, 123.89, 124.72, 127.50, 130.56, 135.05 (8 C, Ind), 160.81 (COO*n*Bu), 167.23 (COOH); MS

(ESI) *m/z*: calcd for $C_{14}H_{13}ClNO_4$ $[M-H]^-$: 294.1; found: 294.0; elemental analysis calcd (%) for $C_{14}H_{14}ClNO_4$ (295.72): C 56.86, H 4.77, N 4.74; found: C 56.77, H 4.80, N 4.72.

***tert*-Butyl 2-butoxycarbonyl-7-chloro-indole-4-carboxylate** (**182**), (DS-03-87).

Carboxylic acid **181** (1.22 g, 4.13 mmol) and CDI (1.00 g, 6.19 mmol) were placed in a flask under argon. THF (20 mL) was slowly added and the solution heated to 50°C while stirring. After 1.5 h *t*BuOH (2 mL, 21.2 mmol) and DBU (930 µL, 6.22 mmol) were added and the reaction heated at reflux for 76 h. The mixture was transferred into a separation funnel with ethyl acetate (100 mL) and washed with satd. aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with ethyl acetate (2 x 80 mL). The combined organic phases were washed with brine (150 mL) and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 30:1 to 25:1) to afford **182** (777 mg, 54%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.00 (t, 3 H, *n*Bu), 1.50 (m, 2 H, *n*Bu), 1.67 (s, 9 H, *t*Bu), 1.78 (m, 2 H, *n*Bu), 4.38 (t, 2 H, *n*Bu), 7.35 (m, 1 H, Ind), 7.83 (m, 2 H, Ind), 9.14 (s, 1 H, NH); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 13.72, 19.19, 30.71, 65.31 (4 C, *n*Bu), 28.31 (3 C, $C(CH_3)_3$), 81.52 ($C(CH_3)_3$), 110.46, 121.92, 123.64, 124.13, 124.96, 127.75, 129.53, 134.54 (8 C, Ind), 161.60 (COO*n*Bu), 165.41 (COO*t*Bu); MS (ESI) *m/z*: calcd for $C_{18}H_{21}ClNO_4$ $[M-H]^-$: 350.1; found: 350.1; elemental analysis calcd (%) for $C_{18}H_{22}ClNO_4$ (351.82): C 61.45, H 6.30, N 3.98; found: C 61.44, H 6.43, N 3.92.

***tert*-Butyl 7-chloro-2-[(4-methyl-1-piperazinyl)carbonyl]-indole-4-carboxylate** (**183**), (DS-03-92, DS-03-104).

Butylester **182** (197 mg, 0.561 mmol) was dissolved in acetone (4 mL) under argon. Aqueous NaOH (0.5 M, 1.15 mL, 0.577 mmol) was added and the reaction stirred for 69 h under protection from light. The mixture was concentrated and dried *in vacuo* overnight. Imidazol (172 mg, 2.53 mmol) was dissolved in acetonitrile (3 mL) under argon and cooled to 0°C. Oxalyl dichloride (54.0 µL, 0.619 mmol) was slowly added and the reaction warmed to r.t.. After stirring for 15 min the dry indole was added in acetonitrile (10 mL) and the mixture was heated to 45°C for 1 h. *N*-Methylpiperazine (70.0 µL, 0.631 mmol) was added and the temperature increased to 55°C. After stirring for 3 h under argon the mixtu re was concentrated under reduced pressure and purified by flash chromatography (CH_2Cl_2/methanol, 20:1) to afford **183** (188 mg, 89%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.65 (s, 9 H, *t*Bu), 2.36 (s, 3 H, CH_3), 2.51 (s, 4 H, Pip H-3, Pip H-5), 3.98 (br, s, 4 H, Pip H-2, Pip H-6), 7.30, 7.47, 7.81 (3 m, 3 H, Ind), 9.39 (s, 1 H, NH); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 28.33 (3 C, C(*C*H_3)$_3$), 46.03 (CH_3), 55.01 (4 C, Pip), 81.26 (*C*(CH_3)$_3$), 107.16, 121.89, 122.81, 123.34, 124.81, 127.88, 131.44, 133.42 (8 C, Ind), 161.41, 165.57 (2 C=O); MS (ESI) *m/z*: calcd for $C_{19}H_{25}ClN_3O_3$ $[M+H]^+$: 378.2; found: 378.1; elemental analysis calcd (%) for $C_{19}H_{24}ClN_3O_3$ (377.87): C 60.39, H 6.40, N 11.12; found: C 60.27, H 6.57, N 11.03.

***tert*-Butyl 2-[(4-methyl-1-piperazinyl)carbonyl]-7-phenyl-indole-4-carboxylate** (**184**), (DS-03-107, DS-03-113, DS-03-121).

$Pd_2(dba)_3$ (1.7 mg, 1.64 μmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos, 3.3 mg, 8.04 μmol) were placed in a flask which was evacuated and flushed with argon several times. Toluene (2 mL) was added and the catalyst stirred under argon for 45 min at 50°C. Arylchloride **183** (60.9 mg, 0.161 mmol), phenylboronic acid (29.7 mg, 0.244 mmol) and Cs_2CO_3 (161 mg, 0.493 mmol) were placed in a microwave tube and dried *in vacuo* at 50°C for 1 h. The tube was flushed with argon and the catalyst was added *via* syringe. After flushing for 10 min with argon, the solvent was degassed in ultrasonic bath for 10 min and the tube flushed with argon for another 10 min. The reaction was heated by microwave irradiation to 90°C for 3 h. The mixture was transferred into a separation funnel with ethyl acetate (10 mL) and extracted with satd. aqueous $NaHCO_3$ (2 x 10 mL). The aqueous layers were each extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2/methanol, 20:1) to afford **184** (68.2 mg, 100%) as crystalline solid.

^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.68 (s, 9 H, *t*Bu), 2.35 (s, 3 H, CH_3), 2.50 (m, 4 H, Pip H-3, Pip H-5), 3.91-4.04 (b, m, 4 H, Pip H-2, Pip H-6), 7.32, 7.44, 7.50-7-53, 7.61-7.63, 7.97 (m, 8 H, Ar-H), 9.31 (b, s, 1 H, NH); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 28.39 (3 C, C(*C*H_3)$_3$), 46.04 (CH_3), 54.98 (4 C, Pip), 80.92 (*C*(CH_3)$_3$), 106.78, 123.26, 123.48, 124.72, 127.22, 128.27, 128.34, 129.32, 130.70, 130.98, 134.10, 37.66 (14 C, Ar-C), 161.88, 166.17 (2 C=O); elemental analysis calcd (%) for $C_{25}H_{29}N_3O_3$ (419.52): C 71.57, H 6.97, N 10.02; found: C 71.17, H 7.07, N 9.77.

Sodium 2-[(4-methyl-1-piperazinyl)carbonyl]-7-phenyl-indole-4-carboxylate (**185**), (DS-03-114, DS-03-122).

Indole **184** (89.1 mg, 0.212 mmol) was dissolved in CH_2Cl_2 (2 mL). The solution was treated with TFA (861 μL), TIS (43.5 μL, 0.212 mmol) and H_2O (33.6 μL) in CH_2Cl_2 (500 μL) and stirred for

70 min. The solvent was removed azeotropically with toluene and *in vacuo*. The residue was redissolved in CH_2Cl_2 (1 mL) and Na_2CO_3 (113 mg, 1.06 mmol) dissolved in H_2O-methanol (1:1, 1 mL) was added. After stirring for 15 min the solvents were removed and the residue was purified by reversed-phase chromatography (methanol/H_2O, 0:10 to 1:5) to afford **185** (59.8 mg, 73%) as colourless film.

^{1}H-NMR (MeOD, 500.1 MHz) δ: 2.34 (s, 3 H, CH_3), 2.53 (m, 4 H, Pip H-3, Pip H-5), 3.90 (b, m, 4 H, Pip H-2, Pip H-6), 7.26, 7.41, 7.50-7.53, 7.56, 7.65-7.67, 7.79 (m, 8 H, Ar-H), ^{13}C-NMR (MeOD, 125.8 MHz) δ: 46.01 (CH_3), 55.92 (4 C, Pip), 108.77, 123.94, 124.46, 128.59, 128.75, 129.46, 129.56, 130.09, 131.19, 131.77, 135.79, 139.92 (14 C, Ar-C), 164.93, 176.23 (2 C=O); MS (ESI) *m/z*: calcd for $C_{21}H_{22}N_3O_3$ $[M+H]^+$: 364.2; found: 364.1.

Methyl 5-benzoyl-indole-3-carboxylate (**187**) and **Methyl 6-benzoyl-indole-3-carboxylate** (**188**), (DS-04-25).

To an ice-cold solution of methyl indole-3-carboxylate (200 mg, 1.14 mmol) in nitromethane (8 mL) was added benzoyl chloride (380 µL, 3.29 mmol) and the mixture was stirred for 15 min. $AlCl_3$ (453 mg, 3.40 mmol) was rapidly added and the reaction stirred for 2.5 h at r.t.. The reaction was then cooled to 0°C, quenched with methanol (10 mL) and poured into an ice-cold solution of $NaHCO_3$ (70 mL). The suspension was extracted with ethyl acetate (100 mL). The organic layer was successively washed with satd. aqueous $NaHCO_3$ (70 mL) and brine (70 mL). The aqueous layers were each extracted with ethyl acetate (2 x 70 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 2:1 to 5:3) to afford the 5-benzoylated indole **187** (227 mg, 71%) and the 6-benzoylated indole **188** (84.8 mg, 27%) as pinkish solids.

Methyl 5-benzoyl-indole-3-carboxylate (**187**):

^{1}H-NMR (DMSO, 500.1 MHz) δ: 3.79 (s, 3 H, CH_3), 7.57 (m, 2 H, Bz), 7.63-7.71 (m, 3 H, H-6, H-7, Bz), 7.73 (m, 2 H, Bz), 8.25 (m, 1 H, H-2), 8.45 (m, 1 H, H-4), 12.32 (s, 1 H, NH); ^{13}C-NMR (DMSO, 125.8 MHz) δ: 50.86 (CH_3), 107.57 (C-3), 112.59 (C-7), 123.96 (C-4), 124.12 (C-6), 125.06 (C-8), 128.39 (2 C, Bz), 129.41 (2 C, Bz), 130.39 (C-5), 132.03 (Bz), 134.37 (C-2), 138.26 (Bz), 138.80 (C-8), 164.33 (*C*OOMe), 196.02 (CO); IR (KBr) ν: 3226 (s), 2923 (vw), 1717 (vs), 1633 (vs), 1618 (s), 1573 (m), 1533 (m), 1449 (vs), 1370 (m), 1334 (s), 1311 (s), 1295 (s), 1245 (m), 1193 (s), 1127 (vs), 1105 (s), 1044 (m), 882 (m), 775, (m), 713 (s), 692 (m) cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{13}NO_3$ (279.29): C 73.11, H 4.69, N 5.02; found: C 73.06, H 4.89, N 4.88.

Methyl 6-benzoyl-indole-3-carboxylate (**188**):

^{1}H-NMR (DMSO, 500.1 MHz) δ: 3.84 (s, 3 H, CH_3), 7.57 (m, 2 H, Bz), 7.67 (m, 2 H, H-5, Bz), 7.75 (m, 2 H, Bz), 7.89 (m, 1 H, H-7), 8.13 (m, 1 H, H-4), 8.34 (m, 1 H, H-2), 12.25 (s, 1 H, NH); ^{13}C-NMR (DMSO, 125.8 MHz) δ: 50.89 (CH_3), 106.82 (C-3), 115.58 (C-7), 120.30 (C-4), 122.68 (C-5), 128.44 (2 C, Bz), 129.06 (C-8), 129.42 (2 C, Bz), 131.06 (C-6), 132.06 (Bz), 135.57, 135.88 (C-2, C-8), 138.12 (Bz), 164.40 (*C*OOMe), 195.76 (CO).

5-Benzoyl-indole-3-carboxylic acid (**189**), (DS-04-38).

Methylester **187** (102 mg, 0.365 mmol) was dissolved in acetonitrile (5 mL) under argon. Aqueous NaOH (1.0 M, 10 mL) was added and the reaction stirred for 10 d. The acetonitrile was removed on a rotary evaporator and the aqueous solution acidified to pH 2.0 with aqueous HCl (6.0 M). Filtration and washing with cold H_2O gave **189** (99.1 mg, 100%) as a brownish solid, the NMR data of which were in accordance with Lit.[RD40]

(1*R*,2*R*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-7-[(1,1'-biphenyl-4-yl-carbonyl)amino]-7-deoxy-L-*glycero*-β-D-*galacto*-heptopyranoside (**190**) and lactone derivative (**191**) and methyl ester thereof (**192**), (DS-03-119).

175 (34.1 mg, 35.2 µmol) was dissolved in CH_2Cl_2 (1.5 mL) and acetonitrile (1 mL). Triethylamine (550 µL) and biphenyl-4-carbonyl chloride (99.6 mg, 460 µmol) were added and the reaction stirred under argon for 30 min. The reaction was quenched with methanol (2 mL) and concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 and extracted with satd. aqueous Na_2CO_3 (2 x 30 mL). The aqueous layers were each extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 2:1 to 1:1) to afford **190** (12.5 mg, 31%) and a mixture of the lactone derivative **191** and methyl ester **192** thereof (**191**+**192**: 10.9 mg) as colourless solids, which were directly used for deprotection.

190:

^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.84-2.03 (m, 21 H, $CyCH_2$, Cy), 1.12 (d, $^{3}J_{F5,F6}$ = 6.4 Hz, 3 H, Fuc H-6), 2.36 (s, 1 H, OH), 3.24 (dd, $^{3}J_{H2,H3}$ = 9.3 Hz, $^{3}J_{H3,H4}$ = 3.1 Hz, 1 H, Hep H-3), 3.27 (m, 1 H, Hep H-5), 3.51-3.57 (m, 2 H, Hep H-7_a, Cy), 3.61-3.73 (m, 5 H, Hep H-2, Hep H-7_b, Cy, 2 OH), 3.76 (m, 1 H, Fuc H-4), 3.94 (m, 1 H, Hep H-4), 4.03 (dd, $^{3}J_{F1,F2}$ = 3.5 Hz, $^{3}J_{F2,F3}$ = 10.1 Hz,

1 H, Fuc H-2), 4.09-4.14 (m, 2 H, Fuc H-3, Hep H-6), 4.23 (m, 1 H, Lac H-2), 4.28 (d, $^{3}J_{H1,H2}$ = 7.7 Hz, 1 H, Hep H-1), 4.47 (m, 1 H, Fuc H-5), 4.63, 4.68, 4.78, 4.78, 4.86, 4.96 (6 m, 6 H, 3 C*H*$_2$Ph), 4.96 (d, $^{3}J_{F1,F2}$ = 3.6 Hz, 1 H, Fuc H-1), 5.14, 5.22 (2 m, 2 H, C*H*$_2$Ph), 6.64 (t, ^{3}J = 5.2 Hz, 1 H, NH), 7.19-7.74 (m, 29 H, Ar-H); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.70 (Fuc C-6), 23.43, 25.98, 26.20, 26.39, 29.31, 29.68, 30.53, 32.12, 33.48, 33.84 (10 C, Cy, $CyCH_2$), 40.90 (Lac C-3), 42.24 (Hep C-7), 66.20 (Fuc C-5), 67.32 (*C*H$_2$Ph), 67.93 (Hep C-4), 70.32 (Hep C-6), 70.61 (Hep C-2), 72.56, 73.04 (2 C, 2 *C*H$_2$Ph), 74.49 (Hep C-5), 74.89 (*C*H$_2$Ph), 75.86 (1 C, Cy), 76.24 (Fuc C-2), 77.13 (Lac C-2), 77.94 (Fuc C-4), 78.47 (1 C, Cy), 79.82 (Fuc C-3), 83.01 (Hep C-3), 94.42 (Fuc C-1), 100.67 (Hep C-1), 127.16, 127.27, 127.41, 127.52, 127.86, 127.92, 128.12, 128.28, 128.56, 128.62, 128.68, 128.88, 132.90, 135.16, 138.72, 138.89, 139.15, 140.05, 144.12 (36 C, Ar-C), 167.27, 174.98 (2 C=O); MS (ESI) *m*/*z*: calcd for $C_{69}H_{81}NNaO_{14}$ $[M+Na]^+$: 1170.6; found: 1170.7.

(1*R*,2*R*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 7-[(1,1'-biphenyl-4-yl-carbonyl)amino]-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-7-deoxy-L-*glycero*-β-D-*galacto*-heptopyranoside sodium salt (**193**), (DS-04-1).

Pd/C (32 mg, 10% Pd) was suspended under argon in dioxane/H_2O (5:1, 3.6 mL). Compound **190** (12.5 mg, 10.9 μmol) and a mixture of **191** and **192** (10.9 mg) were added and the resulting mixture was hydrogenated under 70 psi at r.t.. After 40 h the reaction was filtered through celite, concentrated under reduced pressure, redissolved in methanol (1 mL) and aqueous NaOH (0.5 M, 86.0 μL, 43.0 μmol) was added. After stirring for 50 min, the mixture was neutralized with Dowex 50x8 (H^+) and concentrated *in vacuo*. The residue was purified by reversed-phase column chromatography (RP-18, methanol/H_2O) to give 11.5 mg of **193**. The residue was treated with 1 eq. of aqueous NaOH (0.5 M, 28.4 μL, 14.2 μmol) and purified by Sephadex G15 column to give **193** (10.8 mg, 38% over two steps) as a colourless solid.

$[\alpha]_D^{21}$ = - 58.4 (*c* = 0.32, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.87-1.71 (m, 18 H, $CyCH_2$, Cy), 1.20 (d, $^{3}J_{F5,F6}$ = 6.6 Hz, 3 H, Fuc H-6), 1.92 (m, 1 H, $CyCH_2$), 2.07 (m, 2 H, Cy), 3.26 (dd, $^{3}J_{H2,H3}$ = 9.2 Hz, $^{3}J_{H3,H4}$ = 1.6 Hz, 1 H, Hep H-3), 3.39 (m, 1 H, Hep H-5), 3.51-3.64 (m, 3 H, Hep H-2, Hep H-7_a, Cy), 3.69-3.75 (m, 4 H, Fuc H-2, Fuc H-4, Hep H-7_b, Cy), 4.00 (dd, 1 H, $^{3}J_{F2,F3}$ = 10.1 Hz, $^{3}J_{F3,F4}$ = 3.2 Hz, Fuc H-3), 4.09 (m, 1 H, Hep H-4), 4.12 (m, 1 H, Hep H-6), 4.19 (m, 1 H, Lac H-2), 4.30 (d, 1 H, $^{3}J_{H1,H2}$ = 7.7 Hz, Hep H-1), 4.69 (m, 1 H, Fuc H-5), 4.87 (m, 1 H, Fuc H-1), 7.36-7.95 (m, 9 H, Ar-H); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 16.64 (Fuc C-6), 24.62, 27.22, 27.50, 27.75, 30.36, 31.25, 33.51, 34.66, 35.29 (10 C, $CyCH_2$, Cy), 42.75 (Lac C-3), 43.46 (Hep C-7), 67.45 (Fuc C-5), 69.44 (Hep C-4), 69.96 (Fuc C-2), 71.54, 71.97, 72.29 (4 C, Hep C-2, Hep C-6, Fuc C-3, Fuc C-4), 73.96 (Hep C-5), 75.16 (Cy), 77.61 (Lac C-2), 79.57 (Cy), 84.49

(Hep C-3), 97.38 (Fuc C-1), 102.72 (Hep C-1), 128.04, 128.12, 129.05, 130.02, 134.34, 141.30, 145.68 (12 C, Ar-C), carbonyls were beyond detection level; HR-MS (ESI) *m*/*z*: calcd for $C_{41}H_{57}NNaO_{14}$ $[M+H]^+$: 810.3671; found: 810.3668 (0.4 ppm).

(1*R*,2*R*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 7-[(5-benzoyl-indole-3-carbonyl)amino]-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-7-deoxy-L-*glycero*-β-D-*galacto*-heptopyranoside sodium salt (**194**), (DS-04-111, DS-04-113).

175 (41.5 mg, 42.9 µmol), **189** (22.0 mg, 82.9 µmol) and polymer-bound PPh_3 (3 mmol/g, 55.9 mg, 168 µmol) were suspended in CH_2Cl_2 (4 mL) and CCl_4 (2 mL). *N*-Methylmorpholine (15.0 µL, 136 µmol) was added *via* syringe and the mixture heated to reflux for 5.5 h. The reaction was filtered, and the resin successively washed with THF, acetonitrile, toluene, diethyl ether and petroleum ether (5 mL each). The filtrate was concentrated *in vacuo*, redissolved in CH_2Cl_2 (20 mL) and successively washed with satd. aqueous NH_4Cl (20 mL), satd. aqueous $NaHCO_3$ (40 mL) and brine (40 mL). The aqueous layers were each extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/CH_2Cl_2/methanol, 10:20:1 to 5:20:1) to afford 44.2 mg of a mixture of lactone and benzyl- and methylester, which was directly subjected to deprotection. Pd/C (40 mg, 10% Pd) was placed in a flask and purged with argon. A solution of lactone and benzyl- and methylester in dioxane/H_2O (5:1, 4.8 mL) was added and the mixture was hydrogenated under 70 psi at r.t.. After 4 days the reaction was filtered through celite, concentrated under reduced pressure, redissolved in methanol (1 mL) and aqueous NaOH (0.5 M, 150 µL) was added. After stirring for 6 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/methanol/H_2O, 5:1:0.1 to 2.5:1:0.1) and microfiltration (0.3 µm) to give **194** (10.2 mg, 27%) as a colourless solid.

$[\alpha]_D^{21}$ = - 55.5 (*c* = 0.11, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.82-2.03 (m, 21 H, $CyCH_2$, Cy), 1.19 (d, ^3J= 6.5 Hz, 3 H, Fuc H-6), 3.23 (m, 1 H, Hep H-3), 3.38 (m, 1 H, Hep H-5), 3.53 (m, 1 H, Cy), 3.61 (m, 1 H, Hep H-2), 3.65 (m, 1 H, Hep H-7_a), 3.69-3.74 (m, 2 H, Fuc H-4, Cy), 3.75 (dd, $^3J_{F1,F2}$ = 3.7 Hz, $^3J_{F2,F3}$ = 10.2 Hz, 1 H, Fuc H-2), 3.91 (m, 1 H, Lac H-2), 4.02 (m, 1 H, Fuc H-3), 4.05 (m, 2 H, Hep H-4, Hep H-7_b), 4.11 (m, 1 H, Hep H-6), 4.28 (d, $^3J_{H1,H2}$ = 7.6 Hz, 1 H, Hep H-1), 4.63 (m, 1 H, Fuc H-5), 4.88 (m, 1 H, Fuc H-1), 7.02 (m, 1 H, Ar-H), 7.12 (m, 1 H, Ar-H), 7.18-7.23 (m, 4 H, 4 Ar-H), 7.34 (m, 1 H, Ar-H), 7.96 (m, 2 H, 2 Ar-H); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 16.67 (Fuc C-6), 24.53, 27.24, 27.52, 27.77, 30.15, 31.12, 33.60, 34.64, 35.33, 42.89 (11 C, Cy, $CyCH_2$), 43.22 (Hep C-7), 67.45 (Fuc C-5), 69.18 (Hep C-4), 69.98 (Fuc C-2), 71.38, 71.59 (Hep C-2, Fuc C-3), 72.85 (Hep C-6), 73.90 (Fuc C-4), 74.75 (Hep C-5), 77.42 (Cy), 79.44

(Cy), 80.81 (Lac C-2), 85.23 (Hep C-3), 97.12 (Fuc C-1), 102.69 (Hep C-1), 111.35, 112.92, 121.49, 125.03, 126.80, 127.05, 129.31, 129.83, 130.21, 135.43, 136.80, 143.65 (14 Ar-C), 168.73, 184.17 (3 C, C=O).

(1*R*,2*R*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 7-benzamido-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-7-deoxy-L-*glycero*-β-D-*galacto*-heptopyranoside sodium salt (**195**) and **(1*R*,2*R*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-7-(cyclohexyl-carbonyl)amino-7-deoxy-L-*glycero*-β-D-*galacto*-heptopyranoside sodium salt** (**196**), (DS-05-02, DS-05-39).

175 (77.6 mg, 80.2 µmol), benzoic acid (10.8 mg, 88.4 µmol) and polymer-bound PPh_3 (3 mmol/g, 106.5 mg, 320 µmol) were suspended in CH_2Cl_2 (6 mL) and CCl_4 (3 mL). *N*-Methylmorpholine (29.0 µL, 264 µmol) was added *via* syringe and the mixture heated to reflux for 4 h. The reaction was filtered, and the resin successively washed with THF, acetonitrile, toluene, diethyl ether and petroleum ether (5 mL each). The filtrate was concentrated *in vacuo* and purified by column chromatography (petroleum ether/ethyl acetate, 2:1 to 1:2) to afford 38.1 mg of a mixture of lactone and benzylester, which was directly subjected to deprotection. $Pd(OH)_2$/C (50 mg, 10% Pd) was placed in a flask and purged with argon. A solution of lactone and benzylester in dioxane/H_2O (4:1, 5 mL) was added and the mixture was hydrogenated under 70 psi at r.t.. After 6 d the reaction was filtered through celite, concentrated under reduced pressure, redissolved in methanol (3 mL) and aqueous NaOH (0.5 M, 142 µL) was added. After stirring for 3 h the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/methanol/H_2O, 5:1:0.1 to 2.3:1:0.1), microfiltration (0.3 µm) and Sephadex G15 column to give a mixture of **195** and **196** (**195**:**196** = 2:1, 21.2 mg, 36%) as a colourless solid. Isolation of the pure compounds by preparative reversedphase LC-MS failed.

