Synthesis and Application of Plant Cell Wall Oligogalactans

Andersen, Mathias Christian Franch; Clausen, Mads Hartvig

Publication date:
2014

Document Version
Peer reviewed version

Synthesis and Application of Plant Cell Wall Oligogalactans

PhD Thesis

Mathias Christian Franch Andersen

Department of Chemistry
Technical University of Denmark

March 2014

Synthesis and Application of Plant Cell Wall Oligogalactans

Mathias Christian Franch Andersen

March 2014, Kgs. Lyngby

Preface

This thesis is the result of 3½ years research, as part of the Danish program to obtain a Ph.D. degree. The work has been carried out at the DTU Chemistry, Technical University of Denmark, under the supervision of Professor Mads Hartvig Clausen.

Chapter two describes the structure of the cell wall with an emphasis on galactan-rich polysaccharides, pectin and arabinogalactan protein. Chapter three is an introduction to the structure and function of the carbohydrate-binding protein, Galectin-3. Chapter four deals with the extensive studies of β-(1→4)-galactan synthesis and the final preparation of a series of β-(1→4)-linked galactans including linear and branched structures. Chapter five describes the synthesis of branched and linear β-(1→3)-linked galactans by a convergent block strategy. In chapter six, work regarding synthesis of branched and linear β-(1→6)-linked galactans is outlined. Chapter seven tells of different biological applications of synthesized compounds. In chapter eight the synthesis of Tunicamycin analogues by a chemoenzymatic method is discussed. The work described in this chapter was carried out at the University of Oxford, UK in collaboration with Professor Benjamin G. Davis. Chapter eight is a conclusion and Chapter nine contains experimental protocols and compound data.

Two articles describing the work in chapter three are currently in preparation and will be submitted prior to the Ph.D. defense:

Convenient synthesis of branched and linear β-1,4-linked galactans as ligands for galectin-3.
Mathias C. F. Andersen, Henriette L. Pedersen, Maja G. Rydahl, Gyrithe Lanz, Derek Logan, William G. T. Willats and Mads H. Clausen.

Synthesis of β-1,4 and β-1,6-linked Rhamnogalacturonan-I galactan side chains
Mathias C. F. Andersen and Mads H. Clausen.

An article describing the work in chapter four and five is currently in preparation.

Modular synthesis of oligogalactans related to arabinogalactan protein.
Mathias C. F. Andersen and Mads H. Clausen.

Articles describing the work in chapter six are included in the appendix B

Pectin Biosynthesis: GALS1 in Arabidopsis thaliana Is a β-1,4-Galactan β-1,4-Galactosyl-transferase.
Liwanag A, Ebert B, Verhertbruggen Y, Rennie E, Rautengarten C, Oikawa A, Andersen M, Clausen, M, Scheller H. *Plant Cell*, ***2012, 12,*** 5024-36.

Versatile high resolution oligosaccharide microarrays for plant glycobiology and cell wall research.
Pedersen HL, Fangel JU, McCleary B, Ruzanski C, Rydahl MG, Ralet MC, Farkas V, von Schantz L, Marcus SE, Andersen MC, Field R, Ohlin M, Knox JP, Clausen MH, Willats WG.
J Biol Chem. ***2012, 287, 47,*** 39429-38

Distinct substrate specificities of three glycoside hydrolase family 42 β-galactosidases from Bifidobacterium longum subsp. infantis ATCC 15697.
A. H. Viborg, T. Katayama, M. Abou Hachem, M. C. F. Andersen, M. Nishimoto, M. H. Clausen, T. Urashima, B. Svensson, and M. Kitaoka *Glycobiol.* , Nov. 2013.
Epub ahead of print doi: 10.1093/glycob/cwt104

Acknowledgements

My time as a Ph.D. student has been very fruitful for me not only by means of education and achieving academic and technical qualifications, but also with respect to personal development as an individual and as a scientist. Many people have contributed to the presented work.

First and foremost, I would like to express my gratitude to Professor Mads H. Clausen. During the last four years his support and guidance through critical decisions have had a huge impact on the success of the projects. Thank you for being a great mentor but also a friend with whom I have shared many memorable moments outside the lab.

I would like to express my gratitude to all my colleagues in the Clausen group (Alexandra Zakharova, Mathilde Daugaard, Martin Jæger Pedersen, Mads Holger Rønnest, Faranak Nami, Beatrice Bonara, Christine Kinneart, Henrik Schaarup-Jensen, Hélène Viart, Palle Pedersen, Peter Hammershøj, Asger Bjørn Petersen and Peng Wu) for an outstanding creative and social atmosphere. I would like to give a special thanks to my great lab mate and friend, Alexandra Zakharova. Thank you for inspiring discussions about chemistry and all other matters in life. For your great sense of humor and for showing me that Russia is so much more than vodka and pickles. Thamis Maria Lindorff is gratefully acknowledged for providing priceless support with data for the thesis and for our many lunch dates. Furthermore, Mathilde Daugaard and Martin Jæger Pedersen are thanked for valuable advice at the carbohydrate meetings and their cheerful spirits in the everyday life. I would also like to thank Brian Brylle Dideriksen for always taking time to help me, no matter what time of the day I called, and for great company.

Charlotte Held Gotfredsen for her practical help with NMR experiments and structure elucidation, and for always supporting me, even though I made it hard at times. I have learnt a lot from our small discussions. Claus Gunnar Bang is acknowledged for his friendship and moral support during the difficult times.

Anne Hector, Janne Borg Rasmussen, Brian Ekman-Gregersen, Paul Erik Wibe and Tina Gustafsson all provided superb technical support. Thank you for caring about the NMR instruments, chemicals and equipment in the building and for trying to keep up with my consumption of toluene.

I would like to thank Professor Benjamin G. Davis for giving me the opportunity to work within an interesting field of research in an interdisciplinary and highly dynamic group. The entire Davis group, in particular Hua Wang and Fillipo De Simone are thanked for invaluable help and great times in and outside the lab.

Thanks to our collaborators, Birte Svensson, William Willats, and Henrik Scheller for interesting results and discussions concerning galactans.

I would like to express my deepest gratitude to my parents, Lars and Josefine, brothers, Malthe and Mads and grandparents Hans, Birgitte and Grete for love, support, compliments and criticism. You are all a great inspiration to me. Last but not least, I would like to thank the love of my life, Jeanette Marker Andersen. Words cannot express how grateful I am for your support over the last three years. Without your help I cannot see how I would have achieved what I have.

Abstract

The plant cell walls represent almost 50% of the biomass found in plants and are therefore one of the main targets for biotechnological research. Major motivators are their potential as a renewable energy source for transport fuels, as functional foods, and as a source of raw materials to generate chemical building blocks for industrial processes. To achieve a sustainable development it is necessary to optimize plant production and utilization. This will require a better understanding of the cell wall structure and function at the molecular level.

The cell wall is composed by an intricate network of polysaccharides and proteins that changes during the different developmental stages of the cell. This makes it very challenging to address the function of individual components in living cells. Alternatively, structurally defined oligosaccharides can be used as models for the more complex polysaccharide components in order to investigate a range of properties such as cell wall biosynthesis and protein-carbohydrate interactions. The oligosaccharides can be obtained by chemical or enzymatic degradation of the cell wall. However, although extensive studies have been conducted only a limited range of structures is available and the obtained oligosaccharides require extensive purification. Chemical synthesis, on the other hand, is capable of producing structurally diverse oligosaccharides of excellent purity and in higher quantities.

This thesis presents the chemical synthesis of fragments of galactans and arabinogalactans that are prominent side chains of the pectic polysaccharide rhamnogalacturonan I (RG-I) and the main component of arabinogalactan protein (AGP). In the galactan series, 16 linear or branched β-(1→4)-linked D-galactosides of four to eight residues were prepared by a convergent block strategy. Using a disaccharide donor the number of glycosylations were reduced significantly and late stage regioselective deprotection made it possible to introduce various branches. By the same general strategy, seven linear or branched β-(1→3)-linked- and three linear β-(1→6)-linked D-galactosides were prepared as part of the arabinogalactans series. The fragments were applied in the characterization of a glycosyl transferase, a hydrolase and to study the important cancer biomarker galectin-3. The work done during an external stay at University of Oxford is also presented. This concerns isolation and modification of the carbohydrate-based antibiotic, Tunicamycin. A simple and effective method has been developed for chemo-enzymatic synthesis of the partially protected core tunicaminyl lactol. Furthermore, synthesis of several novel muramic acid donors and attempts to glycosylate the tunicaminyl lactol are discussed.

Dansk Resumé

Plantecellevæggen udgør over 50% af plantens samlede biomasse, hvilket gør den til et interessant forskningsområde indenfor bioteknologi. Det skyldes i høj grad biomassens potentiale som en vedvarende kilde til brændstoffer, funktionelle fødevarer, og som råstof i fremstillingen af byggeblokke til industrielle processer. For at opnå en bæredygtig udvikling er det nødvendigt at optimere produktionen og udnyttelsen af planterne. Dette kræver en indgående forståelse af cellevæggens struktur og funktion på et molekylært niveau.

Cellevæggen består af et indviklet netværk af polysakkarider og proteiner, der ændrer sig i løbet af cellens forskellige udviklingsstadier. Dette besværliggører bestemmelsen af de enkelte molekylers funktion i levende celler. Alternativt kan veldefinerede oligosakkarider anvendes som model-substrater til at undersøge en række egenskaber, såsom cellevæggens biosyntese og interaktioner med kulhydratbindende proteiner. Kemisk eller enzymatisk nedbrydning af cellevæggen har tidligere været den mest anvendte metode til fremstilling af planteoligosakkarider men har kun givet adgang til et begrænset antal strukturer. Dette skyldes hovedsageligt, at en omfattende oprensning er nødvendig for at opnå en tilstrækkelig renhed. Kemisk syntese gør det derimod muligt at fremstille veldefinerede oligosakkarider af høj renhed og i stor mængde.

Denne afhandling beskriver den kemiske syntese af galaktan- og arabinogalaktanfragmenter, der er hyppigt forekomne sidekæder i rhamnogalakturonan I (RG-I), og den vigtigste del af arabinogalaktan protein (AGP). De β-(1→4)-forbundne galaktaner blev fremstillet ved at anvende en konvergent blokstrategi, der gjorde det muligt at syntetisere 16 forskellige lineære eller forgrenede oligosakkarider bestående af fire til otte sukre. Ved at anvende en disakkarid donor kunne antallet af glykosyleringer reduceres og ved hjælp af regioselektiv afbeskyttelse var det muligt at introducere forskellige forgreninger sent i syntesen. Den samme generelle strategi blev benyttet til at syntetisere 10 arabinogalaktan fragmenter i form af syv lineære eller forgrenede β-(1→3)-forbundne D-galaktosider samt tre lineære β-(1→6)-forbundne D-galaktosider. Oligosakkariderne blev benyttet til at karakterisere en glykosyl syntase, en hydrolase og til at studere den vigtige cancer biomarkør galectin-3. Desuden beskrives resultaterne fra et eksternt ophold på University of Oxford, der omhandlede isolering og modifikation af det kulhydrat-baserede antibiotikum Tunicamycin. En enkel og effektiv metode til kemoenzymatisk syntese af grundstrukturen, tunicaminyl laktol blev udviklet. Desuden beskrives syntesen af en række nye muraminsyre glykosyldonorer og forsøgene på at glykosylere tunicaminyl lactolen.

List of Abbreviations

Ac	Acetyl
Acac	Acetylacetone
AG	Arabinogalactan
AGP	Arabinogalactan protein
Alloc	Allyloxycarbonyl
Ara*f*	Arabinofuranosyl
Aq.	Aqueous
AX	Arabinoxylans
BAIB	[bis(acetoxy)iodo]benzene
Bn	Benzyl
BSP	1-Benzenesulfinyl piperidine
BSA	Bovine serum albumin
Bu	Butyl
Bz	Benzoyl
CAN	Cerium(IV) ammonium nitrate
ClAc	Chloroacetyl
CRD	Carbohydrate recognition domain
CSA	Camphor-10-sulfonic acid
COD	1,5-cyclooctadiene
d	Doublet
Da	Dalton
DAST	(Diethylamino)sulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCMME	1,1-Dichloromethyl methyl ether
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DIBAL-H	Diisobutylaluminum hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
DQF-COSY	Double quantum filtered correlation spectroscopy
Et	Ethyl
ESI	Electron spray ionization
Equiv.	Equivalents
f	Furanose
FLA	fascilin-like AGP
Fuc*p*	Fucopyranosyl
Gal*p*	Galactopyranosyl
Gal-3	Galectin-3
Gal*p*A	Galactopyranuronic acid
Glc*p*	Glucopyranosyl
GlcNAc	*N*-Acetyl-D-glucosamine
h	Hours
HG	Homogalacturonan
HMBC	Heteronuclear multiple bond correlation spectroscopy
HMOs	Human milk oligosaccharides
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
HUVEC	Human umbilical vein endothelial cells
Hyp	Hydroxyproline
IDCP	Iodonium di-*sym*-collidine perchlorate
IR	Infrared
LacNAc	*N*-Acetyl-D-lactosamine
LAG	Larch arabinogalactan
m	Multiplet
mAb	Monoclonal antibodies
MALDI	Matrix-assisted laser desorption/ionization
MCP	Modified citrus pectin
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
Mez	2,4,6-Trimethylbenzoyl
MS	Molecular sieves; mass spectrometry
MurNAc	Muramic acid
NAP	2-Naphthylmethyl
NBS	*N*-Bromosuccinimide
ND	N-terminal domain
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
NPhth	*N*-Phthalimidyl
p	Pyranose
PFBz	Pentafluorobenzoyl
Ph	Phenyl
Ph*p*F	*para*-Fluorophenyl
Pr	Propyl
PMB	*para*-Methoxybenzyl
*p*MP	*para*-Methoxyphenyl
PPTS	Pyridinium *para*-toluenesulfonate

p-TSA	*para*-Toluenesulfonic acid
PTFAI	*N*-Phenyl trifluoroacetimidate
RG	Rhamnogalacturonan
Rha*p*	Rhamnopyranosyl
RMSD	Root-mean-square deviation
s	Singlet
sat.	Saturated
Selectride	Lithium tri-*sec*-butylborohydride
SPE	Solid-phase extraction
Super-hydride	Lithium triethylborohydride
t	*Tert*
t	Triplet
TAS-F	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBA	Tetrabutylammonium
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TCA	Trichloroacetimidate
TDS	Thexyldimethylsilyl
TEMPO	2,2,6,6-Tetramethyl-piperidine 1-oxyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSE	Trimethylsilylethyl
TOF	Time-of-flight
Tol	Tolyl, *p*-methylphenyl
Tres	2,2,2-trifluoroethanesulfonate
UDP	Uridine 5’-diphosphate
UV	Ultraviolet

Contents

1 Introduction

Plant science has never been more important. The growing and increasingly prosperous human population needs abundant, safe and nutritious food, clothes, fiber, and renewable energy while addressing the problems generated by climate change. These global challenges can only be met in the context of a strong fundamental understanding of plant biology and translation of this knowledge into applications.

A unique feature of the plant is the presence of a polysaccharide-rich cell wall. The wall encloses the cell but at the same time allows transfer of solutes and signaling molecules between cells via specific pores. Similar to the skeleton in animals, the plant cell wall is the key determinant of the plant form, growth and development. However, in contrast to the specialized skeleton found in animals the shape and strength of plants rely solely on the properties of the wall. Thus, plants would be piles of slime instead of stately trees and other greenery if it was not for the cell wall. The plant cell wall also plays a crucial role in plant defense and response to environmental stresses. Thus, an improved understanding of the plant cell wall will be critical for the development of modified crops. Furthermore, it is generally acknowledged that efficient utilization of plant cell wall material as e.g. food additives and a source of both bioenergy and biochemicals is hampered by a lack of detailed molecular-level information about polysaccharide structure and function. Studies of the structure are complicated by the great complexity of the cell wall. Not only does it constitute a range of polysaccharides, it also has significant microheterogeneity, which makes it extremely challenging to isolate well-defined structures by degradation of plant material. Chemical synthesis, on the other hand, is capable of producing structurally diverse oligosaccharides of excellent purity and in large quantities.

The hypothesis of the research described in this thesis is that we can add to the available information by preparing well-defined, structurally resolved oligosaccharides that resemble the more complex polysaccharide networks found in the plant cell wall. These can function as ligands in characterization of carbohydrate-binding proteins, such as antibodies, lectins and carbohydrate-binding modules that are the probes used to study carbohydrate structure in the complex environment of the cell wall. This, in turn, will lead to a better understanding of the spatial and temporal distribution of polysaccharides in the plant cell wall and their various functions.

We have chosen to focus on galactans and arabinogalactans that are prominent side chains of the pectic polysaccharide, rhamnogalacturonan I (RG-I) (as described in section 2.1) and the main component of arabinogalactan protein (AGP), outlined in section 2.2. Furthermore, galactans have attracted our interest because they are hypothesized to play important roles in modulating mammalian cell biology, exemplified by their role as ligands for the important cancer biomarker galectin-3 (Gal-3), which is introduced in section 3.

2 Structure of the plant cell wall

The primary plant walls are composed mainly of a complex array of polysaccharides (approx. 90%) and protein components (approx. 10%). The types of polysaccharides present in the cell wall vary depending on plant species, cell type and location, developmental stage and history of responses to external stress.[1] All plant cell types are, however, based on a structure of rigid cellulose microfibrils embedded in a gel-like matrix of complex non-cellulosic polysaccharides and pectins. [2,3] The primary cell wall is divided into two categories based on the non-cellulosic polysaccharide composition. Type I walls consist of a cellulosic microfibrils cross-linked by hemicelluloses (mostly xyloglucan) and enmeshed in a non-covalently cross-linked pectic network (Figure 1).[2,3] Type II walls are organized in essentially the same way but in this case the matrix is mainly composed by glucuronoarabinoxylans (GAXs) and β-D-(1→3;1→4)-glucans (mixed-linkage glucans, MLGs).[2,3] The organization and interactions of wall components is not known with certainty and there is still considerable debate about how wall organization is modified to allow cells to expand and grow. A range of models has been published to address this issue but it is outside the scope of this section to describe them. Numerous reviews covering plant cell wall structure and polysaccharide content have been published and can be consulted for further information.[3–5] Plant cells that have ceased to grow and are required to withstand growing compressive forces change character by depositing a secondary cell wall.[5] This serves to increase the strength of the cell and reduce flexibility. The secondary cell wall consists of cellulose and matrix-polysaccharides with a lower degree of backbone branching, mainly xylan and heteromannans that are deposited in a highly ordered fashion. Together with deposition of lignin, a complex polyphenolic polymer, this results in a dehydration of the wall, which becomes more hydrophobic and less dynamic.[5]

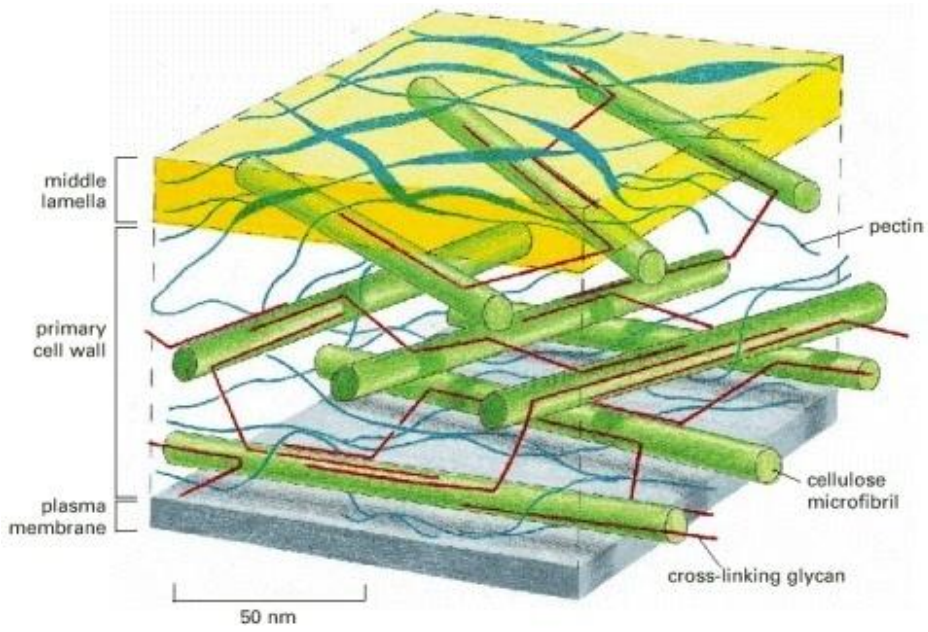


Figure 1. Segment of the primary cell wall. Pectin is shown in blue intertwined in the cellulose network (green cylinders).[6]

The major polysaccharide structures found in the plant cell wall are summarized in Figure 2. Cellulose microfibrils consists of approx. 36 linear β-(1→4)-linked D-Glc*p* chains held tightly together by hydrogen bonds.[7] The diameter, length and crystallinity are highly variable and depend of the age and type of tissue. Xyloglucans are similar in structure to cellulose but xylosyl (Xyl*p*) side chains and their extension prevent hydrogen bonding along the length of the molecules and thereby make them more flexible.[8] MLGs are also similar to cellulose but in this case single β-(1→3)-linked D-Glc*p* residues are located in between blocks of several β-(1→4)-linked D-Glc*p* units. This results in "kinks" and precludes microfibril formation.[9] Heteroxylans consist of a backbone of β-(1→4)-linked Xyl*p* residues of which approx. 10% are C2 or C3 branched with α-D-glucuronic acid (Glc*p*A), α-L-arabinofuranosyl (Ara*f*) residues, or a combination of both to give glucuronoxylan (GX), arabinoxylans (AX), and glucoron-arabinoxylans (GAX). The backbone C2-*O* and C3-*O* can furthermore be acetylated.[10] Heteromannans are a family of mannopyranosyl (Man*p*)-containing polysaccharides that includes mannans, glucomannans, galactomannans and glucogalactomannans. Galactomannans are composed of a β-(1→4)-linked D-Man*p* backbone with C6-branching by β-D-Gal*p* residues. In glucomannans the β-(1→4)-Man*p* backbone is interrupted by β-(1→4)-Glc*p* residues.[11]

Another class of plant polysaccharides, pectins, are among the most complex families of polysaccharides and the focus of our research. In the next section, special attention is therefore given to their structure.

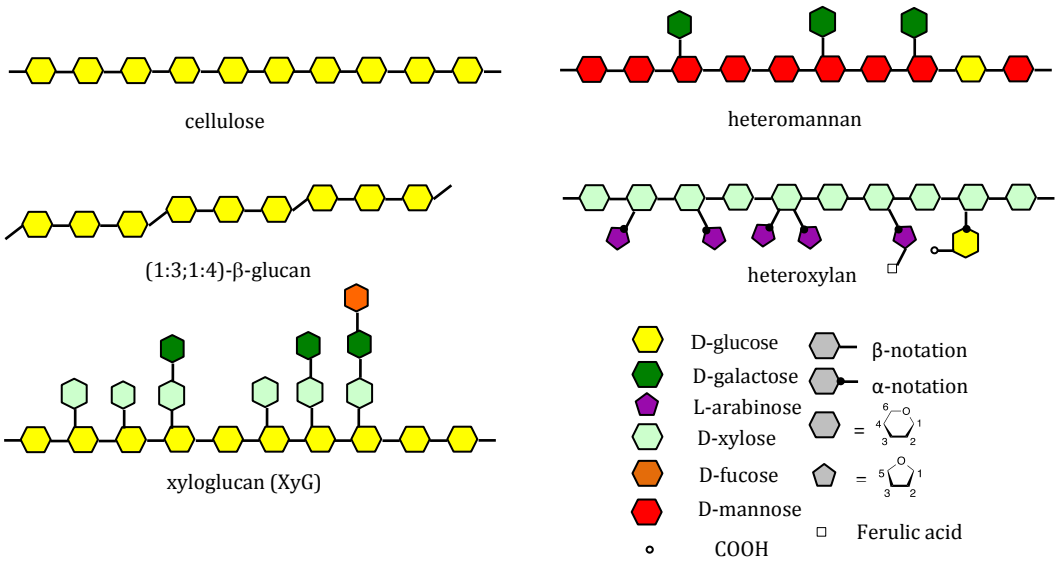


Figure 2. Illustration of the most common plant cell wall polysaccharides.

2.1 The structure of pectin

The pectin backbone is primarily made up from two major units: homogalacturonan (HG) and rhamnogalacturonan I (RG I). HG is an up to 200 residue long homopolymer of (1→4)-α-D-galactopyranuronic acid (Gal*p*A) with varying proportions of methylesterified carboxyl groups and acetylation of the C2-*O* and/or C3-*O* hydroxyls (Figure 3). The free carboxyl groups make it possible for separate HG chains to condense by cross-linking with Ca^{2+} and thereby form 'junction

zones', linking two anti-parallel polysaccharide chains. It is believed that this property is responsible for the porosity of the cell wall, since the pectin chains are condensed in the junction zones, but creates pores where the intervening chains are separated. This correlates with the fact that the methyl-esterification seems to be tightly regulated by the plant both with regard to developmental stage and in a tissue-specific manner.[12–14]

RG I is a heteropolymer of repeating (1→2)-α-L-rhamnopyranosyl-(1→4)-α-D-galactopyranuronic acid disaccharide units (Figure 3). The average length has not been determined, since the RG I domains are generally flanked by HG domains. However, they are all shorter than the HG domains. The backbone Gal*p*A residues may be *O*-acetylated on C2-*O* and/or C3-*O* as seen for HG, but no methyl-esterification has been observed.[12]

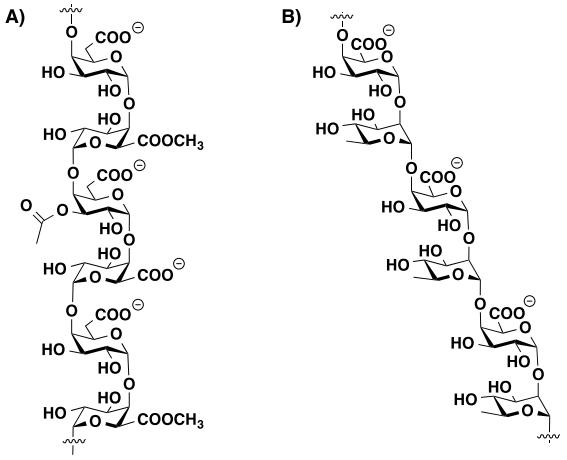


Figure 3. Structure of the two major constituents of the pectic backbone A) homogalacturonan and B) rhamnogalacturonan I.

Both HG and RG I contain side chains, but the degree of substitution, size and diversity of the substituents are very different. HG has a low level of substitution consisting of D-apiose and D-xylose monosaccharides. However, short parts of the HG backbone, also referred to as RG II, are substituted by very diverse side chains. The side chains contain monosaccharide residues such as D-glucose, D-galactose, D-xylose, L-rhamnose, L-arabinose, L-fucose along with many rare sugars.[12,15]

In RG I, the side chains are exclusively attached to the rhamnose residues of the backbone. They consist of four different types of branched oligosaccharides of varying length (1-20 residues): arabinans, galactans and type I or type II arabinogalactans (AG) (Figure 4).[12,15]

Type I arabinogalactan (AG I) is the most abundant neutral pectic structure and is especially abundant in citrus fruits and apple. It is characterized by single interspersed α-(1→5)-linked L-arabinofuranosyl (Ara*f*) residues in a β-(1→4)-linked D-Gal*p* chain. The main chain is furthermore branched by one or more Ara*f* and D-Gal*p* residues or single terminal arabinopyranosyl (Ara*p*) residues.[16] The type II arabinogalactan is constituted by much more branched galactan chains. Thus, they are characterized by a backbone of β-(1→3)-linked D-Gal*p* with branch points of 6-linked β-D-Gal*p* of one, two, or three residues in length. Some of the β-(1→3)-galactan chains are capped by single β-Ara*p* residues.[17] Galactans are simply

β-(1→4)-linked D-galactan chains and have been observed in up to 40 residues length.[18] Finally, the arabinans consists of α-(1→5)-linked L-Ara*f* residues with some degree of (1→3)-bran-ching.[12]

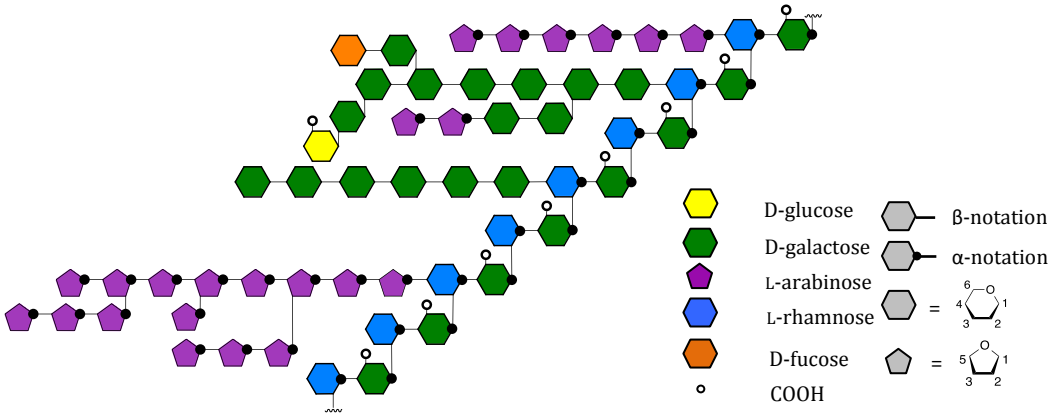


Figure 4. Illustration of the different side chains on the RG I backbone.[12]

Because of the difference in substitution level of the different pectic backbones, they are often described as having alternating "smooth" and "hairy" regions. The "smooth" regions are HG stretches of 25-50 residues with a low substituent level except for methyl esterified or acetylated galacturonic acid residues. This region governs the solubility of the polymer and gives rise to pectin's ability to cross-link.[15]

The "hairy" regions encompass all pectic structures that contain neutral sugars with AG I, AG II and galactans being the "bulk" of the hair.[15] Studies by molecular modeling of the tertiary structure of pectin has implied that AG I's lateral chains are orthogonal to the rhamnogalactan backbone and therefore create plenty of unoccupied space for attachment of other molecules, such as proteins, to the β-galactoside region.[19] The same holds true for AG II, which has an open helical structure. This makes it sterically relaxed and available for both efficient packing and exogenous interactions.[19]

2.2 Arabinogalactan protein

As described previously, the plant cell wall does not only comprise polysaccharides. Wall glycoproteins, which constitute less than 10% of the dry weight of the primary cell wall, are crucial to the structure and function of the wall. In addition to serving a structural role the wall proteins contribute to the wall assembly and remodeling during growth and development, and in stress responses.[5] The proteins includes hydrolases, proteases, glycosidases, peroxidases, esterases, wall-associated kinases, hydroxyproline-rich glycoproteins that includes extensins, arabinogalactan-proteins and proline-rich protein and the glycine rich protein.[20] Detailed description of the wall proteins is beyond the scope of this thesis and readers are referred to reviews.[20] Instead focus will be on arabinogalactan protein, which is very interesting in our context since its backbone is covered with complex galactan polysaccharides.

Arabinogalactan-protein (AGPs) is one of the most complex families of macromolecules found in plants. The complexity arises from a great diversity of glycans decorating the protein backbone and constituting 90-98% of the total mass.[5] Although this has made it impossible to address the precise function of a single AGP, they are known to be involved in several processes in plant growth and development including

differentiation,[67] signaling,[22] root growth,[23] embryogenesis,[24] and programmed cell death[25]. It is outside the scope of this section to describe APGs biological role but excellent reviews have been published on this subject by Seifert & Roberts[26] and Nothnagel[27].

2.3 The structure of arabinogalactan protein

2.3.1 Carbohydrate moiety

Characterization of the glycan structures of AGPs is complicated by difficulties in isolation of single AGPs and the micro heterogeneity found in the constituent chains. Knowledge of the structure is based on NMR-characterization of fragments or binding of carbohydrate-specific monoclonal antibodies for which epitope specificities are partially known.[28] It should therefore only used as a guideline.