195:

HR-MS (ESI) *m*/*z*: calcd for $C_{35}H_{53}NNaO_{14}$ $[M+H]^+$: 734.3358; found: 734.3360 (0.3 ppm).

196:

MS (ESI) *m*/*z*: calcd for $C_{35}H_{58}NO_{14}$ $[M-Na]^-$: 716.4; found: 716.6; MS (ESI): *m*/*z* : calcd for $C_{35}H_{59}NNaO_{14}$ $[M+H]^+$: 740.4; found: 740.6.

(1*R*,2*R*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-7-deoxy-7-{{2-[(4-methyl-1-piperazinyl)carbonyl]-7-phenyl-indole-4-carbonyl}amino}-L-*glycero*-β-D-*galacto*-heptopyranoside sodium salt (**197**) and **(1*R*,2*R*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]cyclohexyl 3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-7-deoxy-7-{{2-[(4-methyl-1-piperazinyl)carbonyl]-7-cyclohexyl-indole-4-carbonyl}amino}-L-*glycero*-β-D-*galacto*-heptopyranoside sodium salt** (**198**), (DS-04-125).

175 (50.5 mg, 52.2 µmol), **185** (22.6 mg, 58.6 µmol) and polymer-bound PPh_3 (3 mmol/g, 69.1 mg, 207 µmol) were suspended in CH_2Cl_2 (4 mL) and CCl_4 (2 mL). *N*-Methylmorpholine (19.0 µL, 173 µmol) was added *via* syringe and the mixture heated to reflux for 3.5 h. The reaction was filtered, and the resin successively washed with THF, acetonitrile, toluene, diethyl ether and petroleum ether (5 mL each). The filtrate was concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2/methanol/Et_3N, 25:1:0.5% to 15:1:0.5%) to afford 55.3 mg of a mixture of lactone and benzylester, which was directly subjected to deprotection. Pd/C (120 mg, 10% Pd) was placed in a flask and purged with argon. A solution of lactone and benzylester in dioxane/H_2O (5:1, 3.6 mL) was added and the mixture was hydrogenated under 70 psi at r.t.. After 9 days the reaction was filtered through celite, concentrated under reduced pressure, redissolved in methanol (1.5 mL) and H_2O (850 µL), and aqueous NaOH (1.0 M, 150 µL) was added. After stirring for 6 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2/methanol/H_2O, 5:1:0.1 to 2:1:0.1) and Sephadex G15 to give a mixture of **197** and **198** (7:3, 15.0 mg, 29%) as a colourless solid. Of this mixture 9.7 mg were separated by preparative LC-MC for analytical purposes to obtain **197** (6.4 mg) in pure form as formiate and **198** as mixture with **197**.

197 (formiate):

$[\alpha]_D^{21}$ = - 58.6 (*c* = 0.55, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.87-2.09 (m, 21 H, $CyCH_2$, Cy), 1.21 (d, ^3J = 6.6 Hz, 3 H, Fuc H-6), 2.81 (s, 3 H, CH_3), 3.20 (b, s, 4 H, Pip H-3, Pip H-5), 3.27 (dd, $^3J_{H3,H4}$ = 3.2 Hz, $^3J_{H2,H3}$ = 9.4 Hz, 1 H, Hep H-3), 3.46 (m, 1 H, Hep H-5), 3.53 (m, 1 H, Cy), 3.61-3.65 (m, 2 H, Hep H-2, Hep H-7_a), 3.68-3.74 (m, 3 H, Cy, Fuc H-4, Fuc H-2), 3.76 (dd, $^3J_{H6,H7b}$ = 4.4 Hz, $^2J_{H7a,H7b}$ = 13.5 Hz, 1 H, Hep H-7_b), 4.02 (dd, $^3J_{F3,F4}$ = 3.3 Hz, $^3J_{F2,F3}$ = 10.2 Hz, 1 H, Fuc H-3), 4.11-4.20 (m, 7 H, Hep H-6, Lac H-2, Hep H-4, Pip H-2, Pip H-6), 4.33 (d, $^3J_{H1,H2}$ = 7.8 Hz, 1 H, Hep H-1), 4.71 (m, 1 H, Fuc H-5), 4.85 (d, $^3J_{F1,F2}$ = 3.8 Hz, 1 H, Fuc H-1), 7.24 (m, 1 H, Ar-H), 7.32 (s, 1 H, Ar-H), 7.44 (m, 1 H, Ar-H), 7.49-7.53 (m, 3 H, Ar-H), 7.61 (m, 2 H, Ar-H), 8.19 (s, 1 H, $HCOO^-$); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 16.67 (Fuc C-6), 24.63, 27.25, 27.53, 27.78, 30.42, 31.26, 33.50, 34.73, 35.40 (10 C, Cy, $CyCH_2$), 43.02 (Lac C-3), 43.42 (Hep C-7), 44.07 (CH_3), 54.49 (4 C, Pip), 67.44 (Fuc C-5), 69.52 (Hep C-4), 69.99 (Fuc C-2), 71.52 (Fuc C-

3), 71.96 (Hep C-2), 72.42 (Hep C-6), 74.03 (Fuc C-4), 75.24 (Hep C-5), 77.61 (Cy), 79.64 (Cy), 79.80 (Lac C-2), 84.61 (Hep C-3), 97.37 (Fuc C-1), 102.78 (Hep C-1), 107.18, 121.86, 124.83, 126.93, 128.39, 129.20, 129.50, 130.18, 130.86, 131.57, 135.84, 139.15 (14 Ar-C), 164.42 (*C*=O), 165.90 (H*C*OO$^-$), 171.06 (*C*=O), 181.89 (*C*OOH); HR-MS (ESI) *m*/*z*: calcd for $C_{49}H_{69}N_4O_{15}$ $[M+H]^+$: 953.4754; found: 953.4750 (0.4 ppm).

198:

HR-MS (ESI) *m*/*z*: calcd for $C_{49}H_{75}N_4O_{15}$ $[M+H]^+$: 959.5223; found: 959.5237 (1.4 ppm).

2-Bromocyclohex-2-en-1-one (**211**).

2-Cyclohexenone (9.8 mL, 101 mmol) was dissolved in CH_2Cl_2 (250 mL) in a light protected flask, then the solution was cooled to 0℃. Bromine (5.4 mL, 105 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 35 min. The clear yellow solution was stirred at 0℃ for 2.5 h, then Et_3N (23.1 mL, 166 mmol) in CH_2Cl_2 (20 mL) was added portion-wise, causing a colour change from clear yellow to brown and formation of a precipitate. The mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 3% HCl (2 x 50 mL). The aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were washed with a mixture of brine (80 mL) and water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were concentrated *in vacuo* to afford a brown residue still dissolved in a few mL of CH_2Cl_2, which was then treated with activated charcoal and filtered through celite. The clear green mixture was concentrated to dryness. Recrystallization from hexane/ethyl acetate gave off-white crystals. The crystals were dried in a desiccator for 12 h affording bromide **211** (11.0 g, 62%), the NMR and IR data of which were in accordance with Lit.[387]

(1*R*)-2-Bromocyclohex-2-en-1-ol (**212**):

Application of MeO-CBS as catalyst: (*S*)-α,α-Diphenylprolinol (290 mg, 1.14 mmol) was dissolved in THF (20 mL) in a flame dried, light protected flask, then under stirring $B(OMe)_3$ (153 μL, 1.37 mmol) was added *via* syringe to the solution. The mixture was stirred for 1 h at r.t., before BH_3·*N*,*N*-diethylaniline (2.00 mL, 11.2 mmol) was added and the resulting solution cooled to –10℃. A solution of bromide **211** (2.00 g, 11.4 mmol) in THF (15 mL) was then added over 45 min. The clear yellow mixture was stirred for 3 h at 0℃. After complete conversion of the ketone the reaction was quenched with HCl (1 M, 20 mL). The resulting mixture was diluted with CH_2Cl_2 (40 mL) and water (50 ml). The organic layer was washed with brine (20 mL) and the aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried with

Na_2SO_4, filtered and concentrated *in vacuo*. Chromatographic purification of the crude product (petroleum ether/Et_2O, 2:1 to 1.5:1) gave **212** (1.89 g, 93%) as a colourless oil and with an optical yield of 96% ee determined by optical rotation and derivatization with (1*R*)-(–)-MTPA-Cl. The NMR data of **212** were in accordance with Lit.[391]

$[\alpha]_D^{21}$ = + 83.0 (*c* = 1.01, $CHCl_3$).

Application of Me-CBS as catalyst: Bromide **211** (2.00 g, 11.45 mmol) was dissolved in THF (12 mL) in a flame dried, light protected flask. The solution was cooled to –20°C and under stirring (*S*)-methyl-CBS-oxazaborolidine (1 M in toluene, 0.570 mL, 1.91 mmol) in THF (8 mL) and borane-dimethyl-sulfide complex (2 M in toluene, 3.4 mL, 6.8 mmol) were simultaneously added dropwise *via* syringe to the solution over 1 h and 10 min. The mixture was stirred for 3 h at –20°C, then quenched with MeOH (11 mL) and warmed to r.t.. After evaporation of the solvent, the yellow oily residue was redissolved in CH_2Cl_2 (20 mL) and washed with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. Chromatographic purification of the crude product (petroleum ether/Et_2O, 2:1 to 3:2) gave **212** (1.70 g, 84%) as a colourless oil and with an optical yield of 90% ee determined by optical rotation and 89% ee determined by derivatization with (1*R*)-(–)-MTPA-Cl.

$[\alpha]_D^{21}$ = + 77.8 (*c* = 1.89, $CHCl_3$).

(1*R*)-2-Bromo-2-cyclohexen-1-yl (*αS*)-*α*-methoxy-*α*-(trifluoromethyl)-phenylacetate (**213**).

212 (5.6 mg, 0.031 mmol) was dissolved in pyridine (500 *µ*L). (1*R*)-(-)-MTPA-Cl (15 *µ*L, 0.080 mmol) and 4-dimethylaminopyridine (2-3 crystals) were added to the mixture. After stirring for 60 h the reaction was stopped. Pyridine was removed azeotropically with toluene *in vacuo* to afford a brown residue. The residue was diluted with CH_2Cl_2 (5 mL) and washed with satd. aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated to dryness. The crude product was purified by column chromatography (petroleum ether/Et_2O, 2:1) to afford **213** as a green resin in quantitative yield with an optical purity of 96% de determined by calculations based on ^{13}C-satellites.

^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.64-1.72 (m, 2 H, H-5_a, H-5_b), 1.97-2.11 (m, 3 H, H-4_a, H-6_a, H-6_b), 2.20 (m, 1 H, H-4_b), 3.43 (s, (1*R*)-OCH_3-satellite), 3.58 (s, 3 H, (1*R*)-OCH_3), 3.64 (s, 3 H, (1*S*)-OCH_3), 3.72 (s, (1*R*)-OCH_3-satellite), 5.66 (s, 1 H, H-1), 6.38 (m, 1 H, H-3), 7.40 (m, 3 H, C_6H_5), 7.59 (m, 2 H, C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.91 (C-5), 27.43 (C-4), 29.93 (C-

6), 55.48 (OCH_3), 73.66 (C-1), 85.00 (*C*-Ph), 117.99 (C-2), 127.64, 128.29, 129.58, 131.98 (6 C, C_6H_5), 136.46 (C-3), 165.86 (C=O).

(1*R*)-Cyclohex-2-en-1-ol (**214**).

212 (7.33 g, 41.4 mmol) was dissolved in Et_2O (43 mL) in a flame dried flask equipped with a dropping funnel. *tert*-BuLi (1.7 M in pentane, 133 mmol) was added dropwise at –78°C over 1 h and 15 min. After complete addition, the clear yellowish mixture was stirred for 1.5 h at –78 °C and then slowly warmed to –20 °C over 3 h and 15 min. The reaction was quenched by addition of satd. aqueous $NaHCO_3$ (50 mL) and stirred for 1 h at r.t.. The mixture was diluted by addition of water (20 mL) and Et_2O (20 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 x 30 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo* (>200 mbar) to afford a yellow mixture (still presence of solvent) which was purified by column chromatography (petroleum ether/Et_2O, 2:1 to 1:1). The product was concentrated to a syrup *in vacuo* (>200 mbar), then the rest of the solvent was removed by distillation under argon with vigreux column to afford alcohol **214** (3.39 g, 85%) as a clear brown oil. The NMR data of **214** were in accordance with Lit.[391]

$[\alpha]_D^{21}$ = + 117.7 (*c* = 0.95, $CHCl_3$).

(1*R*)-1-*O*-Triphenylmethyl-cyclohex-2-en-1-ol (**215**).

Alcohol **214** (1.51 g, 15.3 mmol) was stirred in CH_2Cl_2 (35 mL) at r.t.. Trityl chloride (9.54 g, 34.2 mmol) was added to the mixture, then DBU (5.9 mL, 39.5 mmol) was added *via* syringe. The brown mixture was stirred for 45 h, diluted with CH_2Cl_2 (50 mL) and washed with satd. aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated to dryness. The resulting viscous brown oil was purified by column chromatography (petroleum ether/toluene, 11:1 to 4:1) affording tritylether **215** (3.72 g, 71%) as a yellow solid.

$[\alpha]_D^{21}$ = + 74.6 (*c* = 1.15, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.31-1.41 (m, 3 H, H-5_a, H-6), 1.68-1.76 (m, 1 H, H-5_b), 1.80 (m, 1 H, H-4_a), 1.98 (m, 1 H, H-4_b), 4.06 (s, 1 H, H-1), 5.03 (m, 1 H, H-2), 5.61 (m, 1 H, H-3), 7.21-7.54 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 19.69 (C-5), 25.02 (C-4), 30.18 (C-6), 67.82 (C-1), 86.86 (*C*Ph_3), 129.60 (C-2), 129.97 (C-3), 126.85, 127.68, 129.00, 145.34 (18 C, 3 C_6H_5); IR (KBr) ν: 3031 (vw, C=C-H), 2930 (w), 2833 (vw), 1595 (vw), 1490 (w), 1448 (m), 1393 (vw), 1348 (vw), 1313 (vw), 1215 (w), 1150 (vw), 1043 (s), 1016 (m), 960 (vw), 938 (vw), 900 (vw) cm^{-1}; MS (ESI) *m*/*z*: calcd for $C_{25}H_{24}ONa$ $[M+Na]^+$: 363.2; found: 363.2; elemental analysis calcd (%) for $C_{25}H_{24}O$ (340.46): C 88.20, H 7.10; found: C 88.01, H 7.29.

(1*R*,2*R*,3*R*)-1-*O*-Triphenylmethyl-cyclohexane-1,2,3-triol (**216**).

Tritylether **215** (201 mg, 0.590 mmol) and *N*-methylmorpholine-*N*-oxide monohydrate (239 mg, 1.76 mmol) were dissolved in acetone/water (60 mL, 4:1). Osmium tetroxide (1.5 mg, 5.9 μmol) was added to the stirred solution. The clear colourless mixture was stirred for 19 h at r.t.. During the reaction additional osmium tetroxide (1 crystal, ~ 1 mol%) was added. The reaction was quenched with satd. aqueous sodium dithionite (10 mL) and the mixture was stirred for additional 30 min. Acetone was evaporated *in vacuo* and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 4:1 to 3:1) affording the title compound **216** (192 mg, 87%) as a yellowish solid.

$[\alpha]_D^{21}$ = - 23.9 (*c* = 0.53, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.14 (m, 1 H, H-4_a), 1.24-1.33 (m, 1 H, H-5_a), 1.42-1.50 (m, 3 H, H-4_b, H-5_b, H-6_a), 1.59-1.65 (m, 1 H, H-6_b), 1.90 (br, s, 1 H, OH), 2.22 (br, s, 1 H, OH), 3.49 (dd, ^3J = 2.7, 6.8 Hz, 1 H, H-2), 3.58 (m, 1 H, H-3), 4.04 (m, 1 H, H-1), 7.23-7.31 (m, 9 H, 3 C_6H_5), 7.48-7.50 (m, 6 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 18.61 (C-4), 28.97 (2 C, C-5, C-6), 69.05 (C-1), 73.20 (2 C, C-2, C-3), 86.89 (*C*-Ph_3), 127.18, 127.81, 127.90, 128.70, 128.80, 144.87 (18 C, 3 C_6H_5); IR (KBr) ν: 3414 (m), 3057 (vw), 2936 (w), 1597 (vw), 1490 (w), 1448 (w), 1224 (vw), 1148 (vw), 1069 (m), 1028 (m), 1000 (w), 896 (vw), 764 (w), 746 (w), 703 (m), 632 (vw) cm^{-1}; MS (ESI) *m*/*z*: calcd for $C_{25}H_{26}NaO_3$ $[M+Na]^+$: 397.2; found: 397.2; elemental analysis calcd (%) for $C_{25}H_{26}O_3 \cdot$ ¼ H_2O (378.69): C 79.23, H 7.05; found: C 79.21, H 7.16.

(1*R*,2*S*,3*R*)-2-Hydroxy-3-(triphenylmethoxy)cyclohexyl 4-methylbenzenesulfonate (**217**).

Tritylether **216** (1.70 g, 4.54 mmol) was dissolved in CH_2Cl_2 (55 mL). Tosyl chloride (1.04 g, 5.45 mmol) and dibutyltin oxide (1.13 g, 4.55 mmol) were added to the stirred solution, then Et_3N (1.28 mL, 9.18 mmol) was added *via* syringe causing a change of colour from pink-orange to yellow. After stirring for 19 h at r.t. the reaction was quenched with MeOH (2 mL). The solvents were evaporated *in vacuo* and the crude residue was purified by column chromatography (toluene/ethyl acetate, 12:1 to 11:1, + 1% Et_3N) affording tosylate **217** (2.20 g, 92%) as a white foam.

$[\alpha]_D^{21}$ = + 27.2 (*c* = 0.58, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.88 (m, 1 H, H-4_a), 1.25-1.34 (m, 1 H, H-4_b), 1.37-1.43 (m, 1 H, H-5_a), 1.62-1.77 (m, 2 H, H-6_a, H-5_b), 1.79.1.84 (m, 1 H, H-6_b), 2.35 (s, 1 H, OH), 2.39 (s, 3 H, Ph-CH_3), 3.24 (s, 1 H, H-2), 3.79 (s, 1 H, H-3), 4.80 (m, 1 H, H-1), 7.25-7.36 (17 H, 3 C_6H_5, C_6H_4), 7.78 (m, 2 H, C_6H_4); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 18.77

(C-5), 21.63 (Ph-*C*H_3), 25.76 (2 C, C-6, C-4), 70.20 (C-2), 72.23 (C-3), 81.75 (C-1), 87.30 (*C*-Ph_3), 125.28, 127.18, 127.94, 128.74, 129.81, 133.84, 137.86, 144.46 (24 C, Ar-H); IR (KBr) ν: 3453 (w), 3058 (vw), 2934 (w), 2867 (vw), 1598 (w), 1491 (w), 1449 (m), 1360 (m), 1189 (s), 1177 (vs), 1148 (m), 1097 (w), 1074 (m), 1028 (m), 940 (s), 902 (m), 880 (w), 859 (w), 833 (m), 815 (m), 765 (w), 747 (w), 703 (s), 669 (w), 632 (w), 589 (w), 556 (m) cm^{-1}; MS (ESI) *m*/*z*: calcd for $C_{32}H_{32}NaO_5S$ $[M+Na]^+$: 551.2; found: 551.2; elemental analysis calcd (%) for $C_{32}H_{32}O_5S$ (528.66): C 72.70, H 6.10; found: C 72.76, H 6.35.

(1*R*,2*R*,3*R*)-2,3-Epoxy-1-*O*-triphenylmethyl-cyclohexan-1-ol (***anti*-219**).

Tritylether **215** (948 mg, 2.79 mmol) was dissolved under argon in CH_2Cl_2 (30 mL) and $NaHCO_3$ (281 mg, 3.34 mmol) was added. The mixture was cooled to 0°C and *m*-chloroperbenzoic acid (70%, 960 mg, 5.56 mmol) was added under stirring. After 1.5 h the temperature was gradually raised to r.t. and the mixture was stirred for another 3.5 h. The reaction was diluted with CH_2Cl_2 (50 mL) and transferred to a separation funnel. The excess of *m*-chloroperbenzoic acid was destroyed by washing with satd. aqueous $Na_2S_2O_3$ (2 x 150 mL). The organic layer was then successively washed with satd. aqueous Na_2CO_3 (150 mL) and brine (150 mL). The aqueous layers were each time extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 20:1 to 15:1) affording epoxide ***anti*-219** (714 mg, 72%) as colourless solid and ***syn*-219** (230 mg, 23%) as a yellowish resin.

***anti*-219:**

$[\alpha]_D^{21}$ = + 26.6 (*c* = 0.67, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.02-1.11 (m, 1 H, H-5_a), 1.15-1.22 (m, 1 H, H-6_a), 1.37-1.43 (m, 1 H, H-5_b), 1.53 (m, 1 H, H-6_b), 1.64-1.71 (m, 1 H, H-4_a), 1.90 (m, 1 H, H-4_b), 2.25 (m, 1 H, H-2). 2.97 (m, 1 H, H-3), 3.86 (m, 1 H, H-1), 7.23-7.53 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 15.15 (C-5), 24.05 (C-4). 28.18 (C-6), 53.15 (C-3), 55.44 (C-2), 68.56 (C-1), 87.45 (*C*Ph_3), 127.16, 127.86, 128.88, 144.68 (18 C, 3 C_6H_5); IR (KBr) ν: 3060 (w), 3028 (w), 2976 (w), 2942 (m), 2859 (vw), 1597 (vw), 1490 (m), 1449 (m), 1375 (vw), 1318 (vw), 1215 (w), 1181 (w), 1153 (w), 1055 (s), 1032 (m), 1008 (w), 990 (w) cm^{-1}; MS (ESI) *m*/*z*: calcd for $C_{25}H_{24}O_2Na$ $[M+Na]^+$: 379.2; found: 379.2; elemental analysis calcd (%) for $C_{25}H_{24}O_2$ (356.46): C 84.24, H 6.79; found: C 83.86, H 6.85.

(1*R*,2*R*,3*S*)-3-Azido-1-*O*-triphenylmethyl-cyclohexane-1,2-diol (**218**).

Synthesis from tosylate: **217** (2.12 g, 4.01 mmol) was dissolved in DMF (70 mL) under argon. NaN_3 (1.04 g, 16.1 mmol) was added to the stirred solution and the mixture was heated to 65°C

for 50 h. The reaction was quenched with water (10 mL), diluted with ethyl acetate (100 mL) and washed with H_2O (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 70 mL). The combined organic layers were dried with Na_2SO_4, filtered and co-evaporated with toluene. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 20:1 to 15:1, + 1% Et_3N) to afford azide **218** (1.40 g, 88%) as white solid.

Synthesis from epoxide: ***anti*-219** (111 mg, 0.312 mmol) was dissolved in DMF (10 mL) under argon. CsF (472 mg, 3.12 mmol) was quickly added to the stirred solution, then 15-crown-5 (690 µL, 3.47 mmol) was added *via* syringe. NaN_3 (225 mg, 3.47 mmol) was added and the mixture stirred for 48 h at 65°C then for 43 h at 100°C. The clear yellow reaction mixture was cooled to r.t., quenched with water (10 mL), diluted with ethyl acetate (20 mL) and washed with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried with Na_2SO_4, filtered and co-evaporated with toluene to dryness. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 20:1 to 18:1, + 0.5% Et_3N) to afford **218** (109 mg, 87%).
$[\alpha]_D^{21}$ = - 22.9 (*c* = 0.51, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.74-0.84 (m, 1 H, H-5), 1.17-1.38 (m, 2 H, H-4_a, H-6_a), 1.44-1.52 (m, 2 H, H-5_b, H-6_b), 1.78 (m, 1 H, H-4_b), 2.69 (s, 1 H, OH), 2.90 (ddd, ^3J = 4.1, 8.7, 11.3 Hz, 1 H, H-1), 3.04 (ddd, ^3J = 4.7, 9.4, 12.1 Hz, 1 H, H-3), 3.67 (t, ^3J = 9.0, 9.2 Hz, 1 H, H-2), 7.23-7.49 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 20.86 (C-5), 29.62 (C-4), 31.42 (C-6), 63.76 (C-3), 76.94 (C-1), 77.78 (C-2), 86.90 (*C*-Ph_3), 127.28, 127.88, 128.71, 144.75 (18 C, 3 C_6H_5); IR (KBr) ν: 3554 (w, OH), 3052 (vw), 2932 (w), 2104 (vs, azide), 1594 (vw), 1490 (w), 1448 (w), 1362 (vw), 1309 (w), 1274 (m), 1223 (w), 1118 (vw), 1060 (s), 1032 (m), 992 (m), 934 (w), 901 (vw), 879 (vw), 853 (vw), 776 (w), 754 (m), 699 (s), 651 (vw), 634 (w), 559 (vw), 507 (vw) cm^{-1}; MS (ESI) *m*/*z*: calcd for $C_{25}H_{25}N_3NaO_2$ $[M+Na]^+$: 422.2; found: 422.2; elemental analysis calcd (%) for $C_{25}H_{25}N_3O_2$ (399.48): C 75.16, H 6.31, N 10.52; found: C 75.27, H 6.35, N 10.22.

(1*R*,2*R*,3*R*)-1-*O*-(4-Methoxybenzyl)-cyclohexane-1,2,3-triol (**220**), (DS-04-114, DS-04-116).
NaH (60% in oil, 1.37 g, 34.3 mmol) was suspended in THF (20 mL) under argon, and cooled to 0°C. Alcohol **214** (1.00 g, 10.2 mmol) dissolved in THF (10 mL) was slowly added to the suspension and the mixture stirred at 0°C for 40 min. Tetrabutylammonium bromide (141 mg, 0.437 mmol) was added in one portion to the reaction and 4-methoxybenzyl chloride (2.78 mL, 20.5 mmol) was added dropwise to the suspension. The reaction was warmed to r.t. and stirred for 7 h. After cooling to 0°C, the reaction was quenched with H_2O (4 mL). The mixture was

diluted with THF (20 mL) and washed with H_2O (40 mL). The aqueous layer was extracted with *t*-butylmethyl ether (2 x 30 mL). The combined organic layers were washed with brine (100 mL) and the aqueous layer again extracted with *t*-butylmethyl ether (2 x 100 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated to dryness. The resulting oil was purified by column chromatography (petroleum ether/THF, 100:1 to 70:1), affording the PMB-ether (1.78 g) with some inseparable impurities. The PMB-ether and *N*-methylmorpholine-*N*-oxide monohydrate (3.31 g, 24.5 mmol) were dissolved in acetone/water (820 mL, 4:1). Osmium tetroxide (57.0 mg, 224 *µ*mol) was added to the stirred solution. The mixture was stirred for 47 h at r.t., then quenched with satd. aqueous sodium dithionite (6 g $Na_2S_2O_4$), and the mixture stirred for additional 30 min. Acetone was evaporated *in vacuo* and the aqueous layer was extracted with ethyl acetate (4 x 200 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/diethyl ether, 1:1) affording pure **220** (1.24 g, 48% over two steps) as yellowish oil and 152 mg of unreacted PMB-ether (7%).

$[\alpha]_D^{21}$ = - 71.0 (*c* = 0.64, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.22 (m, 1 H, H-6_a), 1.43 (m, 1 H, H-4_a), 1.55 (m, 1 H, H-5_a), 1.65 (m, 1 H, H-5_b), 1.87 (m, 1 H, H-4_b), 2.10 (m, 1 H, H-6_b), 2.31 (br, s, 2 H, 2 OH), 3.50 (dd, $^3J_{2,3}$ = 2.8 Hz, $^3J_{1,2}$ = 8.7 Hz, 1 H, H-2), 3.60 (ddd, $^3J_{1,6eq}$ = 4.2 Hz, $^3J_{1,2}$ = 8.9 Hz, $^3J_{1,6ax}$ = 10.4 Hz, 1 H, H-1), 3.81 (s, 3 H, CH_3O), 4.10 (m, 1 H, H-3), 4.38, 4.62 (2 m, 2 H, PMB), 6.88-6.90, 7.25-7.27 (m, 4 H, C_6H_4); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 18.38 (C-5), 28.50 (C-6), 29.65 (C-4), 55.27 (CH_3O), 69.14 (C-3), 70.56 (PMB), 75.11 (C-2), 78.00 (C-1), 113.92, 129.37, 130.52 (6 C, C_6H_4); IR (film on NaCl) ν: 3419 (vs, OH), 2938 (vs), 1614 (s), 1587 (w), 1515 (vs), 1456 (m), 1303 (m), 1248 (vs), 1175 (m), 1080 (vs), 999 (m), 818 (m) cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{20}O_4$ (252.31): C 66.65, H 7.99; found: C 66.54, H 8.11.

(1*R*,2*R*,3*S*)-3-Azido-1-*O*-(4-methoxybenzyl)-cyclohexane-1,2-diol (**221**), (DS-04-118, DS-04-119).

PMB-ether **220** (1.24 g, 4.92 mmol) was dissolved in CH_2Cl_2 (60 mL). Tosyl chloride (1.13 g, 5.91 mmol) and dibutyltin oxide (1.23 g, 4.93 mmol) were added to the stirred solution, then Et_3N (1.38 mL, 9.90 mmol) was added *via* syringe. After stirring for 15.5 h at r.t. the reaction was quenched with MeOH (2 mL). The solvents were evaporated *in vacuo* and the crude residue was purified by column chromatography (CH_2Cl_2/diethyl ether, 25:1 to 20:1) affording the monotosylate (1.93 g, 96%) as an inseparable mixture of **3-Ts-220** and **2-Ts-220** (9:1), which was directly used for the next step. The tosylate mixture (1.91 g, 4.69 mmol) was dissolved in DMF (70 mL) under argon. NaN_3 (0.917 g, 14.1 mmol) was added to the stirred solution and the mixture was heated to 65°C for 72 h. After 48 h additional NaN_3 (305 mg, 4.69 mmol) was

added. The reaction was quenched with water (10 mL), diluted with ethyl acetate (100 mL) and washed with H_2O (100 mL). The aqueous layer was extracted with ethyl acetate (3 x 70 mL). The combined organic layers were dried with Na_2SO_4, filtered and co-evaporated with toluene to dryness. The crude product was purified by column chromatography (petroleum ether/diethyl ether, 3:1 to 2:1) to afford azide **221** (1.13 g, 82% over two steps) as yellowish oil.
$[\alpha]_D^{21}$ = - 35.7 (*c* = 0.56, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.17-1.34 (m, 3 H, H-4_a, H-5_a, H-6_a), 1.78 (m, 1 H, H-5_b), 1.95 (m, 1 H, H-4_b), 2.01 (m, 1 H, H-6_b), 2.80 (s, 1 H, OH), 3.21-3.30 (m, 2 H, H-1, H-3), 3.41 (t, ^3J = 9.2 Hz, 1 H, H-2), 3.81 (s, 3 H, OCH_3), 4.44, 4.63 (2 m, 2 H, PMB), 6.88-6.90, 7.25-7.27 (2 m, 4 H, C_6H_4); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 20.79 (C-5), 28.63 (C-6), 29.73 (C-4), 55.26 (OCH_3), 63.69 (C-3), 71.07 (PMB), 77.69 (C-2), 80.79 (C-1), 113.93, 129.38, 130.17, 159.33 (6 C, C_6H_4); IR (film on NaCl) ν: 3445 (w, OH), 2941 (m), 2868 (m), 2097 (vs, N_3), 1613 (m), 1586 (vw), 1514 (s), 1463 (w), 1361 (w), 1303 (m), 1249 (vs), 1174 (w), 1079 (s), 1035 (m) cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{19}N_3O_3$ (277.32): C 60.63, H 6.91, N 15.15; found: C 60.91, H 7.19, N 14.74.

General procedure A for nucleophilic opening of epoxides with cuprate reagents (**222a-d**).
CuCN (3.81 mmol) was dried *in vacuo* at 150ºC for 30 min, suspended in dry THF (10 mL) and cooled to -78ºC. A solution of the appropriate organo lithium compound (7.63 mmol) was slowly added *via* syringe and the temperature was raised over a period of 30 min to -20ºC and the mixture stirred at this temperature for 10 min. The mixture was cooled to -78ºC followed by the addition of freshly distilled BF_3 etherate (1.53 mmol) in THF (2 mL). After stirring for 20 min, epoxide **219** (0.761 mmol) dissolved in THF (8 mL) was added. The reaction was slowly warmed to -50℃ over 5 h and then stirred at this temperat ure for 24 h. After slowly warming the reaction to -30℃ over another 21 h the reaction was quenche d with a 25% aq. NH_3/satd. NH_4Cl (1:9, 20 mL) solution. The mixture was transferred with Et_2O (30 mL) into a separation funnel and extracted with additional 25% aq. NH_3/satd. NH_4Cl (1:9, 30 mL) solution. The layers were separated and the organic layer was washed with brine (50 mL). The aqueous layers were extracted with Et_2O (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/Et_2O, 20:1 to 13:1, + 1% Et_3N) to afford the corresponding Glc*N*Ac mimic.

(1*R*,2*R*,3*S*)-3-Methyl-1-*O*-triphenylmethyl-cyclohexane-1,2-diol (**222a**), (DS-04-147, DS-05-05).
CuCN (935 mg, 10.4 mmol) in THF (50 mL) was treated with MeLi (1.6 M in Et_2O, 13 mL, 20.8 mmol) and BF_3 etherate (875 μL, 6.95 mmol) in THF (10 mL) according to the general procedure

A. Epoxide **219** (1.23 g, 3.45 mmol) in THF (20 mL) was slowly added and the reaction slowly warmed to -30°C (-78°C: 2 h; -78°C to -50°C: 1 h; -50°C: 24 h; -50°C to -30°C: 2 h). Work-up and purification according to the general procedure A yielded **222a** (1.09 g, 85%) as a yellowish resin.

$[\alpha]_D^{21}$ = - 57.6 (*c* = 0.52, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.78 (m, 1 H, H-5_a), 0.94 (m, 1 H, H-4_a), 1.00 (d, ^3J = 6.4 Hz, 3 H, CH_3), 1.17 (m, 1 H, H-3), 1.32 (m, 1 H, H-6_a), 1.40 (m, 1 H, H-5_b), 1.46-1.49 (m, 2 H, H-4_b, H-6_b), 2.67 (s, 1 H, OH), 2.83 (ddd, ^3J = 4.1, 8.6, 11.1 Hz, 1 H, H-1), 3.32 (t, ^3J = 9.2 Hz, 1 H, H-2), 7.21-7.30, 7.49-7.50 (2 m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 18.61 (CH_3), 23.44 (C-5), 32.43, 32.86 (C-4, C-6), 37.53 (C-3), 78.81 (C-1), 79.21 (C-2), 86.45 (O*C*Ph_3), 127.07, 127.75, 128.71, 145.13 (18 C, 3 C_6H_5); IR (KBr) ν: 3577 (w), 3057 (w), 2929 (s), 2856 (m), 1596 (vw), 1490 (m), 1448 (s), 1371 (vw), 1288 (w), 1226 (w), 1064 (vs), 1001 (m), 967 (w), 762 (m), 746 (m), 707 (vs) cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{28}O_2$ (372.51): C 83.83, H 7.58; found: C 83.51, H 7.56.

(1*R*,2*R*,3*S*)-3-Butyl-1-*O*-triphenylmethyl-cyclohexane-1,2-diol (**222b**), (DS-05-34).

CuCN (342 mg, 3.81 mmol) in THF (10 mL) was treated with *n*BuLi (2.5 M in hexane, 3.05 mL, 7.63 mmol) and BF_3 etherate (192 µL, 1.53 mmol) in THF (2 mL) according to the general procedure A. Epoxide **219** (271 mg, 0.761 mmol) in THF (8 mL) was slowly added and the reaction slowly warmed to -30°C (-78°C: 1 h; -78°C to -50°C: 4 h; -50°C: 24 h; -50°C to -30°C: 21 h). Work-up and purification according to the general procedure A yielded **222b** (220 mg, 70%).

$[\alpha]_D^{21}$ = - 37.8 (*c* = 0.66, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.73 (m, 1 H, H-5_a), 0.85 (m, 1 H, H-4_a), 0.86 (t, ^3J = 7.2 Hz, 3 H, H-10), 1.03-1.16 (m, 3 H, H-3, H-7_a, H-8_a), 1.21-1.35 (m, 4 H, H-6_a, H-8_b, H-9_a, H-9_b), 1.38-1.49 (m, 2 H, H-5_b, H-6_b), 1.61 (m, 1 H, H-4_b), 1.75 (m, 1 H, H-7_b), 2.70 (s, 1 H, OH), 2.82 (ddd, ^3J = 4.0, 8.6, 11.2 Hz, 1 H, H-1), 3.40 (t, ^3J = 9.0 Hz, 1 H, H-2), 7.21-7.30, 7.48-7.50 (2 m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 14.11 (C-10), 23.10 (C-9), 23.37 (C-5), 28.73 (C-8), 29.38 (C-4), 32.05 (C-7), 32.30 (C-6), 42.45 (C-3), 77.62 (C-2), 79.05 (C-1), 86.43 (*C*Ph_3), 127.05, 127.74, 128.70, 145.12 (18 C, 3 C_6H_5); elemental analysis calcd (%) for $C_{29}H_{34}O_2$ (414.58): C 84.02, H 8.27; found: C 84.05, H 8.27.

(1*R*,2*R*,3*R*)-3-Cyclopropyl-1-*O*-triphenylmethyl-cyclohexane-1,2-diol (**222c**), (DS-04-147, DS-05-62).

A *c*PrLi solution was generated *in situ* by treating a solution of bromocyclopropane (370 µL, 4.63 mmol) in THF (4 mL) with *t*BuLi (1.7 M in pentane, 5.45 mL, 9.27 mmol) during 80 min at -78°C. CuCN (210 mg, 2.34 mmol) in THF (5 mL) was treated with the *c*PrLi solution and BF_3 etherate

(115 µL, 0.914 mmol) in THF (1 mL) according to the general procedure A. Epoxide **219** (165 mg, 0.463 mmol) in THF (5 mL) was slowly added and the reaction slowly warmed to -30°C (-78°C: 1.5 h; -78°C to -50°C: 1.5 h; -50°C: 24 h; -50 °C to -30°C: 40 min). Work-up and purification according to the general procedure A yielded **222c** (150.7 mg, 82%).

$[\alpha]_D^{21}$ = - 38.8 (*c* = 0.50, CH_2Cl_2); ^{1}H-NMR (CD_2Cl_2, 500.1 MHz) δ: -0.16 (m, 1 H, *c*Pr), 0.13-0.23 (m, 2 H, *c*Pr), 0.34-0.43 (m, 2 H, *c*Pr, H-3), 0.54-0.67 (m, 2 H, *c*Pr, H-5_a), 0.91 (m, 1 H, H-4_a), 1.18 (m, 1 H, H-6_a), 1.27-1.35 (m, 2 H, H-5_b, H-6_b), 1.44 (m 1 H, H-4_b), 2.52 (s, 1 H, OH), 2.71 (ddd, ^3J = 4.1, 8.6, 11.0 Hz, 1 H, H-1), 3.47 (t, ^3J = 9.1 Hz, 1 H, H-2), 7.15-7.23, 7.42-7.43 (2 m, 15 H, 3 C_6H_5); ^{13}C-NMR (CD_2Cl_2, 125.8 MHz) δ: 0.85, 4.26, 14.56 (3 C, *c*Pr), 23.11 (C-5), 29.50 (C-4), 32.15 (C-6), 46.68 (C-3), 78.55 (C-2), 78.92 (C-1), 86.37 (O*C*Ph_3), 127.07, 127.73, 128.82, 145.37 (18 C, 3 C_6H_5); IR (KBr) ν: 3571 (m, OH), 3058 (w), 2930 (m), 2858 (m), 1596 (vw), 1490 (m), 1448 (s), 1284 (w), 1225 (w), 1152 (w), 1063 (vs), 926 (w), 844 (vw), 824 (vw), 761 (m), 746 (m), 707 (vs) cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{30}O_2$ (398.54): C 84.38, H 7.59; found: C 84.16, H 7.78.

(1*R*,2*R*,3*R*)-3-Ethenyl-1-*O*-triphenylmethyl-cyclohexane-1,2-diol (**222d**), (DS-04-143, DS-05-03).

A vinyl lithium solution was generated *in situ* by treating a solution of tetravinyltin (409 µL, 2.25 mmol) in THF (3 mL) with *n*BuLi (2.5 M in hexane, 3.35 mL, 8.38 mmol) during 30 min at 0°C. CuCN (373 mg, 4.16 mmol) in THF (8 mL) was treated with the vinyl lithium solution and BF_3 etherate (209 µL, 1.66 mmol) in THF (1.5 mL) according to the general procedure A. Epoxide **219** (296 mg, 0.830 mmol) in THF (8 mL) was slowly added and the reaction slowly warmed to -30°C (-78°C: 15 min; -78°C to -50°C: 1.5 h; -50°C: 1 3 h; -50°C to -30°C: 1.5 h; -30°C: 24 h). Work-up and purification according to the general procedure A yielded **222d** (258 mg, 81%) as a yellowish resin.

$[\alpha]_D^{21}$ = - 33.7 (*c* = 0.53, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.84 (m, 1 H, H-5_a), 1.15 (m, 1 H, H-4_a), 1.32 (m, 1 H, H-6_a), 1.43-1.55 (m, 3 H, H-5_b, H-6_b, H-4_b), 1.81 (m, 1 H, H-3), 2.66 (s, 1 H, OH), 2.91 (ddd, ^3J = 3.9, 8.6, 11.3 Hz, 1 H, H-1), 3.51 (t, ^3J = 9.3 Hz, 1 H, H-2), 5.02 (A of ABX, $^3J_{A,X}$ = 10.4 Hz, $^2J_{A,B}$ = 1.7 Hz, $^3J_{A,3}$ = 0.7 Hz, 1 H, vinyl H_A), 5.04 (B of ABX, $^3J_{B,X}$ = 17.2 Hz, $^2J_{A,B}$ = 1.7 Hz, $^3J_{B,3}$ = 1.1 Hz, 1 H, vinyl H_B), 5.83 (X of ABX, $^3J_{A,X}$ = 10.4 Hz, $^3J_{B,X}$ = 17.2 Hz, $^3J_{X,3}$ = 7.6 Hz, 1 H, vinyl H_X), 7.21-7.31, 7.48-7.50 (2 m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 23.18 (C-5), 30.39 (C-4), 32.21 (C-6), 47.30 (C-3), 76.74 (C-2), 78.53 (C-1), 114.77 (vinyl C), 127.11, 127.77, 128.75, 145.07 (18 C, 3 C_6H_5), 140.57 (vinyl C); IR (film on NaCl) ν: 3577 (m, OH), 3059 (m), 2932 (vs), 2860 (s), 1641 (vw), 1597 (vw), 1489 (s), 1448 (s), 1278 (m), 1225

(m), 1152 (w), 1064 (vs), 991 (s), 915 (m) cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{28}O_2$ (384.51): C 84.34, H 7.34; found: C 84.15, H 7.33.

General procedure B for α-fucosylation and detritylation (**223a-d**).

A solution of Br_2 (0.837 mmol) in CH_2Cl_2 (1 mL) was added dropwise at 0°C to a solution of ethyl 2,3,4-tri-*O*-benzyl-1-thio-L-fucopyranoside (0.729 mmol) in CH_2Cl_2 (2 mL). After stirring for 50 min at 0°C, cyclohexene (100 μL) was added and the solution stirred for another 20 min. The mixture was added dropwise to a solution of **222a-d** (0.558 mmol) and Et_4NBr (0.733 mmol) in DMF/CH_2Cl_2 (10 mL, 1:1), which has been stirred with activated 3Å molecular sieves (850 mg) for 2 h. The mixture was stirred for 14 h at r.t.. The reaction was quenched with pyridine (1 mL) and filtered over celite with addition of CH_2Cl_2 (20 mL). The solution was washed with brine (40 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvents were removed azeotropically with toluene. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 12:1 to 7:1, + 1% Et_3N) to afford the fucosylated tritylether. To a stirred solution of the tritylether (0.305 mmol) in CH_2Cl_2 (4 mL), $ZnBr_2$ (0.924 mmol) and triethylsilane (0.344 mmol) were added. The reaction was quenched after 8 h by adding water (100 μL). CH_2Cl_2 (10 mL) was added and the reaction mixture extracted with satd. aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with satd. aqueous $NaHCO_3$ (50 mL) and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. Chromatographic purification of the crude product (petroleum ether/toluene/ethyl acetate, 7:7:1 to 4:4:1) afforded **223a-d**.

[(1*R*,2*R*,3*S*)-1-Hydroxy-3-methyl-cyclohex-2-yl] 2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranoside (**223a**), (DS-04-101, DS-04-106).

According to the general procedure B, ethyl 2,3,4-tri-*O*-benzyl-1-thio-L-fucopyranoside (349 mg, 0.729 mmol) in CH_2Cl_2 (2 mL) was treated with a solution of Br_2 (43 μL, 0.837 mmol) in CH_2Cl_2 (1 mL) for 50 min at 0°C. After destroying the excess of bromine, the fucosyl bromide solution was added to a solution of **222a** (208 mg, 0.558 mmol) and Et_4NBr (154 mg, 0.733 mmol) in DMF/CH_2Cl_2 (10 mL, 1:1), which has been stirred with activated 3Å molecular sieves (850 mg) for 2 h. The reaction was stirred for 28 h at r.t. and then quenched with pyridine (1 mL). Work-up was performed according to the general procedure B and the resulting residue was purified by flash chromatography (petroleum ether/toluene/ethyl acetate, 20:5:1, + 1% Et_3N) yielding the pure tritylether (254 mg, 58%) as a colorless foam. To a stirred solution of the tritylether (241

mg, 0.305 mmol) in CH_2Cl_2 (4 mL), $ZnBr_2$ (208 mg, 0.924 mmol) and triethylsilane (55 μL, 0.344 mmol) were added. The reaction was quenched after 8 h by adding H_2O (100 μL). Work-up and purification according to the general procedure B yielded **223a** (140 mg, 84%) as a yellowish solid.

$[\alpha]_D^{21}$ = - 35.0 (*c* = 0.45, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.98 (m, 1 H, H-4_a), 1.08 (d, ^3J = 6.4 Hz, 3 H, CH_3), 1.16 (d, ^3J = 6.5 Hz, 3 H, Fuc H-6), 1.22-1.30 (m, 2 H, H-5_a, H-6_a), 1.51 (m, 1 H, H-3), 1.61-1.67 (m, 2 H, H-4_b, H-5_b), 2.00 (m, 1 H, H-6_b), 2.87 (t, ^3J = 9.3 Hz, 1 H, H-2), 3.37 (m, 1 H, H-1), 3.70 (m, 1 H, Fuc H-4), 3.97 (dd, ^3J = 2.7, 10.2 Hz, 1 H, Fuc H-3), 4.10-4.14 (m, 2 H, Fuc H-2, Fuc H-5), 4.65, 4.70, 4.76, 4.77, 4.86, 4.99 (6 m, 6 H, 3 CH_2Ph), 5.00 (d, 1 H, Fuc H-1), 7.25-7.39 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.61 (Fuc C-6), 18.67 (CH_3), 23.20 (C-5), 32.73 (C-6), 33.70 (C-4), 36.57 (C-3), 67.47 (Fuc C-5), 72.99, 73.02, 73.41 (C-1, 2 CH_2Ph), 74.85 (CH_2Ph), 76.45 (Fuc C-2), 77.50 (Fuc C-4), 78.95 (Fuc C-3), 93.13 (C-2), 98.50 (Fuc C-1), 127.36, 127.44, 127.55, 127.62, 127.89, 128.20, 128.23, 128.33, 128.37, 138.32, 138.42, 138.78 (18 C, 3 C_6H_5); IR (KBr) ν: 3434 (s, OH), 3030 (w), 2929 (s), 2866 (s), 1496 (w), 1454 (m), 1368 (w), 1347 (w), 1306 (w), 1245 (vw), 1208 (vw), 1161 (m), 1138 (s), 1106 (vs), 1059 (vs), 1028 (vs), 735 (s), 696 (s) cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{42}O_6$ (546.69): C 74.70, H 7.74; found: C 74.68, H 7.80.

[(1*R*,2*R*,3*S*)-3-Butyl-1-hydroxy-cyclohex-2-yl] 2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranoside (**223b**), (DS-05-32, DS-05-42).

According to the general procedure B, ethyl 2,3,4-tri-*O*-benzyl-1-thio-L-fucopyranoside (308 mg, 0.644 mmol) in CH_2Cl_2 (3 mL) was treated with a solution of Br_2 (38 μL, 0.740 mmol) in CH_2Cl_2 (1 mL) for 30 min at 0°C. After destroying the excess of bromine, the fucosyl bromide solution was added to a solution of **222b** (205 mg, 0.495 mmol) and Et_4NBr (137 mg, 0.650 mmol) in DMF/CH_2Cl_2 (10 mL, 1:1), which has been stirred with activated 3Å molecular sieves (700 mg) for 3.5 h. The reaction was stirred for 67 h at r.t. and then quenched with pyridine (1 mL). Work-up and purification according to the general procedure B yielded the tritylether (283 mg) as a yellowish resin. To a stirred solution of the tritylether in CH_2Cl_2 (4 mL), $ZnBr_2$ (229 mg, 1.02 mmol) and triethylsilane (81 μL, 0.510 mmol) were added. The reaction was quenched after 1.25 h by adding H_2O (100 μL). Work-up and purification according to the general procedure yielded **223b** (161 mg, 55% over two steps) as a colourless solid.

$[\alpha]_D^{21}$ = - 21.3 (*c* = 0.56, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.82 (t, ^3J = 7.0 Hz, 3 H, H-10), 0.86 (m, 1 H, H-4_a), 0.98 (m, 1 H, H-7_a), 1.15 (d, $^3J_{F5,F6}$ = 6.5 Hz, 3 H, Fuc H-6), 1.09-1.37 (m, 7 H, H-3, H-5_a, H-6_a, H-8_a, H-8_b, H-9_a, H-9_b), 1.66 (m, 1 H, H-5_b), 1.81 (m, 1 H, H-4_b), 1.98 (m, 1 H,

H-6_b), 2.10 (m, 1 H, H-7_b), 2.94 (t, ^3J = 9.3 Hz, 1 H, H-2), 3.36 (m, 1 H, H-1), 3.68 (m, 1 H, Fuc H-4), 3.98 (dd, $^3J_{F3,F4}$ = 2.6 Hz, $^3J_{F2,F3}$ = 10.2 Hz, 1 H, Fuc H-3), 4.09-4.14 (m, 2 H, Fuc H-2, Fuc H-5), 4.65, 4.70, 4.75, 4.78, 4.85 (5 m, 5 H, 3 CH_2Ph), 4.98-5.00 (m, 2 H, Fuc H-1, 1 CH_2Ph), 7.25-7.39 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 14.11 (C-10), 16.57 (Fuc C-6), 22.72 (C-9), 23.19 (C-5), 29.03 (C-8), 30.26 (C-4), 31.24 (C-7), 32.55 (C-6), 41.18 (C-3), 67.54 (Fuc C-5), 72.97 (*C*H_2Ph), 73.26 (C-1), 73.39 (*C*H_2Ph), 74.84 (*C*H_2Ph), 76.38 (Fuc C-2), 77.60 (Fuc C-4), 78.80 (Fuc C-3), 91.47 (C-2), 98.31 (Fuc C-1), 127.40, 127.45, 127.52, 127.61, 127.86, 128.20, 128.21, 128.33, 128.38, 138.32, 138.44, 138.79 (18 C, 3 C_6H_5); elemental analysis calcd (%) for $C_{37}H_{48}O_6$ (588.77): C 75.48, H 8.22; found: C 75.55, H 8.28.