The AGP glycans are predominantly type II arabinogalactan chains of 30-120 carbohydrate residues that are *O*-glycosidically linked to hydroxyproline (Hyp) residues in the protein backbone.[29] The type II AGs are made up by a β-(1→3)-linked D-Gal*p* backbone substituted at C-6 by side-chains of β-(1→6)-linked D-Gal*p*. The side chains are often substituted by a great diversity of sugars including Ara*f*, rhamnopyranosyl (Rha*p*), fucopyranosyl (Fuc*p*) and glucopyranuronic acid (Glc*p*A) (Figure 5). The AGs are generally neutral but Glc*p*A-rich versions have also been found in gum Arabica.[30]

Several groups have reported that the AG backbone is susceptible to periodate oxidation resulting in fragments of approximately seven β-(1→3) Gal*p* units. This suggests that the backbone contains repeating units of seven Gal*p* residues interrupted by periodate-sensitive linkages such as (1→6)-Gal*p* or (1→5)-Ara*f*.[31,32] Besides AG II, single Gal*p* residues linked to serine or threonine and short oligoarabinosides linked to Hyp have also been found.[33] The largest fragment characterized so far is a 15-residue AG-Hyp section isolated by heterologous AGP expression in tobacco BY2 cells followed by alkaline hydrolysis and purification.[34] This confirmed the general held view of AG structure. However, the average chain length is significantly lower than the ones estimated for native AGPs.[29] Furthermore, the "periodate repeats" are much shorter than what was predicted for native AGPs.[32]

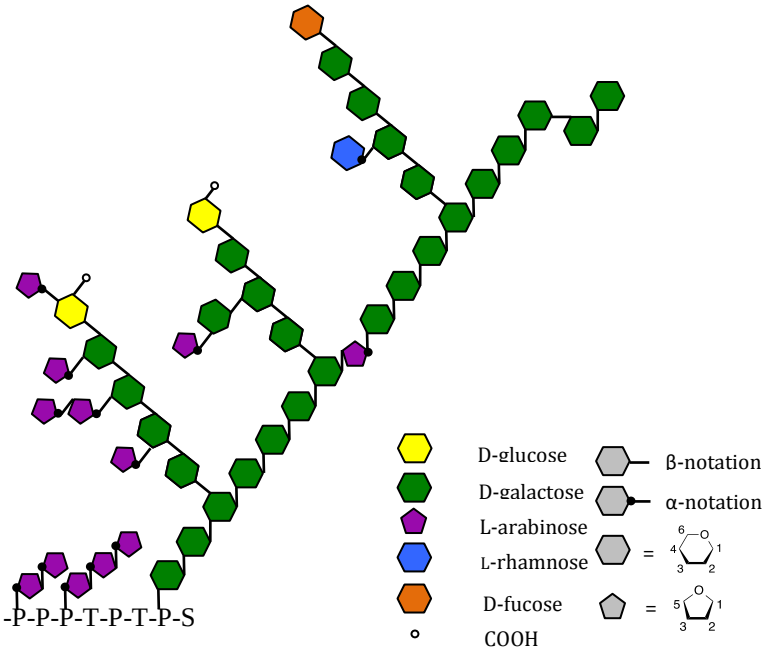


Figure 5. Model of the structure of the carbohydrate moiety of AGPs.[30]

2.3.2 Protein moiety

The first studies of the AGP protein backbone required purification of native AGPs, deglycosylation and Edman degradation[35], which is a difficult and time-consuming process.[36] The emergence of gene sequencing has significantly increased the understanding of AGPs. Like the glycans, the protein backbone has an incredible diversity. For example, Arabidopsis has more than 100 genes coding for proteins with AGP domains.[37] The genes were categorized in four different classes: classical AGPs, Lys-rich AGPs, AG peptides and FLAs (fascilin-like AGPs). The classical AGPs and AG peptides are considered to be the basal form of AGPs, since they have no other functional areas that could interfere with their activity. Thus, the entire backbone is a scaffold for glycosylation. FLAs are a class of chimeric proteins that in addition to an AGP domain, constitutes one or two fasciclin domains. These are believed to be important for protein-protein interaction.[38]

Classical AGPs contain Hyp, alanine, serine, threonine and glycine as the major amino acid constituents and have a backbone of approx. 100 amino acids. AG peptides are made up by the same amino acids but contain only 10 to 13 residues. The Hyp residues are formed by post-translational modification by prolyl 4-hydroxylase, where 80-90% of the proline residues are hydroxylated.[39] There is no well-characterized amino acid sequence motif defining *O*-glycosylation of the AGPs. Instead, it has been hypothesized that single noncontiguous Hyp residues are glycosylated with polysaccharide units whereas clusters of Hyp residues are glycosylated by oligoarabinosides. Further studies are needed to verify this but, for the time being, the prediction correlates with all experimental data.[40]

3 Galectins

This section gives an introduction to the structure and biological role of the β-galactoside binding protein family, galectins. Since there is a remarkable homology between the different galectins most of the discussion is general for all galectins. However, special attention will be given to galectin-3's properties, since this is the most abundant galectin in cancer tissues, together with galectin-1.

3.1 General characteristics of galectins

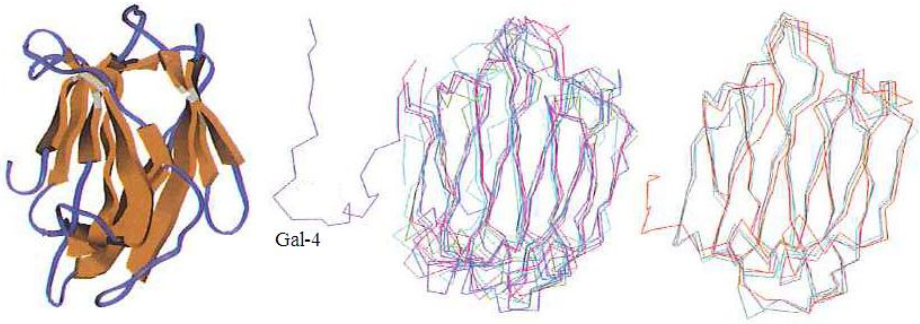
Galectins are a subfamily of the lectins, which is a protein family possessing a relatively high affinity to certain carbohydrate moieties.[41] Galectins are defined by their affinity for β-galactosides, and their significant sequence similarity in the carbohydrate-binding site.[42] They appear to be of very old origin, since galectin-like structures are found in all kingdoms (animal, plant, fungi, protest and prokaryotes).[43] Galectin-1 was the first galectin to be discovered in 1975 in its display of hemagglutinating properties in electric eels and is still by far the most studied of the galectins.[44] Since the discovery, 14 mammalian galectins have been characterized and many more have been found in other organisms.[45] All animal cells appear to express one or more galectins with varying expression level from cell to cell depending on the activation state. The different types of galectins are generally found in high concentration in specific cell types.[46]

3.2 The structure of galectins

The galectins have been divided into three groups based on their structure: prototype (galectin-1, 2, 5, 7, 10, 11, 13 and 14), chimera (Gal-3) and tandem repeat (galectin-4, 6, 8, 9 and 12).[45,47] The prototype only consists of the carbohydrate recognition domain (CRD). Gal-3 is the only mammalian chimera galectin and possesses both a CRD and another N- or C-terminal domain mainly observed as a long peptide extension with various properties. Tandem repeat galectins have two homologous but distinct CRDs, joined either directly or via a linker peptide of variable length.[45,47] The structure seems to have great importance for the galectins' ability to form oligomers.

3.2.1 Structure of the CRD

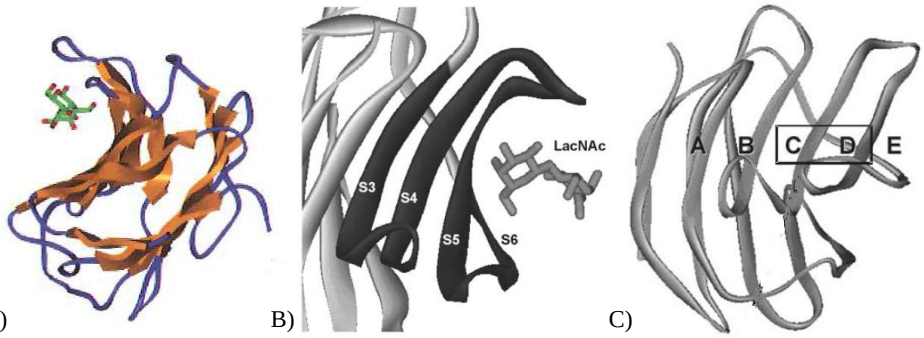
Even though the different types of galectins vary in their overall structure and amino acid sequence they all contain at least one CRD made up from approx. 135 amino acids. Interestingly, the monomer fold of all CRDs is remarkably conserved not only between mammalian galectins, but among all galectins. This is demonstrated in Figure 6B, where the CRD of all known human galectins have been superimposed resulting in a root-mean-square deviation (RMSD) value of only 1.5 Å for the backbone. Similar results are given in Figure 6C where the CRD of galectin-1 originating from different species have been super-imposed.[42,48]



A) Galectin-1 B) Human galectins C) Galectin-1 of different species

Figure 6. A) Cartoon representation of the monomer fold of galectin-1 B) Superimposition of the CRD from all known human galectins C) Superimposition of galectin-1 from different species.[48]

The fold is composed by two slightly bend anti-parallel β-sheets, one of which is formed by six (S1-S6) and the other formed by five (F1-F5) β-strands (see Figure 6A).[42,48] The motif is known as a β-sandwich. The folded structure forms a more or less globular shape, where the hydrophobic residues are packed within the interior to improve the stability in solution. However, due to the bend of the β-sheets, the CRD has a concave and a convex surface. This structural feature is more evident in the crystal structure shown in Figure 7a. Within the concave surface formed by the six-stranded β-sheet, the S3-S6 chains form two fingers, which are steeply bent at the ends and thereby form a negatively charged groove. This is where the carbohydrate is bound (Figure 7B).[48]



A) B) C)

Figure 7. A) Representation of the convex and concave side of Gal-3. B) The carbohydrate binding site C) The five subsites of the carbohydrate binding site.[48]

Based on the observation that the carbohydrate-binding site is able to accommodate a linear tetrasaccharide, it has been proposed to have four subsites (A-D) (Figure 7C).[49] This hypothesis is supported by galectins specificity for small carbohydrates. Using this model, subsite C is the defining β-galactoside binding site and together with subsite D constitutes the core disaccharide-binding site. The binding of galactose in site C is the most conserved feature of galectin binding activities. Six of the seven "motif amino acids" interact with the galactose residue, however, some with weaker binding than others. The D binding site is the second most conserved feature, but here structural requirements are much lower and hence accommodate many different saccharides. Preference for one or the other is one of the sources of variation in the specificity of different galectins. However, the major source of variation in specificity of the different galectins seems to be their different ability to accommodate saccharides and other groups in subsite A and B. The amino acid composition of this area varies to a much higher extent resulting in

some of the differences.[49] Most of the galectins also have an E-site even though it is less defined. This is believed to accommodate interactions with moieties linked to the reducing end of the saccharide (site D), which are large enough to interact with the CRD outside the groove. Thus, for some glycoproteins it has been observed that two proteins with the same glycoconjugate bound Gal-3 with different affinity.[46,50]

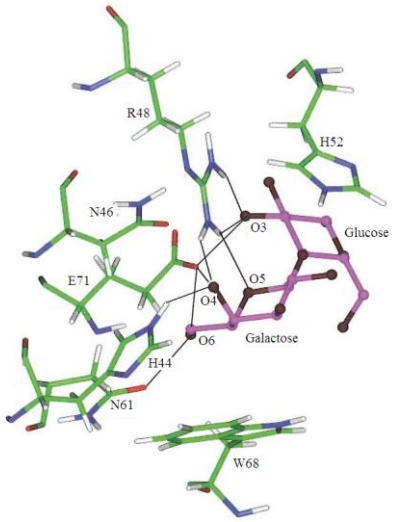


Figure 8. Galectin-1 in complex with the disaccharide lactose.[49]

Seven conserved amino acids constitute subsite C of which only the position in the overall amino acid sequence varies. Hence, the galectins-1 subsite C is composed of H44, N46, R48, H52, N61, W68, and E71 whereas galectins-3's is made up from H158, N164, R162, H169, N174, W181, and E184.[50,51] Figure 8 shows galectin-1 in complex with lactose, the simplest carbohydrate ligand for the galectins. It is seen that three hydroxyl groups of lactose (C4-*OH* and C6-*OH* of galactose and the C3-*OH* of glucose) form hydrogen bonds with the hydrophilic residues from galectins. The galactose ring, in particular, forms several H-bonds between its oxygen atoms C4-*O*, C5-*O* and C6-*O* and H44, E71, and N61, while the C3-*O* of the glucose ring forms H-bonds with the residues R48 and E71.[50] H52 and W68 are proposed to have van der Walls interactions with the non-polar side of the galactose ring, which is almost only substituted by hydrogen. This hydrophobically mediated interaction contributes to the binding free energy and is important for the discrimination of galactose and glucose. This is due to the fact that glucose has its C4-*OH* group in the equatorial position and therefore decreases the apolar nature of the corresponding surface.[52]

3.2.2 Formation of dimers and oligomers

Despite the fact that the galectins are remarkably similar in both structure and sequence, they have several distinct effects and different cellular positions. This is explained by galectins ability to self-associate. Self-association mostly leads to different dimer structures, but also forms higher oligomers depending on the galectin concentration. Despite the similarity of the CRD in all galectins they form different types of dimers. In Figure 9, three examples are given. Galectin-1 forms a dimer through hydrophobic interactions between the N- and C-terminal residues of two monomers with the resulting twofold rotation axis being perpendicular to the plane of the β-sheet.[50] Galectin-2, on the other hand, forms a "non-symmetric" dimer

interface from the convex surfaces of the two monomer stabilized by electrostatic interactions between charged residues.[53] Finally, galectin-7 forms a "symmetric sandwich" dimer also established by electrostatic interactions on the convex surface, but here the interface is reduced compared to the other two.[54] The ability to form different multimer states gives the otherwise very similar proteins a broad range of possible quarternary structures and hence different binding properties.

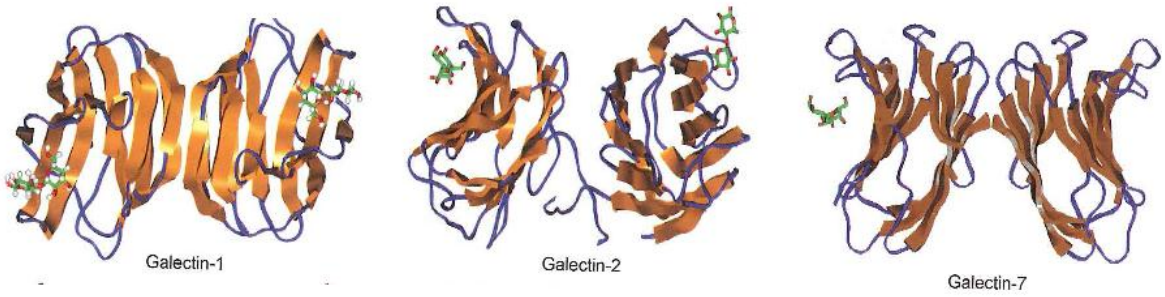


Figure 9. X-ray structures of three different types of dimers formed by galectin-1, -2 and -7.[50,53,54]

3.2.3 The N-terminus of galectins-3

As already mentioned galectins-3 differs from the other galectins due to its N-terminal domain (ND), which is composed of 110-130 amino acids depending on the species. This relatively flexible structure contains 7-14 homologues repeats, which includes the sequence Pro-Gly-Ala-Tyr-Pro-Gly followed by three additional amino acids. Although the ND has been shown to lack carbohydrate-binding activity, it is essential for full biological function of Gal-3.[51] Molecular modeling and mutagenesis studies have indicated that ND participates together with the CRD in oligosaccharide binding and thereby in distinguishing Gal-3 from other galectins. However, the most important property of the ND domain seems to be its responsibility for forming multimers and which makes it possible for Gal-3 to act as a cross-linker.[55] Finally the terminal region of the domain has two phosphorylation sites by residues S6 and S12. These have been shown to be very important for the cellular location of Gal-3 as described in section 3.3.4.[56]

3.3 Gal-3's function in the progression and metastasis of cancer

Galectins generally elicit their biological effects by binding and cross-linking different glycan groups of glycoproteins and/or glycolipids on the surface of various cells. In contrast to most enzymes the binding is not accompanied by a chemical conversion of the ligand. They rather bind them to form non-covalent multivalent complexes that bring the ligands together. This either results in structural interactions that mediate cell-cell and/or cell-matrix adhesion or migration, or in signal transduction to effect intracellular changes necessary for example cell growth and proliferation.[43]

Due to the variety of different galectins and self-associated oligomer states of these, galectins are able to bind a huge array of different ligands and thereby mediate a multitude of effects throughout the body. For example Gal-3, which seems to be one of the most promiscuous galectins, display biological activities including cell growth,[57] cell adhesion,[57] apoptosis,[58] immune response[59] as well as gene transcription

regulation,[60,61] Figure 10 gives an idea of the over-whelming array of ligands to which Gal-3 binds and these are only the extra-cellular binding partners.[61] It is outside the scope of this project to go into details with all the biological functions. The focus will be on Gal-3's involvement in the progression and metastasis of cancer and the potential therapeutic applications of Gal-3. It should be noted that many other galectins are known to be involved in this process with galectin-1 being the most studied together with Gal-3.[62]

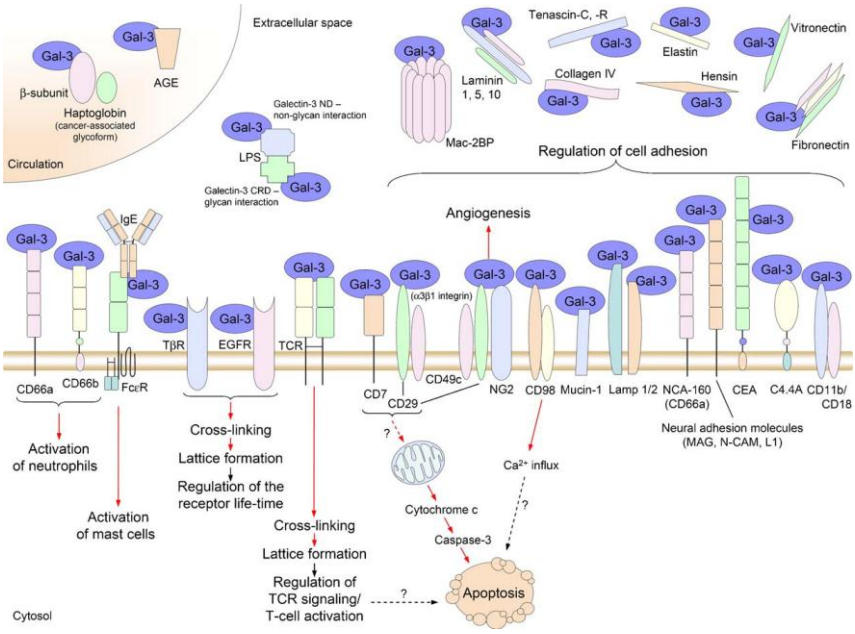


Figure 10. A representation of some of the extracellular receptors and ligands to which Gal-3 has been observed to bind.[61]

Metastasis is a major fatal complication associated with malignant tumors.[63,64] Cancer emerges when a single cell is genetically damaged in ways that result in the formation of a cancer stem cell. The cancer stem cell may undergo uncontrolled mitosis resulting in a rapid increase in the total number of cancer cells. When the area of cancer cells becomes clinically detectable it is called the primary tumor. Cancer cells are able to penetrate and infiltrate surrounding tissue thereby forming "daughter" tumors at the adjacent site. Some cancer cells are able to penetrate the walls of the lymphatic system and/or blood vessels making it possible for them to circulate to other tissues in the body through the lymphatic system and/or blood stream. Once the tumor cell comes to rest at another site it repenetrates the vessels or walls and start multiplying resulting in a new tumor, a metastatic tumor.[63,64] The process is depicted in Figure 11 and can be divided into eight steps 1) growth at the primary site, 2) angiogenesis at the primary site, 3) detachment from the primary site, 4) invasion through the extracellular matrix, 5) dissemination of cells through the blood flow, 6) tumour embolous formation in capillaries, 7) extravasation, 8) growth at the new site.[63]

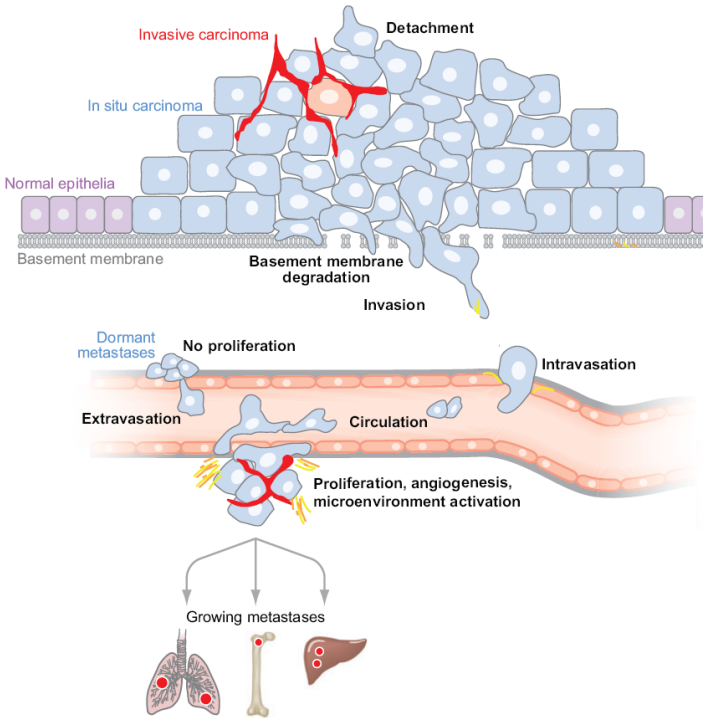


Figure 11. Illustration of some of the steps involved in cancer metastasis.[63]

In several cancer tissues it has been shown, that the expression of Gal-3 correlates with the level of differentiation and that metastases express higher levels of galectins-3 as compared to the primary tumor, from which they arise.[65] This indicates that galectins-3 plays a role in the metastasis biology. The underlying mechanisms of Gal-3 have therefore been studied with great interest in order to discover potential therapeutic targets.[58] It has been demonstrated that Gal-3 is indeed involved in several steps in the metastasis process through various mechanisms, some of which will be described here.

3.3.1 Angiogenesis and galectins-3

Angiogenesis is the formation of new blood vessels by a complex multistep process associated with inflammation, wound healing, and tumor growth. New vessels are required for the growth at the primary and secondary sites and provide gateways to dissemination through the blood flow.[66] Carbohydrate recognition may have an important role in this process, since the angiogenic growth factors responsible for starting the process are bound to extracellular proteoglycans. These are probably guided towards the growth factor receptors by adhesion molecules such as Gal-3.[67,68] Thus, it has been demonstrated, that over-expression of Gal-3 stimulates *in vitro* capillary tube formation by human umbilical vein endothelial cells (HUVEC) and *in vivo* neovascularization (formation of functional microvascular networks). It was furthermore shown, that capillary tube formation was competitively inhibited by the galectin ligands lactose (50mM) and pH-modified citrus pectin (0.1%), which is described in section 3.4.[66]

3.3.2 Anoikis

After the escape from the primary tumor and intravasation, the first obstacle that blood-borne cancer cells encounter is to survive the apoptosis associated with the loss of anchorage (anoikis) and the journey through the circulation. Gal-3 has been shown to protect cancer cells from anoikis by regulation of their transition through the cell cycle. This is obtained by induction of a cell cycle arrest at an anoikis-insensitive point (late G1 phase).[69]

3.3.3 Cell-matrix interaction and homotypic interactions

A crucial step in cancer metastasis is associated with tumor cell arrest in distant organ microvasculature. The cancer cell must attach to the extracellular matrix and then invade the tissue. This takes place by adhesion to the basement membrane. The basement membrane is a thin sheet of fibers that underlies the epithelium, which lines the organs, or the endothelium, which covers the interior surface of blood vessels. This membrane is rich in glycoconjugates such as laminin and fibronectin, and it is therefore believed that cross-linking between Gal-3 on the cancer cell surface and laminin promotes adhesion.[70] For example, breast cancer cells ability to adhere to laminin and fibronectin was improved by 60% in cell lines expressing Gal-3.[71] Furthermore, it was shown that over-expression of Gal-3 enhanced *in vitro* invasion of a solubilized basement membrane.[72] The same results were observed for other Gal-3 ligands such as elastin, which is predominantly found in the lungs.[73] Evidence also exists that Gal-3 interacts with cancer-associated Thomsen–Friedenreich glycoantigen and thereby mediate both the initial adhesion of cancer cells to the vascular wall and subsequent tumor cell homotypic aggregation at the site of primary attachment to the endothelium.[74] Homotypic aggregation is the crosslinking between the already attached cancer cell and circulating cancer cells resulting in accumulation of cells at the point of attachment. This is important, since aggregation with other cancer cells improves the chance of invasion and survival of the early metastatic tumour.[74]

3.3.4 Anti-apoptotic effect

Perhaps the major property that supports the supposed potential for Gal-3 as a therapeutic target is its anti-apoptotic ability.[75] Apoptosis is the process of programmed cell death, which is a natural biological mechanism observed during cell differentiation, immune response or tumour cell death after chemo- or radiotherapy. The resistance to apoptosis enables tumour cells to escape cell death induced by anti-cancer drugs or natural effector cells like natural killer or killer T-cells. This property is of great importance, since the vast majority of cancer cells die due to apoptosis following the arrival to distant organs. Only a few of them (<2%) survive and grow into micrometastases. Hence, the survival of early metastatic colonies is one of the most important steps determining the efficiency of the metastatic process.[75]

It is well established that intracellular Gal-3 protects different cell types against apoptosis in response to various stimuli. For example, Gal-3-transfected Jurkat cells (T lymphoma cells) are more resistant to apoptosis provoked by anti-Fas antibody compared to controls.[76] Furthermore expression of Gal-3 in human breast carcinoma BT549 cells that innately expresses no Gal-3, makes them remarkably more

resistant to apoptosis induced by *cis*-diamminedichloroplatinum(II) (cisplatin).[77] Likewise Gal-3 has been shown to directly regulate sensitivity of cancer cells to various chemotherapeutic agents such a staurosporine,[77] etoposide,[78] bortezomib,[79] dexamethasone,[79] and doxorubicin[80] in various cancerous tissues.

Although the anti-apoptotic effect of the intracellular Gal-3 is well documented, the precise mechanism of this action is still elusive.[81] It seems as if several regulatory pathways are involved. Two main mechanisms of apoptotic regulation have been identified: directly transducing the signal via adaptor proteins to the apoptotic mechanisms or targeting mitochondria functionality of which Gal-3 is involved in the latter. In the response to a variety of apoptotic stimuli, Gal-3 translocate from the cytosol or the nucleus to the perinuclear mitochondrial membrane. Here it prevents mitochondrial damage and inhibits cytochrome-c release, thus downregulating caspase activation and ultimately blocking cell death.[81]

Phosphorylation of Gal-3 at position Ser6 (see section 3.2.3) seems to be essential for its anti-apoptotic activity, since the transfection of Gal-3-null human breast carcinoma BT549 cells with the mutant Gal-3 (S6A and S6E) fails to protect the cells from cisplatin-induced cell death compared to mice transfected with the wild type Gal-3.[56] It has been suggested that post-translational phosphorylation of Gal-3 functions as a type of molecular trigger for the cellular translocation of Gal-3 from the nucleus to the cytoplasm and hinders extracellular release. This is of great importance, since it has been shown, that the cytosolic localization of Gal-3 inhibits apoptosis, whereas extracellular Gal-3 has pro-apoptotic effects.[56]

Another interesting observation is the fact that Gal-3 shares significant sequence similarity (28% identity and 48% similarity) with another anti-apoptotic protein, Bcl-2.[76] Both proteins are rich in proline, glycine, and alanine residues in the N-terminal domain and contain the Asp-Trp-Gly-Arg (NWGR) motif in the C-terminal domain. In Bcl-2 this motif is designated as the anti-death motif and mutagenesis studies have shown that it is critical for the anti-apoptotic function in both proteins. Gal-3 is the only member of the galectin family, known by now, that contains the NWGR motif and which have anti-apoptotic properties. The receptor or ligand for the motif is yet to be found. However, a better understanding of this mechanism would be an important step towards a therapeutic agent, which could be co-administered with the classical chemotherapeutics to increase efficiency against cancer.[76]

3.4 Ligands for inhibition of galectin and their potential therapeutic applications

Due to Gal-3's potential as a therapeutic target, extensive research has been focused on the development of effective inhibitors and the study of their effect on the various Gal-3 functions.

Lactose is the simplest carbohydrate to which galectins bind. Affinities for lactose binding range from millimolar (weak binding affinity) to micromolar (moderate binding affinity) and vary to a great extent depending on the analytical method being used.[42] For example, the dissociation constant for lactose binding to Gal-3 ranges from $26 \cdot 10^{-6}$ M to $1 \cdot 10^{-3}$ M.[82,83] In general, the K_d values indicate a relatively weak binding to Gal-3, which is not surprising, since the lactose unit is the minimal unit required for carbohydrate recognition and binding to galectins.

Improved carbohydrate-binding affinity was obtained using *N*-acetyllactosamine (LacNAc), which binds about a five fold better to Gal-3 (K_d of $0.2 \cdot 10^{-3}$ M).[83] Moreover, it was found that Gal-3 binds more strongly to larger oligosaccharides, for example the K_d value is reduced to app. $1 \cdot 10^{-6}$ M for a linear tri- and pentasaccharide (Gal-α-(1→3)-Gal-β-(1→4)-GlcNAc and Gal-α-(1→3)-Gal-β-(1→4)-GlcNAc-β-(1→3)-Gal-β-(1→4)-Glc).[53]

These observations has given rise to the analysis of a broad range of galactoside rich carbohydrates. In 1992 the field had a breakthrough, when D. Platt and A. Raz reported that modified citrus pectin is able to remarkably decrease experimental melanoma.[84] The term modified citrus pectin (MCP) encompasses a complex formulation of partially depolymerized and hydrolyzed citrus pectic polysaccharides derived by alkaline and acidic treatment of citrus pectin.

Following the first reports indicating MCP's anti-metastatic properties the carbohydrate-formulation sparked significant attention among cancer researchers. Thus, MCP has been shown to be effective either *in vitro* or *in vivo*, or both, against prostate carcinoma,[85] colon carcinoma,[86] breast carcinoma,[87] melanoma,[84,88] multiple myeloma,[79] and hemangiosarcoma.[89] As first postulated the established mechanism of action for MCP is by antagonizing Gal-3. This correlates well with the fact, that MCP have been shown to affect all of the metastatic steps described in the previous section (Figure 12)

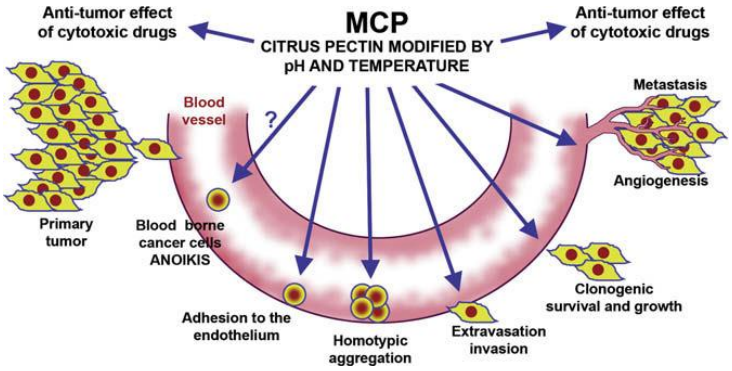


Figure 12. MCP has been demonstrated to have an effect of most of the steps involved in the metastasis of cancer. This figure shows some of the important steps.[75]

The best studied anti-metastatic effect is MCP's anti-adhesive property. It has been demonstrated, that MCP is capable of inhibiting both tumor cell adhesion to the endothelium and homotypic aggregation in both mouse B16 melanoma and rat MAT-LyLu prostate cancer cells.[84,88] Moreover, Nangia-Makker *et al.* established dose-dependent inhibition of the binding of tumor cells (MDA-MB-435 cell line) to human endothelial cells *in vitro*.[86] The anti-adhesive properties have also been studied *in vivo*, where MCP was demonstrated to inhibit the formation of metastatic deposits of human breast and prostate tumour cells in lungs and bones by >90%. Figure 13 shows metastatic deposit formation of prostate carcinoma cells in untreated mice and mice treated with 0.25% MCP.[90] As seen the effect is remarkable with almost zero spread in the MCP treated mice.

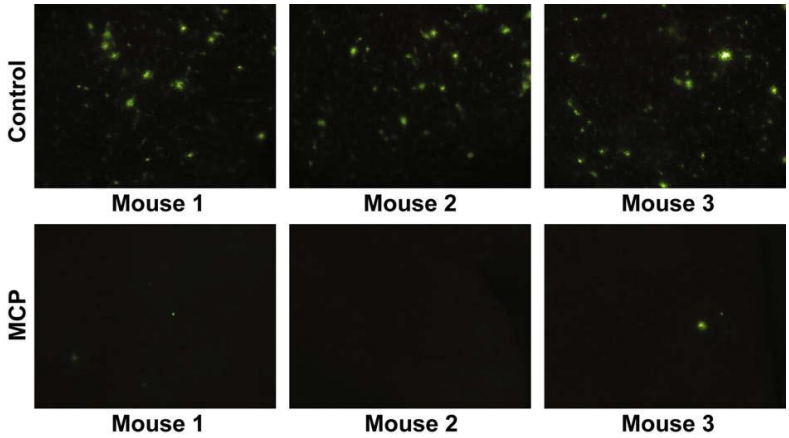


Figure 13. The effect of MCP on *in vivo* metastatic deposit formation of human metastatic prostate carcinoma cells in mice. The cancer cells were fluorescently labeled and injected intravenously.[90]

MCP also inhibits *in vitro* and *in vivo* carbohydrate-mediated angiogenesis by blocking the association of Gal-3 to its receptors in a dose-pendent manner (68% at 0.005% and completely at 0.1%).[66] Finally, as opposed to the observation that over-expression of Gal-3 resulted in increased invasiveness of tumor cells in the basement membrane, MCP was shown to inhibit invasion.[86]

The broad spectrum of targets makes MCP a promising potential anti-metastatic drug for both prophylaxis and therapy. However, MCP may be even more important as a drug co-administered with various "classical" chemotherapeutic agents due its potential inhibition of Gal-3's anti-apoptotic function. One of the first MCP formulations to reach clinical trials was GCS-100.[79] This formulation was demonstrated to inhibit Gal-3 anti-apoptotic function sufficiently to reverse multiple myeloma cell resistance to bortezomib and enhance the response to apoptosis induced by dexamethasone.[79] Moreover, it was demonstrated, that GCS-100 itself could induce apoptosis by activation of the classical extrinsic death-signaling pathway, caspase-8/caspase-3/PARP. A major advantage of GCS-100 is that it is much less toxic to normal cells as compared to classical chemotherapeutics. Even large doses of MCP only led to minor side effects. This is supported by the observation that Gal-3 null mutant mice, corresponding to 100% inhibition, are relatively healthy.[91]

Another example is the increase in sensitivity of hemangiosarcoma cells to doxorubicin-induced apoptosis, when MCP is co-administered. This causes a 10-fold reduction of doxorubicin IC_{50} *in vitro* (from 0.0075 μg/ mL to 0.0007 μg/mL). These results suggest that addition of MCP to a therapeutic regime for treatment of Gal-3 expressing malignancies would improve the effect of chemotherapy.[89]

It should be noted that MCP is not the only effective inhibitor of galectin-dependent tumour metastasis. Other carbohydrate-based inhibitors encompass larch arabinogalactan (LAG). This polysaccharide consists of a β-D-(1→3)-galactan backbone with extensive branching by β-D-(1→6)-galactan chains, which are in turn substituted with different arabinose derived residues.[15] Some fungal polysaccharides have also been demonstrated to lower the adhesion and proliferation potential of tumor cells expressing Gal-3.[82]

An alternative to sugar based inhibitors is artificial peptide inhibitors. These offer the advantage of ease of synthesis along with equally potent immune response. Pentapeptides, based on the common Tyr-X-Tyr motif found in glycomimetic peptides, have been found to be effective in millimolar ranges in preventing binding of several galectins.[92] Recent experiments have shown that 15 residues long peptides made by phage-display are effective at nanomolar affinity for galectins-3 and inhibit metastasis-associated cell adhesion.[93] One of the most extensive studies of Gal-3 inhibitors has been done by Nilsson and co-workers. They showed that derivatization at the C-3' atom in 3'-amino-*N*-acetyllactosamine by *N*-acylation or *N*-sulfonylations resulted in up to 50-fold increase of affinity compared to the parent LacNAc[94]. Second-generation aromatic 3,3′-diester- and 1,4-disubstituted triazole derivatives of thiodigalactoside resulted in affinities down to 29 nM for galectin-3. [95,96] These inhibitors has the advantage that they are more easily synthesized and are expected to have improved hydrolytic stability relative to *O*-glycosides

Even though the results are promising, very little is still known about the exact nature of the carbohydrate inhibitors and their binding to Gal-3. Thus, no crystallographic studies have been published with MCP or defined galactans bound to galectins-3, and the complex MCP has not been separated and characterized.