[(1*R*,2*R*,3*R*)-3-Cyclopropyl-1-hydroxy-cyclohex-2-yl] 2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranoside (**223c**), (DS-05-63).

According to the general procedure B, ethyl 2,3,4-tri-*O*-benzyl-1-thio-L-fucopyranoside (223 mg, 0.466 mmol) in CH_2Cl_2 (1.5 mL) was treated with a solution of Br_2 (27.5 μL, 0.535 mmol) in CH_2Cl_2 (1 mL) for 30 min at 0°C. After destroying the exc ess of bromine, the fucosyl bromide solution was added to a solution of **222c** (142 mg, 0.356 mmol) and Et_4NBr (98.9 mg, 0.471 mmol) in DMF/CH_2Cl_2 (6 mL, 1:1), which has been stirred with activated 3Å molecular sieves (1 g) for 4 h. The reaction was stirred for 67 h at r.t. and then quenched with pyridine (1 mL). Work-up and purification according to the general procedure B yielded the tritylether (237 mg). To a stirred solution of the tritylether in CH_2Cl_2 (4 mL), $ZnBr_2$ (193 mg, 0.859 mmol) and triethylsilane (70 μL, 0.441 mmol) were added. The reaction was quenched after 1.75 h by adding H_2O (100 μL). Work-up and purification according to the general procedure B yielded **223c** (136 mg, 67% over two steps) as a colourless solid.

$[\alpha]_D^{21}$ = - 29.0 (*c* = 0.65, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: -0.06 (m, 1 H, *c*Pr), 0.08 (m, 1 H, *c*Pr), 0.22 (m, 1 H, *c*Pr), 0.33 (m, 1 H, *c*Pr), 0.87 (m, 1 H, H-4_a), 0.96 (m, 1 H, *c*Pr), 1.05-1.27 (m, 6 H, Fuc H-6, H-3, H-5_a, H-6_a), 1.54 (m, 1 H, H-4_b), 1.64 (m, 1 H, H-5_b), 1.96 (m, 1 H, H-6_b), 3.11 (t, ^3J = 9.1 Hz, 1 H, H-2), 3.35 (m, 1 H, H-1), 3.69 (m, 1 H, Fuc H-4), 3.98 (dd, $^3J_{F3,F4}$ = 2.5 Hz, $^3J_{F2,F3}$ = 10.1 Hz, 1 H, Fuc H-3), 4.11-4.16 (m, 2 H, Fuc H-2, Fuc H-5), 4.66-4.68 (m, 2 H, CH_2Ph), 4.76, 4.77, 4.90, 5.01 (4 m, 4 H, CH_2Ph), 5.14 (d, $^3J_{F1,F2}$ = 3.4 Hz, 1 H, Fuc H-1), 7.26-7.41 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 0.76, 4.93, 13.58 (3 C, *c*Pr), 16.56 (Fuc C-6), 22.86 (C-5), 28.32 (C-4), 32.56 (C-6), 44.14 (C-3), 67.64 (Fuc C-5), 73.14, 73.19 (2 *C*H_2Ph), 73.95 (C-1), 74.85 (*C*H_2Ph), 76.74 (Fuc C-2), 77.68 (Fuc C-4), 78.63 (Fuc C-3), 92.33 (C-2), 99.20 (Fuc C-1), 127.42, 127.45, 127.50, 127.64, 128.18, 128.22, 128.35, 128.44, 138.44, 138.58, 138.90 (18 C, 3 C_6H_5); IR (KBr) ν: 3426 (s, OH), 3031 (vw), 3004 (vw), 2933 (s), 1497

(vw), 1453 (m), 1348 (w), 1247 (vw), 1212 (vw), 1161 (m), 1136 (s), 1103 (vs), 1064 (vs), 1026 (vs), 957 (w), 911 (vw), 843 (vw), 736 (s), 696 (s) cm^{-1}; elemental analysis calcd (%) for $C_{36}H_{44}O_6$ (572.73): C 75.50, H 7.74; found: C 75.38, H 7.75.

[(1*R*,2*R*,3*R*)-3-Ethenyl-1-hydroxy-cyclohex-2-yl] 2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranoside (**223d**), (DS-04-148, DS-04-149, DS-05-06, DS-05-09).

According to the general procedure B, ethyl 2,3,4-tri-*O*-benzyl-1-thio-L-fucopyranoside (205 mg, 0.428 mmol) in CH_2Cl_2 (1.5 mL) was treated with a solution of Br_2 (25.5 μL, 0.496 mmol) in CH_2Cl_2 (1 mL) for 40 min at 0°C. After destroying the exc ess of bromine, the fucosyl bromide solution was added to a solution of **222d** (126 mg, 0.329 mmol) and Et_4NBr (90.8 mg, 0.432 mmol) in DMF/CH_2Cl_2 (6 mL, 1:1), which has been stirred with activated 3Å molecular sieves (500 mg) for 4 h. The reaction was stirred for 67 h at r.t. and then quenched with pyridine (1 mL). Work-up and purification according to the general procedure B yielded the tritylether (213 mg). To a stirred solution of the tritylether in CH_2Cl_2 (4 mL), $ZnBr_2$ (179 mg, 0.793 mmol) and triethylsilane (63 μL, 0.397 mmol) were added. The reaction was quenched after 2 h by adding H_2O (100 μL). Work-up and purification according to the general procedure B yielded **223d** (110 mg, 60% over two steps) as a colourless solid.

$[\alpha]_D^{21}$ = - 22.1 (*c* = 0.52, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.15 (d, $^3J_{F6,F5}$ = 6.5 Hz, 3 H, Fuc H-6), 1.17 (m, 1 H, H-4_a), 1.26-1.30 (m, 2 H, H-5_a, H-6_a), 1.72 (m, 1 H, H-5_b), 1.78 (m, 1 H, H-4_b), 2.02 (m, 1 H, H-6_b), 2.13 (m, 1 H, H-3), 3.04 (t, ^3J = 9.5 Hz, 1 H, H-2), 3.45 (m, 1 H, H-1), 3.69 (m, 1 H, Fuc H-4), 3.98 (dd, $^3J_{F3,F4}$ = 2.6 Hz, $^3J_{F2,F3}$ = 10.1 Hz, 1 H, Fuc H-3), 4.10 (dd, $^3J_{F1,F2}$ = 3.6 Hz, $^3J_{F2,F3}$ = 10.1 Hz, 1 H, Fuc H-2), 4.12 (m, 1 H, Fuc H-5), 4.65, 4.70, 4.76, 4.78, (4 m, 4 H, 2 C*H*$_2$Ph), 4.85 (m, 2 H, C*H*$_2$Ph, vinyl H), 4.98 (m, 1 H, vinyl H), 4.99 (m, 1 H, C*H*$_2$Ph), 5.03 (d, $^3J_{F1,F2}$ = 3.6 Hz, 1 H, Fuc H-1), 6.25 (m, 1 H, vinyl H), 7.27-7.40 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.55 (Fuc C-6), 22.81 (C-5), 29.67 (C-4), 32.39 (C-6), 44.33 (C-3), 67.56 (Fuc C-5), 72.97, 73.01 (*C*H$_2$Ph, C-1), 73.38, 74.85 (2 *C*H$_2$Ph), 76.41 (Fuc C-2), 77.54 (Fuc C-4), 78.86 (Fuc C-3), 90.26 (C-2), 97.98 (Fuc C-1), 113.46 (vinyl C), 127.43, 127.48, 127.53, 127.63, 127.82, 128.23, 128.36 (18 C, 3 C_6H_5), 140.43 (vinyl C), IR (KBr) ν: 3429 (s, OH), 3065 (w), 3031 (w), 2932 (s), 2866 (s), 1636 (vw), 1497 (w), 1454 (m), 1348 (m), 1308 (w), 1246 (vw), 1212 (w), 1161 (s), 1138 (s), 1101 (vs), 1064 (vs), 1027 (vs), 953 (m), 911 (w) cm^{-1}; elemental analysis calcd (%) for $C_{35}H_{42}O_6$ (558.70): C 75.24, H 7.58; found: C 74.91, H 7.55.

[(1*R*,2*R*,3*S*)-3-Ethyl-1-hydroxy-cyclohex-2-yl] 2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranoside (**223e**), (DS-05-14).

A solution of **223d** (90.0 mg, 0.161 mmol) in THF (4 mL) was added to Pd/C (45.2 mg, 10% Pd) under argon. The mixture was hydrogenated under atmospheric pressure at r.t.. After 30 min the reaction was filtered through celite, concentrated under reduced pressure and purified by column chromatography (toluene/petroleum ether/ethyl acetate, 7:7:1 to 5:5:1) to yield **223e** (69.8 mg, 77%) as a colourless solid.

$[\alpha]_D^{21}$ = - 37.2 (*c* = 0.50, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.78 (t, ^3J = 7.5 Hz, 3 H, CH_2CH_3), 0.88 (m, 1 H, H-4_a), 1.06-1.26 (m, 3 H, CH_2CH_3, H-5_a, H-6_a), 1.16 (d, $^3J_{F5,F6}$ = 6.5 Hz, 3 H, Fuc H-6), 1.30 (m, 1 H, H-3), 1.67 (m, 1 H, H-5_b), 1.79 (m, 1 H, H-4_b), 1.99-2.07 (m, 2 H, H-6_b, CH_2CH_3), 2.96 (dd, ^3J = 8.6, 10.2 Hz, 1 H, H-2), 3.38 (ddd, ^3J = 4.8, 8.5, 10.6 Hz, 1 H, H-1), 3.70 (m, 1 H, Fuc H-4), 3.98 (dd, $^3J_{F3,F4}$ = 2.7 Hz, $^3J_{F3,F2}$ = 10.2 Hz, 1 H, Fuc H-5), 4.10-4.14 (m, 2 H, Fuc H-2, Fuc H-5), 4.66, 4.70, 4.77, 4.80, 4.84 (5 m, 5 H, CH_2Ph), 4.89-5.00 (m, 2 H, Fuc H-1, CH_2Ph), 7.27-7.40 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 10.99 (CH_2CH_3), 16.60 (Fuc C-6), 23.09 (C-5), 24.17 (CH_2CH_3), 29.50 (C-4), 32.60 (C-6), 42.64 (C-3), 67.48 (Fuc C-5), 72.83, 73.13, 73.47 (C-1, 2 CH_2Ph), 74.84 (CH_2Ph), 76.32 (Fuc C-2), 77.37 (Fuc C-4), 78.86 (Fuc C-3), 91.07 (C-2), 98.31 (Fuc C-1), 127.40, 127.46, 127.50, 127.64, 127.80, 128.21, 128.33, 128.39, 138.31, 138.39, 138.70 (18 C, 3 C_6H_5); HR-MS (ESI) *m*/*z*: calcd for $C_{35}H_{44}NaO_6$ $[M+Na]^+$: 583.3030; found: 583.3018 (2.1 ppm).

[(1*R*,2*R*,3*R*)-1-Hydroxy-3-(2-methoxycarbonyl-ethyl)-cyclohex-2-yl] 2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranoside (**223f**), (DS-05-35).

223d (106 mg, 0.189 mmol) was dissolved in CH_2Cl_2 (5 mL) and Grubbs cat. 2nd gen. (16.0 mg 18.8 μmol) and methyl acrylate (171 μL, 1.90 mmol) were added. The reaction was heated under reflux for 9 d. After 1 d, 2 d and 7 d additional Grubbs cat. 2nd gen. (each 16.0 mg, 18.8 μmol) and methyl acrylate (each 171 μL, 1.90 mmol) were added. The mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether/ethyl acetate, 5:1 to 4:1) to yield an E/Z mixture (53.9 mg), which was directly used for hydrogenation. A solution of the E/Z-mixture in THF (4 mL) was added to Pd/C (28.0 mg, 10% Pd) under argon. The mixture was hydrogenated under atmospheric pressure at r.t.. After 30 min the reaction was filtered through celite, concentrated under reduced pressure and purified by column chromatography (petroleum ether/ethyl acetate, 3:1 to 2:1) to yield **223f** (29.1 mg, 25%) as a brownish oil.

$[\alpha]_D^{21}$ = - 21.2 (*c* = 1.46, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.94 (m, 1 H), 1.14 (d, $^3J_{F6,F5}$ = 6.5 Hz, 3 H, Fuc H-6), 1.19-1.28 (m, 2 H), 1.35-1.47 (m, 2 H), 1.67 (m, 1 H), 1.74 (m, 1 H), 1.99

(m, 1 H), 2.29-2.36 (m, 3 H), 2.97 (t, ^3J = 9.2 Hz, 1 H, H-2), 3.36 (m, 1 H, H-1), 3.57 (s, 3 H, Me), 3.67 (m, 1 H, Fuc H-4), 3.98 (dd, $^3J_{F3,F4}$ = 2.4 Hz, $^3J_{F2,F3}$ = 10.2 Hz, 1 H, Fuc H-3), 4.09-4.13 (m, 2 H, Fuc H-2, Fuc H-5), 4.65, 4.71, 4.76, 4.78, 4.85 (5 m, 5 H, CH_2Ph), 4.96 (d, $^3J_{F1,F2}$ = 3.4 Hz, 1 H, Fuc H-1), 4.99 (1 m, 1 H, CH_2Ph), 7.25-7.41 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.50 (Fuc C-6), 23.03, 27.48, 30.37, 32.02, 32.33 (5 C), 40.72 (C-3), 51.30 (Me), 67.64 (Fuc C-5), 72.97, 73.00 (*C*H_2Ph, C-1), 73.48, 74.82 (2 *C*H_2Ph), 76.01 (Fuc C-2), 77.50 (Fuc C-4), 78.84 (Fuc C-3), 91.25 (C-2), 98.33 (Fuc C-1), 127.43, 127.47, 127.58, 127.62, 127.92, 128.19, 128.28, 128.34, 128.36, 138.23, 138.36, 138.73 (18 C, 3 C_6H_5), 174.33 (*C*OOMe); HR-MS (ESI) *m*/*z*: calcd for $C_{37}H_{46}NaO_8$ $[M+Na]^+$: 641.3085; found: 641.3080 (0.8 ppm).

General procedure C for DMTST promoted glycosylations (**225a-225c**, **225e-225f**).

A solution of the thioglycoside **224** (0.292 mmol) and the appropriate glycosyl acceptor **223** (0.225 mmol) in dry CH_2Cl_2 (8 mL) was added *via* syringe to activated 3Å molecular sieves (2 g) under argon. A suspension of dimethyl(methylthio)sulfonium triflate (DMTST) (0.685 mmol) and activated 3Å molecular sieves (1 g) in CH_2Cl_2 (4 mL) was prepared in a second flask. Both suspensions were stirred at r.t. for 4 h, then the DMTST suspension was added *via* syringe to the other suspension with some additional CH_2Cl_2 (2 ml). The reaction was stopped after 2 d, filtered through celite and the celite washed with CH_2Cl_2 (10 mL). The filtrate was successively washed with satd. aqueous $NaHCO_3$ (25 mL) and water (40 mL). The aqueous layers were extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/toluene/ethyl acetate, 10:10:1 to 5:5:1) to afford the tetrasaccharide mimic **225** as a colourless foam.

{(1*R*,2*R*,3*S*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]-3-methyl-cyclohex-1-yl} 2,4,6-tri-*O*-benzoyl-3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**225a**), (DS-04-107).

Thioglycoside **224** (254 mg, 0.326 mmol) and glycosyl acceptor **223a** (137 mg, 0.250 mmol) in dry CH_2Cl_2 (8 mL) were added *via* syringe to activated 4Å molecular sieves (2 g). A suspension of DMTST (206 mg, 0.797 mmol) and activated 4Å molecular sieves (1 g) in CH_2Cl_2 (4 mL) was prepared in a second flask. Both suspensions were stirred at r.t. for 4 h, then the DMTST suspension was added *via* syringe to the other suspension. The reaction was stopped after 43 h and work-up and purification according to the general procedure C afforded **225a** (187 mg, 59%) as a colourless foam.

$[\alpha]_D^{21}$ = - 51.0 (*c* = 0.51, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.45-1.46 (m, 19 H, $CyCH_2$, MeCy), 1.04 (d, ^3J = 6.3 Hz, 3 H, CH_3), 1.44 (d, $^3J_{F5,F6}$ = 6.4 Hz, 3 H, Fuc H-6), 1.86 (m, 1 H, MeCy), 3.21 (t, ^3J = 9.1 Hz, 1 H, H-2), 3.48 (m, 1 H, H-1), 3.51 (s. 1 H, Fuc H-4), 3.82 (dd, $^3J_{G3,G4}$ = 3.3 Hz, $^3J_{G2,G3}$ = 9.9 Hz, 1 H, Gal H-3), 3.91 (m, 1 H, Gal H-5), 4.02 (dd, $^3J_{F1,F2}$ = 3.3 Hz, $^3J_{F2,F3}$ = 10.3 Hz, 1 H, Fuc H-2), 4.05 (dd, $^3J_{F3,F4}$ = 2.3 Hz, $^3J_{F2,F3}$ = 10.3 Hz, 1 H, Fuc H-3), 4.12 (dd, ^3J = 4.6, 7.9 Hz, 1 H, Lac H-2), 4.24 (dd, $^3J_{G5,G6a}$ = 7.2 Hz, $^2J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6_a), 4.26 (m, 1 H, CH_2Ph), 4.38 (dd, $^3J_{G5,G6b}$ = 5.7 Hz, $^2J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6_b), 4.51 (m, 1 H, CH_2Ph), 4.54 (d, $^3J_{G1,G2}$ = 8.2 Hz, 1 H, Gal H-1), 4.63, 4.67, 4.74, 4.77 (4 m, 4 H, CH_2Ph), 4.88 (m, 1 H, Fuc H-5), 5.05 (m, 1 H, CH_2Ph), 5.06 (d, $^3J_{F1,F2}$ = 3.5 Hz, 1 H, Fuc H-1), 5.11 (m, 1 H, CH_2Ph), 5.60 (m, 1 H, Gal H-2), 5.84 (m, 1 H, Gal H-4), 7.17-7.34, 7.42-7.46, 7.52-7.58, 8.03-8.12 (4 m, 35 H, 7 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.80 (Fuc C-6), 18.68 (CH_3), 22.65, 25.46, 25.72, 26.08, 30.73, 32.63, 33.03, 33.21, 33.40, 38.97, 40.48 (11 C, MeCy, $CyCH_2$), 62.47 (Gal C-6), 66.31 (Fuc C-5), 66.63 (*C*H_2Ph), 70.20 (Gal C-4), 71.43 (Gal C-5), 72.10 (*C*H_2Ph), 72.18 (Gal C-2), 74.19, 74.92 (2 *C*H_2Ph), 76.38 (Fuc C-2), 78.10 (Gal C-3), 78.43 (Lac C-2), 79.46 (Fuc C-4), 79.74 (Fuc C-3), 80.97, 81.20 (2 C, MeCy), 97.88 (Fuc C-1), 100.07 (Gal C-1), 126.91, 127.01, 127.17, 127.37, 127.72, 128.03, 128.07, 128.40, 128.45, 128.49, 128.55, 129.66, 129.74, 129.94, 129.98, 133.04, 133.16, 133.26, 135.43, 138.63, 139.05, 139.25 (42 C, 7 C_6H_5), 164.54, 166.11, 166.22, 172.45 (4 C=O); IR (KBr) ν: 3064, 3032, 2926, 1730 (C=O), 1602, 1497, 1452, 1315, 1267, 1175, 1069, 1098 cm^{-1}; elemental analysis calcd (%) for $C_{77}H_{84}O_{16}$ (1265.48): C 73.08, H 6.69; found: C 73.16, H 6.76.

{(1*R*,2*R*,3*S*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]-3-butyl-cyclohex-1-yl} 2,4,6-tri-*O*-benzoyl-3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**225b**), (DS-05-45).

Thioglycoside **224** (218 mg, 0.279 mmol) and glycosyl acceptor **223b** (126 mg, 0.215 mmol) in dry CH_2Cl_2 (8 mL) were added *via* syringe to activated 3Å molecular sieves (2 g). A suspension of DMTST (166 mg, 0.644 mmol) and activated 3Å molecular sieves (1 g) in CH_2Cl_2 (4 mL) was prepared in a second flask. Both suspensions were stirred at r.t. for 4.5 h, then the DMTST suspension was added *via* syringe to the other suspension with some additional CH_2Cl_2 (2 ml). The reaction was stopped after 65.5 h and work-up and purification according to the general procedure C afforded **225b** (224 mg, 80%) as a colourless foam.

$[\alpha]_D^{21}$ = - 46.7 (*c* = 0.49, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.45-1.84 (m, 26 H, $CyCH_2$, *n*BuCy), 0.80 (d, ^3J = 6.8 Hz, 3 H, *n*Bu), 1.40 (d, ^3J = 6.5 Hz, 3 H, Fuc H-6), 3.36 (t, ^3J = 8.5 Hz, 1 H, H-2), 3.52 (s, 1 H, Fuc H-4), 3.54 (m, 1 H, H-1), 3.83 (dd, $^3J_{G3,G4}$ = 3.0 Hz, $^3J_{G2,G3}$ = 9.8 Hz, 1 H, Gal H-3), 3.92 (m, 1 H, Gal H-5), 4.01 (dd, $^3J_{F1,F2}$ = 3.2 Hz, $^3J_{F2,F3}$ = 10.3 Hz, 1 H, Fuc H-2),

4.04 (dd, $^3J_{F3,F4}$ = 2.0 Hz, $^3J_{F2,F3}$ = 10.4 Hz, 1 H, Fuc H-3), 4.13 (dd, ^3J = 4.6, 7.8 Hz, 1 H, Lac H-2), 4.28 (dd, $^3J_{G5,G6a}$ = 6.7 Hz, $^2J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6_a), 4.28 (m, 1 H, CH_2Ph), 4.39 (dd, $^3J_{G5,G6b}$ = 5.8 Hz, $^2J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6_b), 4.52 (m, 1 H, CH_2Ph), 4.56 (d, $^3J_{G1,G2}$ = 8.1 Hz, 1 H, Gal H-1), 4.65, 4.68, 4.74, 4.76 (4 m, 4 H, CH_2Ph), 4.79 (m, 1 H, Fuc H-5), 5.01 (d, $^3J_{F1,F2}$ = 3.0 Hz, 1 H, Fuc H-1), 5.05, 5.11 (2 m, 2 H, CH_2Ph), 5.61 (m, 1 H, Gal H-2), 5.85 (m, 1 H, Gal H-4), 7.20-7.36, 7.42-7.46, 7.52-7.59, 8.04-8.13 (4 m, 35 H, 7 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 14.26 ($CH_2CH_2CH_2CH_3$), 16.81 (Fuc C-6), 21.84, 22.95, 25.46, 25.71, 26.07, 28.34, 28.55, 30.20, 30.39, 32.61, 33.19, 33.39, 40.48, 42.80 (14 C, $CyCH_2$, *n*BuCy), 62.52 (Gal C-6), 66.37 (Fuc C-5), 66.63 (*C*H_2Ph), 70.15 (Gal C-4), 71.45 (Gal C-5), 72.11 (*C*H_2Ph), 72.21 (Gal C-2), 73.89, 74.92 (2 *C*H_2Ph), 76.17 (Fuc C-2), 78.05 (Gal C-3), 78.38 (Lac C-2), 78.76 (C-2), 79.23 (Fuc C-4), 79.75 (Fuc C-3), 80.79 (C-1), 97.71 (Fuc C-1), 100.03 (Gal C-1), 126.95, 127.04, 127.21, 127.30, 127.80, 128.04, 128.09, 128.15, 128.39, 128.44, 128.48, 128.49, 128.54, 129.66, 129.71, 129.75, 129.92, 129.94, 133.03, 133.16, 133.25, 135.42, 138.70, 138.99, 139.16 (42 C, 7 C_6H_5), 164.56, 166.09, 166.21, 172.47 (4 C=O); elemental analysis calcd (%) for $C_{80}H_{90}O_{16}$ (1307.58): C 73.49, H 6.94; found: C 73.16, H 6.93.

{(1*R*,2*R*,3*R*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]-3-cyclopropyl-cyclohex-1-yl} 2,4,6-tri-*O*-benzoyl-3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**225c**), (DS-05-64).

Thioglycoside **224** (228 mg, 0.292 mmol) and glycosyl acceptor **223c** (129 mg, 0.225 mmol) in dry CH_2Cl_2 (8 mL) were added *via* syringe to activated 3Å molecular sieves (2 g). A suspension of DMTST (177 mg, 0.685 mmol) and activated 3Å molecular sieves (1 g) in CH_2Cl_2 (4 mL) was prepared in a second flask. Both suspensions were stirred at r.t. for 4 h, then the DMTST suspension was added *via* syringe to the other suspension with some additional CH_2Cl_2 (2 ml). The reaction was stopped after 48 h and work-up and purification according to the general procedure C afforded **225c** (253 mg, 87%) as a colourless foam.

$[\alpha]_D^{21}$ = - 43.1 (*c* = 0.61, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: -0.11 (m, 1 H, *c*Pr), 0.16 (m, 1 H, *c*Pr), 0.32-0.35 (m, 2 H, *c*Pr), 0.46-0.53 (m, 2 H, $CyCH_2$), 0.64-1.46 (m, 18 H, $CyCH_2$, Cy, *c*Pr), 1.38 (d, $^3J_{F5,F6}$ = 6.4 Hz, 3 H, Fuc H-6), 1.80 (m, 1 H, H-6_b), 3.52 (t, ^3J = 7.3 Hz, 1 H, H-2), 3.57 (s, 1 H, Fuc H-4), 3.62 (m, 1 H, H-1), 3.84 (dd, $^3J_{G3,G4}$ = 2.8 Hz, $^3J_{G2,G3}$ = 9.8 Hz, 1 H, Gal H-3), 3.93 (m, 1 H, Gal H-5), 4.03 (dd, $^3J_{F1,F2}$ = 3.2 Hz, $^3J_{F2,F3}$ = 10.2 Hz, 1 H, Fuc H-2), 4.07 (dd, $^3J_{F3,F4}$ = 1.7 Hz, $^3J_{F2,F3}$ = 10.4 Hz, 1 H, Fuc H-3), 4.13 (dd, ^3J = 4.5, 7.8 Hz, 1 H, Lac H-2), 4.32-4.40 (m, 3 H, Gal H-6, CH_2Ph), 4.53 (m, 1 H, CH_2Ph), 4.58 (d, $^3J_{G1,\ G2}$ = 8.1 Hz, 1 H, Gal H-1), 4.62, 4.68 (2 m, 2 H, CH_2Ph), 4.74-4.76 (m, 2 H, Fuc H-5, CH_2Ph), 4.78 (m, 1 H, CH_2Ph), 5.05, 5.11 (2 m, 2 H, CH_2Ph), 5.35 (d, $^3J_{F1,F2}$ = 2.8 Hz, 1 H, Fuc H-1), 5.61 (m, 1 H, Gal H-2), 5.87 (m,

1 H, Gal H-4), 7.20-7.36, 7.42-7.44, 7.52-7.59, 8.03-8.14 (4 m, 35 H, 7 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 3.06 (*c*Pr), 5.26 (*c*Pr), 13.55 (*c*Pr), 16.81 (Fuc C-6), 20.97, 25.46, 25.72, 26.07, 27.71, 29.44, 32.62, 33.21, 33.40 (9 C, $CyCH_2$, Cy), 40.46 (Lac C-3), 45.35 (C-3), 62.50 (Gal C-6), 66.34 (Fuc C-5), 66.61 (*C*H_2Ph), 70.10 (Gal C-4), 71.49 (Gal C-5), 72.13 (*C*H_2Ph), 72.32 (Gal C-2), 74.22 (*C*H_2Ph), 74.87 (*C*H_2Ph), 76.15 (Fuc C-2), 77.97 (Gal C-3), 78.38 (Lac C-2), 78.82 (C-2), 79.13 (Fuc C-4), 79.66 (C-1), 79.83 (Fuc C-3), 97.02 (Fuc C-1), 99.60 (Gal C-1), 126.96, 127.05, 127.20, 127.38, 127.78, 128.05, 128.09, 128.37, 128.43, 128.47, 128.53, 129.61, 129.73, 129.89, 129.93, 129.96, 133.03, 133.16, 133.23, 135.44, 138.51, 138.95, 139.21 (42 C, 7 C_6H_5), 164.57, 165.98, 166.16, 172.43 (4 C=O); IR (KBr) ν: 3064 (vw), 3032 (vw), 2927 (s), 2854 (w), 1731 (vs, C=O), 1602 (vw), 1497 (vw), 1452 (m), 1315 (m), 1267 (vs), 1176 (s), 1097 (vs), 1027 (vs), 840 (vw), 713 (vs) cm^{-1}; elemental analysis calcd (%) for $C_{79}H_{86}O_{16}$ (1291.52): C 73.47, H 6.71; found: C 73.32, H 6.81.

{(1*R*,2*R*,3*S*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]-3-ethyl-cyclohex-1-yl} 2,4,6-tri-*O*-benzoyl-3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**225e**), (DS-05-17).

Thioglycoside **224** (112 mg, 0.144 mmol) and glycosyl acceptor **223e** (61.6 mg, 0.110 mmol) in dry CH_2Cl_2 (4 mL) were added *via* syringe to activated 3Å molecular sieves (1 g). A suspension of DMTST (87.0 mg, 0.337 mmol) and activated 3Å molecular sieves (500 mg) in CH_2Cl_2 (2 mL) was prepared in a second flask. Both suspensions were stirred at r.t. for 4 h, then the DMTST suspension was added *via* syringe to the other suspension with some additional CH_2Cl_2 (1 ml). The reaction was stopped after 49.5 h and work-up and purification according to the general procedure C afforded **225e** (110 mg, 78%) as a colourless foam.

$[\alpha]_D^{21}$ = - 51.5 (*c* = 0.42, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ : 0.45-1.61 (m, 20 H, $CyCH_2$, EtCy), 0.75 (t, ^3J = 7.3 Hz, 3 H, CH_2CH_3), 1.41 (d, $^3J_{F5,F6}$ = 6.4 Hz, 3 H, Fuc H-6), 1.84 (m, 1 H, H-6$_b$), 1.92 (m, 1 H, CH_2CH_3), 3.31 (t, ^3J = 8.7 Hz, 1 H, H-2), 3.49-3.52 (m, 2 H, H-1, Fuc H-4), 3.82 (dd, $^3J_{G3,G4}$ = 3.2 Hz, $^3J_{G2,G3}$ = 9.8 Hz, 1 H, Gal H-3), 3.92 (m, 1 H, Gal H-5), 3.99-4.05 (m, 2 H, Fuc H-2, Fuc H-3), 4.12 (dd, ^3J = 4.6, 7.9 Hz, 1 H, Lac H-2), 4.25 (dd, $^3J_{G5,G6a}$ = 7.2 Hz, $^3J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6$_a$), 4.28 (m, 1 H, CH_2Ph), 4.39 (dd, $^3J_{G5,G6b}$ = 5.7 Hz, $^3J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6$_b$), 4.51-4.55 (m, 2 H, CH_2Ph, Gal H-1), 4.63, 4.65, 4.75, 4.78 (4 m, 4 H, CH_2Ph), 4.81 (m, 1 H, Fuc H-5), 4.98 (d, $^3J_{F1,F2}$ = 2.8 Hz, 1 H, Fuc H-1), 5.04, 5.11 (2 m, 2 H, CH_2Ph), 5.60 (m, 1 H, Gal H-2), 5.84 (m, 1 H, Gal H-4), 7.17-7.33, 7.42-7.46, 7.52-7.58, 8.04-8.12 (4 m, 35 H, 7 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 10.94 (CH_2CH_3), 16.82 (Fuc C-6), 23.18 (CH_2CH_3), 22.11, 25.45, 25.71, 26.07, 27.89, 30.41, 32.60, 33.19, 33.40, 40.49 (10 C, EtCy, $CyCH_2$), 44.71 (C-3), 62.50 (Gal C-6), 66.35 (Fuc C-5), 66.64 (*C*H_2Ph), 70.17 (Gal C-4),

71.40 (Gal C-5), 72.07 (*C*H_2Ph), 72.17 (Gal C-2), 74.29, 74.91 (2 *C*H_2Ph), 76.42 (Fuc C-2), 78.06 (Gal C-3), 78.38 (Lac C-2), 79.22, 79.27 (Fuc C-4, C-2), 79.77 (Fuc C-3), 80.95 (C-1), 97.96 (Fuc C-1), 100.05 (Gal C-1), 126.94, 127.06, 127.21, 127.39, 127.77, 128.05, 128.10, 128.38, 128.44, 128.50, 128.54, 129.66, 129.93, 133.03, 133.17, 133.27, 135.40, 138.64, 139.01, 139.17 (42 C, 7 C_6H_5), 164.58, 166.11, 166.22, 172.48 (4 C=O); elemental analysis calcd (%) for $C_{78}H_{86}O_{16}$ (1279.51) + ½ H_2O: C 72.20, H 6.84; found: C 72.37, H 6.82; HR-MS (ESI) *m*/*z*: calcd for $C_{78}H_{86}NaO_{16}$ $[M+Na]^+$: 1301.5808; found: 1301.5855 (3.6 ppm).

{(1*R*,2*R*,3*R*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]-3-(2-methoxycarbonyl-ethyl)-cyclohex-1-yl} 2,4,6-tri-*O*-benzoyl-3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**225f**), (DS-05-47).

Thioglycoside **224** (47.9 mg, 61.3 μmol) and glycosyl acceptor **223f** (29.1 mg, 47.0 μmol) in dry CH_2Cl_2 (4 mL) were added *via* syringe to activated 3Å molecular sieves (500 mg). A suspension of DMTST (37.6 mg, 146 μmol) and activated 3Å molecular sieves (250 mg) in CH_2Cl_2 (2 mL) was prepared in a second flask. Both suspensions were stirred at r.t. for 4 h, then the DMTST suspension was added *via* syringe to the other suspension with some additional CH_2Cl_2 (1 ml). The reaction was stopped after 65.5 h and work-up according to the general procedure C and purification by column chromatography (petroleum ether/ethyl acetate, 4:1 to 3:1) afforded **225f** (49.5 mg, 79%) as a colourless foam.

$[\alpha]_D^{21}$ = - 38.1 (*c* = 0.59, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ : 0.45-1.57 (m, 19 H, $CyCH_2$, Cy), 1.37 (d, ^3J = 6.4 Hz, 3 H, Fuc H-6), 1.61 (m, 1 H, $(CH_2)_2CO_2Me$), 1.82 (m, 1 H, H-6_b), 2.13-2.26 (m, 3 H, $(CH_2)_2CO_2Me$), 3.39 (t, ^3J = 8.1 Hz, 1 H, H-2), 3.51 (s, 1 H, Fuc H-4), 3.53-3.56 (m, 4 H, H-1, Me), 3.84 (dd, $^3J_{G3,G4}$ = 3.3 Hz, $^3J_{G2,G3}$ = 9.9 Hz, 1 H, Gal H-3), 3.93 (m, 1 H, Gal H-5), 3.98-4.03 (m, 2 H, Fuc H-2, Fuc H-3), 4.13 (dd, ^3J = 4.5, 8.0 Hz, 1 H, Lac H-2), 4.28 (dd, $^3J_{G5,G6a}$ = 7.2 Hz, $^2J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6_a), 4.31 (m, 1 H, CH_2Ph), 4.38 (dd, $^3J_{G5,G6b}$ = 5.6 Hz, $^2J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6_b), 4.54 (m, 1 H, CH_2Ph), 4.55 (d, $^3J_{G1,G2}$ = 8.0 Hz, 1 H, Gal H-1), 4.66-4.71 (m, 3 H, CH_2Ph, Fuc H-5), 4.73, 4.77 (2 m, 2 H, CH_2Ph), 5.02 (d, $^3J_{F1,F2}$ = 2.3 Hz, 1 H, Fuc H-1), 5.05, 5.12 (2 m, 2 H, CH_2Ph), 5.60 (m, 1 H, Gal H-2), 5.85 (m, 1 H, Gal H-4), 7.19-7.34, 7.42-7.47, 7.53-7.59, 8.03-8.13 (4 m, 35 H, 7 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.78 (Fuc C-6), 21.18, 25.44, 25.66, 25.70, 26.05, 27.84, 31.26, 32.57, 33.19, 33.38, 40.45 (12 C, $CyCH_2$, Cy, $(CH_2)_2CO_2Me$), 41.94 (C-3), 51.42 (CO_2Me), 62.54 (Gal C-6), 66.50 (Fuc C-5), 66.62 (*C*H_2Ph), 70.09 (Gal C-4), 71.48 (Gal C-5), 72.24 (2 C, *C*H_2Ph, Gal C-2), 73.79, 74.90 (2 *C*H_2Ph), 76.26 (Fuc C-2), 77.91 (Gal C-3), 78.34, 78.38 (Lac C-2, C-2), 79.09 (Fuc C-4), 79.53 (Fuc C-3), 80.22 (C-1), 97.70 (Fuc C-1) 99.93 (Gal C-1), 126.96, 127.06, 127.23, 127.29, 127.83, 128.04, 128.06, 128.08, 128.15, 128.38, 128.44, 128.48, 128.53, 128.57, 129.62,

129.65, 129.69, 129.74, 129.86, 129.88, 129.94, 129.99, 133.05, 133.19, 133.24, 135.39, 138.64, 138.99, 139.07 (42 C, 7 C_6H_5), 164.55, 166.06, 166.17, 172.45, 174.02 (5 C=O); elemental analysis calcd (%) for $C_{80}H_{88}O_{18}$ (1337.54): C 71.84, H 6.63; found: C 71.70, H 6.73.

{(1*R*,2*R*,3*S*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]-3-methyl-cyclohex-1-yl} 2-*O*-benzoyl-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-β-D-galactopyranoside sodium salt (**226a**), (DS-04-139).

Pd/C (20.2 mg, 10% Pd) was suspended under argon in ethanol (3.5 mL) with a catalytic amount of acetic acid. Compound **225a** (68.0 mg, 53.7 μmol) was added and the mixture was hydrogenated under 70 psi at r.t.. After 18 h additional Pd/C (23.1 mg) was added and the hydrogenation continued. After 4 d the mixture was filtered through celite and reacted with fresh Pd/C (23 mg) for another 4 d, until TLC control indicated completion of the reaction. The reaction mixture was filtered through celite and evaporated to dryness. The residue was redissolved in methanol (4 mL) and sodium methoxide (0.161 mmol in 618 μl MeOH) was added. After stirring at r.t. for 18 h the reaction was quenched by addition of acetic acid (15.3 μL). The mixture was concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2/methanol/water, 3.4:1:0.1 to 2:1:0.1), followed by Dowex 50 (Na^+ form) ion exchange column, Sephadex G15 column, microfiltration and lyophilization from *tert.*-butanol/H_2O to give **226a** (30.3 mg, 79%) as a colourless foam.

$[\alpha]_D^{21}$ = - 91.5 (c = 0.46, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.49-1.65 (m, 19 H, $CyCH_2$, MeCy), 1.07 (d, ^3J = 6.4 Hz, 3 H, CH_3), 1.33 (d, ^3J = 6.5 Hz, 3 H, Fuc H-6), 2.02 (m, 1 H, MeCy), 3.11 (t, ^3J = 9.2 Hz, 1 H, H-2), 3.55-3.63 (m, 3 H, H-1, Gal H-3, Gal H-5), 3.71-3.81 (m, 5 H, Gal H-6, Fuc H-2, Fuc H-4, Lac H-2), 3.89 (dd, $^3J_{F3,F4}$ = 3.0 Hz, $^3J_{F2,F3}$ = 10.2 Hz, 1 H, Fuc H-3), 3.94 (m, 1 H, Gal H-4), 4.67 (d, $^3J_{G1,G2}$ = 8.1 Hz, 1 H, Gal H-1), 4.94-4.98 (m, 2 H, Fuc H-1, Fuc H-5), 5.41 (t, ^3J = 8.8 Hz, 1 H, Gal H-2), 7.48-7.51, 7.60-7.62, 8.07-8.08 (3 m, 5 H, C_6H_5); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 16.69 (Fuc C-6), 19.44 (CH_3), 23.94, 26.58, 26.84, 27.42, 32.24, 33.08, 34.47, 34.59, 35.41, 40.23, 43.55 (11 C, MeCy, CH_2Cy), 63.17 (Gal C-6), 67.72 (2 C, Gal C-4, Fuc C-5), 70.32 (Fuc C-2), 71.37 (Fuc C-3), 73.16 (Gal C-2), 73.95 (Fuc C-4), 75.97 (Gal C-5), 80.68 (Lac C-2), 80.75 (C-1), 83.54 (C-2), 83.73 (Gal C-3), 100.15 (Fuc C-1), 100.73 (Gal C-1), 129.59, 130.83, 131.85, 134.17 (6 C, C_6H_5), 166.83 (C=O), 183.26 (CO_2Na); IR (KBr) ν: 3412 (vs, OH), 2927 (vs), 2852 (m), 1723 (m, C=O), 1591 (s), 1450 (m), 1412 (m), 1365 (m), 1316 (w), 1273 (s), 1168 (m), 1079 (vs), 1031 (s), 1000 (w), 970 (vw) cm^{-1}; elemental analysis calcd (%) for $C_{35}H_{51}NaO_{14}$ (718.76) + 3 H_2O: C 54.40, H 7.43; found: C 54.41, H 7.33; HR-MS (ESI) *m/z*: calcd for $C_{35}H_{52}NaO_{14}$ $[M+H]^+$: 719.3249; found: 719.3247 (0.3 ppm).

General procedure D for deprotection with $Pd(OH)_2$/C and sodium methoxide (**226c**, **226e-226f**).

$Pd(OH)_2$/C (50 mg, 10% Pd) was suspended under argon in dioxane/H_2O (4:1, 3.75 mL). The appropriate compound **225** (77.7 μmol) was added and the resulting mixture was hydrogenated under 70 psi at r.t.. After 24 h the mixture was filtered through celite and reacted with fresh $Pd(OH)_2$/C (50 mg) for additional 48 h, until TLC control indicated completion of the reaction. The reaction mixture was filtered through celite and evaporated to dryness. The residue was redissolved in methanol (5 mL) and sodium methoxide (0.194 mmol in 190 μl MeOH) was added. After stirring at r.t. for 16 h the reaction was quenched by addition of acetic acid (22 μL). The mixture was concentrated *in vacuo* and purified by preparative, reversed-phase HPLC to afford the antagonists **226** as colourless solids.

{(1*R*,2*R*,3*S*)-3-butyl-2-[(6-deoxy-α-L-galactopyranosyl)oxy]-cyclohex-1-yl} 2-*O*-benzoyl-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-β-D-galactopyranoside sodium salt (**226b**), (DS-05-46).

225b (100 mg, 76.5 μmol) was hydrogenated with $Pd(OH)_2$/C (50 mg, 10% Pd) in dioxane/H_2O (4:1, 3.75 mL) according the to general procedure D. After 19 h the mixture was filtered through celite and hydrogenated with fresh $Pd(OH)_2$/C (50 mg) for another 30 h. The reaction mixture was filtered through celite and evaporated to dryness. The residue was redissolved in methanol (5 mL) and sodium methoxide (0.191 mmol) was added. After stirring at r.t. for 17 h the reaction was quenched by addition of acetic acid (22 μL). The mixture was concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2/methanol/water, 3.4:1:0.1 to 2:1:0.1), followed by Dowex 50 (Na^+ form) ion exchange column, Sephadex G15 column, microfiltration and lyophilization from dioxane to give **226b** (32.3 mg, 56%) as a colourless foam. For biological testing a small amount was purified by preparative, reversed-phase HPLC to afford the free acid of **226b** as colourless needles.

226b sodium salt:

$[\alpha]_D^{21}$ = - 77.9 (*c* = 0.61, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ : 0.47-1.89 (m, 25 H, $CyCH_2$, *n*Bu, Cy), 0.88 (t, ^3J = 7.1 Hz, 3 H, *n*Bu), 1.31 (d, ^3J = 6.5 Hz, 3 H, Fuc H-6), 2.00 (m, 1 H, H-6_b), 3.24 (t, ^3J = 8.9 Hz, 1 H, H-2), 3.56-3.60 (m, 2 H, Gal H-5, Gal H-3), 3.65 (m, 1 H, H-1), 3.72-3.77 (m, 4 H, Gal H-6_a, Fuc H-2, Fuc H-4, Lac H-2), 3.80 (dd, $^3J_{G5,G6b}$ = 6.9 Hz, $^2J_{G6a,G6b}$ = 11.5 Hz, 1 H, Gal H-6_b), 3.88 (dd, $^3J_{F3,F4}$ = 3.3 Hz, $^3J_{F2,F3}$ = 10.3 Hz, 1 H, Fuc H-3), 3.95 (m, 1 H, Gal H-4), 4.68 (d, $^3J_{G1,G2}$ = 8.1 Hz, 1 H, Gal H-1), 4.85 (m, 1 H, Fuc H-5), 4.94 (d, $^3J_{F1,F2}$ = 4.0 Hz, 1 H, Fuc H-1), 5.41 (dd, $^3J_{G1,G2}$ = 8.5 Hz, $^3J_{G2,G3}$ = 9.2 Hz, 1 H, Gal H-2), 7.48-7.51, 7.60-7.63,

8.07-8.09 (3 m, 5 H, C_6H_5); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 14.48 (*n*Bu), 16.72 (Fuc C-6), 23.27, 23.92, 26.57, 26.82, 27.41, 29.83, 30.04, 31.69, 31.86, 33.06, 34.44, 35.41, 43.54, 44.30 (14 C, *n*Bu, Cy, CH_2Cy), 63.06 (Gal C-6), 67.70 (Gal C-4), 67.84 (Fuc C-5), 70.21 (Fuc C-2), 71.34 (Fuc C-3), 73.08 (Gal C-2), 73.90 (Fuc C-4), 75.92 (Gal C-5), 80.69 (Lac C-2), 80.41 (C-1), 81.37 (C-2), 83.69 (Gal C-3), 99.91 (Fuc C-1), 100.53 (Gal C-1), 129.60, 130.84, 131.76, 134.23 (6 C, C_6H_5), 166.87 (*C*=O), 183.26 (*C*OOH); HR-MS (ESI) *m*/*z*: calcd for $C_{38}H_{58}NaO_{14}$ $[M+H]^+$: 761.3719; found: 761.3710 (1.2 ppm).

226b free acid:

^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.54-1.91 (m, 25 H, $CyCH_2$, *n*Bu, Cy), 0.89 (t, ^3J = 7.1 Hz, 3 H, *n*Bu), 1.32 (d, ^3J = 6.6 Hz, 3 H, Fuc H-6), 1.98 (m, 1 H, H-6_b), 3.23 (t, ^3J = 8.9 Hz, 1 H, H-2), 3.56 (m, 1 H, Gal H-5), 3.62 (m, 1 H, H-1), 3.66 (dd, $^3J_{G3,G4}$ = 3.0 Hz, $^3J_{G2,G3}$ = 9.8 Hz, 1 H, Gal H-3), 3.70-3.75 (m, 3 H, Gal H-6_a, Fuc H-2, Fuc H-4), 3.79 (dd, $^3J_{G6b,G5}$ = 6.9 Hz, $^2J_{G6a,G6b}$ = 11.3 Hz, 1 H, Gal H-6_b), 3.85 (dd, $^3J_{F3,F4}$ = 3.3 Hz, $^3J_{F2,F3}$ = 10.3 Hz, 1 H, Fuc H-3), 3.97 (m, 1 H, Gal H-4), 4.06 (dd, ^3J = 2.9, 9.9 Hz, 1 H, Lac H-2), 4.67 (d, $^3J_{G1,G2}$ = 8.1 Hz, 1 H, Gal H-1), 4.88-4.92 (m, 2 H, Fuc H-1, Fuc H-5), 5.43 (dd, $^3J_{G1,G2}$ = 8.2 Hz, $^3J_{G2,G3}$ = 9.6 Hz, 1 H, Gal H-2), 7.49-7.52, 7.62-7.64, 8.07-8.09 (3 m, 5 H, C_6H_5); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 14.48 (*n*Bu), 16.74 (Fuc C-6), 23.38, 23.90, 26.54, 26.72, 27.28, 29.83, 29.99, 31.71, 31.81, 33.12, 34.19, 35.07, 42.78, 44.51 (14 C, *n*Bu, Cy, CH_2Cy), 62.69 (Gal C-6), 67.79 (2 C, Fuc C-5, Gal C-4), 70.27 (Fuc C-2), 71.43 (Fuc C-3), 73.10 (Gal C-2), 73.94 (Fuc C-4), 75.90 (Gal C-5), 77.93 (Lac C-2), 80.71 (C-1), 81.45 (C-2), 83.57 (Gal C-3), 100.29 (Fuc C-1), 100.52 (Gal C-1), 129.67, 130.85, 131.63, 134.37 (6 C, C_6H_5), 166.77 (*C*=O), 178.84 (CO_2H).

{(1*R*,2*R*,3*R*)-3-cyclopropyl-2-[(6-deoxy-α-L-galactopyranosyl)oxy]-cyclohex-1-yl} 2-*O*-benzoyl-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**226c**), (DS-05-65). **225c** (100 mg, 77.7 μmol) was hydrogenated with $Pd(OH)_2$/C (52 mg, 10% Pd) in dioxane/H_2O (4:1, 3.75 mL) according to the general procedure D. After 24 h the mixture was filtered through celite and hydrogenated with fresh $Pd(OH)_2$/C (50 mg) for another 48 h. The reaction mixture was filtered through celite and evaporated to dryness. The residue was redissolved in methanol (5 mL) and sodium methoxide (194 μmol in 190 μl MeOH) was added. After stirring at r.t. for 16 h the reaction was quenched by addition of acetic acid (22 μL). The mixture was concentrated *in vacuo* and purified by preparative, reversed-phase HPLC to afford **226c** (40.5 mg, 72%) as a colourless solid.