3.5 Modified pectin formulations

It was not until the 90's that pectin formulations found application as potential anti-metastatic agents. However, pectins have been used in the industry for decades as a gelling agent due the HG domains' cross-linking properties.[15] Both the pectin used for gelling in the food industry, and the pectin that has been demonstrated as tumor metastasis inhibitors, are modified extracts of plant pectins. In industry the extraction of pectin is done under mild acidic conditions (pH 3-4). This results in hydrolysis of the methylated galacturonate carboxylic groups and the neutral carbohydrate side chains as well as some degree of depolymerization of the backbone. The increase in galacturonic acid content and the fragmentation of polymer leads to enhanced gelling properties since more carboxylic acid are liberated for cross-linkage.[15]

Interestingly, untreated pectin has been tested in most of the Gal-3 inhibition studies described so far without any observed activity. This indicates that the bulky pectin structure is either too large to bind/reach the galectin or that the target residues are buried within the structure.[15] The name "modified citrus pectins" was given to a therapeutically active formulation of partially depolymerized and hydrolyzed citrus pectin.[84] The starting material had 70-100 kDa molecular weight, high arabinogalactan content (35% of the combined Gal + Ara content) and a low degree of methyl esterification. When the sample was first treated at pH 10 followed by pH 3 the average molecular weight dropped to 10 kDA estimated viscometrically.[84] Although no detailed analysis was made of the MCP it has been suggested that the alkaline treatment will cause β-elimination reactions, which result in depolymerization of the polysaccharide backbone.[97] Alkali treatment will furthermore de-esterify the HG regions and generate lower molecular weight oligomers of polygalacturonic acid plus RG I regions attached to

polygalacturonic oligomers.[97] Acid treatment will preferentially cleave neutral sugars and is expected to result in release of the hairy regions and preferentially remove the arabinose residues.[98] Hence, acid treatment would be expected to generate RG I regions lacking arabinan side chains and with reduced arabinose substitution of the arabinogalactan and galactan chains.[98] The potential importance of arabinogalactans or galactans is supported by the fact that arabinogalactans, just as modified pectin, also has anticancer activity.[99] Moreover, it has been shown that the inhibitory behavior is enhanced in pectic polysaccharides with higher arabinose and galactose contents indicating the importance of arabino-galactans.[100]

4 Synthesis of β-(1→4)-D-galactan oligosaccharides

This section describes the extensive studies of β-(1→4)-galactan synthesis and the final preparation of a series of β-(1→4)-linked galactans including linear and branched structures.

The preparation or isolation of well-defined β-(1→4)-D-galactans has previously turned out to be problematic. Isolation from pectic cell wall material is exceedingly cumbersome and has rarely provided well defined products exceptions being mg quantities of galactobiose, -triose, and -tetraose.[101,102] The generation of β-(1→4)-oligogalactosides by β-galactosidase-induced galactosyl transfer has also been investigated, but despite its simplicity, it has not passed the β-(1→4)-D-galactobiose stage.[103]

The chemical synthesis of β-(1→4)-D-galactans has also proved to be very difficult due to the low reactivity of the axially disposed C4-*OH* of galactosyl acceptors. Not only, are axial hydroxyls less accessible towards glycosylation compared to primary and equatorial alcohols, but the acceptor must also be protected on the C3-*O* and C6-*O*, thereby making the C4-*OH* even more sterically hindered. Thus, only three groups have reported syntheses of β-(1→4)-D-galactooligosaccharides and two of them only reached the trisaccharide level (see Table 1).[104–106]

Table 1. Previous studies of β-(1→4)-D-galactan synthesis.

Synthetic oligosaccharide fragment	Reference
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-β-D-Gal*p*-OMe	Kováč & Taylor[105]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-β-D-Gal*p*-O^{n}Pr	El-Shenawy & Schuerch[104]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-D-Gal*p*	Komba *et al.*[107]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-β-D-Gal*p*-OMe	Lichthenthaler *et al.*[106]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_2$-β-D-Gal*p*-O*p*MP	Lichthenthaler *et al.*[106]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_3$-β-D-Gal*p*-O*p*MP *fully protected*	Lichthenthaler *et al.*[106]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_4$-β-D-Gal*p*-O*p*MP	Lichthenthaler *et al.*[106]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_5$-β-D-Gal*p*-SPh *fully protected*	Oberthür *et al.*[108]

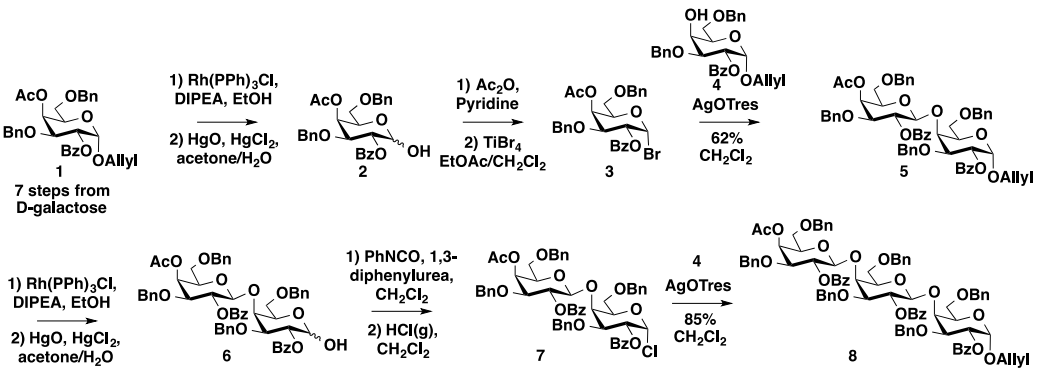
4.1 Previous studies of β-(1→4)-D-galactan synthesis

4.1.1 Synthesis of a linear trisaccharide

The first method used for the synthesis of a trisaccharide, shown in Scheme 1, was developed by Schuerch & El-Shenawy.[104] Their strategy was based on reactivation by exchange of an anomeric protecting group. The building block **1** was protected by electron-donating benzyl (Bn) groups at the 3- and 6-positions to increase the reactivity. A benzoyl was chosen for the 2-position to ensure neighboring group participation and an allyl group was chosen as an exchangeable protecting group at the anomeric position. The acceptor **4** was coupled to glycosyl

bromide **3** in a silver tresylate (2,2,2-trifluoroethanesulfonate, OTres) catalyzed glycosylation reaction to give the disaccharide **5** in 62% yield (Scheme 1).

The disaccharide was converted into the corresponding glycosyl chloride **7** in three steps. The allyl ether was removed by isomerization with $(PPh_3)_3RhCl$ and *N*,*N*-diisopropylethylamine (DIPEA) followed by hydrolysis with $HgO/HgCl_2$ to give the hemiacetal **6**. This was converted to the corresponding glycosyl chloride by activation of the anomeric hydroxyl with *N*-phenyl isocyanate followed by treatment with HCl gas. Glycosylation of the acceptor **4** with the disaccharide donor **7** afforded the trisaccharide **8** in 85% yield. Even though both glycosylations gave good yields the strategy has three major drawbacks. First of all, it was not possible to turn the di- and trisaccharide into acceptors, since selective deprotection of the C4-*O* could not be accomplished. Secondly, the reactivation of the anomeric group by three steps is both time consuming and results in low overall yield. Finally, glycosyl bromide **3** had to be synthesized by a laborious ten-step procedure.

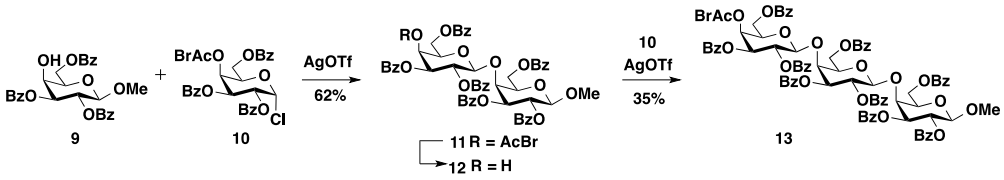


Scheme 1. Synthesis of β-(1→4)-D-galactotriose by Schuerch & El-Shenawy.[104]

4.1.2 Alternative strategy for synthesis of a linear trisaccharide

Kováč and co-workers reported an alternative approach, where they sought to shorten the synthesis by employing a simpler protecting group strategy (see Scheme 2).[105] Hence, methyl glycoside **9** was used as acceptor, which is accessible in just one step from commercially available methyl β-D-galactopyranoside. This was in turn converted to the glycosyl chloride **10** in two steps.

Coupling of acceptor **9** and donor **10** promoted by silver trifluoromethanesulfonate (AgOTf) gave the desired disaccharide **11** in decent yield. The bromoacetyl group was removed with thiourea to give acceptor **12**, which was once again glycosylated with glycosyl chloride **10**. In this case glycosylation was slower and the trisaccharide **13** could only be obtained in a 35% yield. The low reactivity is attributable to negative electronic effects of the ester protecting groups and size of the acceptor. Further elongation was therefore not feasible.

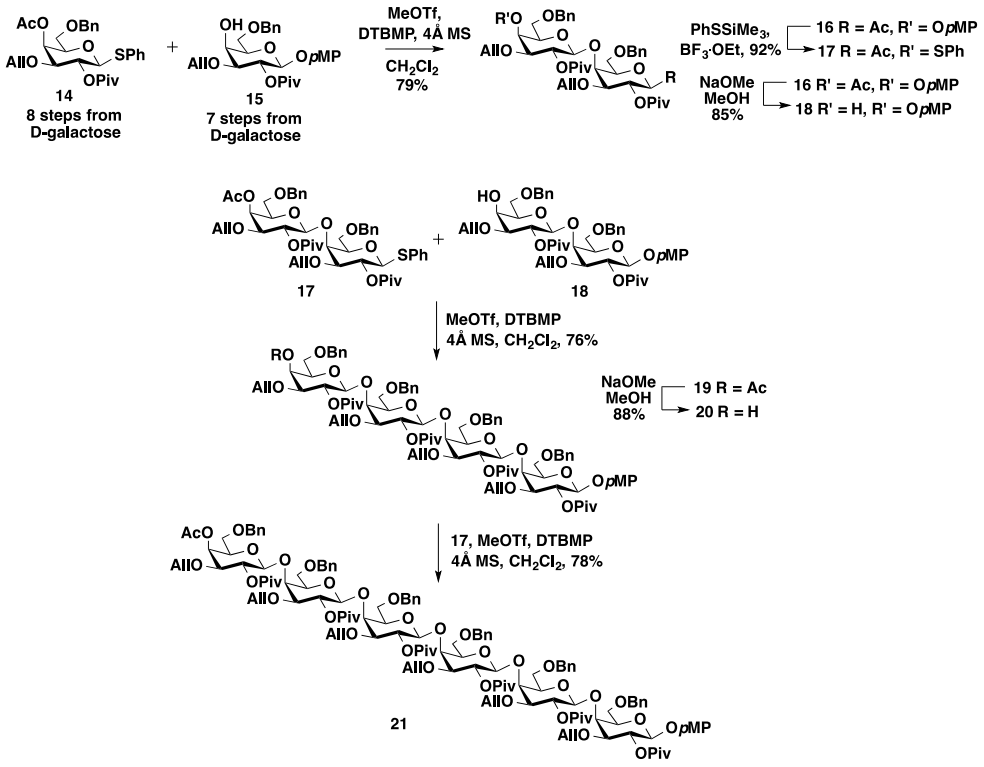


Scheme 2. Synthesis of β-(1→4)-D-trigalactotriose by Kováč.[105]

4.1.3 Synthesis of linear hexagalactoside

Lichtentaler *et al.* has published the only strategy by which longer β-(1→4)-linked galactans have been made (Scheme 3).[106] The method was also based on reactivation by exchange of anomeric protecting group, but as opposed to Schuerch and El-Shenawy, they used thioglycosides for the glycosylations and *p*-methoxyphenyl as the anomeric protecting group.[104] The C3-*O* and the C6-*O* were protected with allyl and/or benzyl groups in order to enhance accessibility and to improve the nucleophilicity of the notoriously unreactive galactosyl C4-*OH*. Pivaloyl esters (Piv) were used to protect the C2-*O* in order to ensure β-stereoselectivity. Moreover, this made it possible to use an acetyl group as temporary protection group for the C4-*OH*.

Protection with *p*-methoxyphenyl is more efficient than allyl groups, since it can be converted to the corresponding thioglycoside in a single step by trimethyl(phenylthio)silane (TMSSPh) and $BF_3{\cdot}OEt_2$ in good yield.



Scheme 3. Synthesis of β-(1→4)-D-hexagalactoside by Lichtentaler *et al.*[106]

As seen in Scheme 3 the strategy is truly convergent. MeOTf-mediated coupling of thioglycoside **14** and acceptor **15** afforded the disaccharide **16** in 79% yield. This could be turned into both disaccharide donor **17** and a disaccharide acceptor **18** by either glycosylation of TMSSPh or mild deacetylation under Zemplén conditions[109]. The building blocks were used in two following glycosylations furnishing the hexasaccharide **21** on gram scale. As an alternative to the toxic MeOTf it was later shown that oxidation of the thioglycoside donors to the corresponding glycosyl sulfoxides followed by activation with triflic anhydride (Tf_2O) gave comparable glycosylation yields.[108]

The purpose for the study was to turn **21** into the corresponding cyclogalactin, an "inside-out" analog of cyclodextrin, by an intramolecular coupling. However, even though several promoters were tried and the

heptasaccharide was later prepared to reduce potential strain, the final coupling was never accomplished.[108] It is remarkable that the glycosylation yields are significantly improved compared to the two other strategies. This can either result from use of small electron-donating protecting groups at the 3- and 6-position or application of thioglycosides as donors. The strategy is, however, not without problems. Deprotection of the allyl ether groups turned out to be complicated and a five-step procedure was necessary to deprotect the linear hexasaccharide. This results in loss of almost 50% of the final product. Furthermore, the final product is the unnatural *p*-methoxyphenyl glycoside and a low yielding oxidation (70% for a trisaccharide) is necessary if the reducing sugar is needed.

4.2 Results & Discussion

The aim of the project was to synthesize a range of β-D-galactooligosaccharides and test these in binding assay with lectins (e.g. Gal-3) or various antibodies for epitope mapping.

The oligosaccharide should comprise at least four residues in order to exploit the entire CRD of Gal-3 and other carbohydrate binding proteins. Secondly, it should be an oligomer of D-Gal*p* and have a β-(1→4)-linked backbone with possibly (1→3) or (1→6)-branching to mimic the structure of the galactans present in pectin. Finally, the protecting group strategy should allow global deprotection to give the fully unprotected oligosaccharide. This would make it possible to conjugate the oligosaccharide to proteins and linkers via the reducing end and it would increase the similarity to natural polysaccharides.

The results and discussion section is divided into two parts. The first part describes the stereoselective synthesis of three branched tetragalactans with various α/β binding patterns. The synthesis is done by a stepwise approach, since only a few glycosylations are needed. The second part deals with the synthesis of the longer oligosaccharides. In order to prepare these a more advanced method was needed to limit the number of glycosylations. Different block strategies were investigated towards the synthesis of a disaccharide donor and ultimately linear and branched hepta- and octasaccharides.

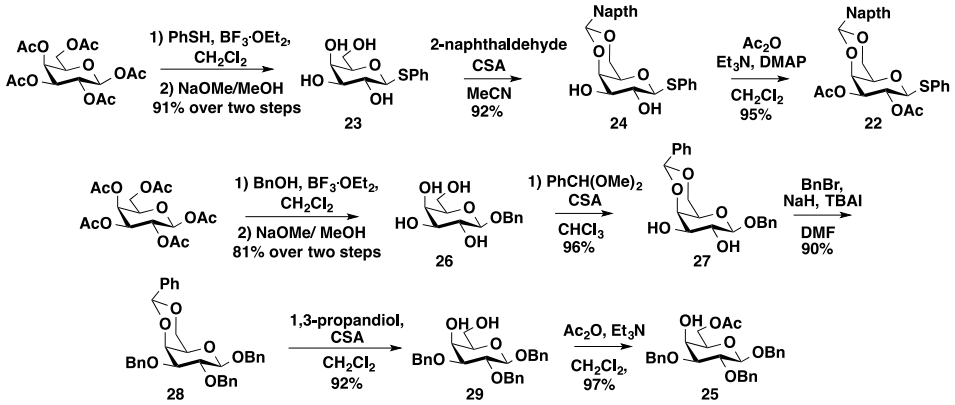
4.3 Synthesis of branched and linear tetrasaccharides

The first aim was to prepare branched- and linear tetrasaccharides with either natural β-linkages or unnatural α-linkages. These would be interesting for epitope mapping of antibodies and test of Gal-3 specificity. The synthesis was furthermore used to develop a robust protecting group strategy for introduction of branching on larger oligosaccharides.

In order to glycosylate the C4- and C6-*OH* in a sequential manner, it was necessary to find a protecting group strategy that allowed regioselective deprotection of first the 4-position and at a later point the 6-position. The benzylidene acetal is often used as a temporary protecting group for the 4- and/or 6-position, since it can be regioselectively opened under reductive conditions.[110–112] Its use is, however, limited by the fact that the resulting benzyl ether is a permanent protecting group in most strategies. Several other acetals have been developed that allow selective deprotection of the corresponding ether. The most common is the *p*-methoxybenzylidene acetal.[113–115] Regioselective cleavage of the

p-methoxybenzylidene acetal results in a *p*-methoxybenzyl (PMB) group, which can be cleaved using oxidative conditions without affecting benzyl- and acyl protecting groups. The standard oxidation agents are 2,3-dichloro-5,6-di-cyano-1,4-benzoquinone (DDQ)[116] or ceric ammonium nitrate (CAN)[117]. Unfortunately, the *p*-methoxybenzylidene acetal is much more acid labile than its unsubstituted counterpart. Especially the C6-*O*-PMB is prone to acidic cleavage and therefore could give rise to problems in glycosylation reactions.[118,119]

Instead it was decided to use the less common (2-naphthyl)methylene acetal as a double-acting temporary protecting group. This acetal and its corresponding ether are less sensitive to acid, but due to the electron-withdrawing second aromatic ring, they still have many of PMB's advantages.[114] Not only has it been shown that (2-naphthyl)methyl (NAP) ethers can be hydrogenolysed in the presence of benzyl ethers or esters, more interestingly, regioselective opening of the acetal with $NaCNBH_3$/HCl-OEt_2 results in the C6-*O*-NAP ether, which can be removed by oxidation with DDQ.[120,121] This ability would make it possible to selectively deprotect first the 4-position and later on selectively cleave the C4-*O*-NAP.

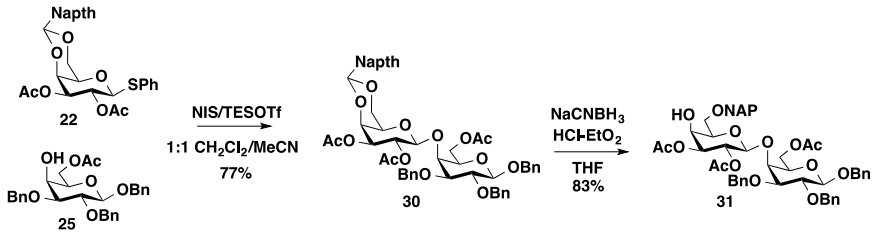


Scheme 4. Synthesis of monosaccharide building block 22 and 25.

The fully protected donor **22** was prepared from commercially available β-D-galactose pentaacetate in four steps. $BF_3{\cdot}OEt_2$-promoted glycosylation of thiophenol followed by deacetylation under Zemplén conditions afforded known thioglycoside **23**.[122] Treatment with 2-naphtaldehyde and camphor-10-sulfonic acid (CSA) gave the diol **24** which was converted to **22** by 4-dimethylaminopyridine (DMAP)-catalyzed acetylation (Scheme 4). The acceptor **25** was prepared from β-D-galactose pentaacetate in six steps by a literature procedure.[123] $BF_3{\cdot}OEt_2$-mediated glycosylation of benzyl alcohol and deacetylation under Zemplén conditions afforded tetraol **26**. Temporary protection of the 4- and 6-position was achieved by treatment with benzaldehyde dimethyl acetal and CSA to give diol **27**. This made it possible to protect the C2-*O* and C3-*O* with benzyl groups by alkylation with benzyl bromide and NaH to give fully protected galactoside **28**. The benzylidene acetal was hydrolyzed with 1,3-propandiol/CSA to afford **29** followed by regioselective acetylation of the C6-*OH* to give the acceptor **25** in 58% overall yield.

Condensation of donor **22** and acceptor **25** with *N*-iodosuccinimide (NIS) and triethylsilyl trifluoromethanesulfonate (TESOTf)[124] as promoter afforded β-glycoside **30** in 77% yield (Scheme 5). Use of acetonitrile (MeCN) as co-solvent resulted in shorter reaction time and higher yield. This effect

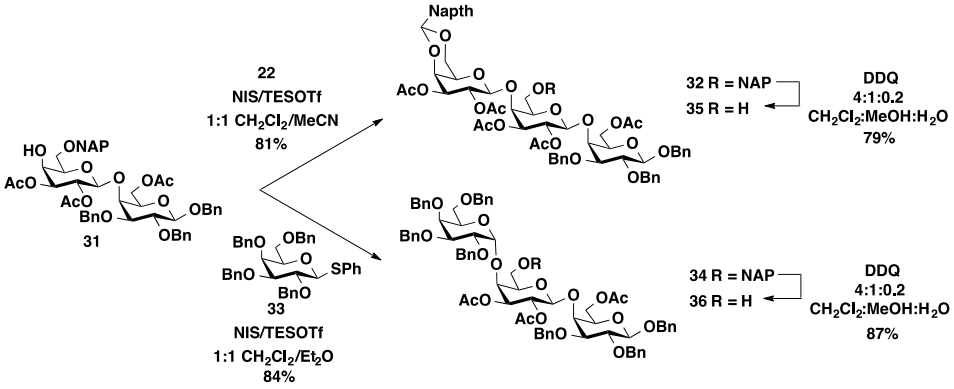
can either be explained by improved solubility of the promoter or by participation of the solvent also known as the *"nitrile effect"*.[125] Regioselective reductive opening of the naphthylidene acetal was achieved by treatment with $NaCNBH_3/HCl{\cdot}OEt_2$[126] to give the disaccharide acceptor **31** in 83% yield. The identity of the product was verified by heteronuclear multiple bond correlation spectroscopy (HMBC).



Scheme 5. Synthesis of disaccharide acceptor.

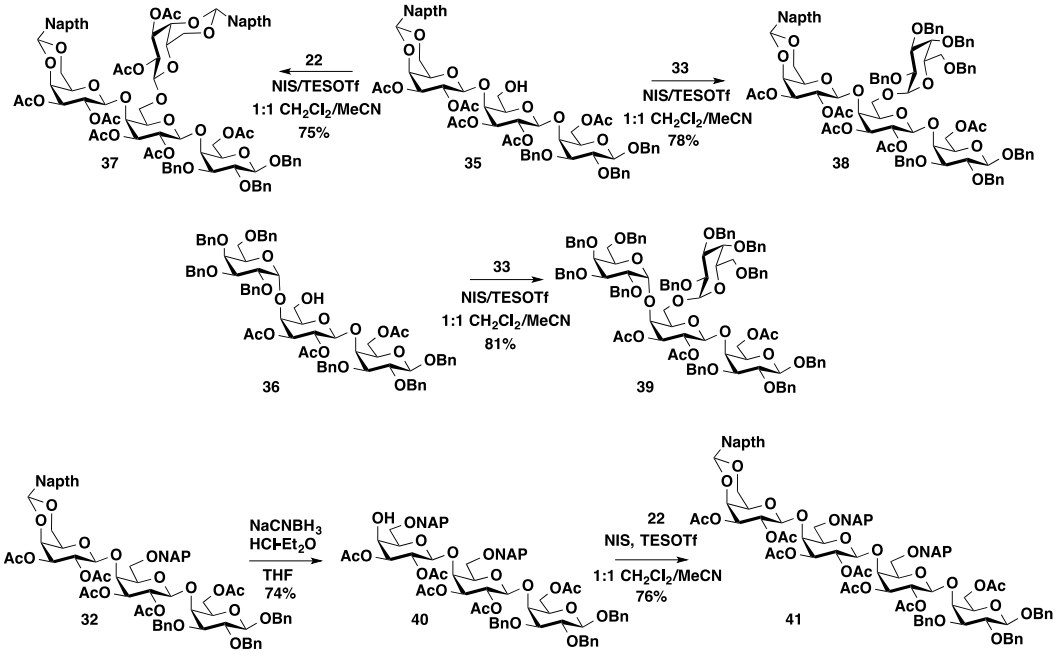
NIS/TESOTf-mediated coupling of donor **22** and acceptor **31** afforded the β-linked trisaccharide **32** in 81% yield (Scheme 6). Compound **31** was furthermore coupled to the perbenzylated thioglycoside donor **33**[127] to give the α,β-linked trisaccharide **34** in 84% yield. In this case, the use of a 1:1 CH_2Cl_2/Et_2O solvent mixture resulted in improved α-selectivity compared to pure CH_2Cl_2. This is most likely a result of the lower reactivity of the donor in CH_2Cl_2/Et_2O, which promotes formation of the thermodynamic product. Alternatively, the effect has been explained by formation of an equatorial diethyl-glycosyl-oxonium ion that blocks the β-face.[128]

The NAP group on both trisaccharides was selectively removed with DDQ to give β,β-linked acceptor **35** and α,β-linked acceptor **36**. The oxidation is generally done in wet CH_2Cl_2 (0.5-10% water).[129,130] However, it was observed that addition of 20% methanol was crucial in order to avoid concurrent deprotection of the benzyl groups. It is noteworthy, that the naphthylidene acetal is not hydrolyzed under these conditions.



Scheme 6. Synthesis of β,β- and α,β- linked trisaccharide acceptors 32 and 34.

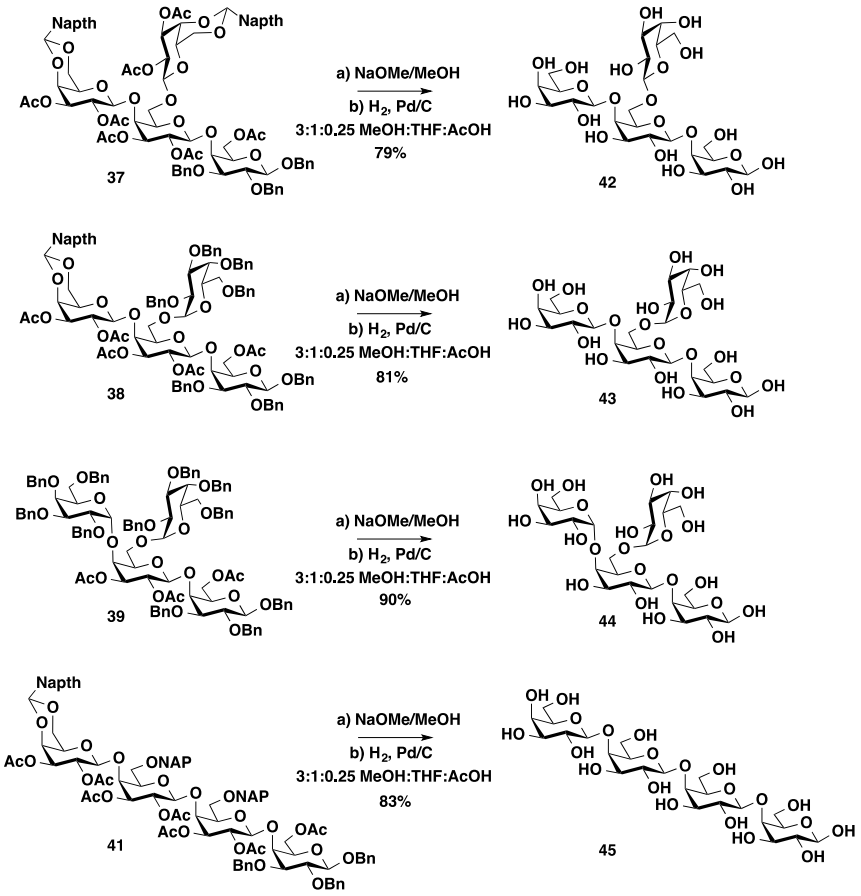
Coupling of the two trisaccharides to either donor **22** or donor **33** by NIS/TESOTf-mediated glycosylations, afforded the three tetrasaccharides **37**, **38** and **39** in acceptable yield (Scheme 7). Moreover, trisaccharide **32** was regioselectively deprotected followed by glycosylation with thioglycoside **22** to give the linear tetrasaccharide **41** in 56% yield over two steps.



Scheme 7. Synthesis of the four tetrasaccharides 37, 38, 39 and 41.

Transesterification with NaOMe/MeOH followed by hydrogenation over Pd/C provided the four unprotected tetrasaccharides **42**, **43**, **44** and **45** (Scheme 8). A high amount of palladium (20 mol%) and addition of acetic acid was necessary to obtain full conversion. This is in agreement with reports by Gaunt *et al.* who have shown that (2-naphthyl)methane formed during the reaction poisons the palladium catalyst.[120]

In summary, we have developed a simple, and efficient strategy for the synthesis of (1→6)-branched (1→4)-D-tetragalactosides, where the naphthylidene acetal acts as temporary protecting group for first the 4-position and later the 6-position. This strategy can potentially be expanded to larger branched oligosaccharides, preferably via block synthesis. The four galactosides were conjugated to bovine serum albumin (BSA) and printed on a microarray that made it possible to test binding to Gal-3 and various monoclonal antibodies (mAb). The conjugation and preliminary results are described in section 7.3.



Scheme 8. Global deprotection of four tetrasaccharides.

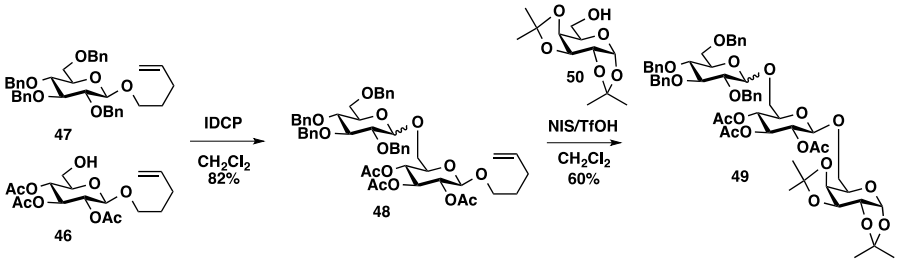
4.4 Synthesis of β-(1→4)-galactans by block-wise approach

Larger oligosaccharides were needed if the full binding site of Gal-3 and other carbohydrate binding proteins were to be studied. The tetrasaccharides discussed in section 4.3, were synthesized by a stepwise strategy. The synthesis only consists of 19 steps, of which most are high yielding and can be done on large scale. However, synthesis of longer oligosaccharides by this approach is untenable. The high number of steps will result in very low overall yields and a laborious synthesis. Instead, a block strategy should be used where di- or trisaccharide donors are coupled. This reduces the total number of steps and in particular the number of glycosylations that are usually the critical steps in oligosaccharide synthesis. This section describes the work leading up to development of a strategy for synthesis of β-(1→4)-linked galactans.