$[\alpha]_D^{21}$ = - 85.4 (*c* = 0.75, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: -0.04 (m, 1 H, *c*Pr), 0.33 (m, 1 H, *c*Pr), 0.45-0.52 (m, 2 H, *c*Pr), 0.56-1.65 (m, 20 H, $CyCH_2$, *c*PrCy), 1.30 (d, $^3J_{F5,F6}$ = 6.6 Hz, 3 H, Fuc H-6), 1.94 (m, 1 H, H-6_b), 3.45 (t, ^3J = 8.5 Hz, 1 H, H-2), 3.56 (m, 1 H, Gal H-5), 3.62 (m, 1 H, H-1), 3.66 (dd, $^3J_{G3,G4}$ = 3.1 Hz, $^3J_{G2,G3}$ = 9.8 Hz, 1 H, Gal H-3), 3.71-3.74 (m, 2 H, Gal H-6_a, Fuc H-2), 3.78 (m, 1 H, Fuc H-4), 3.83 (dd, $^3J_{G5,G6b}$ = 7.1 Hz, $^2J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6_b), 3.95 (dd, $^3J_{F3,F4}$ = 3.3 Hz, $^3J_{F2,F3}$ = 10.2 Hz, 1 H, Fuc H-3), 3.97 (m, 1 H, Gal H-4), 4.06 (dd, ^3J = 2.9, 9.8 Hz, 1 H, Lac H-2), 4.66 (d, $^3J_{G1,G2}$ = 8.0 Hz, 1 H, Gal H-1), 4.88 (m, 1 H, Fuc H-5), 5.37 (d, $^3J_{F1,F2}$ = 3.9 Hz, 1 H, Fuc H-1), 5.39 (dd, $^3J_{G1,G2}$ = 8.1 Hz, $^3J_{G2,G3}$ = 9.6 Hz, 1 H, Gal H-2), 7.49-7.52, 7.61-7.65, 8.07-8.09 (3 m, 5 H, C_6H_5); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 3.96, 7.18, 15.53 (3 C, *c*Pr), 16.72 (Fuc C-6), 22.94, 26.54, 26.73, 27.27, 30.78, 31.45 (6 C, $CyCH_2$, Cy), 33.13, 34.20, 35.07, 42.76 (4 C, $CyCH_2$), 48.49 (C-3), 62.72 (Gal C-6), 67.61 (Fuc C-5), 67.88 (Gal C-4), 70.24 (Fuc C-2), 71.34 (Fuc C-3), 73.16 (Gal C-2), 73.97 (Fuc C-4), 76.02 (Gal C-5), 78.01 (Lac C-2), 80.29 (C-1), 80.52 (C-2), 83.45 (Gal C-3), 98.97 (Fuc C-1), 100.41 (Gal C-1), 129.66, 130.82, 131.63, 134.36 (6 C, C_6H_5), 166.76 (*C*=O), 178.83 (*C*O_2H); HR-MS (ESI) *m*/*z*: calcd for $C_{37}H_{54}NaO_{14}$ $[M+Na]^+$: 745.3406; found: 745.3407 (0.1 ppm).

{(1*R*,2*R*,3*S*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]-3-ethyl-cyclohex-1-yl} 2-*O*-benzoyl-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**226e**), (DS-05-67).

225e (38.2 mg, 29.9 μmol) was hydrogenated with $Pd(OH)_2$/C (50 mg, 10% Pd) in dioxane/H_2O (4:1, 3.75 mL) according to the general procedure D. After 24 h the reaction mixture was filtered through celite and evaporated to dryness. The residue was redissolved in methanol (5 mL) and sodium methoxide (74.6 μmol in 73 μl MeOH) was added. After stirring at r.t. for 16 h the reaction was quenched by addition of acetic acid (8.5 μL). The mixture was concentrated *in vacuo* and purified by preparative, reversed-phase HPLC to afford **226e** (16.3 mg, 77%) as a colourless solid.

$[\alpha]_D^{21}$ = - 89.3 (*c* = 0.47, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.55-1.69 (m, 20 H, $CyCH_2$, EtCy), 0.83 (t, ^3J = 7.3 Hz, 3 H, CH_2CH_3), 1.32 (d, ^3J = 6.6 Hz, 3 H, Fuc H-6), 1.90 (m, 1 H, CH_2CH_3), 1.99 (m, 1 H, H-6_b), 3.24 (t, ^3J = 8.9 Hz, 1 H, H-2), 3.57 (m, 1 H, Gal H-5), 3.62 (m, 1 H, H-1), 3.67 (dd, $^3J_{G3,G4}$ = 3.0 Hz, $^3J_{G2,G3}$ = 9.8 Hz, 1 H, Gal H-3), 3.70-3.75 (m, 3 H, Gal H-6_a, Fuc H-2, Fuc H-4), 3.79 (dd, $^3J_{G5,G6b}$ = 6.9 Hz, $^2J_{G6a,G6b}$ = 11.3 Hz, 1 H, Gal H-6_b), 3.86 (dd, $^3J_{F3,F4}$ = 3.3 Hz, $^3J_{F2,F3}$ = 10.3 Hz, 1 H, Fuc H-3), 3.97 (m, 1 H, Gal H-4), 4.07 (dd, ^3J = 3.0, 9.8 Hz, 1 H, Lac H-2), 4.67 (d, $^3J_{G1,G2}$ = 8.1 Hz, 1 H, Gal H-1), 4.90 (m, 1 H, Fuc H-5), 4.91 (m, 1 H, Fuc H-1), 5.43 (dd, $^3J_{G1,G2}$ = 8.3 Hz, $^3J_{G2,G3}$ = 9.4 Hz, 1 H, Gal H-2), 7.49-7.52, 7.61-7.64, 8.08-8.09 (3 m, 5 H, C_6H_5); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 11.12 (CH_2CH_3), 16.72 (Fuc C-6), 23.39, 24.59,

26.54, 26.72, 27.27, 29.47, 31.86, 33.14, 34.20, 35.06, 42.76 (11 C, EtCy, CH_2Cy), 45.96 (C-3), 62.68 (Gal C-6), 67.77 (Fuc C-5), 67.83 (Gal C-4), 70.30 (Fuc C-2), 71.38 (Fuc C-3), 73.12 (Gal C-2), 73.92 (Fuc C-4), 75.90 (Gal C-5), 77.94 (Lac C-2), 80.77 (C-1), 81.11 (C-2), 83.55 (Gal C-3), 100.20 (Fuc C-1), 100.52 (Gal C-1), 129.67, 130.84, 131.63, 134.37 (6 C, C_6H_5), 166.79 (*C*=O), 178.76 (*C*O_2H); HR-MS (ESI) *m/z*: calcd for $C_{36}H_{54}NaO_{14}$ $[M+Na]^+$: 733.3406; found: 733.3409 (0.4 ppm).

{(1*R*,2*R*,3*R*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]-3-(2-methoxycarbonyl-ethyl)-cyclohex-1-yl} 2-*O*-benzoyl-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**226f**), (DS-05-48).

225f (46.0 mg, 34.4 μmol) was hydrogenated with $Pd(OH)_2$/C (25 mg, 10% Pd) in dioxane/H_2O (4:1, 3.75 mL) according to the general procedure D. After 42 h the mixture was filtered through celite and hydrogenated with fresh $Pd(OH)_2$/C (27 mg) for additional 24 h. The reaction mixture was filtered through celite and evaporated to dryness. The residue was redissolved in methanol (3 mL) and sodium methoxide (51.6 μmol in 55 μl MeOH) was added. After stirring at r.t. for 16 h the reaction was quenched by addition of acetic acid (6 μL). The mixture was concentrated *in vacuo* and purified by preparative, reversed-phase HPLC to afford **226f** (19.2 mg, 73%) as a colourless solid.

$[\alpha]_D^{21}$ = - 78.3 (*c* = 0.63, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.55-0.75 (m, 4 H, $CyCH_2$), 0.84-0.96 (m, 2 H, $CyCH_2$, H-4_a), 1.04 (m, 1 H, H-6_a), 1.14 (m, 1 H, H-5_a), 1.21-1.36 (m, 5 H, $CyCH_2$), 1.32 (d, ^3J = 6.6 Hz, 3 H, Fuc H-6), 1.39-1.60 (m, 6 H, $CyCH_2$, H-3, H-5_b, (CH_2)$_2CO_2$Me), 1.66 (m, 1 H, H-4_b), 1.97 (m, 1 H, H-6_b), 2.18-2.38 (m, 3 H, $CyCH_2$, (CH_2)$_2CO_2$Me), 3.27 (t, ^3J = 8.4 Hz, 1 H, H-2), 3.57 (m, 1 H, Gal H-5), 3.63-3.68 (m, 5 H, CH_3, Gal H-3, H-1), 3.71-3.75 (m, 3 H, Gal H-6_a, Fuc H-2, Fuc H-4), 3.79 (dd, $^3J_{G5,G6b}$ = 6.8 Hz, $^2J_{G6a,G6b}$ = 11.3 Hz, 1 H, Gal H-6_b), 3.84 (dd, $^3J_{F3,F4}$ = 3.3 Hz, $^3J_{F2,F3}$ = 10.2 Hz, 1 H, Fuc H-3), 3.98 (m, 1 H, Gal H-4), 4.07 (dd, ^3J = 3.0, 9.9 Hz, 1 H, Lac H-2), 4.67 (d, $^3J_{G1,G2}$ = 8.1 Hz, 1 H, Gal H-1), 4.83 (m, 1 H, Fuc H-5), 4.92 (m, 1 H, Fuc H-1), 5.43 (dd, $^3J_{G1,G2}$ = 8.2 Hz, $^3J_{G2,G3}$ = 9.6 Hz, 1 H, Gal H-2), 7.49-7.52, 7.62-7.65, 8.08-8.09 (3 m, 5 H, C_6H_5); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 16.73 (Fuc C-6), 22.77 (C-5), 26.55, 26.73, 27.28, 27.34 (4 C, $CyCH_2$), 29.49 (C-4), 31.34 (C-6), 32.16 ((CH_2)$_2CO_2$Me), 33.13, 34.20, 35.07 (3 C, $CyCH_2$), 42.78 ((CH_2)$_2CO_2$Me), 43.52 (C-3), 52.03 (Me), 62.62 (Gal C-6), 67.81 (Gal C-4), 67.89 (Fuc C-5), 70.25 (Fuc C-2), 71.41 (Fuc C-3), 73.09 (Gal C-2), 73.90 (Fuc C-4), 75.92 (Gal C-5), 77.98 (Lac C-2), 80.36 (C-1), 80.96 (C-2), 83.50 (Gal C-3), 100.34 (Fuc C-1), 100.50 (Gal C-1), 129.68, 130.85, 131.62, 134.39 (6 C, C_6H_5), 166.77, 176.09, 178.86 (3 C=O); elemental analysis calcd (%) for $C_{38}H_{56}O_{16}$

(768.84) + 1½ H_2O: C 57.35, H 7.47; found: C 57.57, H 7.36; HR-MS (ESI) *m/z*: calcd for $C_{38}H_{56}NaO_{16}$ $[M+Na]^+$: 791.3461; found: 791.3463 (0.3 ppm).

{(1*R*,2*R*,3*S*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]-3-methyl-cyclohex-1-yl} 3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-β-D-galactopyranoside sodium salt (**226g**), (DS-04-115).

Pd/C (49.6 mg, 10% Pd) was suspended under argon in ethanol (3 mL) containing a catalytic amount of acetic acid. Compound **225a** (101 mg, 79.8 μmol) was added and the mixture was hydrogenated under 70 psi at r.t.. After 24 h additional Pd/C (50.0 mg) was added and the hydrogenation was continued for another 5 d. The reaction was quenched with CH_2Cl_2, filtered through celite and the celite washed with methanol. The filtrate was concentrated under vacuo, redissolved in methanol/water (3:1, 4 mL) and lithium hydroxide (100 mg, 4.18 mmol) was added. After stirring for 2 d, the mixture was neutralized with Dowex 50x8 (H^+), filtered through a Dowex 50 (Na^+ form) ion exchange column and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/methanol/water, 5:1:0.1 to 2:1:0.1), followed by Sephadex G15 column and lyophilization from dioxane to give **226g** (36.5 mg, 74%) as colourless foam.

$[\alpha]_D^{21}$ = - 84.8 (*c* = 0.32, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.87-1.00 (m, 2 H, $CyCH_2$, MeCy), 1.04-1.38 (m, 6 H, $CyCH_2$, MeCy), 1.13 (d, ^3J = 6.3 Hz, 3 H, CH_3), 1.20 (d, ^3J = 6.5 Hz, 3 H, Fuc H-6), 1.55-1.74 (m, 10 H, $CyCH_2$, MeCy), 1.92 (m, 1 H), 2.13 (m, 1 H, MeCy), 3.20 (t, ^3J = 9.3 Hz, 1 H, H-2), 3.24 (dd, $^3J_{G3,G4}$ = 2.8 Hz, $^3J_{G2,G3}$ = 9.3 Hz, 1 H, Gal H-3), 3.42 (m, 1 H, Gal H-5), 3.62-3.68 (m, 3 H, Gal H-2, Gal H-6_a, H-1), 3.70-3.75 (m, 3 H, Fuc H-2, Fuc H-4, Gal H-6_b), 3.85 (dd, $^3J_{F3,F4}$ = 3.3 Hz, $^3J_{F2,F3}$ = 10.3 Hz, 1 H, Fuc H-3), 3.88 (m, 1 H, Gal H-4), 4.07 (dd, ^3J = 3.1, 9.3 Hz, 1 H, Lac H-2), 4.29 (d, $^3J_{G1,G2}$ = 7.8 Hz, 1 H, Gal H-1), 4.89 (m, 1 H, Fuc H-5), 5.00 (d, $^3J_{F1,F2}$ = 3.9 Hz, 1 H, Fuc H-1); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 16.84 (Fuc C-6), 19.65 (CH_3), 24.28, 27.31, 27.58, 27.83, 31.92, 33.62, 34.79, 35.00, 35.41, 40.45, 42.95 (11 C, MeCy, CH_2Cy), 63.14 (Gal C-6), 67.60 (Fuc C-5), 67.94 (Gal C-4), 70.37 (Fuc C-2), 71.41 (Fuc C-3), 71.62 (Gal C-2), 73.88 (Fuc C-4), 75.80 (Gal C-5), 79.90 (2 C, Lac C-2, MeCy), 84.60 (1 C, MeCy), 85.00 (Gal C-3), 100.41 (Fuc C-1), 102.36 (Gal C-1), 182.16 (CO_2Na); IR (KBr) ν: 3413 (OH), 2926, 2852, 1716 (C=O), 1587, 1449, 1413, 1376, 1164, 1078, 1034, 972 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{47}NaO_{13}$ + 1 H_2O (614.65): C 53.16, H 7.81; found: C 53.22, H 7.91; HR-MS (ESI) *m/z*: calcd for $C_{28}H_{48}NaO_{13}$ $[M+H]^+$: 615.2987; found: 615.2991 (0.7 ppm).

{(1*R*,2*R*,3*S*)-2-[(6-deoxy-α-L-galactopyranosyl)oxy]-3-ethyl-cyclohex-1-yl} 3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-β-D-galactopyranoside sodium salt (**226h**), (DS-05-18).

Pd/C (20 mg, 10% Pd) was suspended under argon in ethanol (3 mL) containing a catalytic amount of acetic acid. Compound **225e** (65.5 mg, 51.2 μmol) was added and the mixture was

hydrogenated under 70 psi at r.t.. The mixture was several times filtered through celite and set up with fresh Pd/C (20 mg). After 50 d the catalyst was exchanged with $Pd(OH)_2/C$ (100 mg, 10% Pd) in dioxane/H_2O (4:1, 4.8 mL) and the mixture was hydrogenated under 70 psi at r.t. for additional 10 d. The reaction mixture was filtered through celite and evaporated to dryness. The residue was redissolved in methanol/H_2O (4:1, 5 mL) and lithium hydroxide (65.0 mg, 2.71 mmol) was added. After stirring for 32 h, the mixture was neutralized with Dowex 50x8 (H^+), filtered through a Dowex 50 (Na^+ form) ion exchange column and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/methanol/water, 3.4:1:0.1 to 2:1:0.1), followed by Sephadex G15 column, microfiltration and lyophilization from dioxane to give **226h** (9.8 mg, 30%) as a colourless foam.

$[\alpha]_D^{21}$ = - 73.9 (*c* = 0.39, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.82-2.03 (m, 21 H, $CyCH_2$, EtCy), 0.89 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.20 (d, ^3J = 6.6 Hz, 3 H, Fuc H-6), 2.13 (m, 1 H, H-6_b), 3.18 (dd, $^3J_{G3,G4}$ = 2.8 Hz, $^3J_{G2,G3}$ = 9.4 Hz, 1 H, Gal H-3), 3.33 (m, 1 H, H-2), 3.43 (m, 1 H, Gal H-5), 3.60-3.76 (m, 6 H, Gal H-6, Gal H-2, H-1, Fuc H-4, Fuc H-2), 3.84-3.87 (m, 3 H, Gal H-4, Fuc H-3, Lac H-2), 4.30 (d, $^3J_{G1,G2}$ = 7.9 Hz, 1 H, Gal H-1), 4.84 (m, 1 H, Fuc H-5), 4.98 (d, $^3J_{F1,F2}$ = 3.9 Hz, 1 H, Fuc H-1); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 11.13 (CH_2CH_3), 16.79 (Fuc C-6), 23.91, 24.87, 27.28, 27.58, 27.84, 30.05, 31.69, 33.51, 34.77, 35.50, 43.32 (11 C, EtCy, CH_2Cy), 46.24 (C-3), 63.27 (Gal C-6), 67.68 (Fuc C-5, Gal C-4), 70.24 (Fuc C-2), 71.25 (Fuc C-3), 71.32 (Gal C-2), 73.79 (Fuc C-4), 75.83 (Gal C-5), 79.84 (C-1), 80.73 (Lac C-2), 82.00 (C-2), 85.57 (Gal C-3), 100.07 (Fuc C-1), 102.23 (Gal C-1), 183.44 (COONa); HR-MS (ESI) *m*/*z*: calcd for $C_{29}H_{50}NaO_{13}$ $[M+H]^+$: 629.3144; found: 629.3144 (0.0 ppm).

Dimethyl *cis*-4-cyclohexene-1,2-dicarboxylate (**235**).

Amberlyste 15 (50.0 g) was placed in a flask and dried *in vacuo* for 1 h. Methanol (1 L) was added, followed by *cis*-1,2,3,6-tetrahydrophthalic anhydride (50.0 g, 328 mmol) and trimethylorthoformate (100 mL, 914 mmol). The reaction mixture was then vigorously stirred. After 5 d, additional trimethylorthoformate (50 mL, 457 mmol) was added. The reaction was stopped after 9 d, filtered through celite and the celite washed with methanol. The solvent was removed *in vacuo* (20 mbar). The brown residue was dissolved in CH_2Cl_2 (150 mL) and washed with satd. aqueous $NaHCO_3$ and brine (each 150 mL). The aqueous layers were extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* (20 mbar) to afford diester **235** (57.5 g, 88%) as a brownish oil, the NMR data of which were in accordance with Lit.[445]

***cis*-2-(Methoxycarbonyl)-cyclohex-4-ene-1-carboxylic acid** (**236**).

To a stirred suspension of diester **235** (2.00 g, 10.1 mmol) in phosphate buffer (pH 7.00, 103 mL, 0.07 M), PLE (8.00 mg, 216 units) was added. The pH was kept at 7 by adding continuously NaOH solution (1.0 M) *via* syringe pump. The reaction was stirred at 20ºC until one equivalent of NaOH (10 mL) was consumed (56.5 h). The reaction mixture was transferred into a separation funnel with ethyl acetate (100 mL). The layers were separated and the organic layer was extracted with phosphate buffer (pH 7.00, 2 x 60 mL). The combined aqueous layers were acidified to pH 2 with 1 M HCl solution and extracted with ethyl acetate (4 x 150 mL). To separate the layers NaCl was added. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the monoester **236** (1.67 g, 90%) as a yellowish oil, the NMR data of which were in accordance with Lit.[E14] **236** showed an optical yield of 96.4% ee determined by optical rotation and 96.0% ee determined by chiral GC.

$[\alpha]_D^{21}$ = + 15.2 (*c* = 0.20, EtOH), (Lit. + 15.8, *c* = 0.2, EtOH).[446]

Methyl (*R*)-cyclohex-3-ene-carboxylate (**237**).

A solution of monoester **236** (0.992 g, 5.38 mmol) in dry CH_2Cl_2 (18 mL) was treated with $(COCl)_2$ (0.7 mL, 8.15 mmol) and DMF (14 μL), stirred for 3 h at r.t. and evaporated. A solution of the residue in dry THF (20 mL) was added dropwise over a period of 20 min to a boiling suspension of 2-mercaptopyridine-1-oxide sodium salt (975 mg, 6.49 mmol), *t*-BuSH (3.1 mL, 27.5 mmol), and 4-DMAP (26.3 mg, 0.216 mmol) in dry THF (50 mL). The solution was stirred at reflux for 3 h. The reaction mixture was then cooled to r.t., transferred into a separation funnel with ethyl acetate (50 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* (200 mbar). The crude product was purified by column chromatography (petroleum ether/Et_2O, 30:1 to 15:1) to afford methylester **237** (585 mg, 83%) as a yellowish oil, the NMR data of which were in accordance with Lit.[307]

$[\alpha]_D^{21}$ = + 78.2 (*c* = 1.01, $CHCl_3$).

(*R*)-Cyclohex-3-ene-carboxylic acid (**128**).

To a stirred suspension of methylester **237** (5.19 g, 37.0 mmol) in phosphate buffer (pH 7.00, 520 mL, 0.07 M), PLE (51.2 mg, 1382 units) was added. The pH was kept at 7 by adding NaOH solution (1.0 M) *via* syringe pump. The reaction was stirred at r.t. until one equivalent of NaOH (37 mL) was consumed (11 h). The reaction mixture was washed with ethyl acetate (2 x 300 mL). The organic layers were extracted with phosphate buffer (pH 7.00, 2 x 300 mL). The combined aqueous layers were acidified to pH 2 with aqueous HCl (30 mL, 4 M) and extracted

with ethyl acetate (3 x 400 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* (100 mbar). The crude product was filtered through a pad of silica affording acid **128** (3.92 g, 84%) as a pale yellowish oil, the NMR data of which were in accordance with Lit.[309] **128** showed an optical yield of 94.3% ee determined by optical rotation and 96.3% ee determined by chiral GC.
$[\alpha]_D^{21}$ = + 89.1 (*c* = 6.73, MeOH), (Lit. + 94.5, *c* = 7, MeOH).[447]

(1*R*,2*R*,5*R*)-2-Iodo-7-oxabicyclo[3.2.1]octan-6-one (**238**).
Acid **128** (8.30 g, 65.7 mmol) was suspended in water (180 mL) under argon. The reaction mixture was cooled to 0℃ and $NaHCO_3$ (16.6 g, 197 mmol) was added, followed by a solution of KI (65.4 g, 394 mmol) and iodine (17.5 g, 68.9 mmol) in water (150 mL). The reaction was stirred at r.t. for 24 h and then extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with a solution of $Na_2S_2O_3$ (50 g) in water (250 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic layers were protected from light, dried over Na_2SO_4, filtered and concentrated *in vacuo* (20 mbar) and quickly *in vacuo* to afford iodolactone **238** (15.8 g, 95%) as an off-white solid, the NMR data of which were in accordance with Lit.[309]
$[\alpha]_D^{21}$ = + 36.0 (*c* = 0.57, $CHCl_3$).

(1*R*,5*R*)-7-Oxabicyclo[3.2.1]oct-2-ene-6-one (**129**).
Iodolactone **238** (15.7 g, 62.2 mmol) was dissolved in dry THF (340 mL). Then, DBU (14 mL, 93.3 mmol) was added and the mixture was refluxed for 20 h. The reaction mixture was cooled to r.t., diluted with Et_2O (200 mL) and extracted with aqueous HCl (400 mL, 0.5 M) and brine (400 mL). The aqueous layers were extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* (350 mbar). The crude product was purified by column chromatography (petroleum ether/CH_2Cl_2/Et_2O, 20:5:1 to 8:5:1) to afford lactone **129** (7.28 g, 94%) as a yellowish oil, the NMR data of which were in accordance with Lit.[309]
$[\alpha]_D^{21}$ = + 187.3 (*c* = 1.08, $CHCl_3$).

Methyl (1*R*,3*R*)-3-*O*-(*tert*-butyldimethylsilyl)-3-hydroxy-cyclohex-4-ene-1-carboxylate (**239**).
$NaHCO_3$ (4.36 g, 51.8 mmol) was dried *in vacuo* for 2 h. Then, freshly distilled methanol (268 mL) was added, followed by lactone **129** (6.38 g, 51.4 mmol). The reaction mixture was stirred under argon for 12 h. The solvent was evaporated, the residue transferred into a separation funnel with CH_2Cl_2 (60 mL), and extracted with water (60 mL) and brine (60 mL). The aqueous layers were extracted with CH_2Cl_2 (2 x 60 mL). The combined organic layers were dried over

Na_2SO_4, filtered and concentrated *in vacuo* (50 mbar) to obtain the alcohol as yellowish oil. To a solution of the alcohol in dry CH_2Cl_2 (150 mL), *tert*-butyldimethylsilyl chloride (14.93 g, 99.1 mmol) was added in small portions, followed by DBU (18.4 mL, 123 mmol). The reaction was stirred at r.t. for 12 h and then quenched with methanol (20 mL). The mixture was diluted with CH_2Cl_2 (100 mL) and washed with satd. aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The aqueous layers were extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated (200 mbar). The crude product was purified by column chromatography (petroleum ether/Et_2O, 40:1 to 20:1) to afford silylether **239** (14.0 g, quant.) as colourless oil.

$[\alpha]_D^{21}$ = + 2.0 (*c* = 1.05, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.08 (2 s, 6 H, 2 SiC*H*$_3$), 0.89 (s, 9 H, SiC(C*H*$_3$)$_3$), 1.64 (m, 1 H, H-2$_a$), 2.02-2.24 (m, 3 H, H-6$_a$, H-6$_b$, H-2$_b$), 2.64 (m, 1 H, H-1), 3.69 (s, 3 H, Me), 4.35 (m, 1 H, H-3), 5.60 (m, 1 H, H-4), 5.70 (m, 1 H, H-5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: -4.72 (Si*C*H$_3$), -4.57 (Si*C*H$_3$), 18.19 (Si*C*(CH$_3$)$_3$), 25.84 (C(*C*H$_3$)$_3$), 27.37 (C-6), 34.87 (C-2), 38.58 (C-1), 51.78 (Me), 67.73 (C-3), 126.24 (C-4), 131.90 (C-5), 175.10 (C=O); IR (film on NaCl) ν: 2954 (s), 2857 (s), 1740 (vs, C=O), 1436 (w), 1389 (w), 1251 (m), 1200 (m), 1170 (m) cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{26}O_3Si$ (270.44): C 62.18, H 9.69; found: C 62.38, H 9.62.

Methyl (1*R*,3*R*,4*R*,5*R*)-3,4-epoxy-5-(*tert*-butyldimethylsilyloxy)-cyclohexane-1-carboxylate (228).

To a solution of silylether **239** (1.21 g, 4.47 mmol) in CH_2Cl_2 (36 mL), *m*-CPBA (1.92 g, 11.1 mmol) was added in one portion at 10°C. The reaction mixture was stirred at 10°C for 15 h. The temperature was then slowly raised to r.t. (2 h) and the reaction stopped. The mixture was diluted with CH_2Cl_2 (150 mL) and washed with satd. aqueous $Na_2S_2O_3$ (2 x 150 mL), satd. aqueous $NaHCO_3$ (150 mL) and brine (150 mL). The aqueous layers were each extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/Et_2O, 12:1 to 10:1) to obtain epoxide **228** (1.00 g, 78%) as yellowish oil.

$[\alpha]_D^{21}$ = - 25.6 (*c* = 0.99, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.10 (s, 3 H, SiC*H*$_3$), 0.12 (s, 3 H, SiC*H*$_3$), 0.91 (s, 9 H, SiC(C*H*$_3$)$_3$), 1.33 (m, 1 H, H-6$_a$), 1.92 (m, 1 H, H-2$_a$), 2.08 (m, 1 H, H-6$_b$), 2.31-2.41 (m, 2 H, H-2$_b$, H-1), 3.05 (m, 1 H, H-4), 3.32 (m, 1 H, H-3), 3.68 (s, 3 H, Me) 3.95 (m, 1 H, H-5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: -4.95 (Si*C*H$_3$), -4.76 (Si*C*H$_3$), 18.11 (Si*C*(CH$_3$)$_3$), 25.76 (C(*C*H$_3$)$_3$), 27.33 (C-2), 32.88 (C-1), 33.72 (C-6), 51.90 (Me), 53.44 (C-3), 56.89 (C-4), 6.65 (C-5), 175.23 (C=O); IR (film on NaCl) ν: 2954 (vs), 2858 (vs), 1740 (vs, C=O), 1463 (s), 1436 (s),

1369 (s), 1307 (s), 1259 (vs), 1174 (vs), 1095 (vs), 1053 (s), 1006 (s), 986 (m), 902 (s), 838 (vs), 778 (vs), 669 (m), 636 (w) cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{26}O_4Si$ (286.44): C 58.70, H 9.15; found: C 58.92, H 9.12.

Methyl (1*R*,3*R*,4*R*,5*S*)-3-(*tert*-butyldimethylsilyloxy)-4-hydroxy-5-methyl-cyclohexane-1-carboxylate (**240**).

CuCN (635 mg, 7.09 mmol) was dried *in vacuo* at 150ºC for 30 min, suspended in dry THF (10 mL) and cooled to -78ºC. MeLi (1.6 M in Et_2O, 8.90 mL, 14.2 mmol) was slowly added *via* syringe and the temperature was raised over a period of 30 min to -10ºC. The mixture was again cooled to -78ºC and freshly distilled BF_3 etherate (360 μL, 2.86 mmol) in THF (2 mL) was added. After stirring for 20 min, epoxide **228** (408 mg, 1.42 mmol) in THF (10 mL) was added. The reaction was stopped after stirring for 5 h at -78ºC. The excess of MeLi was quenched with a mixture of methanol (4 mL) and triethylamine (4 mL). The mixture was diluted with Et_2O (100 mL) and extracted with 25% aq. NH_3/satd. NH_4Cl (1:9). The organic layer was then successively washed with brine (60 mL), 5% aqueous acetic acid (60 mL), satd. aqueous $NaHCO_3$ (60 mL) and brine (60 mL). The aqueous layers were extracted with Et_2O (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/Et_2O, 10:1 to 8:1) to afford **240** (337 mg, 78%) as a reddish oil.

$[\alpha]_D^{21}$ = - 28.3 (*c* = 1.02, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.09 (s, 3 H, SiCH_3), 0.10 (s, 3 H, SiCH_3), 0.89 (s, 9 H, SiC(CH_3)$_3$), 1.07 (d, $^3J_{Me,5}$ = 6.4 Hz, 3 H, Me), 1.25 (m, 1 H, H-6$_a$), 1.47-1.57 (m, 2 H, H-5, H-2$_a$), 1.90 (m, 1 H, H-6$_a$), 2.07 (m, 1 H, H-2$_a$), 2.43 (m, 1 H, H-1), 2.98 (t, ^3J = 9.3 Hz, 1 H, H-4), 3.41 (ddd, $^3J_{2eq,3}$ = 4.5 Hz, $^3J_{3,4}$ = 8.5 Hz, $^3J_{2a,3}$ = 11.3 Hz, 1 H, H-3), 3.67 (s, 3 H, Me); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: -4.75 (SiCH$_3$), -4.10 (SiCH$_3$), 17.95 (C(CH$_3$)$_3$), 18.09 (Me), 25.74 (C(CH$_3$)$_3$), 35.46 (C-6), 35.64, 35.69 (C-2, C-5), 40.62 (C-1), 51.80 (Me), 75.51 (C-3), 80.12 (C-4), 174.85 (C=O); IR (film on NaCl) ν: 3584 (w, OH), 2954 (vs), 2858 (s), 1738 (vs, C=O), 1462 (m), 1378 (w), 1257 (m), 1173 (m), 1123 (m), 1100 (s), 1075 (vs), 1052 (w), 973 (vw), 924 (vw), 873 (m), 836 (vs), 778 (s), 667 (vw) cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{30}O_4Si$ (302.48): C 59.56, H 10.00; found: C 59.75, H 9.93.

Methyl (1*R*,3*R*,4*R*,5*S*)-4-*O*-(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)-3-*O*-(*tert*-butyldimethylsilyl)-3,4-dihydroxy-5-methyl-cyclohexane-1-carboxylate (**241**), (DS-05-57).

A mixture of **240** (348 mg, 1.15 mmol), ethyl 2,3,4-tri-*O*-benzyl-L-fucothiopyranoside (**166**) (1.11 g, 2.32 mmol), $(Bu)_4NBr$ (1.12 g, 3.48 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (713 mg, 3.47 mmol), and powdered 4Å molecular sieves (3 g) in CH_2Cl_2 (12 mL) and DMF (3 mL) was stirred

at r.t. under argon for 4 h. Then, $CuBr_2$ (776 mg, 3.47 mmol) was added and the reaction mixture was stirred at r.t. for 20 h. The reaction mixture was filtered through celite, the filtrate was diluted with CH_2Cl_2 (20 mL) and successively washed with satd. aqueous $NaHCO_3$ and brine (each 40 mL). The aqueous layers were extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried with Na_2SO_4, filtered and co-evaporated with toluene to dryness. The residue was purified by column chromatography (petroleum ether/Et_2O, 7:1 to 5:1) to yield compound **241** (631 mg, 76%) as a yellowish oil.

$[\alpha]_D^{21}$ = - 40.7 (*c* = 0.79, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.01 (s, 3 H, SiCH_3), 0.07 (s, 3 H, SiCH_3), 0.86 (s, 9 H, SiC(CH_3)$_3$), 1.07 (d, $^3J_{Me,5}$ = 6.4 Hz, 3 H, Me), 1.09 (d, $^3J_{F5,F6}$ = 6.4 Hz, 3 H, Fuc H-6), 1.25 (m, 1 H, H-6$_a$), 1.55 (m, 1 H, H-2$_a$), 1.64 (m, 1 H, H-5), 1.79 (m, 1 H, H-6$_b$), 2.05 (m, 1 H, H-2$_b$), 2.38 (m, 1 H, H-1), 3.29 (t, ^3J = 9.2 Hz, 1 H, H-4), 3.63 (m, 1 H, Fuc H-4), 3.65-3.68 (m, 4 H, H-3, Me), 4.02-4.07 (m, 2 H, Fuc H-2, Fuc H-3), 4.37 (m, 1 H, Fuc H-5), 4.63, 4.73, 4.74, 4.82, 4.84, 4.98 (6 m, 6 H, 3 CH_2Ph), 5.22 (m, 1 H, Fuc H-1), 7.27-7.39 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: -5.03 (Si*C*H$_3$), -3.32 (Si*C*H$_3$), 16.94 (Fuc C-6), 18.12 (*C*(CH$_3$)$_3$), 19.45 (Me), 26.12 (C(*C*H$_3$)$_3$), 36.30 (C-6), 37.41 (C-2), 37.64 (C-5), 40.60 (C-1), 51.75 (Me), 66.26 (Fuc C-5), 72.78 (*C*H$_2$Ph), 74.12 (*C*H$_2$Ph), 74.25 (C-3), 74.88 (*C*H$_2$Ph), 76.49 (Fuc C-2), 78.28 (Fuc C-4), 79.17 (Fuc C-3), 82.34 (C-4), 97.13 (Fuc C-1), 127.41, 127.60, 128.13, 128.17, 128.25, 128.32, 128.35, 138.47, 138.84, 138.89 (18 C, 3 C_6H_5), 174.87 (C=O); IR (film on NaCl) ν: 3031 (vs), 2929 (vs), 1732 (vs, C=O), 1497 (m), 1455 (s), 1361 (m), 1103 (br), 836 (w), 696 (w), 667 (vw) cm^{-1}; MS (ESI) *m/z*: calcd for $C_{42}H_{58}NaO_8Si$ $[M+Na]^+$: 741.4; found: 741.5; elemental analysis calcd (%) for $C_{42}H_{58}O_8Si$ (718.99): C 70.16, H 8.13; found: C 70.18, H 8.20.

Methyl (1*R*,3*R*,4*R*,5*S*)-4-*O*-(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)-3,4-dihydroxy-5-methyl-cyclohexane-1-carboxylate (**242**), (DS-05-58).

To a solution of **241** (606 mg, 0.842 mmol) in THF (5 mL), TBAF (1 M, in THF, 4.21 mL, 4.21 mmol) was added. The reaction was stirred for 13 h and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 3:1) to afford **242** (399 mg, 78%) as a white solid.

$[\alpha]_D^{21}$ = - 43.0 (*c* = 1.09, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 1.11 (d, $^3J_{F5,F6}$ = 6.4 Hz, 3 H, Fuc H-6), 1.15 (d, $^3J_{Me,5}$ = 6.5 Hz, 3 H, Me), 1.23 (m, 1 H, H-6$_a$), 1.48 (m, 1 H, H-2$_a$), 1.59 (m, 1 H, H-5), 1.92 (m, 1 H, H-6$_b$), 2.24 (m, 1 H, H-2$_b$), 2.39 (m, 1 H, H-1), 2.89 (dd, ^3J = 8.6, 10.0 Hz, 1 H, H-4), 3.43 (ddd, ^3J = 4.7, 8.4, 11.5 Hz, 1 H, H-3), 3.67 (s, 3 H, Me), 3.70 (m, 1 H, Fuc H-4), 3.96 (dd, $^3J_{F3,F4}$ = 2.7 Hz, $^3J_{F2,F3}$ = 10.2 Hz, 1 H, Fuc H-3), 4.08-4.12 (m, 2 H, Fuc H-2, Fuc H-5), 4.65, 4.69, 4.67, 4.78, 4.85, 4.99 (6 m, 6 H, 3 CH_2Ph), 4.97 (d, $^3J_{F1,F2}$ = 3.8 Hz, 1 H, Fuc H-1), 7.26-7.39 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.61 (Fuc C-6), 18.35 (Me), 34.77

(C-2), 35.44 (C-5), 35.84 (C-6), 40.33 (C-1), 51.77 (Me), 67.63 (Fuc C-5), 71.99 (C-3), 72.97 (*C*H_2Ph), 73.52 (*C*H_2Ph), 74.86 (*C*H_2Ph), 76.32 (Fuc C-2), 77.38 (Fuc C-4), 78.87 (Fuc C-3), 92.12 (C-4), 98.74 (Fuc C-1), 127.36, 127.49, 127.63, 127.66, 127.91, 128.23, 128.27, 128.35, 128.38, 138.23, 138.35, 138.70 (18 C, 3 C_6H_5), 174.89 (C=O); IR (KBr) ν: 3424 (s, OH), 3031 (vw), 2998 (w), 2952 (s), 2904 (s), 1737 (vs, C=O), 1497 (w), 1454 (m), 1384 (w), 1344 (s), 1305 (m), 1273 (w), 1248 (w), 1191 (s), 1138 (s), 1157 (s), 1102 (vs), 1037 (vs), 973 (w), 957 (w), 909 (w), 823 (vw), 802 (vw), 743 (s), 720 (w), 697 (m) cm^{-1}; elemental analysis calcd (%) for $C_{36}H_{44}O_8$ (604.73): C 71.50, H 7.33; found: C 71.51, H 7.36.

{(1*R*,3*R*,4*R*,5*S*)-4-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]-1-methoxycarbonyl-5-methyl-cyclohex-3-yl} 2,4,6-tri-*O*-benzoyl-3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**243**).

Dry CH_2Cl_2 (16 mL) was added to a mixture of thioglycoside **224** (562 mg, 0.719 mmol), glycosyl acceptor **242** (336 mg, 0.555 mmol) and activated 4Å molecular sieves (4 g) under argon. A suspension of DMTST (441 mg, 1.71 mmol) and activated 4Å molecular sieves (2 g) in CH_2Cl_2 (8 mL) was prepared in a second flask. Both suspensions were stirred at r.t. for 4 h, then the DMTST suspension was added *via* syringe to the other suspension with some additional CH_2Cl_2 (1 mL). The reaction was stopped after 63 h, filtered through celite and the celite washed with CH_2Cl_2. The filtrate was successively washed with satd. aqueous $NaHCO_3$ (40 mL) and water (100 mL). The aqueous layers were extracted with DCM (3 x 60 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/Et_2O, 1:1) to afford **243** (485 mg, 66%) as a white foam.

$[\alpha]_D^{21}$ = - 52.8 (*c* = 1.05, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.45-2.23 (m, 18 H, CyCH_2, Cy), 1.07 (d, $^3J_{Me,5}$ = 6.4 Hz, 3 H, Me), 1.43 (d, $^3J_{F5,F6}$ = 6.4 Hz, 3 H, Fuc H-6), 1.51 (m, 1 H, H-5), 3.21 (t, ^3J = 9.5 Hz, 1 H, H-4), 3.53-3.56 (m, 5 H, H-3, Fuc H-4, Me), 3.81 (dd, $^3J_{G3,G4}$ = 3.2 Hz, $^3J_{G2,G3}$ = 9.9 Hz, 1 H, Gal H-3), 3.91 (m, 1 H, Gal H-5), 4.00-4.05 (m, 2 H, Fuc H-2, Fuc H-3), 4.12 (dd, ^3J = 4.5, 7.9 Hz, 1 H, Lac H-2), 4.24-4.28 (m, 2 H, Gal H-6_a, C*H*$_2$Ph), 4.36 (dd, $^3J_{G5,G6b}$ = 5.6 Hz, $^2J_{G6a,G6b}$ = 11.4 Hz, 1 H, Gal H-6_b), 4.51, 4.62, 4.67, 4.74, 4.79 (5 m, 5 H, 3 C*H*$_2$Ph), 4.56 (d, $^3J_{G1,G2}$ = 8.2 Hz, 1 H, Gal H-1), 4.89 (m, 1 H, Fuc H-5), 5.04 (m, 1 H, C*H*$_2$Ph), 5.04 (m, 1 H, Fuc H-1), 5.12 (m, 1 H, C*H*$_2$Ph), 5.61 (m, 1 H, Gal H-2), 5.85 (m, 1 H, Gal H-4), 7.19-7.33, 7.42-7.48, 7.53-7.58, 8.04-8.12 (4 m, 35 H, 7 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.77 (Fuc C-6), 18.51 (Me), 25.46, 25.71, 26.07, 32.60, 33.19, 33.40, 35.37, 38.04, 40.21, 40.46 (11 C, Cy, CH_2Cy), 51.68 (Me), 62.50 (Gal C-6), 66.38 (Fuc C-5), 66.65 (*C*H_2Ph), 70.20 (Gal C-4), 71.60 (Gal C-5), 71.99 (Gal C-2), 72.05 (*C*H_2Ph), 74.39 (*C*H_2Ph), 74.90 (*C*H_2Ph), 76.18 (Fuc C-2),

78.02 (Gal C-3), 78.41 (Lac C-2), 79.23 (Fuc C-4), 79.84 (Fuc C-3), 80.08 (C-3), 80.64 (C-4), 98.11 (Fuc C-1), 100.13 (Gal C-1), 126.91, 127.05, 127.20, 127.45, 127.71, 128.04, 128.09, 128.12, 128,42, 128.45, 128.52, 128.56,129.56, 129.65, 129.75, 129.93, 133.09, 133.21, 133.30, 135.40, 138.49, 138.95, 139.15 (42 C, 7 C_6H_5), 164.60, 166.08, 166.15, 172.43, 174.09 (5 C=O); IR (KBr) ν: 4925 (s), 1731 (vs, C=O), 1602 (w), 1497 (w), 1452 (m), 1267 (vs), 1176 (m), 1097 (vs), 712 (s) cm^{-1}; elemental analysis calcd (%) for $C_{79}H_{86}O_{18}$ (1323.53): C 71.69, H 6.55; found: C 71.73, H 6.65.

{(1*R*,3*R*,4*R*,5*S*)-4-[(6-deoxy-α-L-galactopyranosyl)oxy]-1-methoxycarbonyl-5-methyl-cyclohex-3-yl} 2-*O*-benzoyl-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**244**), (DS-05-60).

A mixture of **243** (133 mg, 0.100 mmol), $Pd(OH)_2/C$ (50.5 mg), dioxane (3 mL) and water (0.75 mL) was hydrogenated under 70 psi at r.t.. After 20 h the mixture was filtered through celite and set up with fresh $Pd(OH)_2/C$ (50.7 mg) for additional 26 h. The reaction mixture was filtered through celite and evaporated to dryness. The residue was redissolved in methanol (4 mL) and sodium methoxide (0.150 mmol in 160 μL MeOH) was added. After stirring at r.t. for 16 h the reaction was quenched by addition of acetic acid (17 μL). The mixture was concentrated *in vacuo* and purified by preparative, reversed-phase HPLC to afford compound **244** (57.1 mg, 76%) as a white solid.

$[\alpha]_D^{21}$ = - 85.0 (*c* = 0.57, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.55-0.75 (m, 4 H, Cy), 0.92 (m, 1 H, Cy), 1.04-1.15 (m, 2 H, H-6_a, H-2_a), 1.10 (d, ^3J = 6.5 Hz, 3 H, CH_3), 1.21-1.36 (m, 5 H, Cy), 1.33 (d, ^3J = 6.5 Hz, 3 H, Fuc H-6), 1.43 (ddd, $^3J_{L2,L3a}$ = 3.0 Hz, $^3J_{L3a,L4}$ = 9.6 Hz, $^2J_{L3a,L3b}$ = 13.9 Hz, 1 H, Lac H-3_a), 1.52 (ddd, $^3J_{L3b,L4}$ = 4.0 Hz, $^3J_{L2,L3b}$ = 10.0 Hz, $^2J_{L3a,L3b}$ = 14.0 Hz, 1 H, Lac H-3_b), 1.60 (m, 1 H, Cy), 1.64 (m, 1 H, H-5), 1.76 (m, 1 H, H-6_b), 2.28 (m, 1 H, H-2_b), 2.40 (m, 1 H, H-1), 3.10 (t, ^3J = 9.6 Hz, 1 H, H-4), 3.56-3.58 (m, 4 H, Gal H-5, Me), 3.63-3.68 (m, 2 H, Gal H-3, H-3), 3.71-3.79 (m, 4 H, Gal H-6, Fuc H-2, Fuc H-4), 3.85 (dd, $^3J_{F3,F4}$ = 3.3 Hz, $^3J_{F2,F3}$ = 10.3 Hz, 1 H, Fuc H-3), 3.97 (m, 1 H, Gal H-4), 4.07 (dd, $^3J_{L2,L3a}$ = 3.0 Hz, $^3J_{L2,L3b}$ = 9.9 Hz, 1 H, Lac H-2), 4.69 (d, $^3J_{G1,G2}$ = 8.1 Hz, 1 H, Gal H-1), 4.94 (d, $^3J_{F1,F2}$ = 4.0 Hz, 1 H, Fuc H-1), 4.99 (m, 1 H, Fuc H-5), 5.43 (dd, $^3J_{G1,G2}$ = 8.2 Hz, $^3J_{G2,G3}$ = 9.7 Hz, 1 H, Gal H-2), 7.49-7.52, 7.62-7.65, 8.07-8.09 (3 m, 5 H, C_6H_5); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 16.72 (Fuc C-6), 19.18 (Me), 26.59, 26.78, 27.32, 33.13, 34.23 (5 C, Cy), 34.95 (C-2), 35.12 (Cy), 36.98 (C-6), 39.17 (C-5), 41.40 (C-1), 42.80 (Lac C-3), 52.27 (Me), 62.68 (Gal C-6), 67.72 (Fuc C-5), 67.78 (Gal C-4), 70.35 (Fuc C-2), 71.47 (Fuc C-3), 73.11 (Gal C-2), 74.00 (Fuc C-4), 75.92 (Gal C-5), 77.91 (Lac C-2), 79.97 (C-3), 83.06 (C-4), 83.60 (Gal C-3), 100.53 (Fuc C-1), 100.76 (Gal C-1), 129.71, 130.96, 131.60, 134.40 (6 C, C_6H_5), 166.88 (O(*C*=O)Ph), 176.18 (*C*OOMe), 178.81 (*C*OOH);

elemental analysis calcd (%) for $C_{37}H_{54}O_{16} \cdot 1\ H_2O$ (754.82): C 57.50, H 7.30; found: C 57.53, H 7.16; HR-MS (ESI) *m*/*z*: calcd for $C_{37}H_{53}O_{16}$ $[M-H]^-$: 753.3339; found: 753.3331 (1.1 ppm).

rac-**(1*S*,2*R*,5*S*)-5-*tert*-Butyl-2-hydroxycyclohexyl benzoate** (*rac*-**248**) and *rac*-**(1*S*,2*R*,4*S*)-4-*tert*-Butyl-2-hydroxycyclohexyl benzoate** (*rac*-**249**), (DS-05-91/92).
4-*tert*-Butylcatechol (2.02 g, 12.2 mmol), Rh/Al_2O_3 (98.9 mg), cyclohexane (4 mL) and THF (0.5 mL) were hydrogenated under 5 bar at r.t.. After 24 h the mixture was filtered through celite and evaporated to dryness. The residue was purified by MPLC on silica (CH_2Cl_2/ethyl acetate, 3:1 to 1:3) to afford a mixture of *syn*-diols (1.64 g, 78%, *rac*-**246**:*rac*-**247**, 1.4:1) as a white solid. The mixture (1.64 g, 9.55 mmol) and dibutyltin oxide (2.37 g, 9.52 mmol) were dissolved in CH_2Cl_2 (50 mL) and cooled to 0°C. Et_3N (2.68 mL, 19.2 mmol) and benzoyl chloride (1.32 mL, 11.45 mmol) were slowly added *via* syringe. The mixture was warmed to r.t. during 3 h and then quenched with MeOH (2 mL). The solvents were evaporated *in vacuo* and the crude residue was purified by MPLC on silica (toluene/ethyl acetate, 10:0 to 10:1) affording *rac*-**248** (1.15 g, 44%) and *rac*-**249** (688 mg, 26%) as white solids.

rac-**248**:
^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.90 (s, 9 H, *t*Bu), 1.23 (m, 1 H, H-5), 1.42 (m, 1 H, H-4_a), 1.50-1.57 (m, 2 H, H-3_a, H-4_b), 1.68 (m, 1 H, H-6_a), 1.85 (m, 1 H, H-6_b), 2.04 (m, 1 H, H-3_b), 4.17 (m, 1 H, H-2), 5.05 (ddd, ^3J = 2.7, 4.7, 11.9 Hz, 1 H, H-1), 7.44-7.47, 7.56-7.59, 8.05-8.07 (3 m, 5 H, C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 19.59 (C-4), 26.42 (C-6), 27.51 (3 C, *t*Bu), 30.57 (C-3), 32.49 (*t*Bu), 46.35 (C-5), 67.10 (C-2), 76.47 (C-1), 128.39, 129.58, 130.27, 133.07 (6 C, C_6H_5), 165.62 (C=O); HR-MS (ESI) *m*/*z*: calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$: 299.1618; found: 299.1621 (1.0 ppm).

rac-**249**:
^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.89 (s, 9 H, *t*Bu), 1.18 (m, 1 H, H-5_a), 1.34 (m, 1 H, H-3_a), 1.56 (m, 1 H, H-4), 1.83-1.98 (m, 3 H, H-5_b, H-6), 2.04 (m, 1 H, H-3_b), 4.25 (m, 1 H, H-2), 4.98 (ddd, ^3J = 2.8, 4.9, 11.7 Hz, 1 H, H-1), 7.44-7.47, 7.56-7.59, 8.04-8.06 (3 m, 5 H, C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 25.07 (C-5), 25.27 (C-6), 27.48 (3 C, *t*Bu), 31.91 (*t*Bu), 31.98 (C-3), 39.43 (C-4), 68.14 (C-2), 75.87 (C-1), 128.39, 129.58, 130.28, 133.06 (6 C, C_6H_5), 165.72 (C=O); HR-MS (ESI) *m*/*z*: calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$: 299.1618; found: 299.1621 (1.0 ppm).

rac-(**1*R*,2*R*,4*R*)-2-(Benzoyloxy)-4-*tert*-butylcyclohexyl 3,5-dinitrobenzoate** (*rac*-**250**), (DS-05-94).

rac-**248** (400 mg, 1.45 mmol), triphenylphosphine (1.14 g, 4.33 mmol) and 3,5-dinitrobenzoic acid (921 mg, 4.34 mmol) were dissolved in toluene (25 mL). Diethyl azodicarboxylate (680 µL, 4.32 mmol) was slowly added to the reaction *via* syringe. The mixture was warmed to 50°C and stirred for 1 d. The solvent was evaporated *in vacuo* and the residue, redissolved in a small amount of CH_2Cl_2, was purified by MPLC on silica (petroleum ether/ethyl acetate, 10:0 to 10:1) affording *rac*-**250** (428 mg, 63%) and recovered starting material *rac*-**248** (103 mg, 26%) as white solids.