4.4.1 Armed-disarmed strategy

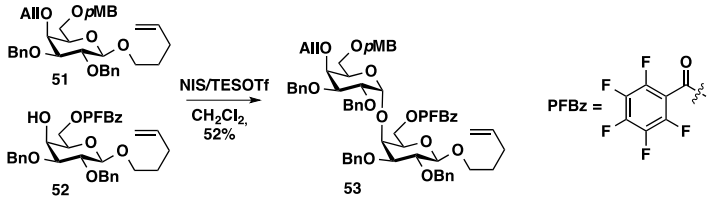
The first strategy was based on previous work done by Madsen and Clausen.[131] Their method relies on the armed-disarmed concept first described by Fraser-Reid.[132,133] As opposed to most other block strategies, this method does not rely on the use of orthogonal anomeric leaving groups. Instead, it is based on the observation that the substituents on the carbohydrate ring, mostly protecting groups, influence the reactivity in glycosylation reactions. Electron-withdrawing protecting groups, such as esters, deactivate (disarm) the glycosylating capability, because they decrease the nucleophilicity of the anomeric leaving

group and destabilize the carbocationic transition state. Electron donating substituents, such as ethers, activates (arm) the donor.[134] This makes it possible to couple an armed donor with a disarmed donor without activating the latter. Fraser-Reid and co-workers introduced the concept by showing that the acetylated "disarmed" *n*-pentenyl glycoside **46** could be selectively glycosylated with a perbenzylated "armed" *n*-pentenyl glycoside **47** using iodonium di-*sym*-collidine perchlorate (IDCP) as promoter (Scheme 9). The disaccharide **48** could afterwards be used as a donor to give the trisaccharide **49** after glycosylation with isopropylidene-protected acceptor **50**.[132] It was later discovered by van Boom and co-workers that IDCP could also selectively activate armed ethyl thiorhamnosides in presence of disarmed thioglycosides and soon after the armed-disarmed concept found application for other thioglycosides.[135]



Scheme 9. Example of an armed-disarmed glycosylation.[132]

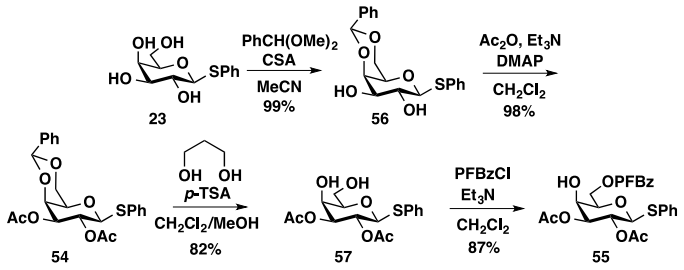
The first armed/disarmed strategies were usually between a perbenzylated- and a peracylated glycosides resulting in a limited scope of protecting groups. Madsen and Clausen showed that sufficient difference in reactivity could be obtained by a minimal difference in protecting group pattern between donor and acceptor. Based on screening of several acyl groups, it was found that the 2,3,4,5,6-pentafluorobenzoyl (PFBz) was sufficiently electron-withdrawing to allow armed/disarmed coupling of acceptor **51** and donor **52** to give the disaccharide **53** in 52% yield (Scheme 10).[132] The scope of the method was later expanded to also include thioglycosides.[136]



Scheme 10. Armed-disarmed strategy based on deactivation by 2,3,4,5,6-pentafluorobenzoyl.[124]

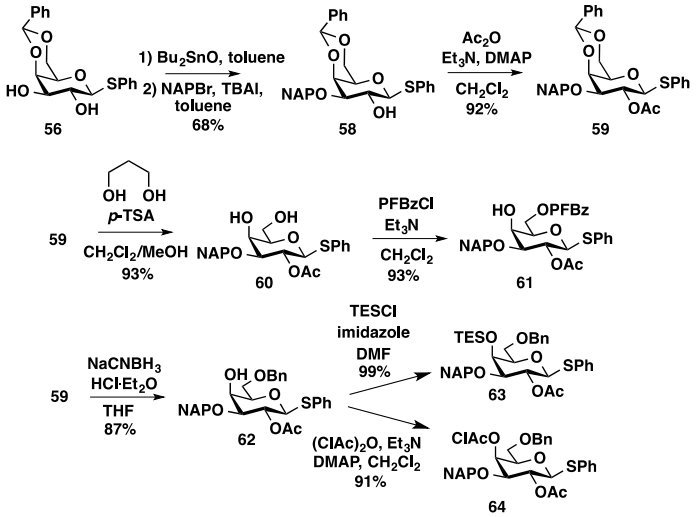
Our target structures only differ from Madsen and Clausen by the configuration of the anomeric center. For synthesis of β-(1→4)-linked galactans, the 2- and 3-position should also be permanently blocked, but as opposed to disaccharide **53,** it is necessary to have a 2-*O*-acyl group for anchimeric assistance during the glycosylation.

The donor **54** and acceptor **55** were both synthesized starting from thioglycoside **23** (Scheme 11). The 4- and 6-position were protected by a benzylidene acetal by treatment with $PhCH(OMe)_2$ and CSA to give diol **56**. This was converted to donor **54** by acetylation of the C2- and C3-*OH*.



Scheme 11. Synthesis of donor 54 and acceptor 55 for use in armed-disarmed coupling.

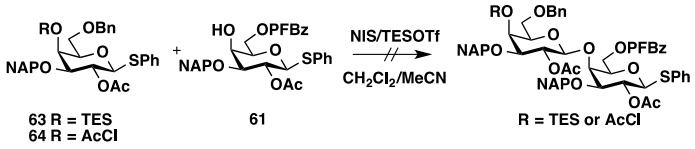
The acceptor was prepared from donor **54** in two additional steps. First, the benzylidene acetal was hydrolyzed. Standard conditions such aq. AcOH[137] and MeOH/*para*-toluenesulfonic acid (*p*-TSA)[138] resulted in moderate yields and long reaction time, but propane-1,3-diol and *p*-TSA[131] gave diol **57** in 82% yield after 12 h. It was observed that a longer reaction time (48 h) resulted in almost complete hydrolysis of the C3-*O*-acetyl group, but not the C2-*O*-acetyl. The 6-position was regioselectively protected by treatment of diol **57** with 2,3,4,5,6-pentafluorobenzoyl chloride and Et_3N to afford acceptor **55**. Coupling of donor **54** and acceptor **55** with NIS/TESOTf as promoter resulted in a complex mixture of products. The expected product could be isolated in less than 5% yield and only in an impure form. The reaction was repeated at various temperatures without significant change in outcome. Increased reactivity of the donor and acceptor could be achieved by exchanging one or more of the electron-withdrawing groups with ether functionalities. Hence, the C3-*O*-acetyl group was exchanged for a NAP ether in both acceptor and donor. Moreover, Jensen *et al.* has reported that the benzylidene acetal is disarming due to torsional strain.[139] It was therefore opened regioselectively and a triethylsilyl group was introduced as a temporary protecting group of the C4-*OH*. The synthesis of donor **63** and acceptor **61** is shown in Scheme 12.



Scheme 12. Synthesis of more reactive acceptor/donor pair 61 and 63 for armed/disarmed coupling.

The armed-disarmed glycosylation of **63** and **61** was carried out with the same conditions as the first coupling (Scheme 13). The reactivity seemed to be improved since full conversion of the donor was observed after less than one hour. However, the reaction resulted in several products. Separation and characterization of the most prominent products showed that a disaccharide donor was indeed formed in

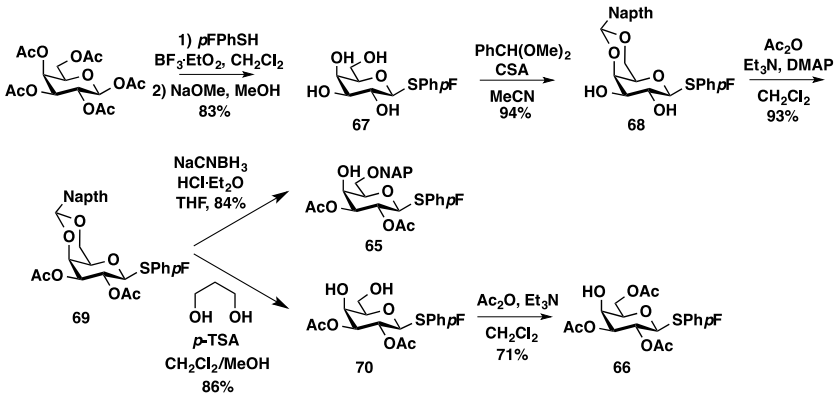
approx. 10% yield, but that the TES group had been cleaved during the glycosylation. The homologation product of **63** was also observed, which is consistent with the formation of a more reactive acceptor after the TES group is cleaved.



Scheme 13. Coupling of donor 63/64 and acceptor 61.

The C4-*OH* was instead protected with a chloroacetyl (ClAc) group. Coupling of **64** and **61** using the general coupling conditions again resulted in a complex mixture of products with the unchanged acceptor and hydrolyzed donor as the most prominent. The 4-position exerts the greatest influence on the reactivity in galactose[140] and since the chloroacetyl is very electron withdrawing, the overall reactivity of donor **64** is probably not much higher than for thioglycoside **61**. One of the major problems in the chemoselective synthesis seemed to be low reactivity of the disarmed acceptors. The very electron-withdrawing protecting group at the 6-position appears to make the C4-*OH* such a poor nucleophile that reaction is not possible.

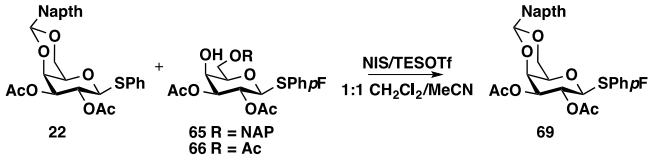
Another way to alter the reactivity of a donor/acceptor pair is by using different anomeric thiofunctions. For example electron-withdrawing substituents will lower the nucleophilicity of the sulfur. One of the advantages of this approach is that the disarming effect is manifested far from the nucleophilic *C4*-OH. Lahmann and Oscarson have prepared a range of oligosaccharides by chemoselective couplings between *p*-bromophenyl thioglycosides and phenyl thioglycosides with great success.[141] In order to obtain even greater difference in reactivity the more deactivated *p*-fluorophenyl (Ph*p*F) thioglycosides were used. This also has the advantage that the products have characteristic ^{19}F-NMR signals. Syntheses of C6-*O*-NAP acceptor **65** and C6-*O*-acetyl acceptor **66** are shown in Scheme 14.



Scheme 14. Synthesis of *p*-fluorophenyl thioglycosides 65 and 66.

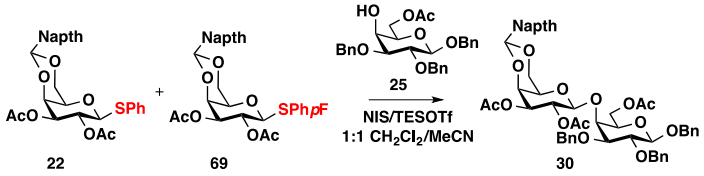
The two acceptors **65** and **66** were glycosylated with donor **22** with NIS/TESOTF as promoter (Scheme 15). Both reactions resulted in similar outcome, but the glycosylation of acceptor **65** was four times faster. The acceptor was fully consumed and the major product co-eluted with the donor. To our surprise, it was neither disaccharide nor excess donor, but instead thioglycoside **69**. This could either have been formed

by activation of the acceptor followed by glycosylation of **22** with the liberated *p*-fluorothiophenol or via direct attack by from the *p*-fluorothiophenol on the activated thioglycoside **22** resulting in aglycon transfer.



Scheme 15. Formation of aglycon-transfer product in armed-disarmed glycosylation.

This result made us question whether the reactivity of the acceptor was sufficiently decreased by the *p*-fluorophenyl. In order to test this, a competition experiment was conducted, where a 1:1 mixture of **22** and **69** was used to glycosylate acceptor **25** (Scheme 16). It was not possible to separate the mixture of donors due to structural similarity, but based on NMR it consisted of approx. 5:1 mixture of **69**/**22**. This confirms, that **69** is indeed deactivated by the electron withdrawing fluorine.



Scheme 16. Competition experiment between donor 69 and 22.

In both chemoselective strategies, the low reactivity of the electron-poor C4-*OH* and/or insufficient reactivity difference seems to be the problem. One way to improve the glycosylation outcome would be to use a more reactive donor. Thus, a stable, orthogonal arming protecting group should be found for the 4-position. Alternatively, another thiofunction could be used to lower the reactivity of the acceptor even further. For example, 2,4- or 3,4-difluorothiophenol are more electron withdrawing and are not much more expensive than 4-fluorothiophenol.

4.4.2 Orthogonal strategy

It had not been possible to find protecting group pattern that gave a sufficient difference in reactivity of the donor/acceptor pair, while retaining the nucleophilicity of the acceptor. Another approach was therefore undertaken. The orthogonal strategy is based on the use of two different anomeric functionalities that can be activated by orthogonal promoter systems. This has the advantage that the anomeric center of the acceptor is unreactive under the glycosylation conditions and it is therefore possible to couple a electron-poor donor with an electro-rich acceptor.[142]

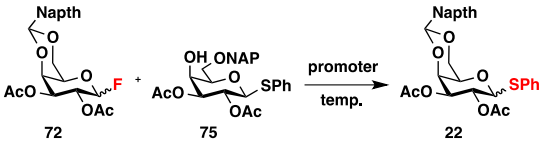
Thioglycosides can be converted into almost all other donors directly or by a two-step procedure. The new donor can then be coupled to the thioglycoside under orthogonal conditions. This feature makes thioglycosides ideal for orthogonal couplings since it is possible to start from a single building block.[142]

Five different donors were synthesized from thioglycoside **22** or **54**: A glycosyl sulfoxide **71**, glycosyl fluoride **72**, glycosyl bromide **73**, glycosyl trichloroacetimidate (TCA) **74** and glycosyl *N*-phenyl trifluoroacetimidate (PTFAI) **75**. The synthesis and outcome of glycosylation of acceptor **76** are compiled

in Table 2. The first orthogonal donor to be examined was a glycosyl sulfoxide which had been used by Lichtentaler *et al.* to synthesize a β-D-(1→4)-disaccharide thioglycosides (section 4.1).[106] Donor **71** was prepared in one step by titration with *m*-CPBA (*meta*-chloroperbenzoic acid).[143] The reaction had to be carefully monitored in order to avoid over-oxidation to the sulfone. The couplings were carried out by the Kahne procedure using triflic anhydride as promoter and a hindered base to keep the reaction from becoming too acidic. Both 2,6-lutidine and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) were tested as bases.[144,145] Lutidine is much cheaper than DTBMP, but is less sterically hindered. This seems to be critical, since the outcome of the reaction was degradation of the donor, whereas most of the acceptor could be recovered. In the next experiment, DTBMP was used as base. In this case full conversion of the acceptor was achieved but the expected product was not observed.

Glycosyl fluoride **72** was prepared in one step from the corresponding thioglycoside by treatment with diethylaminosulfur trifluoride (DAST) and *N*-bromosuccinimide (NBS).[146] Against expectations **72** was obtained as a 2:3 α/β mixture (**72a** = α-fluoride and **72b** = β-fluoride) even though the α-glycosyl fluoride is favored as a result of stabilization by the anomeric effect. The stereochemical outcome is probably a result of neighboring-group participation of the acetyl group. It was possible to increase the selectivity (95:5 β/α) by changing the solvent to acetonitrile but this also resulted in lowered yield (60%).

The first choice of promoter, $BF_3{\cdot}OEt_2$[147] afforded disaccharide **77** in 28% yield. It was observed that the β-glycosyl fluoride **72b** was fully consumed within one hour, whereas the α-glycosyl fluoride **72a** remained unchanged. Increasing the temperature or amount of promoter only increased the yield to 32%. Even though the turnover of **72a** was improved, the harsher conditions gave rise to formation of the thioglycoside **22** as the major product (Scheme 17). This result is very similar to the observations for the *p*-fluorothiophenol aglycon and strongly suggests that aglycon transfer causes the problem.



Scheme 17. Aglycon transfer in glycosylation with glycosyl fluorides.

A reaction was performed with only the β-glycosyl fluoride **72b**. This resulted in higher yield (42%) but the effect was not as pronounced as expected due to concurrent conversion of **72b** into the unreactive α-fluoride **72a**. BF_4^- probably acts as fluoride source and converts the activated species into the thermodynamically favored **72a**.

Three other promoter systems were investigated. Both $SnCl_2$-AgOTf[148] and Cp_2ZrCl_2-$AgClO_4$[149] resulted in degradation of the acceptor leading to a complex product mixture. Cp_2ZrCl_2-$AgClO_4$ is the most reactive group IV_B metallocenes and the reaction with both acceptor and donor was almost instantaneous. Unfortunately, the milder promoters Cp_2HfCl_2[150] and Cp_2TiCl_2[150] were not available. Activation with $SnCl_2$-$AgClO_4$ gave results similar to $BF_3{\cdot}OEt_2$ with regard to difference in reactivity of the α- and β-glycosyl fluoride, but the yields were generally lower.[151]

The major problem with the glycosyl fluorides was their low reactivity. An obvious alternative was to use the more reactive glycosyl bromides. Glycosyl bromide **73** was prepared *in situ* by titration with bromine. The glycosylation was carried out at -50 °C with AgOTf as promoter. 4Å molecular sieves (MS) were added to reduce the acidity and thereby avoid decomposition of the acceptor. Even though these are rather mild conditions, the acceptor was degraded and formation of thioglycoside **22** was again observed among many other by-products.

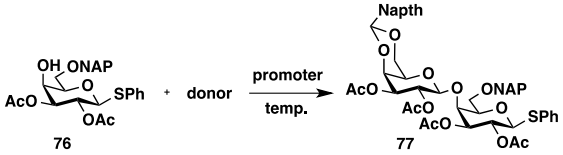
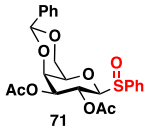
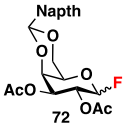
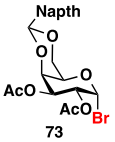
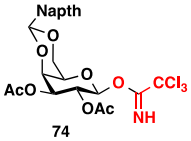
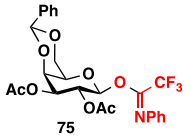


Table 2. Synthesis and glycosylation with orthogonal donors.

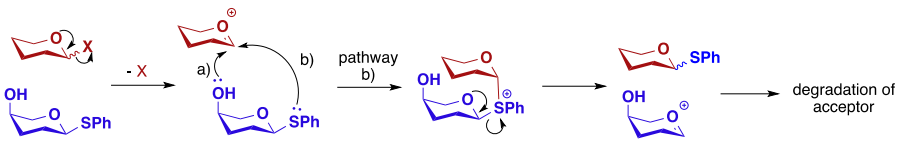
	Donor synthesis	Glycosylation cond.	Temp.	Yield
	*m*-CPBA, CH_2Cl_2, -78 °C	Tf_2O, 2,6-lutidine CH_2Cl_2	-78 °C	Donor degraded, no product
		Tf_2O, DTBMP CH_2Cl_2	-78 °C	Acceptor degraded, no product
	NBS, DAST, CH_2Cl_2, 2:3 α/β-mix	$BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2	-15→0 °C	22-28 %
		$BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2	5 °C	32%
		$SnCl_4$, $AgClO_4$, 4Å MS, CH_2Cl_2	-15 °C	19-24%
		Cp_2ZrCl_2-$AgClO_4$, 4Å MS, CH_2Cl_2	-20 °C	0%
	NBS, DAST, MeCN	$BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2	-15→0 °C	42%
		$SnCl_2$-$AgClO_4$, 4Å MS, CH_2Cl_2	-15 °C	31-34%
	Br_2, CH_2Cl_2, 0 °C, quant.	AgOTf, 4Å MS, CH_2Cl_2	-50 °C	Acceptor degraded
	1) NBS, H_2O, CH_2Cl_2 2) Cl_3CCN, DBU, CH_2Cl_2	TESOTf, CH_2Cl_2	-20 °C	Only formation of the corresponding trichloro-acetamide
	1) NBS, H_2O, CH_2Cl_2 2) $CF_3CClNPh$, Cs_2CO_3, CH_2Cl_2	TESOTf, CH_2Cl_2	-40 °C	12%

The final donor-types investigated were glycosyl imidates. The general significance of *O*-glycosyl trichloroacetimidates lies in their ability to act as strong glycosyl donors in presence of only catalytic amounts of Brønsted or Lewis acids. The mild conditions were anticipated to limit the risk of acceptor activation and the high reactivity of the donor should make both the α- and β-glycoside reactive. Compared to glycosyl bromides, glycosyl imidates have the advantage that they are more compatible with chromatographic purification.[152]

Thioglycoside **22** was converted to the corresponding trichloroacetimidate (TCA) **73** by hydrolysis with NBS and H_2O followed by treatment with trichloroacetonitrile and a base. In this case, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used since it favors formation of the more stable α-glycosyl trichloroacetimidate.[153] Instead of the frequently used TMSOTf, the more easily handled TESOTf was employed for the coupling. Full conversion of the donor was observed after only 20 min, while the acceptor remained unchanged. The trichloroacetimidate had instead rearranged into the unreactive glycosyl trichloroacetamide due to the low reactivity of the acceptor.[154]

In an effort to solve this problem the corresponding glycosyl *N*-phenyl trifluoroacetimidate was prepared. This rather new donor has the advantage that the leaving group is not nucleophilic and the rearrangement product is therefore not observed.[155] Nonetheless, it still has reactivity similar to TCAs and can be activated under mild condition (e.g. TMSOTf or $BF_3{\cdot}OEt_2$[156,157], TBSOTf[158], $Bi(OTf)_3$[159], $Yb(OTf)_3$[160]).

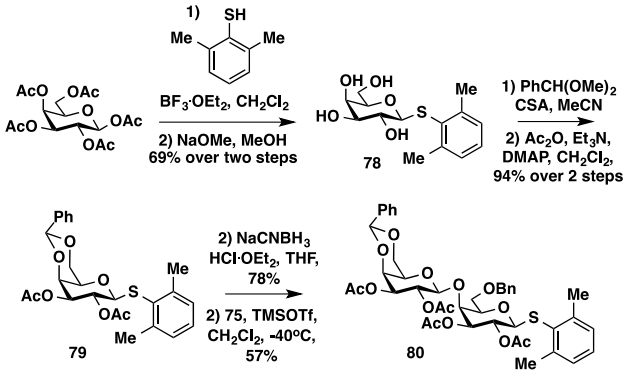
Donor **75** was prepared by treating the lactol with *N*-phenyl trifluoroacetimidoyl chloride and Cs_2CO_3.[161] The imidoyl chloride can be prepared by refluxing aniline with trifluoroacetic acid (TFA) in CCl_4 in the presence of Ph_3P and Et_3N followed by distillation.[162] However, PTFAICl was purchased from commercial suppliers for the remainder of the reported reactions due to the toxicity of the reagents. TMSOTf-catalyzed glycosylation at -40 °C resulted in full conversion of donor and acceptor. The expected product **70** was formed, but only in 12% yield. Instead, **54** was isolated as the major product, just as it was the case for glycosyl fluorides and *p*-fluorophenyl thioglycosides. As opposed to the previous examples, 0.1 equiv. TESOTf was unlikely to activate the acceptor. Instead it was hypothesized that degradation of the acceptor was effected by attack of the acceptors' sulfur atom onto the activated glycosyl donor (Scheme 18). Pathway b is only favored because of the very low reactivity of the axial C4-*OH*.



Scheme 18. Proposed mechanism for aglycon transfer.[163]

A similar mechanism has previously been described by Li *et al.*, who named the phenomenon "aglycon transfer".[163] They described that aglycon transfer could be prevented by decreasing the nucleophilicity of the acceptor aglycon by steric hindrance or with electron withdrawing substituents. Screening of a wide range of donors showed that electron withdrawing substituents only had a minor effect whereas better results were obtained when 2,6-dimethylthiophenol.[163] Based on these results, 2,6-dimethylthiophenyl

acceptor was prepared in five steps from β-D-galactose pentaacetate to test if this would prevent aglycon transfer (Scheme 19).



Scheme 19. Synthesis and 2,5-dimethylthiophenyl disaccharide 80.

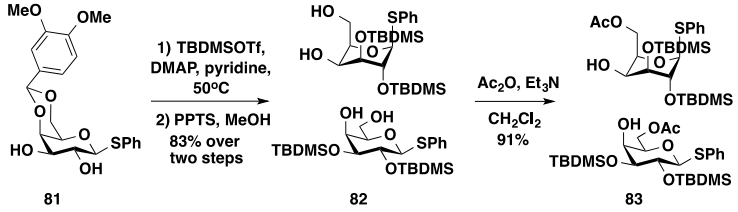
Coupling of PTFAI donor **75** and acceptor **79** in a TMSOTf-catalyzed glycosylation still resulted in formation of several products, but the disaccharide **80** could be isolated in 57% yield. This result strongly suggests that aglycon transfer is the reason for the poor yield in both the chemoselective- and orthogonal glycosylations. Even though the yield was remarkably improved, it was still evident that the choice of thiofunctionalities as aglycons for unreactive acceptors is unfavorable. Furthermore, the 2,5-dimethylthioglycosides has been shown to be poor donors, which could be problematic in couplings to the unreactive C4-*OH*.

4.5 Study of 1,6-anhydro sugars as precursors for thioglycosides

One of the major issue in the synthesis of a β-(1→4)-digalactoside is the low reactivity of the axial C4-*OH*. This gives rise to degradation and aglycon transfer of the more reactive anomeric functionalities. One way to increase the reactivity would be to use less bulky and/or less electron withdrawing protecting groups. Alternatively, a drastic change was expected if the ring was flipped from a $^4C_1$- towards a $^1C_4$- conformation. In this way the C4-*OH* would be the only equatorial hydroxyl group, thus, a much better nucleophile. Unfortunately, the $^1C_4$- conformation is strongly disfavored due to 1,3-diaxial interactions between the -CH_2OR and two -OR groups and therefore has to be forced to change conformation.

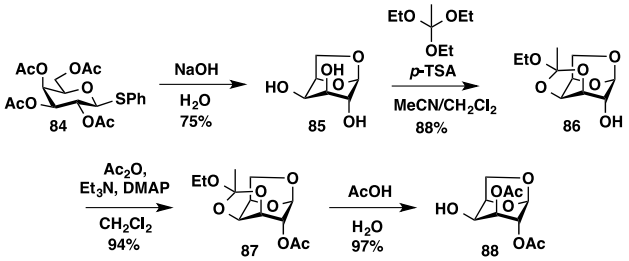
The preliminary studies were based on work by Pedersen *et al.*[164] They had shown that a ring flip could be achieved by introduction of two or more bulky silyl groups (*tert*-butyldimethylsilyl (TBDMS) or triisoproylsilyl (TIPS)). These cannot be accommodated in a $^4C_1$ conformation, thus, force the pyranose ring into an axial-rich conformation. Instead of the expected $^1C_4$ conformation they obtained a twisted boat conformation but this would still be a remarkable improvement.[164] It was decided to introduce TBDMS groups at the 2- and 3-position followed by selective protection of the 6-position. Hydrolysis of a benzylidene acetal resulted in concurrent deprotection of the silyl ethers. Instead, the more acid labile 3,4-dimethoxybenzylidene acetal was introduced followed by protection of the diol with TBDMSOTf and DMAP in pyridine (Scheme 20).[165], [164] The more common reagent combination, TBDMSCl and

imidazole in *N*,*N*-dimethylformamide (DMF), only resulted in monosilylation.[166] Next the 2,4-methoxy-benzylidene was hydrolyzed under almost neutral conditions with pyridinium *p*-toluenesulfonate (PPTS) in methanol to give diol **82**. At this point, the $^1C_4$ should be favored over the $^4C_1$, but judging from the coupling constants in ^{1}H-NMR, the ring was still in the $^4C_1$ conformation. Regioselective acetylation afforded **83** but did not change the conformation. The approach was therefore abandoned.



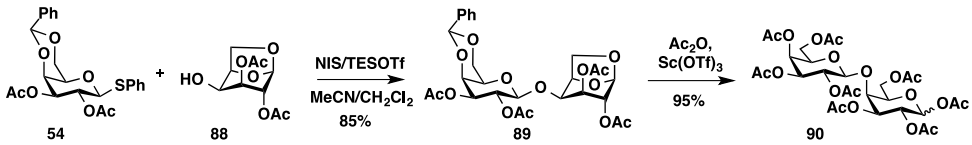
Scheme 20. Preliminary attempts to force D-galactose into a $^1C_4$-like conformation.

Another way to force D-galactose into a $^1C_4$ conformation is by converting it into the 1,6-anhydro derivative. 1,6-anhydrides can either be formed by selective tosylation followed by intramolecular attack by the anomeric hydroxyl or via displacement of an anomeric leaving group by the C6-*OH* under basic conditions.[167,168] In this case the peracetylated thioglycoside **84** was treated with aq. NaOH resulting in both deacetylation and formation of the 1,6-anhydride **85** (Scheme 21). Ring flip to the $^1C_4$-conformation was evident from the changes in coupling constants (J) in ^{1}H-NMR. For example, the $J_{2,3}$ changes from 10.5 to 1.4 Hz whereas the $J_{3,4}$ goes from 3.4 to 5.5 Hz. Regioselective protection of the 3- and 4-position with triethylorthoacetate and *p*-TSA afforded the ethyl orthoester **86**. The free C2-*OH* was acetylated and finally the orthoester was hydrolyzed with aq. acetic acid to give the 2,3-diacetylanhydro sugar **88** in four steps (Scheme 21).



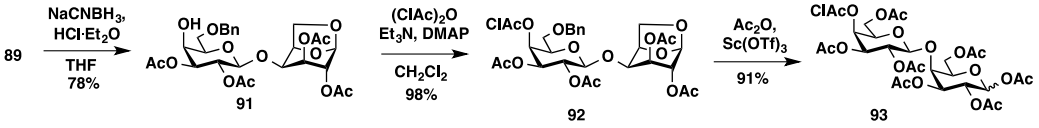
Scheme 21. Synthesis of 1,6-anhydro building block 88.

This is an improvement to previously published procedures with regard to both overall yield and length of synthesis.[169] The 1,6-anhydride **88** was glycosylated with thioglycoside **54** to give the disaccharide **89** (Scheme 22). As expected the reaction was fast and gave a high yield even though both acceptor and donor were electron-deficient.



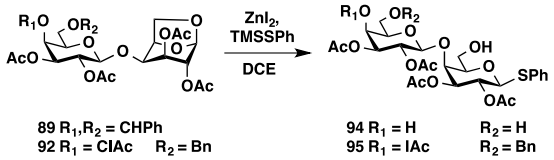
Scheme 22. Glycosylation of 1,6-anhydride 88 followed by acetolysis.

The 1,6-anhydro acetal had to be opened and converted to a donor. One of the classical ways to cleave the acetal is by acetolysis. In this reaction the anhydro sugar is treated with acetic anhydride and a Lewis- or Brønsted acid, which breaks the 1,6-anhydro ring and acetylates the 1- and 6-position.[170–172] A catalytic amount of scandium(III) triflate was chosen as Lewis acid, since it had previously been used to open anhydro sugars on complex oligosaccharides.[173] Acetolysis of **89** did not give rise to the desired product. Instead, peracetylated galactobiose **90** was formed as a result of concurrent acetolysis of the benzylidene acetal. This result is apprehensible, since the 1,6-anhydro acetal is generally more stable towards hydrolysis than the benzylidene acetal. To solve the issue, the benzylidene acetal was regioselectively opened with $NaCNBH_3/HCl{\cdot}OEt_2$ to give **91** followed by protection of the C4-*OH* with a chloroacetyl group to afford disaccharide **92** in 76% yield over two steps (Scheme 23). Acetolysis of **92** with Ac_2O and $Sc(OTf)_3$ again resulted in formation of a single product, but also in this case not the expected. The harsh conditions give rise to concurrent acetolysis of the primary benzyl ether resulting in formation of disaccharide **93**. Several attempts to avoid cleavage of the benzyl ether were made. TFA, TMSOTf, and AcOH were used as acid catalysts without any significant difference. The best result was obtained when the reaction was performed with only 1% $Sc(OTf)_3$ at -30 °C. In this case, an approx. 1:1 mixture of the desired product and the C6'-*OAc* was observed by NMR (the two compound were not separable by flash chromatography). This is still far from acceptable and the approach was abandoned.



Scheme 23. Introduction of chloroacetyl and acetolysis of 1,6-anhydride 92.

Disaccharide **93** could be converted to a thioglycoside or glycosyl imidate, but the many acetyl groups would make it a poor donor and acceptor. Wang *et al.* have reported that 1,6-anhydro sugars can be turned directly into the corresponding thioglycoside with zinc(II) iodide and trimethyl(phenylthio)silane, also known as Hanessian conditions.[174,175] Treatment of the disaccharide **89** with $TMSSPh/ZnI_2$ resulted in concurrent hydrolysis of the benzylidene acetal to give triol **94** (Scheme 24). Opening of the chloroacetyl-protected disaccharide **92** resulted in a complex mixture of products with compound **95** as the major product. The iodoacetyl must arise from substitution of the primary chloride. Moreover, it was found that one of the other by-products was the triol, which derives from cleavage of the benzyl group.



Scheme 24. Opening of 1,6-anhydride under Hanessian conditions.

In the final experiment, the C4'-*OTBDMS* analogue **96** was applied. The silyl ether was stable under the reaction conditions, but significant deprotection of the benzyl was still observed. A range of conditions was screened in order to optimize the reaction. Some of the results are shown in Table 3.

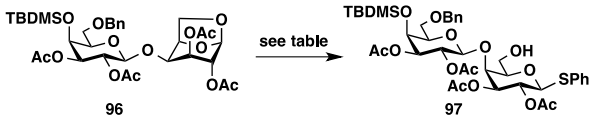
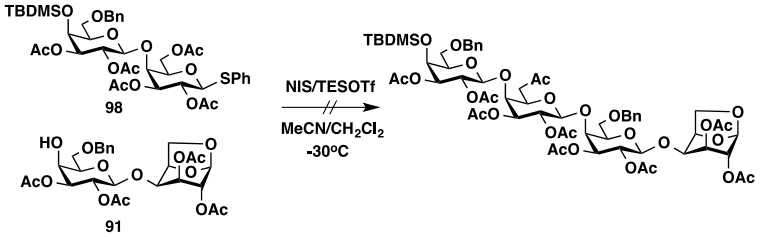


Table 3. Optimization of 1,6-anhydride opening under Hanessian conditions.

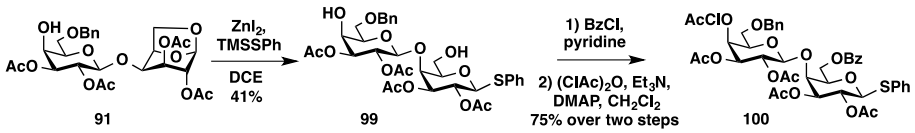
Entry	ZnI_2 (equiv.)	TMSSPh (equiv.)	Solvent	Time (h)	Recovered st. mat	Yield (%)
1	3	3	DCE	48	0	0
2	3	3	DCE	8	4	50
3	1.1	3	DCE	48	61	28
4	3	1.1	DCE	48	95	0
5	**1.75**	**3**	**DCE**	**14**	**16**	**58**
6	1.75	3	1,4-dioxane	8	20	40

In the first entry, the original conditions published by Hanessian and Guindon were used.[175] This resulted in complete deprotection of the benzyl ether. If the reaction was stopped after 8h the product could be isolated in 50% yield (entry 2). Next, the reagent loading was changed (entry 3-5). The results indicate that 3 equiv. of TMSSPh is necessary, but that it is possible to lower the amount of ZnI_2. The best result was obtained with 1.75 equiv., where **97** was isolated in 58% yield together with 16% of the starting material. It was tested whether the thioglycoside could be used as a donor. The C6-*OH* was acetylated to give the fully protected disaccharide **98**, which was used as donor in a NIS/TESOTf-promoted glycosylation reaction with disaccharide acceptor **91** (Scheme 25). No coupling product was observed and the acceptor could be fully recovered. This can be explained by the observation that the TBDMS group was too acid labile to be used under these glycosylation conditions.



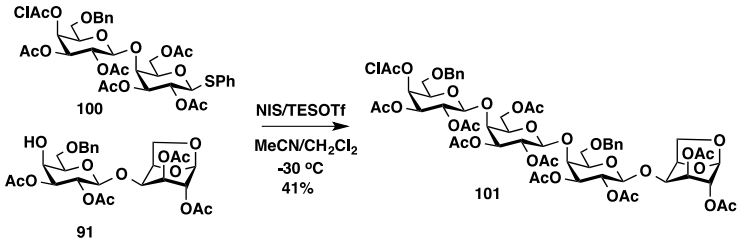
Scheme 25. Attempts to glycosylate with donor 98.

None of the applied protecting groups had been stable to both 1,6-anhydride opening and the subsequent glycosylation. Instead, it was decided not to protect the 4-position until after the acetal opening. Using the optimized conditions, the disaccharide **91** could be converted to the corresponding thioglycoside **99** in 41% yield (Scheme 26). This is unacceptable for large-scale synthesis, but sufficient to study the subsequent coupling. The C6-*OH* was selectively protected with a benzoyl group followed by protection of the C4'-*OH* by a chloroacetyl to give the fully protected thioglycoside **100** in 75% yield over two steps.



Scheme 26. Synthesis of fully protected thioglycoside 100.

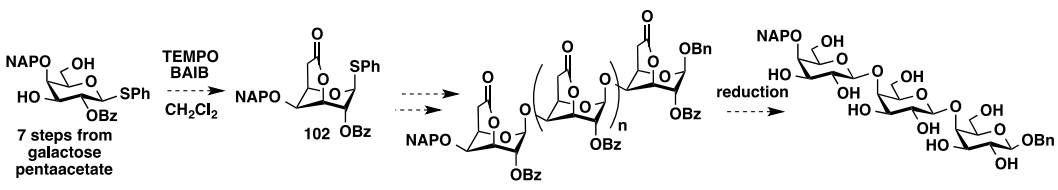
NIS/TESOTf-catalyzed condensation of **100** and **91** afforded the tetrasaccharide **101** in 41% yield (Scheme 27). The poor yield may be caused by the low reactivity of donor and acceptor. This shows that even though the strategy solves the first coupling, the subsequent glycosylations remain challenging.



Scheme 27. Synthesis of fully protected tetrasaccharide 101.

In conclusion, it was shown, that 1,6-anhydro acceptor **88** is indeed more reactive than the other acceptors studied so far. It was, however, not possible to convert the 1,6-anhydro disaccharide into a donor in acceptable yield. Both acetolysis and Hanessian conditions resulted in deprotection of one or more protecting groups. The major challenge is that the opening conditions are not compatible with primary benzyl ethers. Another issue in this strategy is that the use of 1,6-anhydrosugars only solves the problem in the first coupling. Subsequent glycosylations will still be to an axial hydroxyl group and will be further complicated by the steric hindrance manifested by the second ring in the disaccharide. An alternative would be to synthesize the oligosaccharide from the reducing end by sequential couplings to 1,6-anhydro monosaccharides. This would, however, result in a large number of glycosylations and 1,6-anhydro acetal openings.

A recent report by Van der Marel and co-workers described the chemo- and regioselective 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)/[bis(acetoxy)iodo]benzene (BAIB)-mediated oxidation of 3,6-dihydroxy 1-thio glycopyranosides to the corresponding 1-thio uronic acid lactones.[176] Based on these results, it may be possible to prepare donor **102** and use it for the consecutive coupling (Scheme 28). In that case, all of the glycosylation would be to an equatorial hydroxyl group and the conformation would favor formation of the β-product due to neighboring group participation. In the final step, reduction, hydrolysis or transesterification would either give the C6-hydroxyl, C6-acid or C6-ester.



Scheme 28. Alternative strategy based on 1-thio uronic acid lactones.

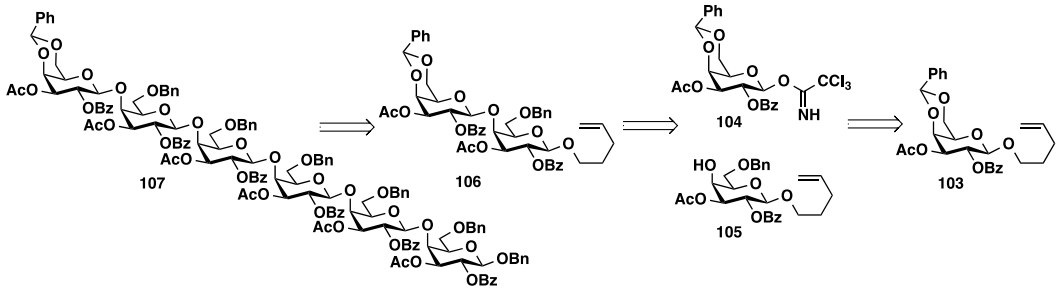
Interestingly, the original paper by Van der Marel shows that excellent 1,2-cis glycosylation are obtained when the 2-position is protected with a benzyl group and the donor is pre-activated with Ph_2SO and Tf_2O. The α-selectivity can be explained by formation of the axial triflate followed by a "S_N2"-like attack similar Crich's β-mannosylation approach.[176,177]

4.6 Synthesis of β-(1→4)-linked pentenyl disaccharide and its use in oligosaccharide synthesis.

As described in section 4.4.2, aglycon transfer was the major problem in glycosylation of unreactive thioglycoside acceptors. The simplest way to eliminate this side-reaction would be to use an acceptor without a nucleophilic aglycon. One way to accomplish this is by using an aglycon with a very electron withdrawing functionality that makes the sulfur less nucleophilic. This approach was applied in the active/latent strategy described by Roy and co-workers.[178] They used *p*-nitrothiophenol as aglycon, which makes the thiofunctionality virtually unreactive. After the glycosylation, the aglycon can be turned into a better leaving group by reduction and acetylation and used in the following coupling. However, the two steps after every glycosylation make the strategy less favorable.

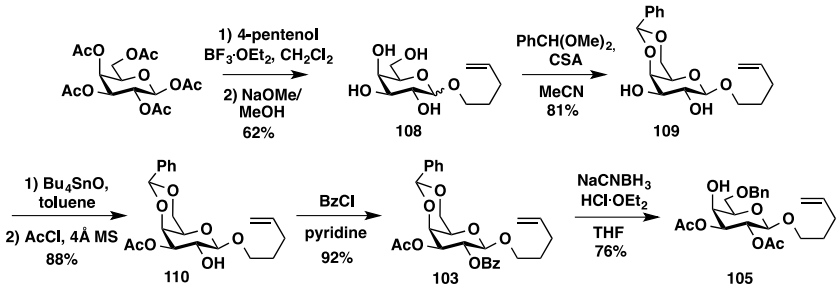
Alternatively, the thioglycoside could be exchanged for an *O*-glycoside, either in the form of a potential donor or a protecting group. The oxygen is significantly less nucleophilic than sulfur and the *O*-glycosides are therefore not expected to undergo aglycon transfer. Typical examples of anomeric protecting groups are allyl ether[179], silyl ethers[180] and *p*-methoxyphenyl ethers[181]. These all serve as temporary protecting group and can be turned into a donor in one or two steps in the presence of most common protecting groups. A more elegant strategy would be to use an orthogonal *O*-glycoside donor. This makes it possible to use the product directly in the following glycosylation and thereby avoid low-yielding protecting group manipulations. Glycosyl imidates[182] and glycosyl phosphates[183] are too reactive to act as acceptors, but *n*-pentenyl glycosides[132] and *ortho*-alkenyl benzoates[184] have been applied with great success.

It was decided to use pentenyl glycosides, since they allow many of the same manipulations as thioglycosides. The strategy was to make a single building block **103** that could be converted to an orthogonal donor **104** and an acceptor **105** (Scheme 29**)**. These could be coupled to give a disaccharide donor **106**, which could be used in the following glycosylations in the synthesis of hexasaccharide **107**. Glycosyl imidates were chosen as orthogonal donors because of their high reactivity and ease of synthesis. In some of the preliminary experiments, extensive migration during hydrolysis formation was observed with an acetyl in the 2-position. Instead, it was decided to protect the C2-*OH* with a benzoyl. The 3-position, on the other hand, was protected with an acetyl to avoid steric hindrance of the 4-position from the larger benzoyl ester.



Scheme 29. Retrosynthetic analysis of *n*-pentenyl glycoside-based strategy.

The fully protected pentenyl glycoside **103** was prepared in five steps from D-galactose pentaacetate (Scheme 30). $BF_3{\cdot}OEt_2$-mediated glycosylation of 4-penten-1-ol with β-D-galactose pentaacetate followed by Zemplén deacetylation afforded the unprotected pentenyl glycoside **108** as a 6:1 β/α-mixture. Treatment of **108** with benzaldehyde dimethylacetal and CSA gave the diol **109**. Activation of diol **109** with dibutyltinoxide followed by treatment with acetyl chloride in presence of 4Å MS gave the partially protected glycoside **110** in excellent yield. The molecular sieves both removed residual water but also acted as acid-scavenger. Finally, benzoylation of the 2-position with BzCl in pyridine afforded building block **103**. The acceptor **105** was prepared by regioselective ring opening of the benzylidene acetal with $NaCNBH_3$/ $HCl{\cdot}OEt_2$.[126]



Scheme 30. Synthesis of building block 103 and 105.

Next, the pentenyl glycoside **103** had to be hydrolyzed in order to prepare the glycosyl imidate. This turned out to be challenging due to the low reactivity of the donor and instability of the benzylidene acetal. The optimization results are shown in Table 4. Activation with NIS/TESOTf and NBS/TESOTf in presence of water resulted in concomitant hydrolysis of the benzylidene acetal (entry 1-2). The higher yield observed for NBS can be explained by a shorter reaction time. Hydrolysis with NBS/H_2O[132] (entry 3) also resulted in low yield, due to hydrolysis of the benzylidene acetal and formation of the halohydrin. The electron-poor ring makes the intramolecular attack on the bromonium ion slow and competing intermolecular attack by water therefore takes place.

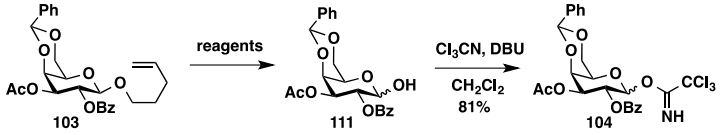


Table 4. Hydrolysis of disarmed pentenyl glycoside 103.

Entry	Reagents	Yield
1	NIS, TESOTf, H_2O	0%
2	NBS, TESOTf, H_2O	21%
3	NBS, H_2O	35%
4	Br_2, TBAB, H_2O	29%
5	Br_2, TBAB, Et_3N, H_2O	82%

Instead we developed a method based on Lemieux conditions (entry 5). Lemieux and coworkers observed that glycosyl bromides could anomerize in presence of a bromide source (e.g. tetrabutylammonium

bromide (TBAB)) and that the β-glycosyl bromide was more reactive than the α-glycosyl bromide.[185] Thus, in the absence of promoters, β-glycosyl bromide could slowly react with an alcohol by "S_N2-like" displacement to give the α-glycosides with high stereoselectivity. In this case, mutarotation would lead to an α/β-mixture, but the reaction would be a mild alternative to the use of NBS or NIS. The pentenyl glycoside was titrated with bromine followed by treatment with TBAB and water in a one-pot reaction. A temperature of 55 °C was necessary to obtain full conversion. The yield was significantly improved, but hydrolysis of the benzylidene acetal was still observed. This was solved by addition of Et_3N, which resulted in excellent yields of hemiacetal **111**. Even though the reaction is a two-step conversion, the fact that it can be made one-pot makes it a simple and efficient alternative to the known methods.

The hemiacetal **111** was converted to glycosyl trichloroacetimidate **104** by treatment with trichloroacetonitrile and DBU[186] which was used in a TMSOTf-promoted glycosylation of pentenyl acceptor **105** (Table 5, entry 1). Just as for the coupling to the thioglycoside acceptor **76**, only little conversion of the acceptor was observed, since most of the donor rearranged to the trichloroacetamide. A range of conditions was tested in order to optimize the reaction.

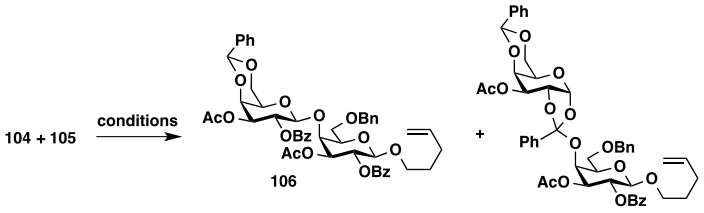


Table 5. Optimization of orthogonal coupling between TCA donor 104 and pentenyl acceptor 105.

Entry	Method	Promoter	Temp.	Yield
1	Classic	TMSOTf	0 °C	13%
2	Inverse	TMSOTf	0 °C	35%
3	Inverse	TMSOTf	-15 °C	57%
4	Inverse	TMSOTf	-40 °C	0%
5	Classic	BF_3OEt_2	-15 °C	25%
6	Inverse	BF_3OEt_2	-15 °C	37%
7	Classic	$Bi(OTf)_3$	0 °C	21%
8	Classic	$HClO_4$/silica	0 °C	0%
9	Inverse	TBSOTf	-15 °C	56%

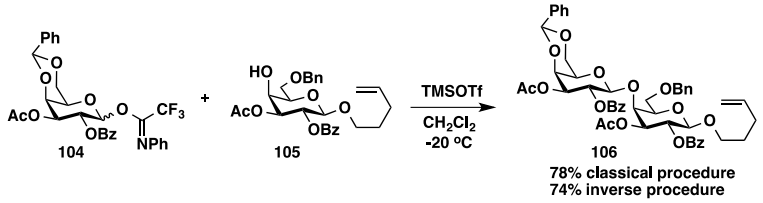
Rearrangement of imidates is most frequently observed when unreactive acceptors are used. Schmidt and Weingart showed that the reaction outcome could often be improved by an "inverted" addition procedure.[187] Instead of mixing acceptor and donor prior to activation, the acceptor and promoter were first mixed followed by slow addition of donor. In this way the acceptor concentration will be significantly higher than the donor concentration and glycosylation is therefore favored over rearrangement.

The inverted procedure was tested at three different temperatures (entry 2-4) with variable success. The best result was obtained at -15 °C, where disaccharide **106** could be isolated in 57% yield. Use of the

second-most common catalyst, $BF_3{\cdot}OEt_2$,[188] did not give rise to better results even though the yield for the classic procedure was improved (entry 5-6). $Yb(OTf)_3$ and H_2SO_4-silica have both been described to be milder alternatives to TMSOTf but procedures resulted in low yield (entry 7-8).[189,190] It has previously been reported that TMSOTf-catalyzed glycosylations of hindered acceptors can give rise to concurrent TMS silylation.[158] This can be avoided if the more bulky TBSOTf is used. In this case the yield was similar, which suggests that silylation of the acceptor is not the issue (entry 9).

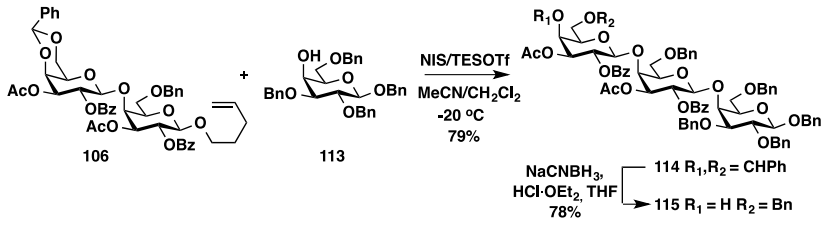
In most of the reactions, a by-product was isolated in 5-15% yield. This was first believed to be the α-anomer, but further characterization proved that it was instead the orthoester. Orthoesters can be avoided if the glycosylation is sufficiently acidic (>0.25 equiv. TMSOTf).[191] Unfortunately, this would also result in faster rearrangement of the imidate. Alternatively, additional promoter could be added after the glycosylation was finished. The conditions from entry 3 were used and after finished reaction an extra 0.25 equiv. was added. This afforded the disaccharide **106** in 62% yield.

The major problem with the TCA donor was rearrangement to the glycosyl trichloroacetamide prior to attack from the acceptor. The PTFAI donor is not affected by this problem, since the leaving group is a poor nucleophile. The PTFAI donor **104** was used to glycosylate acceptor **105** with TMSOTf as promoter by both the classic and "inverse" procedure affording disaccharide **105** in 78% and 74% yield, respectively (Scheme 31).



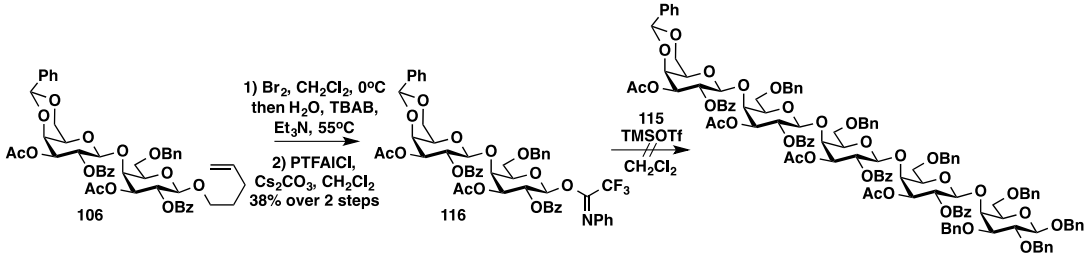
Scheme 31. Orthogonal coupling between pentenyl glycoside 105 and PTFAI donor 112.

Glycosylation of monosaccharide **113** with disaccharide **106** using NIS/TESOTf as promoter afforded the trisaccharide **114** in excellent yield (Scheme 32). Trisaccharide **114** was converted to acceptor **115** by regioselective ring opening of the benzylidene acetal using $NaCNBH_3$/ $HCl{\cdot}OEt_2$.[126] Coupling of the trisaccharide **115** and the pentenyl disaccharide **106** only resulted in hydrolysis of the donor and almost no conversion of the acceptor. The reaction was repeated at -40 °C, -20 °C, and 0 °C without a significant change in outcome. The low reactivity of trisaccharide acceptor **115** compared to monosaccharide **113** can be explained by the disarming protecting groups and steric hindrance manifested by the disaccharide unit.



Scheme 32. Introduction of reducing end residue by [2+1]-coupling.

The reactivity of the acceptor could not be changed without significant modifications to the strategy. Instead, we focused on changing the reactivity of the donor. Thioglycosides and glycosyl imidates are known to be more reactive than pentenyl glycosides.[192] The pentenyl glycoside **106** was therefore converted to the PTFAI donor **116** in two steps. Hydrolysis by the conditions described in Table 4 turned out to be much slower than for the monosaccharide and migration of the C2-*O*-benzoyl was observed. Nonetheless, the hemiacetal was isolated in 51% yield. Treatment of the hemiacetal with PTFAICl and Cs_2CO_3 afforded the PTFAI donor. Coupling of PTFAI donor **116** and trisaccharide acceptor **115** resulted in almost complete conversion of the acceptor and formation of a single product. Unfortunately, this turned out to be the orthoester and not the desired product.



Scheme 33. Synthesis of PTFAI donor 106 and condensation with trisaccharide 115.

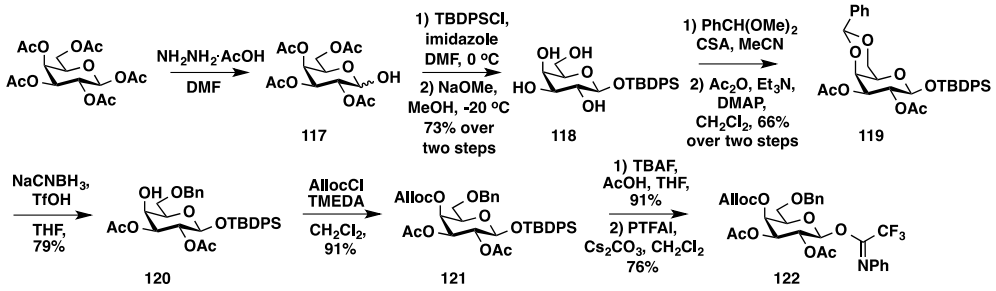
Changing the temperature and promoter did not change the outcome and attempts to rearrange the orthoester into the product were also unsuccessful. The low yields for the two-step conversion to the PTFAI donor made this strategy unfavorable no matter what and it was therefore decided to change the strategy for synthesis of the disaccharide donor.

4.7 Use of TBDPS as anomeric protecting group in synthesis of β-(1→4)-linked tri-, tetra- and pentasaccharides

Very reactive donors e.g. *N*-phenyl trifluoroacetimidates, are essential for couplings to acceptors with low reactivity. Unfortunately, it had not been possible to find an efficient method for conversion of pentenyl glycosides to PTFAI donors. All the same, it is not favorable to install a pentenyl moiety via a low-yielding two-step procedure, just to use it as a protecting group. Instead it was decided to introduce a more common protecting group that would allow simple conversion to the PTFAI donor.

An obvious choice would be to use an allyl group. The ease of formation, mild methods for its cleavage in the presence of other protecting groups and its stability to various glycosylation conditions has made it mainstay in many protecting group strategies.[192] However, deprotection of allyl groups had previously been shown to be challenging in several projects in the group. The isomerization is often incomplete and concurrent reduction of the alkene is often observed.[193] The problematic isomerization is evident from the range of catalysts that have been developed including $PdCl_2$, $(PPh_3)_3RuCl/BuLi$[124], (1,5-cyclooctadiene)-bis(methyldiphenylphosphine)-iridium(I) hexafluorophosphate $[Ir(COD)(Ph_2MeP)_2]PF_6$[194] and $[(Ph_3P)_4Pd]$[195][196]. Instead, we decided to use silyl ethers as anomeric protecting groups. Silyl ethers can be deprotected under acidic conditions or with fluoride ion sources such as TBAF or hydrogen fluoride.[197,198]

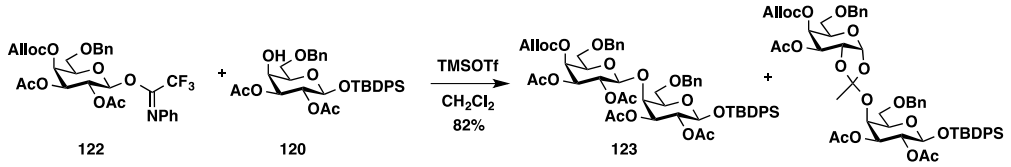
This is attributed to the fluoride ions' high affinity for silicon with the Si-F bond strength being approximately 30 kcal/mol higher than the Si-O bond.[199] Since the first reports by Schmidt and co-workers, anomeric TBDMS ethers have often been used as a precursor for TCAI donors.[196,200,201] Their application is, however, limited to the synthesis of 2-amino-2-deoxy sugars because the TBDMS group is prone to migrate if the 2-position is not protected. Schmidt and co-workers showed that the tendency to migrate could be significantly reduced by using the sterically hindered thexyldimethylsilyl (TDS) ether.[202] This made it possible to remove acyl groups under Zemplén conditions. We expected that a *tert*-butyl-diphenylsilyl (TBDPS)-ether would be even more stable and therefore set out to make a building block with an anomeric TBDPS group. The synthesis is shown in Scheme 34.



Scheme 34. Synthesis of donor 122 and acceptor 120 from C1-*O*-TBDPS building block.

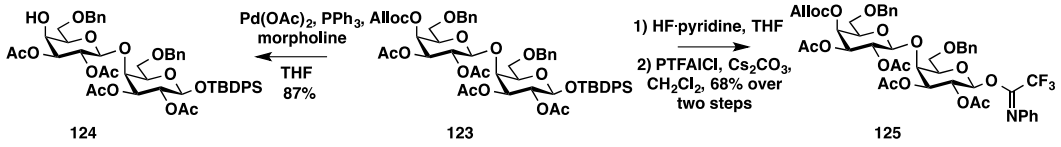
Selective anomeric deacetylation of galactose pentaacetate with hydrazine acetate in DMF afforded the hemiacetal **117**.[203] This was treated with TBDPSCl and imidazole in DMF at 0 °C to give only the kinetic product, the β-anomer **118**. The acetyl groups were removed with the Zemplén procedure but in this case the reaction was performed in only 0.01 M NaOMe in MeOH at -20 °C to avoid migration. The 4- and 6-position were protected with a benzylidene acetal followed by acetylation of the diol to give **119**. The low yield is caused by migration of the TBDPS group during the acetal formation. This could possibly be avoided if a lower temperature and milder acids were used. The benzylidene acetal was opened regioselectively with $NaCNBH_3$/TfOH[204] to give the free C4-*OH* **120**. The use of triflic acid instead of HCl/Et_2O improved the reaction outcome, because the stoichiometry was more easily controlled.[204]

Next, an allyloxycarbonyl (Alloc) group was introduced at the C4-*OH* by treatment with AllocCl and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to give **121**.[205] The TBDPS group was removed in excellent yield with TBAF and AcOH to give the hemiacetal.[206] Addition of acetic acid was crucial to avoid simultaneous migration and/or deprotection of the acetyl groups. Finally, the hemiacetal was converted to the PTFAI donor **122** with PTFAICl and Cs_2CO_3.[207] The coupling of donor **122** and acceptor **120** with 0.1 equiv TMSOTf as promoter resulted in a 3:2 mixture of disaccharide **123** and the corresponding orthoester (Scheme 35). The reaction was repeated using 0.25 equiv. of TMSOTf. In this case, the orthoester was not observed and the disaccharide **123** could be isolated in 81% yield.



Scheme 35. Condensation of donor 122 and acceptor 120.

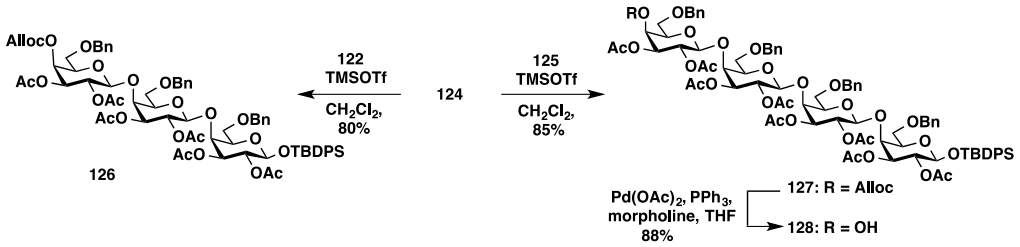
The disaccharide was converted into acceptor **124** by deprotection of allyloxycarbonyl. This was accomplished by Pd(0)-catalyzed transfer of allyl to the weak base morpholine. Instead of the air-sensitive $Pd[PPh_3]_4$, it was possible to use the cheaper and more stable $Pd(OAc)_2$, which is reduced *in situ* with PPh_3 (Scheme 36).[208] Dimedone was also tested as scavenger but this resulted in slower conversion and similar yield.[209]



Scheme 36. Transformation of disaccharide 123 into a donor 125 and acceptor 124.

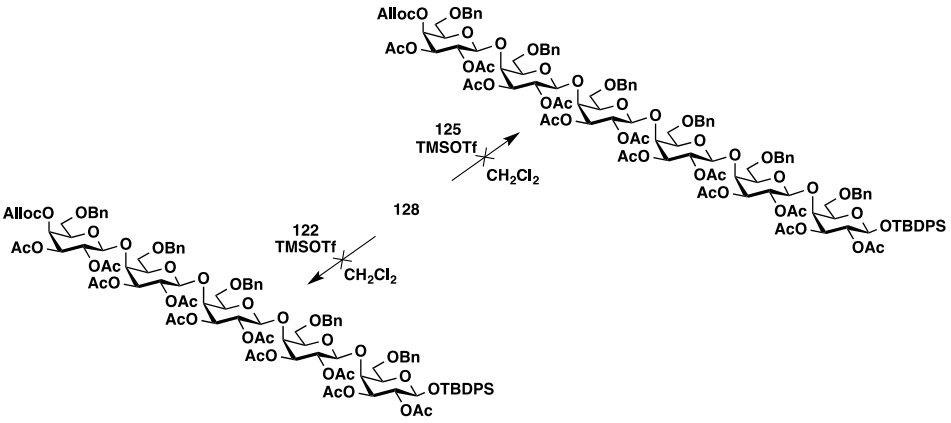
Disaccharide **123** was also turned into the corresponding PTFAI donor **125** by deprotection of the TBDPS group followed by treatment with PTFAICl and Cs_2CO_3. As opposed to deprotection of the monosaccharide, no reaction was observed with TBAF and acetic acid at 22 °C. Even with a large excess of the reagents in refluxing tetrahydrofuran (THF), it was not possible to get more than 10% conversion. HF-pyridine in THF, on the contrary, afforded the hemiacetal in 88% yield after 10 h at 22 °C.[198]

Glycosylation of acceptor **124** with either donor **122** or donor **125** using 0.25 equiv. TMSOTf as promoter afforded trisaccharide **126** and tetrasaccharide **127** in excellent yield (Scheme 37). No orthoester by-products were observed in any of the reactions. The Alloc group was removed with $Pd(OAc)_2$, PPh_3 and morpholine to give the acceptor **128**, which only needed to be glycosylated once more in order to obtain the target hexasaccharide.



Scheme 37. Glycosylation of disaccharide 124 with mono- and disaccharide donors.

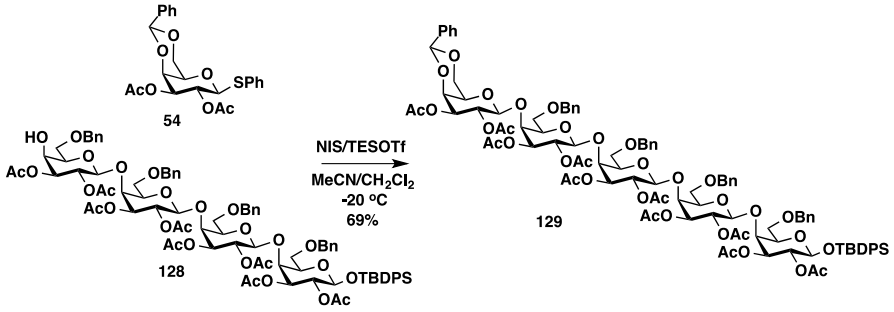
TMSOTf-promoted coupling of the tetrasaccharide **128** and disaccharide **125** only resulted in degradation of the donor (Scheme 38). The reaction was repeated at different temperatures (-40 °C, -20 °C and 0 °C), with 4 Å MS and with two other promoters ($BF_3{\cdot}OEt_2$[188] and TBSOTf[158]) without any significant change in outcome. Attempts to glycosylate **128** with monosaccharide donor **122** also resulted in degradation of the donor (Scheme 38). This indicates that it is not the donor but rather the acceptor that caused the problems.



Scheme 38. Unsuccessful attempts to glycosylate tetrasaccharide 128.

It had been confirmed by NMR that the Alloc group had been removed, but the poor glycosylation results made us question whether a free hydroxy group was present. The tetrasaccharide was treated with BzCl and Et_3N resulting in formation of a single product. NMR and LC-MS confirmed that it was the monobenzoylated tetrasaccharide. Based on this result, there must be a free C4-*OH* on the tetrasaccharide, but it is simply too unreactive. Hence, the donor is degraded, before it has a chance to react with the acceptor. This is in agreement with work by Kováč *et al.* (section 4.1), who observed a remarkable drop in yield in glycosylations to a disaccharide acceptor compared to a monosaccharide acceptor.[105]

It was investigated if a different type of donor would be a better match. To our surprise, we found that NIS/TESOTf-promoted glycosylation of the tetrasaccharide **128** with thioglycoside **54** afforded the pentasaccharide **129** in 69% yield with 18% of recovery of the acceptor (Scheme 39). The activation of the thioglycoside was much slower than for the PTFAI donors, which may have been the reason for the improvement.