^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.93 (s, 9 H, *t*Bu), 1.25-1.47 (m, 3 H, H-3_a, H-4, H-5_a), 1.68 (m, 1 H, H-6_a), 1.94 (m, 1 H, H-5_b), 2.29-2.35 (m, 2 H, H-3_b, H-6_b), 5.27 (ddd, ^3J = 4.9, 9.7, 11.4 Hz, 1 H, H-1), 5.35 (ddd, ^3J = 4.7, 9.9, 10.5 Hz, 1 H, H-2), 7.36-7.39, 7.48-7.52, 7.96-7.98 (3 m, 5 H, C_6H_5), 9.06, 9.14-9.15 (2 m, 3 H, C_6H_3); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 24.79 (C-5), 27.52 (3 C, *t*Bu), 29.76 (C-6), 31.79 (C-3), 32.36 (*t*Bu), 45.73 (C-4), 74.80 (C-2), 77.55(C-1), 122.31, 128.39, 129.44, 129.58, 129.74, 133.17, 133.81, 148.54 (12 C, C_6H_5, C_6H_3), 162.16, 165.89 (2 C=O); HR-MS (ESI) *m*/*z*: calcd for $C_{24}H_{26}N_2NaO_8$ $[M+Na]^+$: 493.1581; found: 493.1582 (0.2 ppm).

rac-(**1*R*,2*R*,5*R*)-5-*tert*-Butyl-2-hydroxycyclohexyl benzoate** (*rac*-**251**), (DS-05-96).

rac-**250** (135 mg, 0.287 mmol) was suspended in methanol (5 mL). Et_3N (1 mL) was added and the reaction stirred for 1 h. The solvents were evaporated *in vacuo* and the residue was purified by MPLC on silica (toluene/ethyl acetate, 6:0 to 6:1) affording *rac*-**251** (63.2 mg, 80%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ : 0.88 (s, 9 H, *t*Bu), 1.12 (m, 1 H, H-4_a), 1.19-1.32 (m, 2 H, H-5, H-6_a), 1.41 (m, 1 H, H-3_a), 1.80 (m, 1 H, H-4_b), 2.12-2.18 (m, 2 H, H-3_b, H-6_b), 3.69 (ddd, ^3J = 4.9, 9.3, 11.3 Hz, 1 H, H-2), 4.88 (ddd, ^3J = 4.7, 9.4, 10.7 Hz, 1 H, H-1), 7.43-7.46, 7.55-7.58, 8.06-8.07 (3 m, 5 H, C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 24.89 (C-4), 27.54(3 C, *t*Bu), 31.44 (C-6), 32.28 (*t*Bu), 32.61 (C-3), 46.01 (C-5), 73.33 (C-2), 79.47 (C-1), 128.34, 129.64, 130.23, 133.05 (6 C, C_6H_5), 166.82 (C=O); HR-MS (ESI) *m*/*z*: calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$: 299.1618; found: 299.1619 (0.3 ppm).

[(1*R*,2*R*,5*R*)-5-*tert*-Butyl-1-hydroxy-cyclohex-2-yl] 2,3,4-tris-*O*-benzyl-6-deoxy-L-galactopyranoside (**252**) and **[(1*S*,2*S*,5*S*)-5-*tert*-Butyl-1-hydroxy-cyclohex-2-yl] 2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranoside** (**253**), (DS-05-100).

A mixture of *rac*-**251** (76.9 mg, 0.278 mmol), ethyl 2,3,4-tri-*O*-benzyl-L-fucothiopyranoside (**166**) (202 mg, 0.421 mmol), $(Bu)_4NBr$ (274 mg, 0.850 mmol) and powdered 4Å molecular sieves (1 g) in CH_2Cl_2 (4 mL) and DMF (1 mL) was stirred at r.t. under argon for 3.5 h. Then, $CuBr_2$ (188 mg, 0.844 mmol) was added and the reaction mixture was stirred at r.t. for 11 h. The reaction mixture was filtered through celite and the filtrate was diluted with CH_2Cl_2 (30 mL). The organic layer was successively washed with satd. aqueous $NaHCO_3$ and brine (each 30 mL) and the aqueous layers were extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried with Na_2SO_4, filtered and co-evaporated with toluene to dryness. The residue was purified by MPLC on silica (petroleum ether/CH_2Cl_2/diethyl ether, 2:1:0 to 2:1:1) to afford the fucosylated diastereomers. To a stirred solution of these diastereomers in methanol/water (5:1, 6 mL), lithium hydroxide (200 mg) was added and the mixture warmed to 50°C. After stirring for 4 h the reaction mixture was diluted with CH_2Cl_2 (30 mL) and the organic layer was washed with brine (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by MPLC on silica (petroleum ether/ethyl acetate, 4:0 to 4:1) to yield **252** (72.1 mg, 44%, α:β = 1:0.12, yield over two steps) as an anomeric mixture and **253** (63.0 mg, 38%, yield over two steps) as pure α-anomer.

α-**252:**

$[\alpha]_D^{21}$ = - 41.3 (*c* = 0.31, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.86 (s, 9 H, *t*Bu), 0.97-1.38 (m, 7 H, Fuc H-6, H-3$_a$, H-4$_a$, H-5, H-6$_a$), 1.74 (m, 1 H, H-4$_b$), 1.99-2.06 (m, 2 H, H-3$_b$, H-6$_b$), 3.22 (m, 1 H, H-2), 3.47 (m, 1 H, H-1), 3.70 (m, 1 H, Fuc H-4), 3.94 (dd, $^3J_{F3,F4}$ = 2.4 Hz, $^3J_{F2,F3}$ = 10.1 Hz, 1 H, Fuc H-3), 4.05-4.09 (m, 2 H, Fuc H-2, Fuc H-5), 4.65, 4.66, 4.75, 4.82, 4.87 (5 m, 5 H, C*H*$_2$Ph), 4.97-5.00 (m, 2 H, Fuc H-1, C*H*$_2$Ph), 7.26-7.41 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.65 (Fuc C-6), 25.17 (C-4), 27.55 (3 C, *t*Bu), 29.54 (C-3), 32.19 (*t*Bu), 33.63 (C-6), 45.82 (C-5), 66.97 (Fuc C-5), 73.15, 73.33 (2 *C*H$_2$Ph), 73.52 (C-1), 74.86 (*C*H$_2$Ph), 76.16 (Fuc C-2), 77.41 (Fuc C-4), 79.21 (Fuc C-3), 84.09 (C-2), 96.33 (Fuc C-1), 127.40, 127.48, 127.64, 127.69, 127.90, 128.21, 128.35, 128.44, 138.41, 138.50, 138.81 (18 C, 3 C_6H_5); HR-MS (ESI) *m*/*z*: calcd for $C_{37}H_{48}NaO_6$ $[M+Na]^+$: 611.3343; found: 611.3346 (0.5 ppm).

253:

$[\alpha]_D^{21}$ = - 40.7 (*c* = 0.38, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.85 (s, 9 H, *t*Bu), 1.01-1.17 (m, 6 H, Fuc H-6, H-4_a, H-5, H-6_a), 1.29 (m, 1 H, H-3_a), 1.70 (m, 1 H, H-4_b), 1.97-2.04 (m, 2 H, H-3_b, H-6_b), 3.17 (m, 1 H, H-2), 3.45 (m, 1 H, H-1), 3.69 (m, 1 H, Fuc H-4), 3.96-4.05 (m, 3 H, Fuc H-2, Fuc H-3, Fuc H-5), 4.66, 4.73, 4.76, 4.81, 4.87, 4.97 (6 m, 6 H, C*H*$_2$Ph), 4.98 (m, 1 H, Fuc H-1), 7.26-7.41 (m, 15 H, 3 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.69 (Fuc C-6), 25.32 (C-4), 27.58 (3 C, *t*Bu), 31.26 (C-3), 32.25 (*t*Bu), 32.88 (C-6), 45.78 (C-5), 66.57 (Fuc C-5), 72.63, 74.19 (2 *C*H$_2$Ph), 74.66 (C-1), 74.80 (*C*H$_2$Ph), 76.33 (Fuc C-2), 77.40 (Fuc C-4), 80.01 (Fuc C-3), 87.22 (C-2), 101.01 (Fuc C-1), 127.34, 127.52, 127.58, 127.84, 128.18, 128.22, 128.34, 128.39, 128.47, 137.95, 138.53, 138.65 (18 C, 3 C_6H_5).

{(1*R*,2*R*,5*R*)-2-[(2,3,4-tris-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)oxy]-5-*tert*-butyl-cyclohex-1-yl} 2,4,6-tri-*O*-benzoyl-3-*O*-[(1*S*)-1-benzyloxycarbonyl-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**254**), (DS-05-101).

Thioglycoside **224** (125 mg, 0.161 mmol) and glycosyl acceptor **252** (71.4 mg, 0.121 mmol) in dry CH_2Cl_2 (4 mL) were added *via* syringe to activated 4Å molecular sieves (1 g). A suspension of DMTST (120 mg, 0.465 mmol) and activated 4Å molecular sieves (500 mg) in CH_2Cl_2 (2 mL) was prepared in a second flask. Both suspensions were stirred at r.t. for 2 h, before adding the DMTST suspension *via* syringe to the other suspension with some additional CH_2Cl_2 (1 mL). The reaction was stopped after 45 h and worked-up according to the general procedure C. The crude product was purified by MPLC on silica (toluene/ethyl acetate, 11.5:0 to 11.5:1) to yield **254** (107 mg, 68%) as a colourless foam.

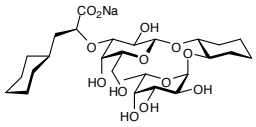
$[\alpha]_D^{21}$ = - 57.9 (c = 0.50, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500.1 MHz) δ: 0.46-1.43 (3 m, 17 H, CyCH_2, Cy), 0.58 (s, 9 H, *t*Bu), 1.36 (d, ^3J = 6.0 Hz, 3 H, Fuc H-6), 1.60 (m, 1 H, H-4_b), 1.81 (m, 1 H, H-6_b), 1.99 (m, 1 H, H-3_b), 3.45 (m, 1 H, H-2), 3.55 (m, 1 H, H-1), 3.58 (s, 1 H, Fuc H-4), 3.87-3.90 (m, 2 H, Gal H-3, Gal H-5), 3.97-4.04 (m, 2 H, Fuc H-2, Fuc H-3), 4.16 (m, 1 H, Lac H-2), 4.29 (m, 2 H, Gal H-6), 4.39 (m, 1 H, C*H*$_2$Ph), 4.55-4.57 (m, 2 H, Gal H-1, C*H*$_2$Ph), 4.63 (m, 1 H, C*H*$_2$Ph), 4.69-4.74 (m, 2 H, C*H*$_2$Ph), 4.79-4.83 (m, 2 H, Fuc H-5, C*H*$_2$Ph), 4.88 (d, $^3J_{F1,F2}$ = 2.1 Hz, 1 H, Fuc H-1), 5.04, 5.13 (2 m, 2 H, C*H*$_2$Ph), 5.56 (m, 1 H, Gal H-2), 5.91 (m, 1 H, Gal H-4), 7.17-7.35, 7.39-7.48, 7.54-7.55, 8.04-8.11 (m, 35 H, 7 C_6H_5); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ: 16.62 (Fuc C-6), 24.43 (C-4), 25.40, 25.71, 26.06 (3 C, CyCH_2), 27.19 (3 C, *t*Bu), 28.97 (C-3), 31.95 (*t*Bu), 32.23 (C-6), 32.49, 33.17, 33.44 (3 C, CyCH_2), 40.44 (Cy*C*H$_2$), 45.50 (C-5), 62.21 (Gal C-6), 65.98 (Fuc C-5), 66.58 (*C*H$_2$Ph), 69.86 (Gal C-4), 71.19 (Gal C-5), 72.53, 72.56 (Gal C-2, *C*H$_2$Ph), 73.02 (*C*H$_2$Ph), 74.90 (*C*H$_2$Ph), 75.25 (C-2), 76.44 (Fuc C-2), 77.51 (Gal C-3), 78.08 (Lac C-2), 79.24 (Fuc C-4), 79.64 (Fuc C-3), 81.37 (C-1), 94.16 (Fuc C-1), 100.24 (Gal C-

1), 126.87, 126.95, 127.22, 127.38, 127.93, 127.95, 128.03, 128.15, 128.34, 128.42, 128.47, 128.50, 129.64, 129.74, 129.83, 129.88, 129.91, 133.04, 133.16, 133.21, 135.43, 138.86, 139.08, 139.14 (42 C, 7 C_6H_5), 164.56, 165.65, 166.11, 172.47 (4 C=O); elemental analysis calcd (%) for $C_{80}H_{90}O_{16}$ (1307.56): C 73.48, H 6.94; found: C 73.50, H 6.95.

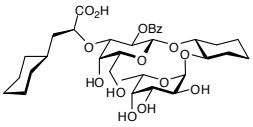
{(1*R*,2*R*,5*R*)-5-*tert*-Butyl-2-[(6-deoxy-α-L-galactopyranosyl)oxy]-cyclohex-1-yl} 2-*O*-benzoyl-3-*O*-[(1*S*)-1-carboxy-2-cyclohexyl-ethyl]-β-D-galactopyranoside (**255**), (DS-05-102). A mixture of **254** (102 mg, 77.9 *µ*mol), $Pd(OH)_2/C$ (49.4 mg), dioxane (3 mL) and water (0.75 mL) was hydrogenated under 4 bar at r.t.. After 37 h TLC control indicated completion of the reaction and the mixture was filtered through celite and evaporated to dryness. The residue was redissolved in methanol (5 mL) and sodium methoxide (0.195 mmol in 255 *µ*L MeOH) was added. After stirring at r.t. for 14 h the reaction was quenched by addition of acetic acid (23 *µ*L). The mixture was concentrated *in vacuo* and purified by preparative, reversed-phase HPLC to afford compound **255** (50.9 mg, 88%) as a white solid.

$[\alpha]_D^{21}$ = - 93.2 (*c* = 0.91, MeOH); ^{1}H-NMR (MeOD, 500.1 MHz) δ: 0.60-0.77 (m, 5 H, H-6_a, $CyCH_2$), 0.65 (s, 9 H, *t*Bu), 0.84 (m, 1 H, H-4_a), 0.93 (m, 1 H, $CyCH_2$), 1.01 (m, 1 H, H-5), 1.15 (m, 1 H, H-3_a), 1.26 (d, $^3J_{F5,F6}$ = 6.6 Hz, 3 H, Fuc H-6), 1.29-1.39 (m, 5 H, $CyCH_2$), 1.43 (m, 1 H, Cy*C*H_2), 1.53 (m, 1 H, Cy*C*H_2), 1.60-1.66 (m, 2 H, H-4_b, $CyCH_2$), 1.95 (m, 1 H, H-6_b), 2.05 (m, 1 H, H-3_b), 3.33 (m, 1 H, H-2), 3.56-3.61 (m, 2 H, H-1, Gal H-5), 3.69-3.74 (m, 4 H, Fuc H-2, Fuc H-4, Gal H-3, Gal H-6_a), 3.79 (m, $^3J_{G6b,G5}$ = 6.9 Hz, $^2J_{G6a,G6b}$ = 11.3 Hz, 1 H, Gal H-6_b), 3.91 (dd, $^3J_{F3,F4}$ = 3.4 Hz, $^3J_{F2,F3}$ = 10.1 Hz, 1 H, Fuc H-3), 4.00 (m, 1 H, Gal H-4), 4.10 (dd, ^3J = 2.9, 10.0 Hz, 1 H, Lac H-2), 4.67 (d, $^3J_{G1,G2}$ = 8.0 Hz, 1 H, Gal H-1), 4.77 (m, 1 H, Fuc H-5), 4.82 (d, $^3J_{F1,F2}$ = 3.8 Hz, 1 H, Fuc H-1), 5.36 (dd, $^3J_{G1,G2}$ = 8.0 Hz, $^3J_{G2,G3}$ = 9.8 Hz, 1 H, Gal H-2), 7.49-7.52 (m, 2 H, C_6H_5), 7.61-7.64 (m, 1 H, C_6H_5), 8.10-8.12 (m, 2 H, C_6H_5); ^{13}C-NMR (MeOD, 125.8 MHz) δ: 16.53 (Fuc C-6), 25.74 (C-4), 26.60, 26.82, 27.30 (3 C, $CyCH_2$), 27.78 (3 C, *t*Bu), 29.73 (C-3), 32.83 (*t*Bu), 33.11 ($CyCH_2$), 33.74 (C-6), 34.26 (Lac C-4), 35.12 ($CyCH_2$), 42.76 (Lac C-3), 47.02 (C-5), 62.69 (Gal C-6), 67.38 (Fuc C-5), 67.99 (Gal C-4), 70.03 (Fuc C-2), 71.57 (Fuc C-3), 73.63 (Gal C-2), 73.96 (Fuc C-4), 76.02 (Gal C-5), 76.90 (C-2), 78.03 (Lac C-2), 81.57 (C-1), 83.17 (Gal C-3), 96.51 (Fuc C-1), 101.13 (Gal C-1), 129.74, 130.90, 131.70, 134.40 (6 C, C_6H_5), 166.83 (*C*=O), 178.78 (*C*OOH); HR-MS (ESI) *m*/*z*: calcd for $C_{38}H_{58}NaO_{14}$ $[M+H]^+$: 761.3719; found: 761.3723 (0.5 ppm).

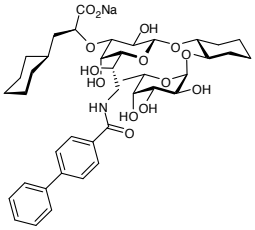
6. Formula Overview of E-Selectin Antagonists



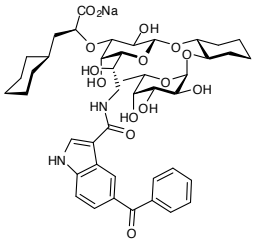
41



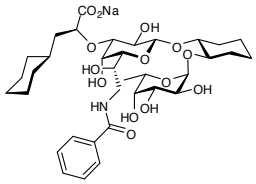
56



193



194



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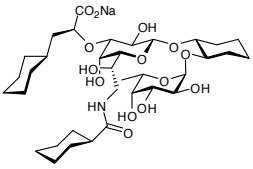

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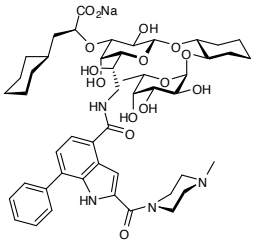

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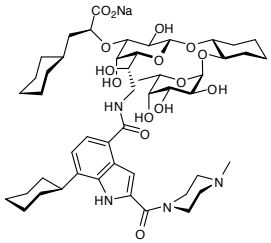
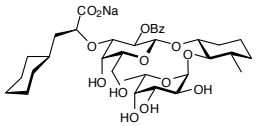
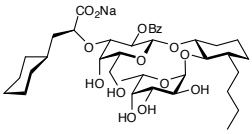


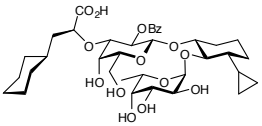
198



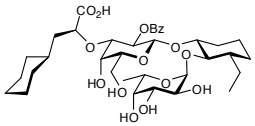
226a



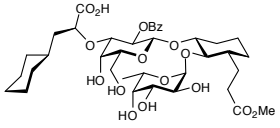
226b (Na)



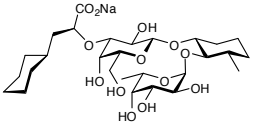
226c



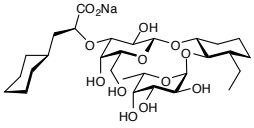
226e



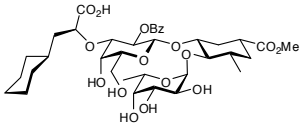
226f



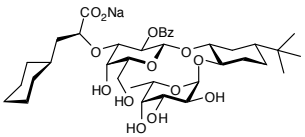
226g



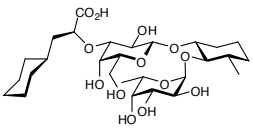
226h



244



255



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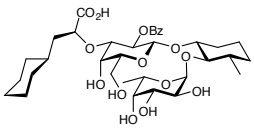

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8. Curriculum Vitae

Daniel Schwizer
St. Gallerring 50
CH-4055 Basel
SWITZERLAND

daniel.schwizer@unibas.ch
Phone +41 (0)61 301 52 49
Mobile +41 (0)79 532 30 88

Born on January 15th, 1977
Martial status: unmarried
Cititzen of Pfaffnau, LU, Switzerland
Swiss nationality

EDUCATION

02/2004 – present	**University of Basel: PhD studies**	
	Topic:	Design and Synthesis of new E-Selectin Antagonists
	Institute:	Institute of Molecular Pharmacy, University of Basel
2003	**University of Basel: Diploma work**	
	Topic:	Studies on the Synthesis of Biphenyl Oligosaccharide Mimetics
	Institute:	Institute of Molecular Pharmacy, University of Basel
	Grade:	6/6
1998 – 2003	**University of Basel: Pharmacy degree**	
	Grade:	5.88/6
1990-1997	High school Sursee University entrance examination certificate type C	
1984-1990	Primary school Pfaffnau	

LANGUAGES

German	Native language
English	Fluently written and spoken Certificate in Advanced English (CAE) International House, Cairns, Australia
French	Basic knowledge

PUBLICATIONS

Antagonists of the myelin-associated glycoprotein: A new class of tetrasaccharide mimics, D. Schwizer, H. Gäthje, S. Kelm, M. Porro, O. Schwardt, B. Ernst, *Bioorg. Med. Chem.* **2006,** *14*(14), 4944-57.

Patent application filed on the synthesis of new E-selectin antagonists.

PRESENTATIONS

'Preorganization of E-Selectin Antagonists in the Bioactive Conformation', **D. Schwizer**, A. Kato, M. Porro, B. Cutting, B. Ernst, Swiss Chemical Society Fall Meeting, University of Zürich, October 13, 2006.

AWARDS

Amedis award 2003 for diploma thesis.

TEMPORARY EMPLOYMENT

2002/2003	Apotheke Tychboden, Parkweg 2, 4665 Oftringen, Switzerland
2001/2002	Ahorn Apotheke, Ahornstrasse 24, 4055 Basel, Switzerland
2000/2001	3rd year pharmacy studies: Hardhofapotheke, Hardstrasse 103, 4052 Basel, Switzerland
1998/1999	UBS AG, financial affairs personnel, 4002 Basel
1998	Credit Suisse First Boston, 8000 Zürich
1997/1998	Armstrong Ins. Products AG, 6264 Pfaffnau
1995/1996	Ringier AG, 4800 Zofingen

REFERENCES

- Prof. Dr. Beat Ernst, University of Basel, Institute for Molecular Pharmacy, Pharmacenter, Klingelbergstrasse 50, 4056 Basel (Switzerland).
  +41 (0)61 267 15 51
  beat.ernst@unibas.ch

- Dr. Oliver Schwardt, University of Basel, Institute for Molecular Pharmacy, Pharmacenter, Klingelbergstrasse 50, 4056 Basel (Switzerland).
  +41 (0)61 267 15 57
  oliver.schwardt@unibas.ch

- Dr. Brian Cutting, University of Basel, Institute for Molecular Pharmacy, Pharmacenter, Klingelbergstrasse 50, 4056 Basel (Switzerland).
  +41 (0)61 267 15 63
  brian.cutting@unibas.ch

- Marco Ferrari, Apotheke Tychboden, Parkweg 2, 4665 Oftringen (Switzerland).
  +41 (0)62 797 20 00
  mferrari@bluewin.ch