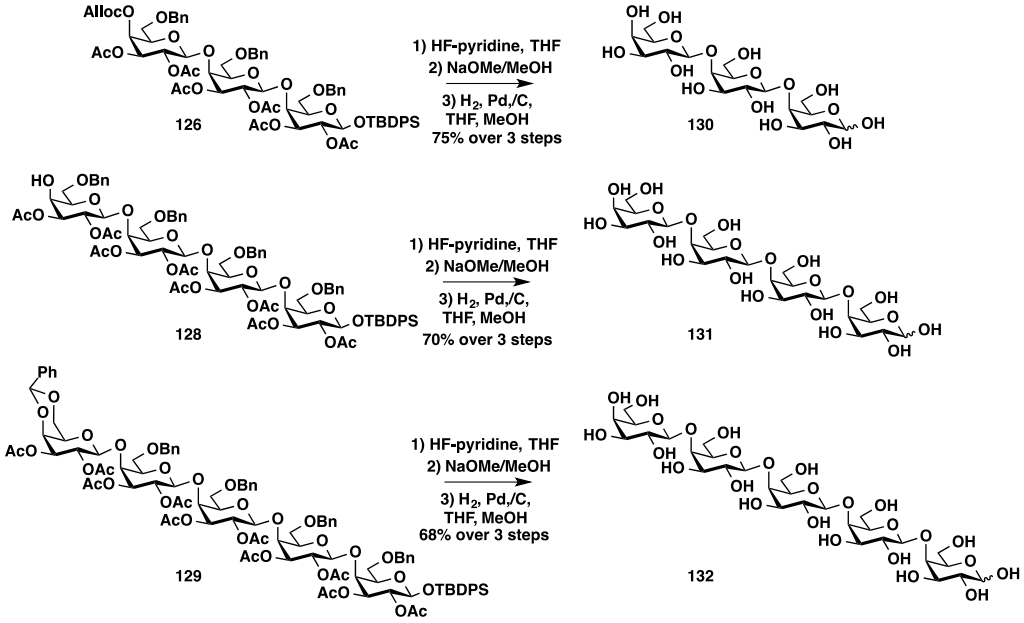
Scheme 39. Successful glycosylation of tetrasaccharide 128 using thioglycoside donor 54.

It had not been possible to prepare the target hexasaccharide by this strategy, but the tri, tetra- and pentasaccharide were still in high demand from our collaborators. Global deprotection of the three oligosaccharides was accomplished in three steps (Scheme 40). First, the TBDPS group was removed with HF-pyridine, followed by Zemplén deacetylation and hydrogenation over Pd/C to give the fully unprotected oligosaccharides in 68-75% yield.[198]

In summary, it was demonstrated that the TBDPS group is an interesting alternative to the common anomeric protecting groups, allyl ether and *p*-methoxyphenyl. The high yield in the selective desilylation shows that the strategy can be used to prepare tri-, tetra- and pentasaccharide donors that could have been

used as building blocks in larger oligosaccharides. It was possible to make a fully protected tetrasaccharide from galactose pentaacetate in just 14 steps based on the C1-*O*-TBDPS strategy.

Unfortunately, the reactivity of the C4-*OH* decreases with increasing size of the acceptor, which precluded the final [2+4] glycosylation with PTFAI donor **125**. One way to increase reactivity of the C4-*OH* would be to use small electron-donating protecting groups (e.g. benzyl or allyl). However, these protecting groups are not compatible with TBDPS protection of the anomeric center, since it has a tendency to migrate under typical alkylation conditions.

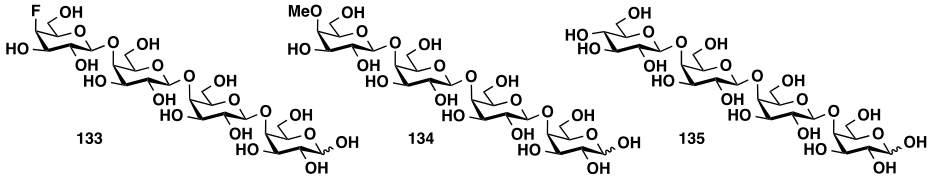


Scheme 40. Global deprotection of tri-, tetra- and pentasaccharide.

4.8 Synthesis of unnatural tetrasaccharides for co-crystallization studies with GALS1 from Arabidopsis thaliana

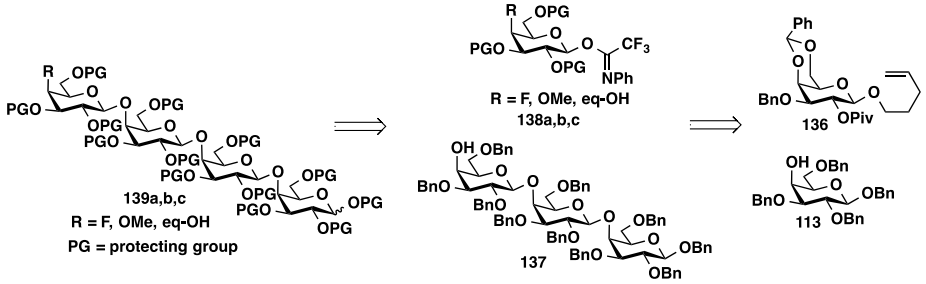
In a study by Scheller and co-workers, the galactotriose, -tetraose and -pentaose described in the previous section were used as substrates in the identification of a novel β-(1→4)-galactosyl-transferase, GALS1. The results are summarized in section 7.1. The functional properties of proteins depend upon their three-dimensional structure. It is therefore essential to understand the folding in order to understand the protein's specificity and mode of action. In spite of considerable efforts over the last 40 years, it is still not possible to predict the folding of individual proteins in sufficient detail. The three-dimensional structure is instead determined experimentally by X-ray crystallography, electron crystallography or nuclear magnetic resonance. Even though the crystal structure is only a static representation of the protein fold, it still gives valuable information about the protein structure.[210] The next step in the study of GALS1 was to obtain a high-resolution crystal structure of the enzyme. Thus, members of H. Scheller's group have been performing extensive crystallization studies, but so far without success. Without a ligand the enzyme seemed to be too flexible and when natural substrate was used it was modified by the enzyme to give a mixture of ligands.

In an attempt to solve this issue, we decided to make competitive inhibitors, which maintain the binding affinity but does not act as substrates. This was done by modification of the axial C4-*OH* in the non-reducing end of a natural ligand. The new substituent should be very similar to the natural hydroxy group in order to maintain the ligands binding properties. It was therefore decided to make three different analogs: A C4-*F* (**133)**, C4-*OMe* (**134)**, and C4-*epimer* (**135)** (Scheme 41). This would not only make us more likely to find a good inhibitor, but also give information about the promiscuity of the active site.



Scheme 41. Structures of the potential GALS1 inhibitors.

As described in section 4.4.2, it was possible to make a β-(1→4)-linked trisaccharide acceptor by orthogonal coupling of pentenyl glycosides and PTFAI donors. The synthesis was, however, complicated by formation of orthoesters during glycosylation and migration during hydrolysis of the pentenyl moiety. One way to solve this is by using the more hindered pivaloyl ester, which only migrates under harsh conditions. The only drawback is that pivaloyl groups must be removed under strong alkaline conditions (e.g. LiOH in refluxing MeOH), which could result in elimination of the axial fluorine under the global deprotection. It was therefore decided to exchange the pivaloyl groups with benzyl groups after synthesis of the trisaccharide followed by glycosylation with three different monosaccharide donors. We furthermore sought to improve the reactivity of the donor and acceptor by introducing a benzyl group at the 3-position. The retrosynthetic analysis for synthesis of the three inhibitors is shown in Scheme 42. Starting from pentenyl glycoside **136** and acceptor **113** it was possible to make perbenzylated trisaccharide acceptor **137**. This was coupled to three different donors **138a,b,c** followed by global deprotection to give the three inhibitors **139a,b,c**.

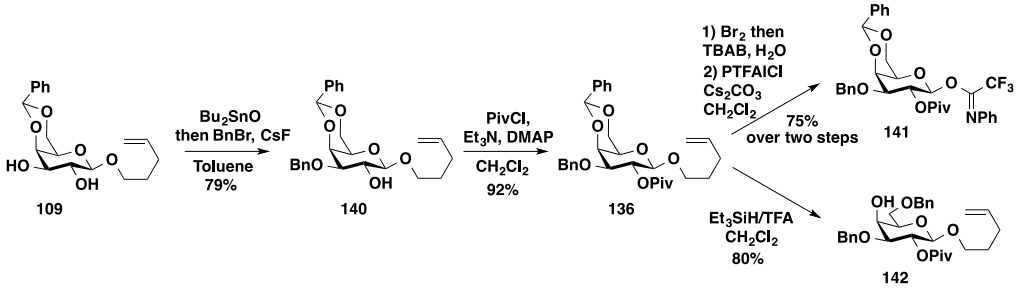


Scheme 42. Retrosynthetic analysis of tetrasaccharide synthesis.

4.8.1 Synthesis of trisaccharide acceptor

Starting from pentenyl glycoside **109**, regioselective benzylation of the C3-*OH* via a stannylene acetal afforded **140** in 79% yield (Scheme 43). The use of CsF[211] as activator resulted in approx. 10% higher yield than TBAB[212] and TBAI[212]. Next, the 2-position was protected with a pivaloyl group to give the fully protected donor **136**. It was necessary to use rather forceful conditions for the protection due to the steric bulk of the *tert*-butyl group and the low reactivity of the C2-*OH*. Pentenyl glycoside **136** was

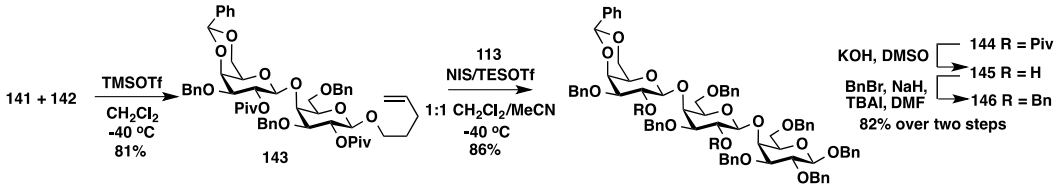
converted to the PTFAI donor **141** in two steps by the method described in section 4.6. The benzylidene acetal had to be opened to form the acceptor **142**. Against expectations, very little conversion was observed with $NaCNBH_3/HCl{\cdot}OEt_2$.[126] Opening was instead achieved by treatment of **136** with Et_3SiH/TFA to give **142** in 76% yield.[213] It should be mentioned, that the original paper states that reductive opening of benzylidene-protected galactose derivatives does not take place under these conditions. Since our result suggests otherwise, it was decided to validate the finding by acetylating the liberated C4-*OH*. This resulted in a characteristic downfield shift of the H-4 proton, whereas the H-6 proton remained unchanged. The method has the advantage that it is easily scaled up compared to the $NaCNBH_3/HCl{\cdot}OEt_2$-procedure.[213]



Scheme 43. Synthesis of donor 141 and acceptor 142 from common building block 109.

TMSOTf-catalyzed coupling of donor **141** and acceptor **142** afforded disaccharide **143** in excellent yield (Scheme 44). No orthoester by-products were observed and the reaction was significantly faster than the glycosylation described in section 4.7. The disaccharide was used as donor in the following glycosylation of the monosaccharide acceptor **113** to give the fully protected trisaccharide **144**. The reaction turned out to be very fast compared to the similar coupling of **105** and **113** (section 4.6). It was therefore possible to perform the reaction at -40 °C, which resulted in less by-products and an impressive 86% yield.

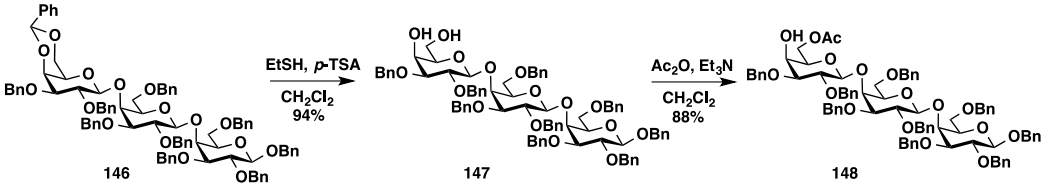
The pivaloyl groups were deprotected using KOH in dimethylsulfoxide (DMSO) to give diol **145**. In DMSO the hydroxide ion is not solvated to the same extent as in water or methanol and therefore becomes a better nucleophile (and base).[214] The conditions made it possible to cleave both pivaloyl groups in less than 12 h at 22 °C which makes it a promising alternative to known methods e.g. 48 h with LiOH in refluxing MeOH.[106] The liberated hydroxyl groups were benzylated to give **146** in 82% yield over two steps.



Scheme 44. Synthesis of disaccharide donor 143 followed by coupling to acceptor 113.

The regioselective opening of the benzylidene acetal to give a trisaccharide acceptor **137** turned out to be problematic. No reaction was observed for $NaCNBH_3/HCl$[126] or $NaCNBH_3/I_2$,[215] whereas Et_3SiH/TFA[213] and $Et_3SiH/Cu(OTf)_2$[216] only resulted in slow hydrolysis of the benzylidene. Instead, the benzylidene was

hydrolyzed by treatment with EtSH and *p*-TSA to give **147** in 94% yield (Scheme 45).[217] These conditions gave significantly better results than 1,3-propanediol/ *p*-TSA and aq. AcOH, that had been used previously.[124,218] Regioselective acetylation of the 6-position afforded the acceptor **148** in 88% yield.

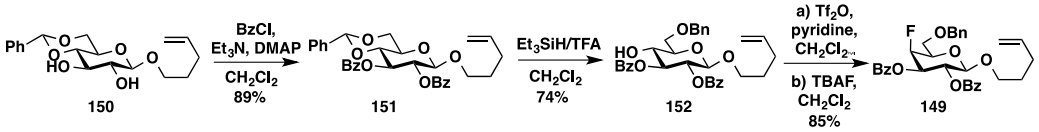


Scheme 45. Synthesis of trisaccharide acceptor 148 by hydrolysis and regioselective acetylation.

4.8.2 Synthesis of 4-deoxy-4-fluoro-, 4-*O*-methyl- and glucose donor

With access to the acceptor, the next step was to prepare the three donors. It was decided to use pentenyl glycosides, since they are stable under methylation and fluorination conditions.

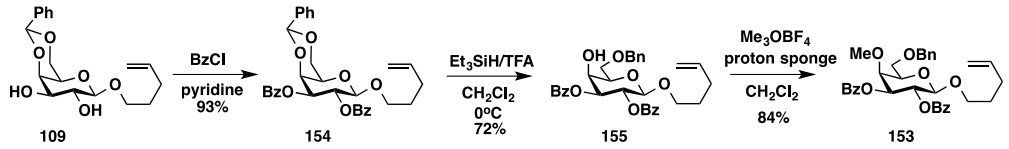
The common way to prepare fluorine analogues is with DAST.[219] Starting from the free alcohol, DAST both activates the hydroxyl group and displaces it via an S_N2 mechanism. Unfortunately, this method is not applicable for the C4-*F* galactose analogues because axial attack is hampered by steric hindrance.[220] Instead, the fluorine analogue **149** was prepared in four steps from the known pentenyl glucoside **150** (Scheme 46).[221,222] Benzoylation of the diol followed by regioselective opening of the benzylidene acetal afforded **152**. Next the C4-*OH* was converted to the corresponding triflate with Tf_2O and pyridine.[220] The more hindered base, 2,6-lutidine resulted in slightly cleaner reactions, but was harder to remove during work-up. The triflate is a better leaving group than the DAST-species and made it possible to introduce the fluorine by S_N2 substitution with TBAF to give the donor **149** in 85% yield over two steps. It was critical that the TBAF solution was completely anhydrous since concurrent hydrolysis, elimination and deacylation was otherwise observed.



Scheme 46. Synthesis of 4-deoxy-4-fluoro donor 149.

The methyl analogue **153** was prepared in two steps from the known pentenyl galactoside **154** (Scheme 47). Regioselective ring opening of the benzylidene acetal was achieved with Et_3SiH/TFA to give **155**. The methylation of the C4-*OH* turned out to be challenging due to the low reactivity and since only neutral conditions could be used in order to avoid migration or deprotection of the benzoyl groups. Methyl iodide and silver(I) oxide should meet these criteria but resulted in almost 40% of the migration product.[223] On the contrary, no conversion was observed with MeOTf and DTBMP[224] even after 24 h at reflux. The methylation was finally accomplished with Meerweins' salt and Proton-sponge®, which afforded **153** in 84% yield after just 6 h at 22 °C.[225] To the best our knowledge, this is the first time that this combination of reagent has been used for methylation of carbohydrates.

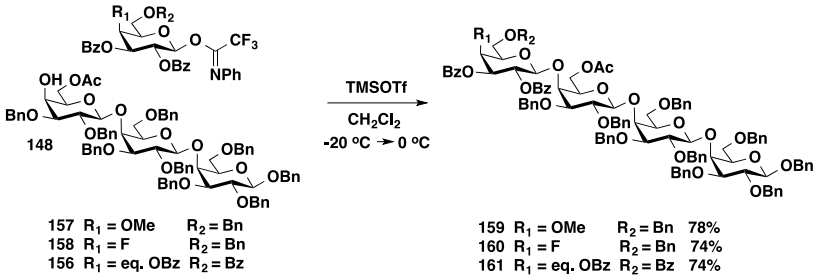
The perbenzoylated PTFAI glucoside **156** was used for the glucose analogue. This was synthesized in three steps from D-glucose based on a literature procedure.[226]



Scheme 47. Synthesis of 4-*O*-methyl donor 153.

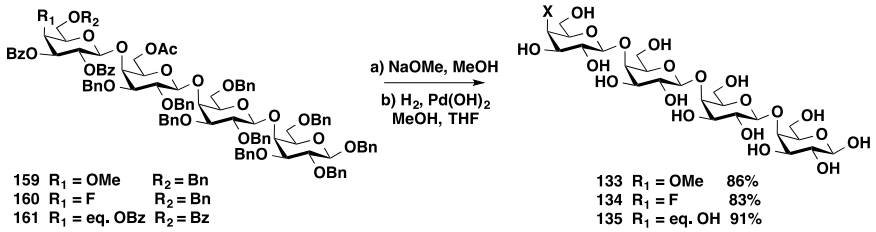
4.8.3 Final glycosylation and deprotection of tetrasaccharide inhibitors

Glycosylation of trisaccharide **148** with the pentenyl glycoside **149** using NIS/TESOTf as promoter only resulted in degradation of the donor. The poor result was most likely attributable to the electron-poor nature of the donors. The pentenyl glycosides were instead converted to the more reactive PTFAI donors (**157** and **158)** by hydrolysis with NBS/H_2O followed by treatment with PTFAICl and Cs_2CO_3. TMSOTf-catalyzed glycosylation of acceptor **148** with the three PTFAI donors gave the corresponding tetrasaccharides **159**, **160** and **161** in excellent yield (Scheme 48). The three reactions had to be performed at 0 ºC, since no conversion was observed at lower temperatures. The reactivity of the different donors followed the expected trends. Thus, methyl analogue **157** reacted much faster than electron-poor fluorine donor **158** and glucose donor **156** had intermediate reactivity.



Scheme 48. Glycosylation of trisaccharide acceptor 148 with three PTFAI donors.

Global deprotection of the three tetrasaccharides was achieved by transesterification with NaOMe in MeOH followed by $Pd(OH)_2$-catalyzed hydrogenolysis to give the target molecules: **133**, **134**, and **135** (Scheme 49). A final purification by reverse-phase chromatography was necessary in order to remove $Pd(OH)_2$/C traces. The three analogues were sent to University of California, Berkley, USA and we are currently waiting for results of the crystallization studies.



Scheme 49. Global deprotection of the three tetrasaccharides 159, 160 and 161.

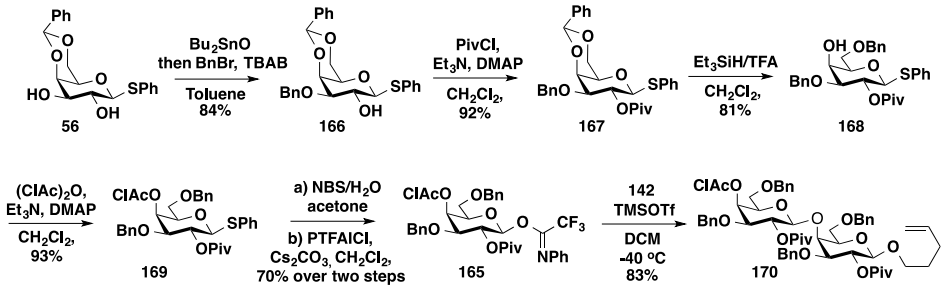
In conclusion, it was possible to prepare three tetrasaccharide analogues by glycosylation of a mutual trisaccharide acceptor with various PTFAI donors. The very effective coupling of **143** and **113** suggests that the acceptor reactivity is more influenced by the C3-*O* protecting group than first anticipated. The final couplings showed that careful choice of donors and glycosylation conditions are necessary to achieve successful couplings to the C4-*OH* of galactose.

4.9 Block-synthesis of β-(1→4)-linked linear penta- and heptagalactans

The coupling of the disaccharide donor **143** and monosaccharide acceptor **113** was very promising but the following conversion to an acceptor by hydrolysis and regioselective acetylation was problematic. Not only was it a two-step procedure, but previous results also showed that a C6-*O*-acetyl significantly lowered the reactivity of the C4-*OH*.[227] This observation was confirmed by the low reactivity of trisaccharide **148** in couplings to pentenyl glycosides. Instead, it was decided to open the benzylidene acetal on the monosaccharide stage and protect the C4-*OH* with a temporary protecting group. The chloroacetyl was chosen, since it can be easily removed either with thiourea or under mild basic conditions.[228]

4.9.1 Synthesis of disaccharide donor

For large-scale synthesis of the disaccharide donor, it was favorable to make the PTFAI donor **165** from the corresponding thioglycoside, since the first steps of the pentenyl glycoside synthesis result in mediocre yields (Scheme 50). Regioselective benzylation of diol **56** afforded **166** in excellent yield. As opposed to the synthesis of pentenyl glycoside **140**, the best results were obtained with TBAB rather than CsF. The C2-*OH* was acylated to give thioglycoside **167** followed by regioselective reductive opening of the benzylidene acetal with Et_3SiH/TFA. The opening resulted in higher yields for thioglycosides, since by-product formation from hydrosilylation or reduction of the double bond was avoided. Treatment of the free C4-*OH* of **168** with $ClAc_2O$ and Et_3N afforded the fully protected thioglycoside **169**. Finally, hydrolysis with NBS/H_2O followed by treatment with PTFAICl and Cs_2CO_3 gave the PTFAI donor **165** in 40% total yield over six steps. TMSOTf-catalyzed glycosylation of pentenyl acceptor **142** with PTFAI glycoside **165** afforded disaccharide donor **170** in 83% yield. Careful control of the temperature was necessary, since formation of the α-anomer was observed at higher temperatures (-10 °C). All of the reactions were easily performed at large scale and it was possible to prepare disaccharide **170** in 30 g.

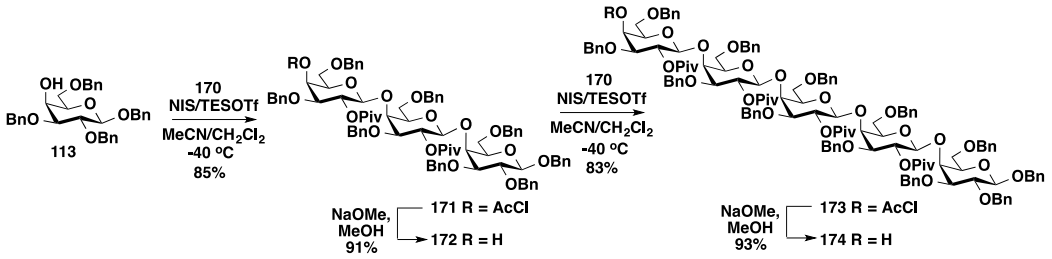


Scheme 50. Large-scale synthesis of disaccharide 170.

4.9.2 Block-synthesis of penta- and heptasaccharide

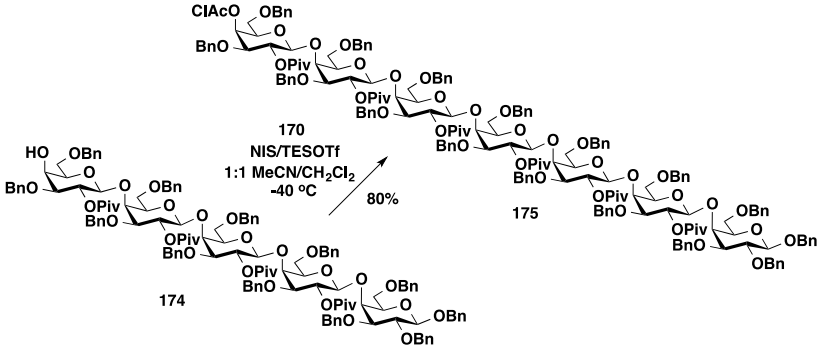
NIS/TESOTf-promoted glycosylation of acceptor **113** with disaccharide donor **170** afforded trisaccharide **171** (Scheme 51). Just like the coupling of **143** and **113** the 3-*O*-benzyl seemed to improve the reactivity of the donor remarkably. The chloroacetyl group was removed with thiourea, $NaHCO_3$ and TBAI to give **172** in 88% yield.[228] This was acceptable but it was found that the cumbersome work-up to remove

thiourea could be avoided, if 0.02M NaOMe in MeOH at 0 ºC was used instead. The pivaloyl group is stable under mild basic conditions and the C3-*O*-benzyl group prevents migration.



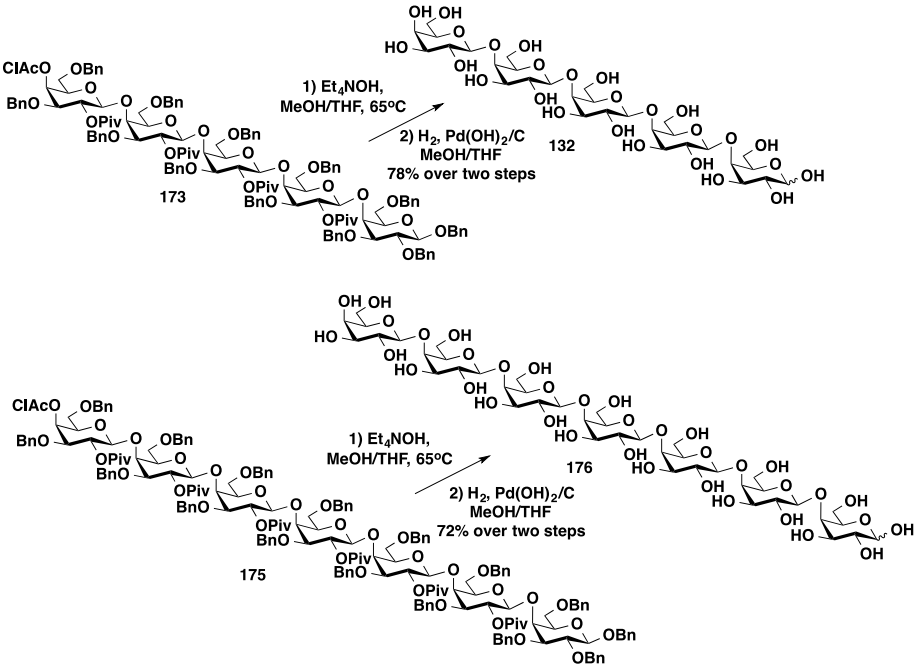
Scheme 51. Block-synthesis of pentasaccharide 173.

The trisaccharide acceptor **172** was glycosylated with the disaccharide donor **170** to give the pentasaccharide **174** in 83% yield. As opposed to all previous efforts to synthesize longer β-(1→4)-linked galactans, the reaction was fast and almost no by-products were observed. Deprotection with NaOMe/MeOH followed by glycosylation with donor **170** gave the fully protected heptasaccharide **175** (Scheme 52). The reaction was slower than the two previous glycosylations (3 h vs. 1 h) but resulted in a similar yield.



Scheme 52. [2+5]-glycosylation to give the fully protected heptasaccharide 175.

Cleavage of the pivaloyl groups with KOH/DMSO resulted in complete deprotection but also in significant degradation of the heptasaccharide. The product was isolated in only 46% yield. A range of conditions was investigated in an effort to improve the yield. Deprotection with NaOMe in refluxing MeOH,[229] aq. $MeNH_2$,[230] LiOH in refluxing MeOH[106] and aq. Bu_4NOH/H_2O[193] resulted in incomplete deprotection after 72 h. $MeLi/Et_2O$[231] and *i*-Bu_2AlH/CH_2Cl_2[232] gave rise to pronounced degradation. Global deprotection was possible by Birch reduction but it was necessary to acetylate the product in order to purify it.[233] Attempts to remove the benzyl ethers first followed by depivaloation under Zemplén conditions also resulted in degradation, most likely due to reaction with the hemiacetal. The best result was achieved with aq. Bu_4NOH, but poor solubility seemed to be a problem. The deprotection was instead done with Et_4NOH in MeOH/THF at 60 °C, which resulted in full conversion and a minimum of by-products (Scheme 53). The benzyl groups were cleaved by $Pd(OH)_2$-catalyzed hydrogenolysis to give the fully unprotected oligosaccharides **132** and **176** in 78 and 72% yield over two steps, respectively.



Scheme 53. Global deprotection of penta- and heptasaccharide.

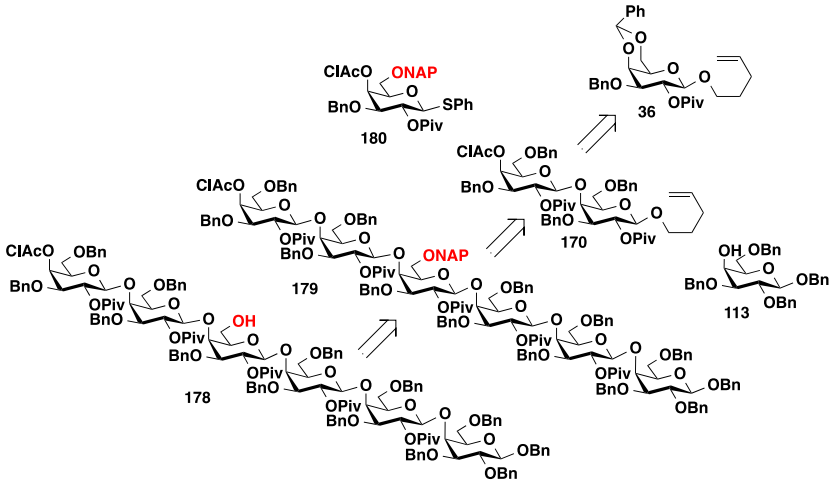
Judging from the high glycosylation yields, the 3-*O*- and 6-*O*-benzyl protection made the acceptors more reactive. The increased nucleophilicity can be ascribed to both electronic and steric effects. Not only are benzyl groups electron donating, but their flexibility also allow them to adopt conformations, where the C4-*OH* is significantly less hindered. It would be interesting to make even longer linear oligosaccharides by this method to investigate if the reactivity will decrease at some point, as it was the case for the 2,3-*O*-diacetylated oligosaccharides. This is, however, outside the scope of this project.

The method is similar to the report by Oberthür *et al.* (section 4.1.3), but has several advantages.[108] In this case the disaccharide can be used directly as donor in the next coupling. Furthermore, allyl groups were avoided which resulted in a more effective global deprotection and enabled us to use iodonium-based promoters instead of toxic MeOTf. Finally, the two-step deprotection gives direct access to the natural reducing oligosaccharide instead of the *p*-methoxyphenyl glycoside.

4.10 Branched β-(1→4)-linked galactans

As described in section 2.1, the structure of RG-I is highly complex and includes several branchings. The linear galactans are therefore not necessarily the best ligands for the carbohydrate-binding proteins (e.g. Gal-3) and antibodies. This is exemplified in section 7.3, where the antibody LM16 was shown to bind a branched tetrasaccharide but not a linear. In order to study how branching would influence the binding, it was decided to prepare a linear β-(1→4)-linked hexasaccharide core with branchings at the 4th residue. The synthetic strategy was based on results from section 4.3, where it was shown that a C6-*O*-NAP could be selectively removed in the presence of benzyl ethers and acyl groups. This made it possible to design a convergent strategy where the linear hexasaccharide **178** with only one free hydroxyl was glycosylated with various glycosyl donors. The NAP group has the advantage that it is sterically and electronically

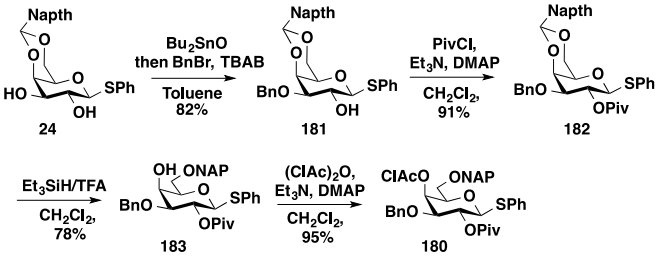
similar to the benzyl groups. The glycosylations were therefore likely to follow the same trend as the previous examples. It was decided to use the NAP-protected monosaccharide **180** for introduction of the branching point and disaccharide donor **170** for the remaining glycosylations. The retrosynthetic analysis of the hexasaccharide backbone is shown in Scheme 54.



Scheme 54. Retrosynthetic analysis of the hexasaccharide acceptor 178.

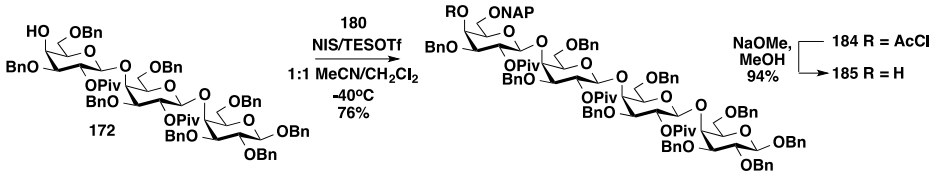
4.10.1 Synthesis of hexasaccharide acceptor

The NAP-protected building block **180** was prepared by the same route as thioglycoside **169**, but in this case a naphthylidene acetal was used (Scheme 55). Stannylene-promoted regioselective benzylation of diol **24** gave thioglycoside **181** followed by acylation of the C2-*OH* to afford the fully protected thioglycoside **182**. Regioselective opening of the naphthylidene acetal was achieved by treatment with Et_3SiH/TFA to give **183**. It is remarkable that the NAP group is stable under the Et_3SiH/TFA conditions, since 10% TFA in CH_2Cl_2 has previously been used to deprotect NAP ethers.[234] Finally, the chloroacetyl group was introduced with $(ClAc)_2O$, Et_3N and DMAP to afford **180** in 55% yield over four steps.



Scheme 55. Synthesis of NAP-protected building block.

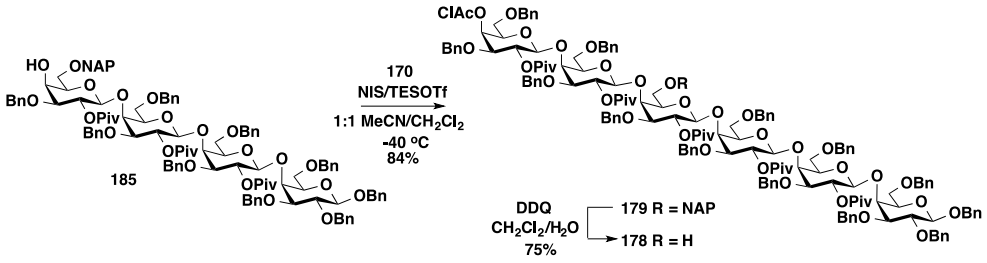
The branching point was installed at the 4th sugar by glycosylation of trisaccharide acceptor **172** (described in section 4.9.2) with thioglycoside **180** to give tetrasaccharide **184** in 73% yield (Scheme 56). The low yield compared to glycosylations with the disaccharide donor is most likely attributable to the C4-*O*-chloroacetyl. In the monosaccharide, it is much closer to the aglycon, which results in a rather electron poor system. The effect is further enhanced since the 4-position on galactose has been shown to have the largest effect on the donor reactivity.[140] Deprotection of the chloroacetyl group with NaOMe/MeOH gave the tetrasaccharide acceptor **185** in 94% yield.



Scheme 56. NIS/TESOTf-promoted glycosylation of trisaccharide 172 with NAP-protected donor 180.

A second glycosylation with disaccharide donor **170** gave the fully protected hexasaccharide **179** in 84% yield (Scheme 57). As expected the NAP ether did not negatively impact the glycosylation outcome.

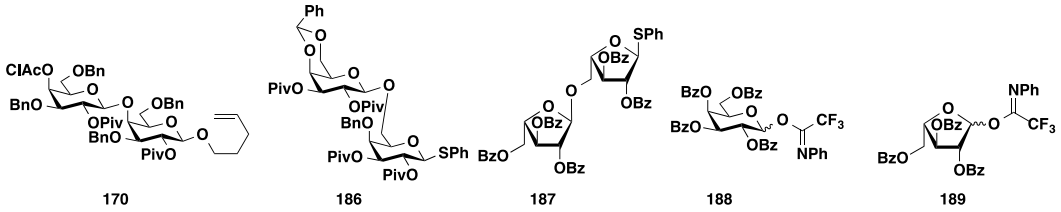
The first attempt to cleave the NAP ether with DDQ in a 4:1:0.2 CH_2Cl_2/MeOH/H_2O-mixture resulted in a slow conversion and several by-products. Much better results were obtained without methanol, where the product **178** could be isolated in 75% yield after a special work-up described by Boltje *et al.*.[235] Characterization of the byproducts showed that they were a mixture of hexasaccharides where one or more of the benzyl groups had been cleaved.



Scheme 57. Glycosylation and NAP-cleavage to give target hexasaccharide 178.

4.10.2 Synthesis and introduction of branchings

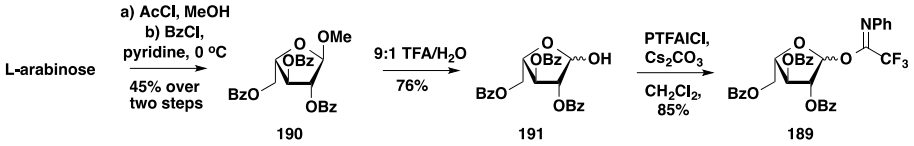
The hexasaccharide acceptor could now be glycosylated with a range of donors. It was decided to introduce three disaccharides and two monosaccharides: β-(1→4)-linked D-digalactan **170**, β-(1→6)-linked D-digalactan **186**, α-(1→5)-linked L-diarabinan **187**, D-galactose **188** and L-arabinose **189,** since they are all found in nature.[12] The structures of the five donors are shown in Scheme 58.



Scheme 58. Structure of the five donors used for branching.

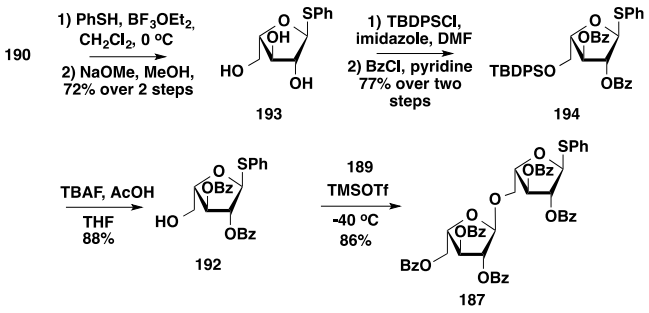
L-Arabinofuranosyl donors

The perbenzoylated PTFAI donor **189** was chosen as donor for the L-arabinose branch. It could be prepared from commercially available L-arabinose in four steps (Scheme 59). First, L-arabinose was transformed into the methyl glycoside by a Fischer glycosylation of methanol under kinetic control.[236] This ensures formation of the furanoside. Benzoylation with benzoyl chloride in pyridine afforded **190** as the α-isomer in 45% yield over two steps.[237] The methyl glycoside **190** was hydrolyzed with 90% aqueous TFA to give the hemiacetal **191** in 68% yield and finally the PTFAI donor **189** was formed after treatment with PTFAICl and Cs_2CO_3.[207]



Scheme 59. Synthesis of L-arabinose PTFAI donor 189.

Donor **189** was not only used in the glycosylation of the hexasaccharide but also acted as donor in the synthesis of diarabinan donor **187**. Thioglycoside acceptor **192** was prepared in five steps from methyl glycoside **190** based on literature procedure for the corresponding D-arabinofuranosyl thioglycoside (Scheme 60).[238] Compound **190** was treated with thiophenol and BF_3OEt_2 followed by debenzoylation under Zemplén conditions to give the phenyl thioglycoside **193** in 72% yield over two steps. Next, the primary C5-*OH* was selectively protected with the bulky TBDPS group using TBDPSCl and imidazole followed by benzoylation of the diol to afford **194** in 77% yield over two steps. Finally, the TBDPS group was removed with TBAF/AcOH to give the acceptor **192** in 88% yield. It was necessary to add AcOH to avoid concurrent deprotection or migration of the benzoyl esters. TMSOTf-mediated glycosylation of thioglycoside acceptor **192** with PTFAI donor **189** afforded disaccharide **187** in an excellent yield (Scheme 60).

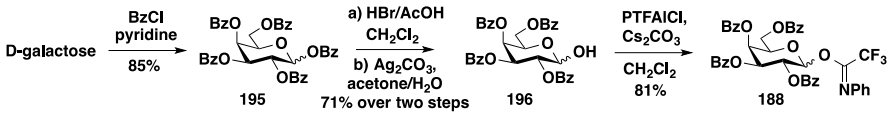


Scheme 60. Synthesis of diarabinan thioglycoside 187.

D-Galactose donors

Synthesis of the β-(1→6)-linked D-digalactan donor **186** is described in section 6.2 and the β-D-(1→4)-digalactan was introduced with disaccharide donor **170,** discussed in section 4.9.1.

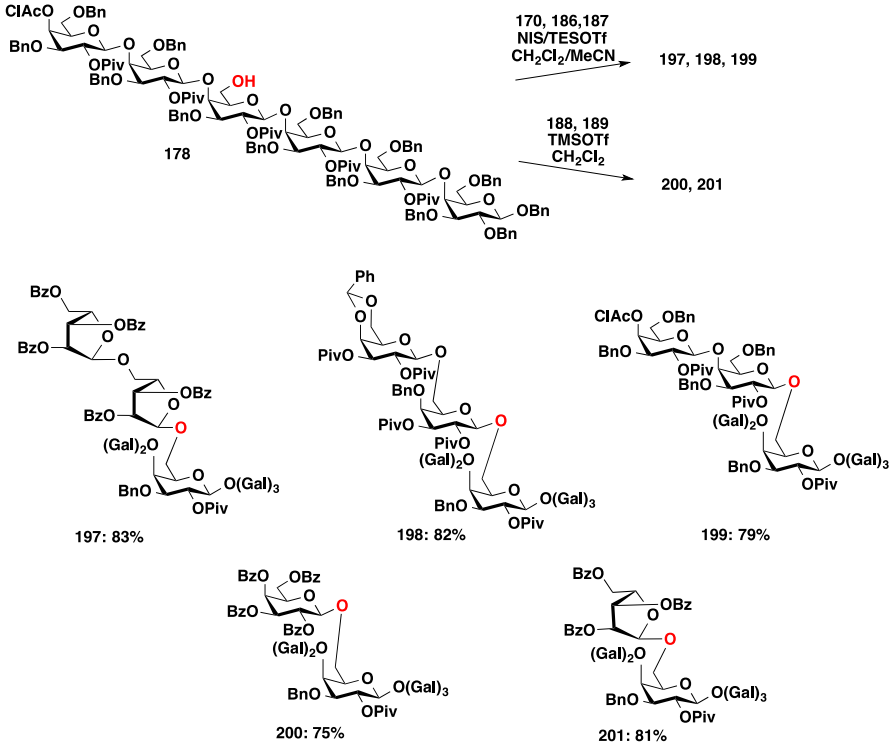
The galactose monomer was introduced using the perbenzoylated PTFAI donor **188** which was prepared in four steps from commercially available D-galactose according to a literature procedure (Scheme 61).[239] D-Galactose was treated with benzoyl chloride in pyridine to give the perbenzoylated sugar **195** in 85% yield. The anomeric center was brominated with HBr/AcOH and the crude glycosyl bromide was subjected to silver(I) carbonate in the mixture of acetone and water to afford hemiacetal **196** in 71% yield over two steps. Hemiacetal **196** was converted to the PTFAI donor **188** with PTFAICl and Cs_2CO_3.[207]



Scheme 61. Synthesis of PTFAI donor 188.

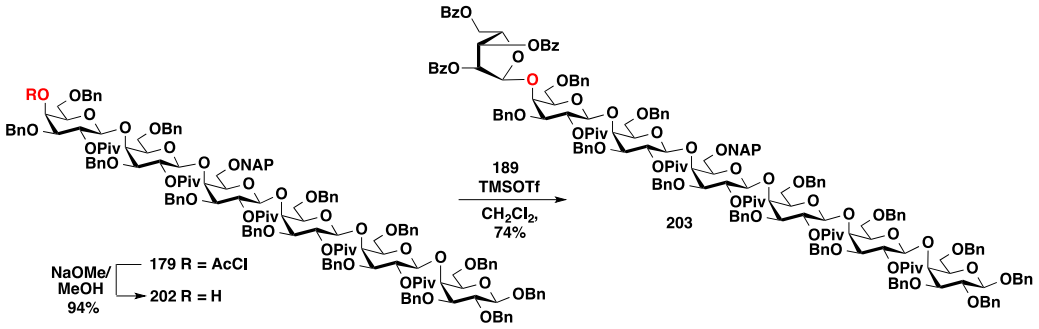
4.10.3 Glycosylations of hexasaccharide acceptor 178

With all the donors at hand, it was possible to make the branched oligosaccharides. The glycosylations with pentenyl and thioglycosides were promoted by NIS/TESOTf in a 1:1 acetonitrile (MeCN)/CH_2Cl_2 mixture, whereas the glycosyl imidates were activated with TMSOTf in CH_2Cl_2 (Scheme 62). All of the reactions were performed at -40 ºC to enhance the stereoselectivity. All of oligosaccharides **197-201** were isolated in over 70% yield. Against expectations, the disaccharide donors gave the best results. This can perhaps be explained by their lower reactivity, which often results in better α/β-selectivity. It is remarkable that couplings to the primary C6-*OH* gives lower yields than glycosylations to the hindered C4-*OH*. The low reactivity of the C6-*OH* is probably attributable to its position in the middle of the oligosaccharide chain and is further reduced by β-(1→4)-D-galactans tendency to fold into helical structures.[240] The knowledge of the 3-dimensional structure of protected carbohydrates is, however, limited.



Scheme 62. Glycosylation of hexasaccharide 178 with various donors.

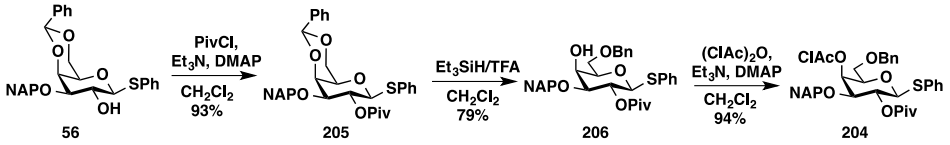
Structural studies of RG-I have shown that linear galactans are often capped by a single L-arabinose residue. We were interested to see how this affects binding and decided to prepare a heptasaccharide with a L-arabinofuranosyl in the non-reducing end. The compound was synthesized from hexasaccharide **179**. Instead of deprotecting the NAP-ether, the chloroacetyl group was removed with NaOMe/MeOH to give the hexasaccharide acceptor **202** in 94% yield (Scheme 63). This was glycosylated with perbenzoylated PTFAI donor **189** with TMSOTf as promoter to afford the heptasaccharide **203** in 74% yield.



Scheme 63. Synthesis of L-arabinofuranosyl-capped heptasaccharide.

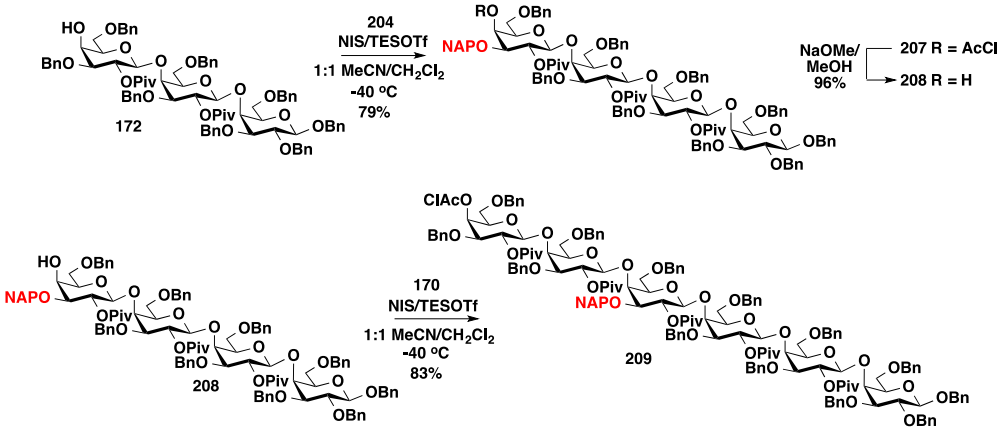
The final type of branched oligogalactans that we were interested in were C3-branched oligogalactans. As described in section 2.1, this class includes a range of sugars with L-arabinose being the most common. The strategy was based on the same approach as for the C6-branched oligosaccharides. A C3-*O*-NAP-protected monosaccharide was introduced at the branching point and once the hexasaccharide core had been prepared the NAP group was selectively deprotected.

The synthesis of the monosaccharide donor **204** is shown in Scheme 64. Acylation of thioglycoside **56** with PivCl, Et_3N and DMAP afforded **205** in 93% yield. The benzylidene acetal was regioselectively opened with Et_3SiH/TFA to give **206** followed by protection of the liberated C4-*OH* with $ClAc_2O$ and Et_3N to give the fully protected thioglycoside **204** in 94% yield.



Scheme 64. Synthesis of C3-*O*-NAP building block.

NIS/TESOTf-mediated glycosylation of trisaccharide acceptor **172** with the monosaccharide donor **204** afforded the tetraasaccharide **207** in 79% yield (Scheme 65). As expected, the reactivity was similar to thioglycoside **180**. The chloroacetyl group was deprotected with NaOMe/MeOH to afford **208** followed by glycosylation with disaccharide donor **170** to give the fully protected hexasaccharide **209** in 83% yield.

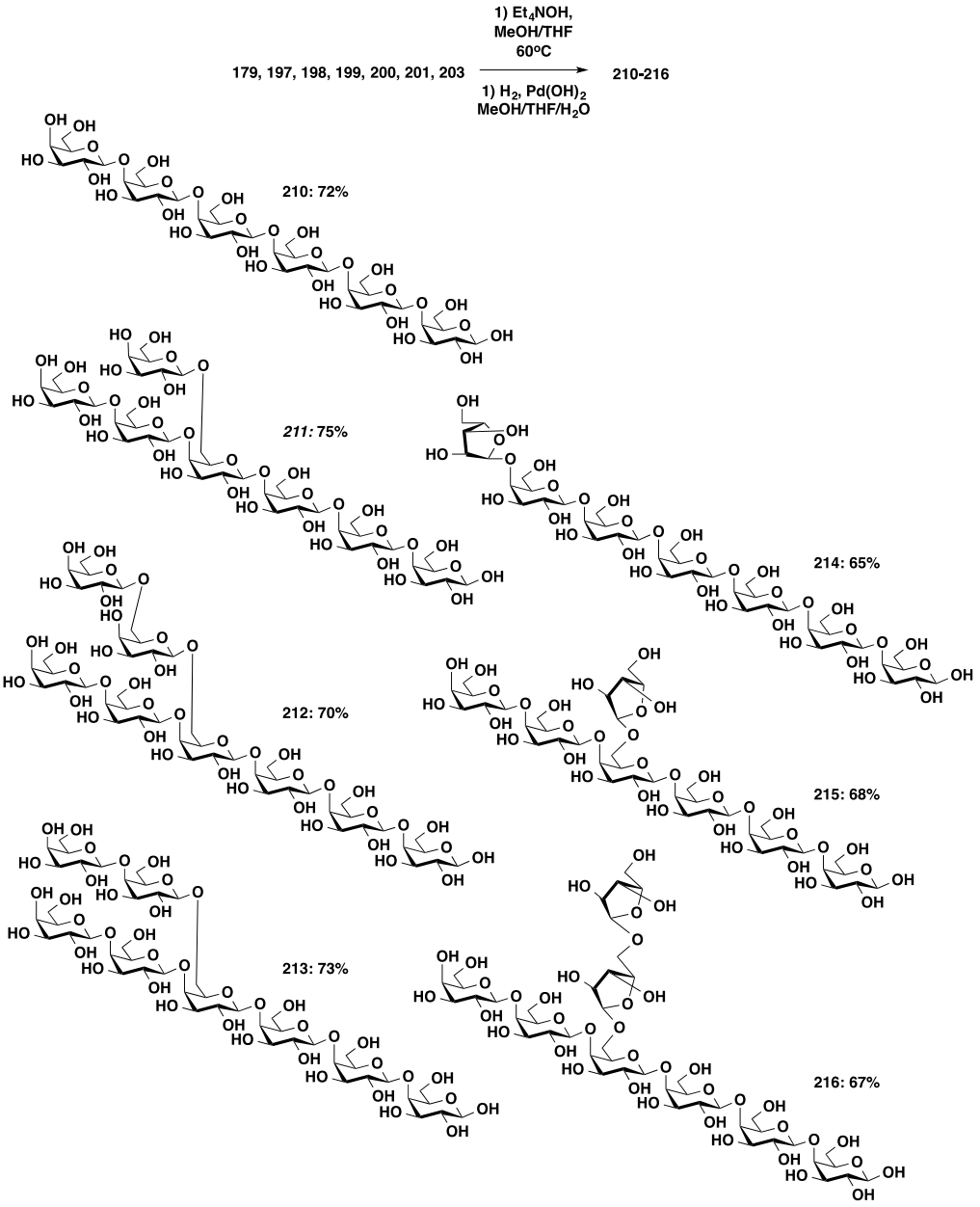


Scheme 65. Synthesis of C3-*O*-NAP protected hexasaccharide 209.

The final step in the synthesis of the hexasaccharide acceptor was selective removal of the NAP group. Unfortunately, treatment of **209** with DDQ in CH_2Cl_2/H_2O[234] gave a complex mixture of products. Lower temperature or addition of methanol resulted in a slower reaction but not a change in reaction outcome. Fuwa *et a*l. have reported that NAP ethers are selectively cleaved by 9:1 CH_2Cl_2/TFA, but in our hands the reaction was slow and only resulted in degradation.[234] Selective hydrogenolysis of a NAP-ether in presence of benzyl groups has been reported but in this case no selectivity was observed.[120] In hindsight, the problems in the final deprotection should have been anticipated. Deprotection of C6-*O*-NAP gave rise to notable cleavage of the benzyl ethers and since the C3-*O*-NAP is considerably more sterically hindered, this problem was likely to be increased. Other methods for selective NAP deprotection have to be screened in order to solve the problem. Alternatively, the NAP-group should have been exchanged for another protecting group e.g. an acetyl or silyl group.

Global deprotection of the linear hexasaccharide (**179**), three branched heptasaccharides (**200**, **201** and **203**) and three octasaccharides (**197**, **198** and **199**) was accomplished with the conditions described in section 4.9.2 to give the fully unprotected oligosaccharides **210-216** in yields ranging between 65% and 75% (Scheme 66). This was acceptable considering the difficult deprotection of the pivaloyl groups.

In conclusion, a convergent strategy for (1→6)-branched β-(1→4)-D-galactans was developed and a small library of hepta- and octasaccharides was prepared. The late-stage introduction of the branchings significantly reduces the overall number of steps and makes it possible to introduce different donors. The use of pivaloyl groups is favorable throughout the synthesis but results in reduced yields in the final deprotection. It would be interesting to study if the pivaloyl groups could be exchanged for an alternative protecting group. One possibility is the 2-chloro-2-methyl-propanoyl group developed by Carreira and Szpilman.[241] This reduces formation of orthoesters and can be cleaved under mild Zemplén conditions due to the electron withdrawing chloro substituent. Unfortunately, it was not possible to apply the same strategy to synthesis of (1→3)-branched galactans. In this case, a different orthogonal protecting group is needed. The problem will be addressed in future studies in the group.



Scheme 66. Global deprotection of the branched β-(1→4)-linked ligogalactans.

5 Synthesis of β-(1→3)-D-galactan oligosaccharides

The equatorial C3-*OH* of D-galactose is significantly less sterically hindered than the axial C4-*OH*. Problems such as aglycon transfer and unreactive acceptors are therefore less common and it is possible to make glycosylations between electron-deficient acceptors and -donors in high yields. However, the higher reactivity is not without its challenges. The increased nucleophilicity makes the glycosylation reactions faster and more difficult to control which typically results in poorer stereoselectivity.[192] Electron-withdrawing substituents reduce electron density of the neighboring hydroxyl group and thereby lower its nucleophilicity. This may improve the stereoselectivity as the reaction can be carried out in a more controlled manner.[242]

As described in section 2.2, the β-(1→3)-linked galactans are widespread in nature in the form of AG-II. Nevertheless, very little work has been done regarding synthesis of defined oligosaccharide fragments. Table 6 summarizes the published work.

Table 6. Published work on synthesis of β-(1→3)-linked galactans.

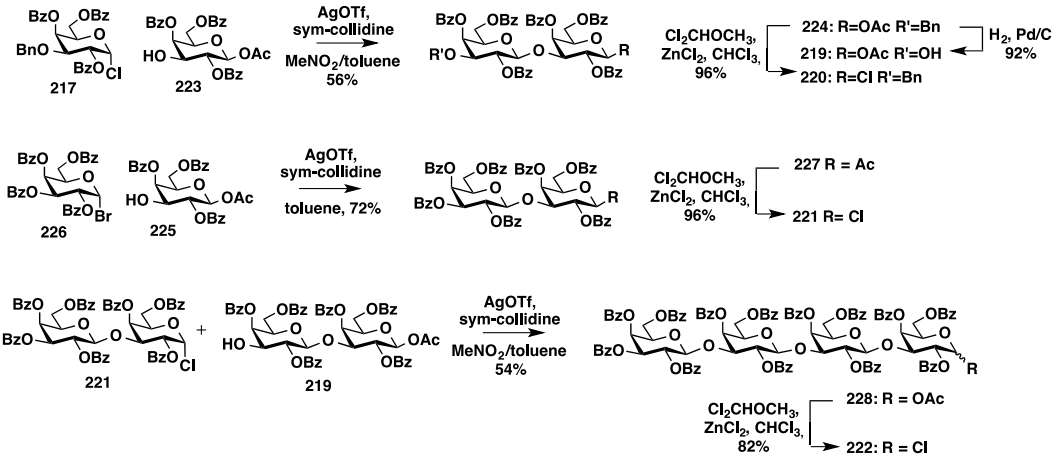
Synthetic oligosaccharide fragment	Reference
Trisaccharides	
β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*	Komba *et al.*[107]
β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*-HMBA	Komba & Machida[243]
β-D-Gal*p*-(1→3)-[β-D-Gal*p*-(1→6)]-β-D-Gal*p*-HMBA	Komba & Machida[243]
β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p* *fully protected*	Ziegler *et al.*[244]
β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*-OMe *partially protected*	Fenger & Madsen[245]
β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*-OMe	Kováč *et al.*[246]
β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*-O$(CH_2)_8N_3$	McGill & Williams[247]
β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-D-Gal*p*	Chowdhary *et al.*[248]
Tetrasaccharides and larger oligomers	
β-D-Gal*p*-(1→3)-{β-D-Gal*p*-(1→3)}$_2$-β-D-Gal*p*-OMe	Kováč *et al.*[246]
β-D-Gal*p*-(1→3)-{β-D-Gal*p*-(1→3)}$_3$-β-D-Gal*p*-OMe	Kováč *et al.*[246]
β-D-Gal*p*-(1→3)-{β-D-Gal*p*-(1→3)}$_5$-β-D-Gal*p*-OMe	Kováč *et al.*[246]

5.1 Previous studies of β-(1→3)-D-galactan synthesis

5.1.1 Synthesis of linear β-(1→3)-linked tri, tetra, penta and heptagalactans

The elegant work by Kováč and co-workers is so far the only published strategy for synthesis of higher members of the β-(1→3)-D-galactan series.[246] They showed that it was possible to prepare the entire series of linear methyl β-glycosides of DP 2-7 from a single building block, namely methyl 2,4,6-tri-*O*-benzoyl-3-*O*-benzyl-β-D-galactopyranoside. This could either be converted to the corresponding glycosyl chloride **217** by treatment with 1,1-dichloromethyl methyl ether (DCMME) or turned into acceptor **218**

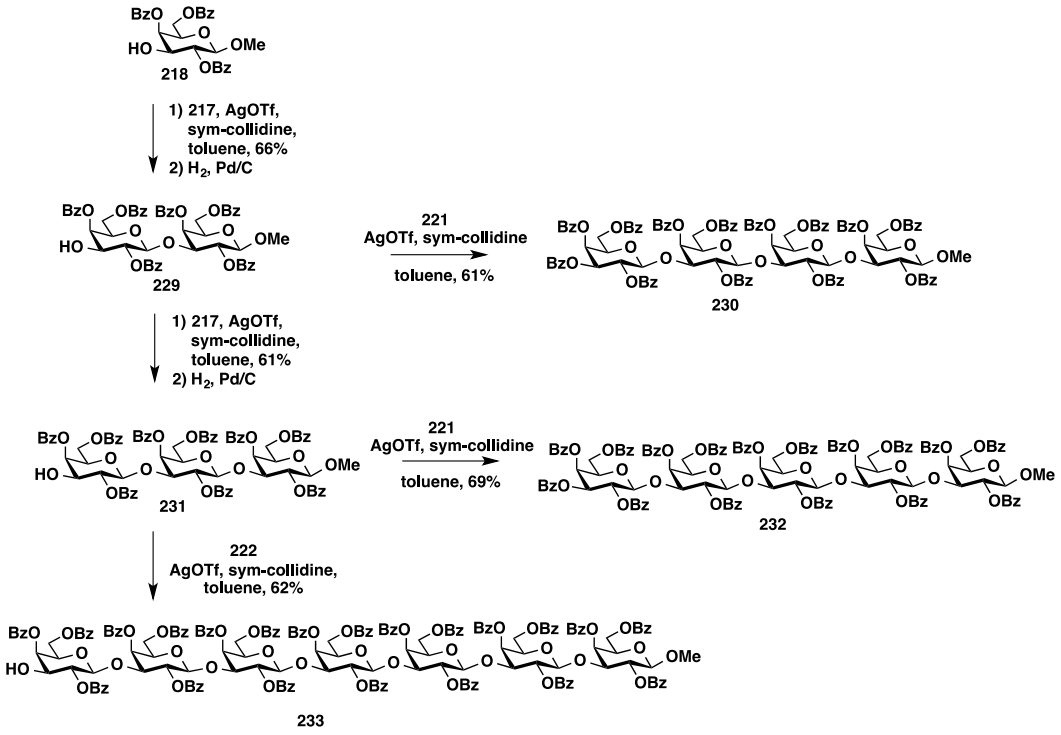
by hydrogenolysis of the 3-*O*-benzyl group. Glycosyl chlorides were chosen over glycosyl bromides, since they are easier to purify and have longer shelf life. Syntheses of the disaccharide and tetrasaccharide building blocks **219**, **220**, **221** and **222** are outlined in Scheme 67. AgOTf-mediated glycosylation of acceptor **223** with glycosyl chloride **217** afforded disaccharide **224** in 56% yield. Like the monosaccharide, this was converted to either a disaccharide donor **220** with DCMME or a disaccharide acceptor **219** by hydrogenolysis. Disaccharide building block **221** was prepared by AgOTf-mediated glycosylation of **225** with perbenzoylated glycosyl bromide **226** to give disaccharide **227** followed by activation with DCMME. Condensation of donor **221** and acceptor **219** with AgOTf as activator afforded fully protected D-galactotetraose **228** in 54% yield. By careful control of the amount of Lewis acid it was possible to convert acetate **228** into the corresponding glycosyl chloride **222** in 82% yield.



Scheme 67. Synthesis of β-(1→3)-linked disaccharide and tetrasaccharide building blocks.[246]

It was now possible to prepare all the methyl glycosides (Scheme 68). Condensation of glycosyl halide **217** and acceptor **218** followed by hydrogenolysis gave disaccharide acceptor **229**. This was coupled to donor **221** to give fully protected tetrasaccharide **230**. Alternatively, glycosylation with donor **217** followed by deprotection of the 3-*O*-benzyl group afforded trisaccharide acceptor **231**. Coupling to either donor **221** or **222** gave the fully protected pentose **232** and heptaose **233**. Debenzoylation was achieved by transesterification under Zemplén conditions to give the fully unprotected methyl glycosides.

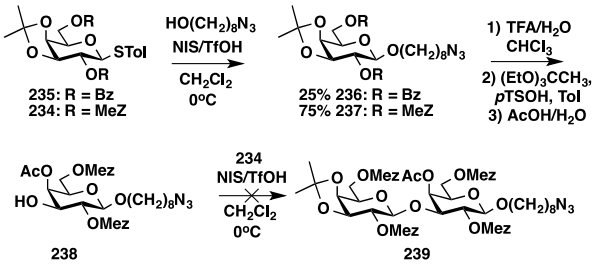
Kováč's synthesis excels by its simplicity, but suffers from low glycosylation yields and cumbersome purifications. This is mainly explained by poor stereoselectivity resulting in formation of α-glycoside by-products even though the 2-*O*-benzoyl group should facilitate formation of the β-product. Furthermore, the mediocre glycosylation yields are caused by formation of orthoesters, transesterification of the 2-*O*-acyl group or acyl migration on the acceptor.



Scheme 68. Assembly of the methyl β-D-(1→3)-galactose series.[246]

5.1.2 2,6-Disubstitued benzoates as neighboring groups in galactosylation reactions

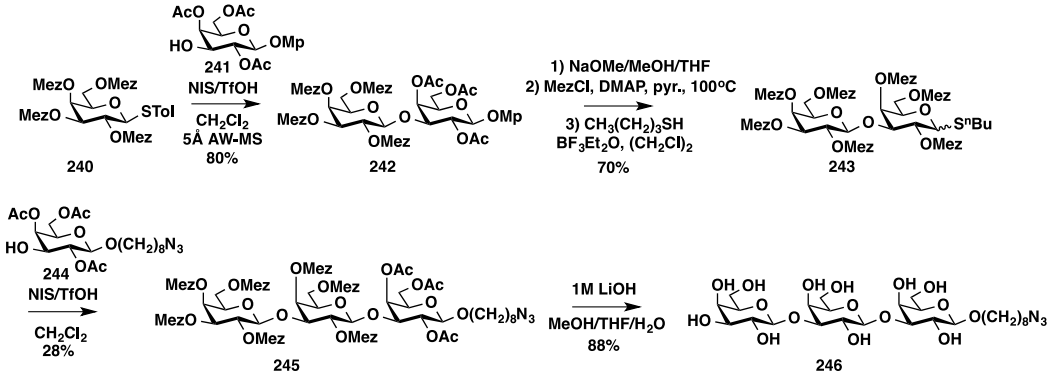
In a more recent work by McGill and Williams, it was studied whether more bulky 2,6-substituted benzoates could overcome the issue of poor stereoselectivity.[247] Glycosylation of 8-azidooctanol with a range of thioglycosides showed that 2,4,6-trimethylbenzoyl (Mez) protected donor **234** gave significantly higher yield than the corresponding benzoate donor **235** (Scheme 69). In order to test the applicability of the new protecting group, **237** was converted to acceptor **238** in three steps and glycosylated with donor **234**. However, in this case none of the expected product **239** was observed. The failed glycosylation was explained by steric hindrance manifested by the 2-*O*-mesitoyl of the acceptor.



Scheme 69. Comparison of the glycosylation with 2-*O*-mesitoyl and a 2-*O*-benzoyl donor.[247]

To solve the problem, the target trisaccharide was instead prepared by a [2+1]-strategy. Tetramesitoate **240** was coupled to methoxyphenyl glycoside **241** in a NIS/TfOH-promoted glycosylation to give disaccharide **242** in 80% yield. This was converted to the heptamesiotate thioglycoside **243** by deacetylation, acylation and exchange of the anomeric protecting group. Glycosylation of acceptor **244** with donor **243** afforded the trisaccharide **245** in just 28% yield. Deprotection of the hindered mesitoyl ester was achieved by saponification with LiOH for five days to give **246** in 88% yield.

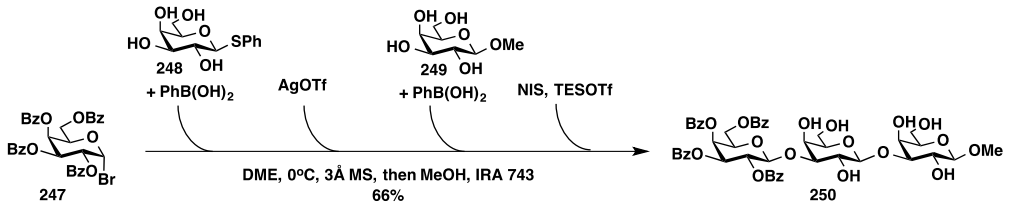
Even though the mesitoyl ester lowers the amount of α- and orthoester byproducts, its use in oligosaccharide synthesis seems to be limited by the additional steric hindrance induced by the three methyl groups.



Scheme 70. Synthesis of (1→3)-linked trisaccharides with Mez-protected glycosyl donors.[247]

5.1.3 One-pot synthesis of β-(1→3)-galactans by transient protecting group strategy

Significant progress has been made in oligosaccharide synthesis over the last two decades but the fundamental principle remains the same.[192] A fully protected glycosyl donor is activated by a promoter and reacts with a partially protected acceptor with only one or two free hydroxy groups. Most common methods therefore involve far more protective group manipulations than glycosylations, resulting in poor atom-economy and a time-consuming synthesis. In an effort to address this problem Madsen & Fenger developed a simple method for synthesis of β-(1→3)-linked di- and trisaccharides.[245] They were able perform regioselective glycosylations of unprotected glycosyl acceptors by transient protection of the 4- and 6-position with phenyl boronic acid. The method also works for unprotected thioglycoside acceptors and, thus, gives access to valuable disaccharide building blocks for oligosaccharide synthesis. Alternatively, the thioglycosides could be used directly in a second regioselective glycosylation to give gluco- or galactotrioses. An example is shown in Scheme 71, where the perbenzoylated glycosyl bromide **247** was first coupled to thioglycoside **248** under Koenigs-Knorr conditions. Next, the pre-formed 4,6-*O*-phenylboronate **249** was added followed by activation of the thioglycoside with NIS/TESOTf. The boronates were removed by weakly basic ion-exchange resin IRA 743 and after purification trisaccharide **250** was isolated in 66% yield.

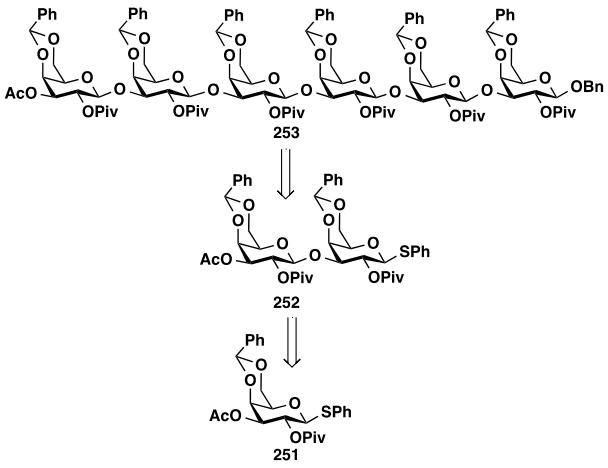


Scheme 71. One-pot glycosylation of unprotected glycosyl acceptors.[245]

5.2 Synthesis of β-(1→3)-linked linear hexa- and tetragalactans

Because of the lack of defined substrates, knowledge of the AGP glycan backbones' biological functions is very limited. It was therefore decided to make a range of linear and branched β-1→3)-linked galactans and test binding of lectins and antibodies with the microarray technology described in section 4.3. Novozymes® was furthermore interested in β-(1→3)-linked oligo-saccharides for characterization of new glycosidases.

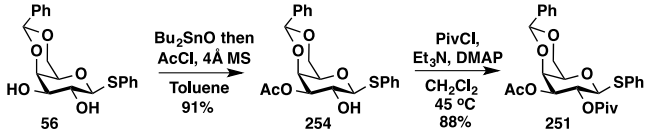
The strategy for synthesis of β-(1→3)-linked galactans was very similar to the block strategy described in section 4.4. We aimed to prepare a single building block, which could be converted to a disaccharide donor. This would lower the number of critical glycosylations in the rest of the synthesis. As described in the previous section it is possible to glycosylate the 3-position of galactose even though the 2-position is unprotected. The yields were, however, mediocre and it was necessary to protect the 2-position after every glycosylation.[245] Instead, we decided to protect the 2-, 4- and 6-position with permanent protecting groups and the 3-position with a temporary protecting group. A pivaloyl group was chosen for the 2-position since neighboring group participation was necessary to ensure β-selectivity. The pivaloyl group furthermore has the advantage that it reduces the risk of orthoester formation, which had been a problem in the synthesis by Kováč.[244] The 4- and 6-position was protected with a benzylidene acetal, which is easily introduced and is sterically small. An acetyl group was chosen for temporary protection of the 3-position, since it had previously been selectively removed in presence of the more bulky pivaloyl esters.[106] A retrosynthetic analysis of the synthesis of a linear hexasaccharide is shown in Scheme 72. Starting from building block **251**, it was possible to make a disaccharide donor **252** by coupling to an orthogonal PTFAI donor. The disaccharide could then be used to build the hexasaccharide **253** by three glycosylations.



Scheme 72. Retrosynthetic analysis of the synthesis of fully protected hexasaccharide 253.

5.2.1 Synthesis of disaccharide donor 252

Thioglycoside **56** was regioselectively acetylated via formation of the stannylene acetal with Bu_2SnO followed by treatment with AcCl and 4Å molecular sieves (Scheme 73).[249] The molecular sieves removed residual water, but also helped to quench the HCl formed during the reaction. Treatment of **254** with PivCl, Et_3N and DMAP afforded the fully protected thioglycoside **251** in 88% yield.



Scheme 73. Synthesis of the common building block 251.

In order to make the PTFAI donor the thioglycoside had to be hydrolyzed. This turned out to be very challenging and several reagent combinations were tested before a suitable set was found. The results are compiled in Table 7. NBS in acetone/H_2O (entry 1) gave rise to hydrolysis of the benzylidene acetal and no product was observed. Instead, the glycosyl bromide was formed by titration with bromine followed by hydrolysis under basic conditions as described in section 4.4.2 (entry 2). This gave the expected product **255**, but the reaction was slow and gave rise to several by-products. The corresponding glycosyl iodide was expected to be more reactive. However, it was not possible to obtain full conversion of the thioglycoside (entry 3). A similar compound had been hydrolyzed with chloramine-T (entry 4) as activator but in this case only low conversion was observed.[250]

There had to be acid present in order for the benzylidene acetal to be hydrolyzed. This could either derive from HBr already present in the NBS or it could be formed during the hydrolysis by reaction between NBS and water. In entries 5-7 different bases were screened as acid-scavengers. No hydrolysis of the benzylidene was observed with triethylamine but instead migration of the pivaloyl resulted in low yields. The milder bases, pyridine and 2,6-lutidine, afforded **255** in high yields. The better results observed with 2,6-lutidine may be explained by its lower tendency to react with the bromonium ion or act as a competing nucleophile.

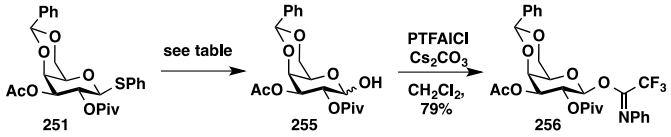


Table 7. Hydrolysis of benzylidene-protected thioglycoside 251.

Entry	Conditions	Yield (%)
1	NBS, H_2O/MeCN	-
2	Br_2 then TBAB/H_2O/MeCN, Et_3N	55
3	I_2 then H_2O/MeCN	20
4	Chloramine-T, H_2O/MeCN	35
5	NBS, Et_3N, H_2O/MeCN	41
6	NBS, pyridine, H_2O/MeCN	75
7	NBS, 2,6-lutidine, H_2O/MeCN	84

The selective deacetylation to give acceptor **257** also turned out to be far from simple. The results of the experiments are shown in Table 8. It was expected that the acetyl could be removed by Zemplén condition without affecting the pivaloyl group just as it had been the case for the chloroacetyl group in section 4.9. However, this resulted in extensive migration as well as deprotection of the pivaloyl (entry 1). Most likely, the pivaloyl group first migrates to the 3-position, where it is more accessible and is therefore cleaved. Lowering the temperature only made the reaction slower but gave a similar outcome (entry 2). Decreasing both NaOMe concentration and temperature improved the yield to 59% but this was still far from acceptable. Xu *et al*. had reported that $Mg(OMe)_2$ can be used as a milder alternative to NaOMe (entry 4).[251] In this case no deprotection of the pivaloyl was observed but it did not solve the migration problem. The same was the case for the even milder conditions with ammonia in methanol (entry 5).[252] All the methods described in entries 1-5 follow the same mechanism. In order to change the conditions more drastically, it was attempted to remove the acetal by reduction (entries 6 and 7). DIBAL-H did not give rise to migration but deprotection of the pivaloyl was still observed, which had also been reported by Nicolaou and co-workers.[232] On the contrary, the more bulky reducing agent, $LiEt_3BH$ (superhydride) solved the problem and the product **257** was obtained in excellent yield.[253]

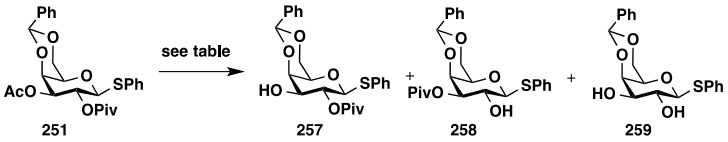


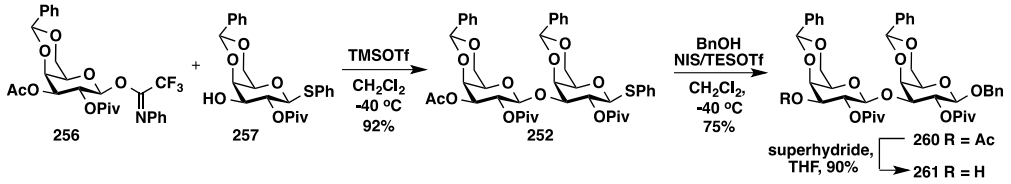
Table 8. Optimization of conditions for selective deacetylation.

Entry	Conditions	**257** (%*)	**258** (%*)	**259** (%*)
1	NaOMe/MeOH (0.1 M), rt	37	35	20
2	NaOMe/MeOH (0.1 M), 0 °C	40	37	10
3	NaOMe/MeOH (0.01 M), 0 °C	59	25	11
4	$Mg(OMe)_2$ (0.1 M), 0 °C	61	32	0
5	NH_3/MeOH	74	15	0
6	1M DIBAL-H in toluene, CH_2Cl_2, 0 °C	70	0	22
7	1M superhydride in THF, CH_2Cl_2, 0 °C	94	0	0

*isolated yields

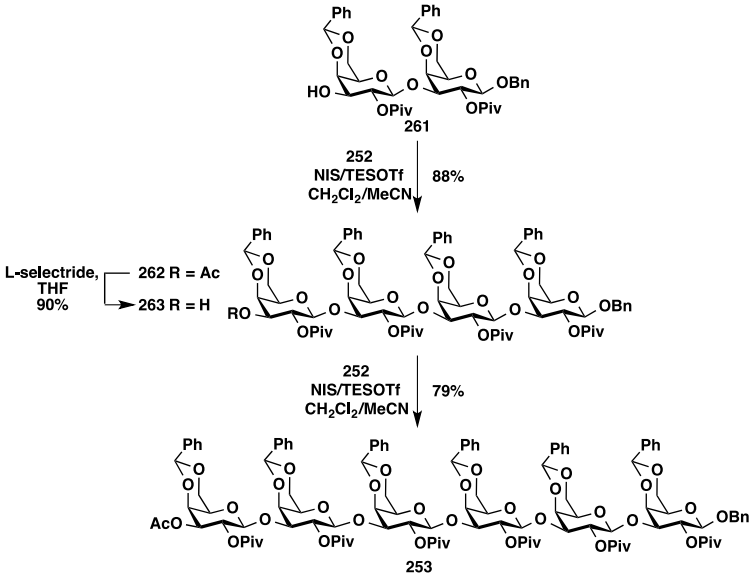
With access to both donor **256** and acceptor **257,** the disaccharide donor **252** was prepared in 92% by a TMSOTf-mediated glycosylation (Scheme 74). The disaccharide was converted to an acceptor in two steps. NIS/TESOTf-promoted glycosylation of benzyl alcohol with disaccharide **252** gave the β-benzyl glycoside **260** in 75% yield. It was crucial to use only a small surplus of benzyl alcohol and to carry out the reaction at low temperature, since significant amounts of the α-glycoside were otherwise formed. Selective deacetylation with superhydride afforded acceptor **261** in 90% yield. Scale up of the reaction resulted in a minor explosion, since triethylborane formed during workup reacted with oxygen and ignited. To avoid accidents superhydride was substituted for the more bulky reducing agent,

Li(*sec*-Bu)$_3$BH (L-selectride). This did not affect the yields and the corresponding borane is less volatile and therefore less likely to react with oxygen. However, the reductions were generally slower due to the increased bulk of the *sec*-butyl groups.



Scheme 74. Synthesis of disaccharide donor and disaccharide acceptor.

Condensation of disaccharide acceptor **261** and disaccharide donor **252,** promoted by NIS/TESOTf, afforded tetrasaccharide **262** in 88% yield. Tetrasaccharide **262** was converted to acceptor **263** by reduction with L-selectride. Finally, this was glycosylated with disaccharide donor **252** to give the fully protected hexasaccharide in 79% yield.



Scheme 75. Synthesis of β-(1→3)-linked hexasaccharide.

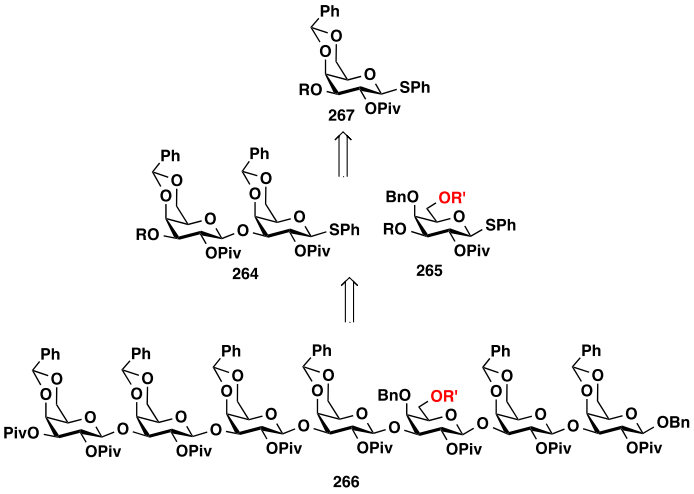
5.3 Synthesis of branched β-(1→3)-linked galactans

As described earlier, the glycan backbone of AGP is decorated by a wide variety of branchings. It is therefore likely that proteins bind motifs that include both the backbone and part of the branching. Nonetheless, only one group has reported synthesis of well-defined oligosaccharides with both backbone and branching.[254]

We decided to prepare a small library of (1→6)-branched β-(1→3)-linked oligosaccharides. In order to have a sufficient size for proteins to recognize the oligosaccharide, it was decided to make octa- and nonasaccharides. We furthermore aimed to introduce branching at either the third or fifth sugar residue to test how the position would affect protein binding and enzymatic degradation.

The strategy was the same as for the branched β-(1→4)-linked galactans. Monosaccharide donor **265** with a temporary C6-*O* protecting group was introduced at the branching point and the rest of the backbone

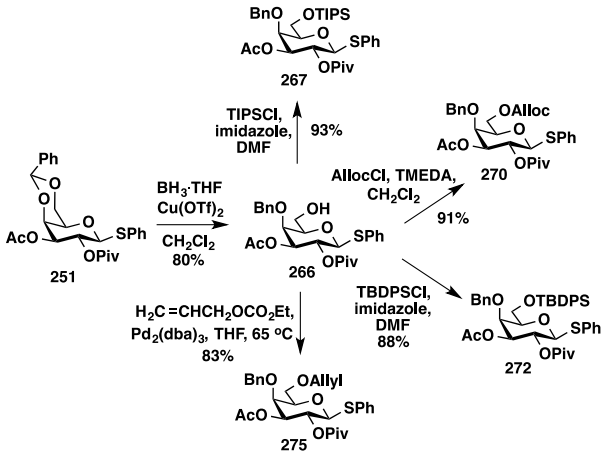
was constructed using disaccharide donor **264**. After preparation of the linear heptasaccharide **266**, the temporary protecting was to be removed to give an acceptor, which could be glycosylated with different donors. The retrosynthetic strategy is shown in Scheme 76.



Scheme 76. Retrosynthetic analysis for synthesis of heptasaccharide acceptor. R and R' are orthogonal protecting groups

5.3.1 Synthesis of donor for introduction of C6-branching

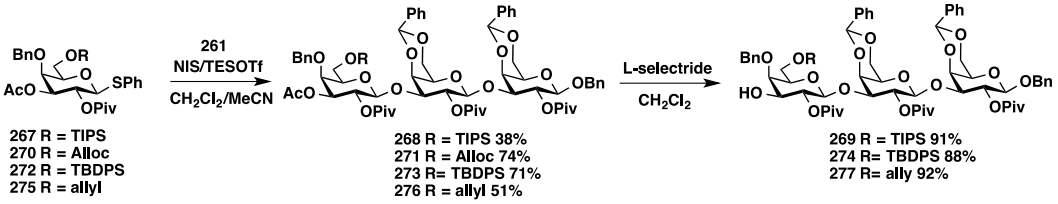
The monosaccharide donor **265** could be prepared in two steps from thioglycoside **251** (Scheme 77). The benzylidene acetal was regioselectively opened with borane-tetrahydrofuran complex and copper(II) triflate to afford the free C6-*OH* **266**.[216] Next, a temporary protecting group had to be found which was stable under the glycosylation conditions and during reductive deacetylation. The first choice of temporary protecting group was a TIPS ether, which could be introduced with TIPSCl and imidazole in DMF to give **267** in 93%.[255]



Scheme 77. Synthesis of potential donors for introduction of branching point.

Glycosylation of the disaccharide **261** with TIPS donor **267** resulted in several by-products and the trisaccharide **268** was only isolated in 38% yield (Scheme 78). The degradation of the donor is most likely caused by formation of the corresponding 1,6-anhydrosugar as a result of intramolecular attack from the 6-position. Bols and co-workers have previously reported this issue when TBDMS protected donors were used.[164] Deprotection of the acetyl group with L-selectride was effective and the acceptor

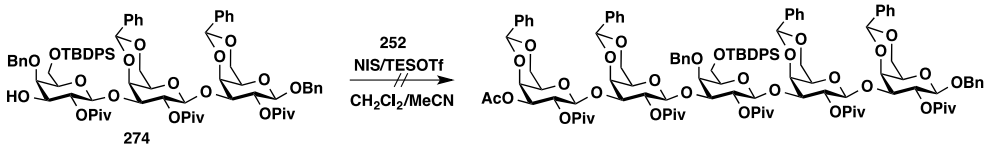
269 could be isolated in 91% yield but the low glycosylation yield made us look for an alternative protective group.



Scheme 78. Glycosylation of disaccharide acceptor 261 with C6-*O* protected donors.

Carbonates, like esters, can be cleaved by basic hydrolysis but are normally far less susceptible due to resonance stabilization by the second oxygen.[199] The same trend was expected with regard to reduction. The C6-*OH* of **266** was therefore protected with an Alloc group by reaction with allyl chloroformate and TMEDA (Scheme 77).[205] Coupling of **270** to disaccharide acceptor **261** afforded the trisaccharide **271** in 74% yield even though minor by-products were observed from reaction between NIS and the Alloc alkene. This is problematic since these by-products could also be formed in the following glycosylations. Against expectations the reduction with L-selectride was not selective even at low temperatures. The difference in lability is probably evened out by the greater accessibility of the 6-position. It was possible to obtain selectivity with $Mg(OMe)_2$, but as described in the previous section, this gave rise to migration of the pivaloyl group.

Instead, the TIPS ether was replaced with the less acid-labile TBDPS group to prevent it from acting as an internal acceptor. In this case glycosylation of disaccharide **261** with donor **272** gave trisaccharide **273** in 71% yield. The acetyl group was deprotected with L-selectride to give **274**, which was used as acceptor in a NIS/TESOTf-mediated glycosylation with donor **252** (Scheme 79**)**. Unfortunately, no conversion of the acceptor was observed. The low reactivity is presumably caused by the bulky TBDPS ether that blocks the 3-position.



Scheme 79. Unsuccessful glycosylation of TBDPS-protected acceptor 274.

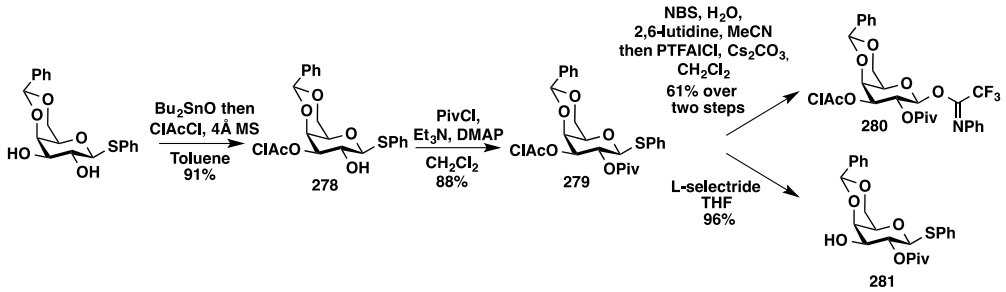
The final choice of protecting group was an allyl ether. Due to the acyl groups, it was not possible to introduce the allyl ether by Williamson ether synthesis. Instead, a method developed by Sinou and co-workers was used where allyl groups can be introduced under neutral conditions with ethyl allyl carbonate and bis(dibenzylidene-acetone)palladium(0) (Scheme 77).[256] This made it possible to prepare donor **275** in 83% yield. The glycosylation of acceptor **261** with donor **275** turned out to be very slow and several by-products were formed. This is probably due to competing reaction of iodonium with the allylic alkene. Since iodonium ions seemed to be the problem, different pre-activation methods were instead tested. However, glycosylation promoted by 1-benzenesulfinyl piperidine (BSP)/Tf_2O,[257] Ph_2SO/Tf_2O[258]

or Me_2S_2/Tf_2O[259] (with or without DTBMP) did not give significantly higher yields (33-65%). Me_2S_2/Tf_2O was the most successful.

5.3.2 Synthesis of chloroacetyl protected building blocks

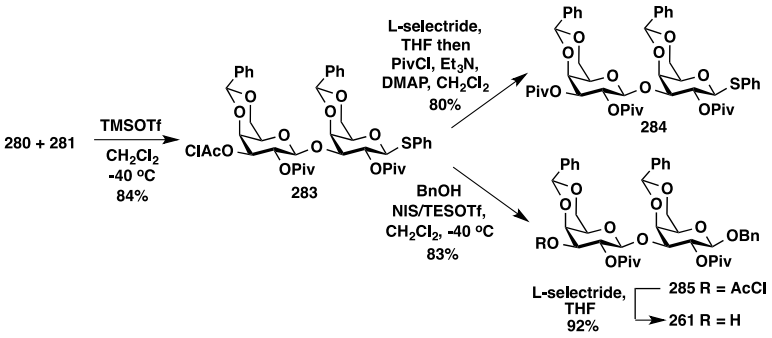
Since no suitable orthogonal protecting group could be found, we decided to change the strategy. The 3-position was instead protected with a chloroacetyl group. This made it possible to use an acetyl group for the 6-position, which could be removed by L-selectride reduction at the end of the synthesis.

The synthesis of the disaccharide donor was very similar to what was previously described. First, the chloroacetyl group was regioselectively introduced at the 3-position via the stannylene acetal. The preliminary experiments were done with $ClAc_2O$ but the liberated ClAcOH seemed to disrupt the stannylene acetal and resulted in poor selectivity. When chloroacetyl chloride was used instead, the product **278** was obtained in excellent yield (Scheme 80). The 2-position was protected with a pivaloyl ester by treatment with PivCl, Et_3N, and DMAP to give the fully protected thioglycoside **279**. Hydrolysis with NBS/H_2O/2,6-lutidine followed by treatment with PTFAICl and Cs_2CO_3 afforded PTFAI donor **280**. The thioglycoside **279** could furthermore be transformed to the acceptor **281** by deprotection of the chloroacetyl group with L-selectride.



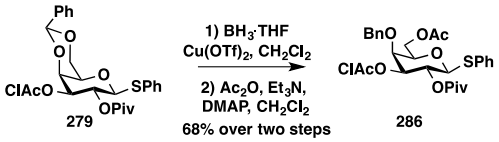
Scheme 80. Synthesis of orthogonal PTFA donor and thioglycoside acceptor.

TMSOTf-catalyzed coupling of donor **280** and acceptor **281** afforded disaccharide donor **283** in 84% yield (Scheme 81). It would be unfavorable to have a chloroacetyl in the non-reducing end of the heptasaccharide, since it would be removed during reduction of the C6-*O*-acetyl. Hence, the chloroacetyl was exchanged with a pivaloyl to give disaccharide **284** by reduction with L-selectride followed by treatment with PivCl, Et_3N, and DMAP. Furthermore, the disaccharide donor **283** was converted to acceptor **261** by glycosylation of benzyl alcohol to give **285** followed by deprotection of the chloroacetyl group with L-selectride.



Scheme 81. Synthesis of the three disaccharide building blocks 261, 283 and 284.

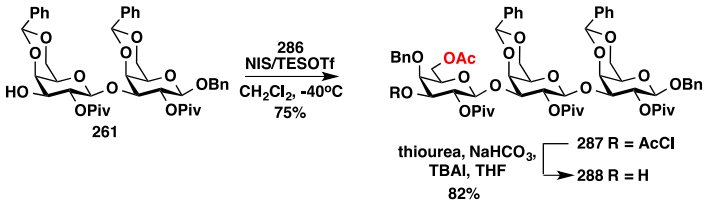
The final building block **286** was prepared by regioselective opening of the benzylidene acetal of **279** with borane-THF complex and copper(II) triflate followed by acetylation (Scheme 82).



Scheme 82. Synthesis of C6-*O*-acetyl donor 286.

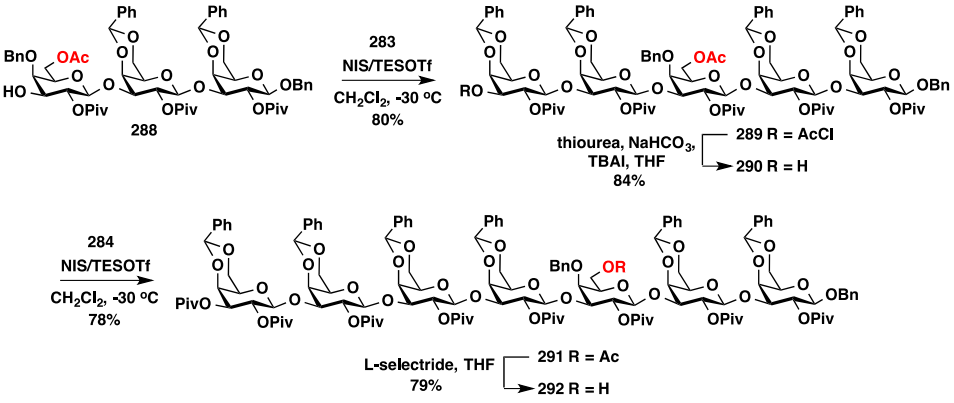
5.3.3 Synthesis of heptasaccharides acceptors

With all the building blocks at hand it was now possible to syntheize the two heptasaccharides. Trisaccharide **287** was prepared by NIS/TESOTf-promoted coupling of donor **286** and acceptor **261** (Scheme 83). The new protecting group combination resulted in decent yields, but it was necessary to use 1.5 equiv. of donor in order to obtain full conversion of the acceptor. This can be ascribed to degradation of the donor because of the primary acetyl or simply that the donor was rather unreactive due to the three acyl groups.



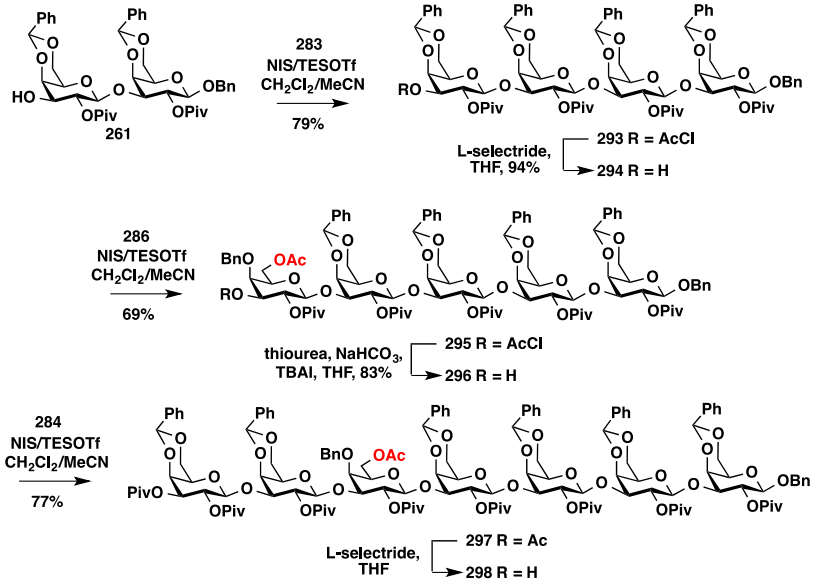
Scheme 83. Introduction of branching point.

Trisaccharide **287** was converted to trisaccharide acceptor **288** by deprotection of the chloroacetyl group with thiourea, $NaHCO_3$ and TBAI.[228] A second NIS/TESOTf-mediated glycosylation of **288** with disaccharide donor **283** afforded the pentasaccharide **289** in 80% yield. We were pleased to find that the reaction gave fewer by-products and that only 1.2 equiv. of donor was necessary. This confirms that it was the donor rather than degradation of the product that caused the problems in the first glycosylation. The chloroacetyl group was again removed with thiourea, $NaHCO_3$ and TBAI to give acceptor **290**, which could be glycosylated with the tripivaloyl donor **284** to give the fully protected heptasaccharide **291**. Finally, the C6-*O*-acetyl was removed selectively with L-selectride to give the acceptor **292**.



Scheme 84. Synthesis of heptasaccharide with branching point at 3rd residue.

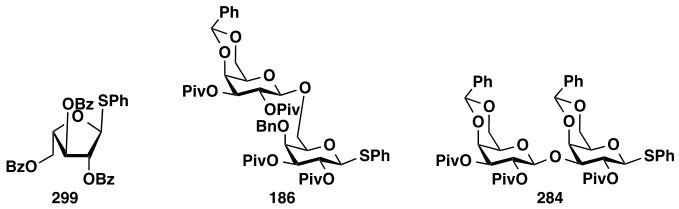
The second heptasaccharide was synthesized in the same way. NIS/TESOTf-promoted coupling of disaccharide donor **283** and acceptor **261** afforded tetrasaccharide **293** in 79% yield. Deprotection of the chloroacetyl group with L-selectride afforded tetrasaccharide acceptor **294,** which was coupled to monosaccharide donor **286** by a NIS/TESOTf-mediated glycosylation reaction to give the pentasaccharide **295** in 69% yield. The chloroacetyl group was removed with thiourea, $NaHCO_3$ and TBAI to give pentasaccharide acceptor **296**, which could be glycosylated with tripivaloyl donor **284** to give the fully protected heptasaccharide **297**. Finally, selective deprotection of the acetyl with L-selectride afforded the second heptasaccharide acceptor **298**.



Scheme 85. Synthesis of heptasaccharide with C6-*O*-acetyl on the 5th residue.

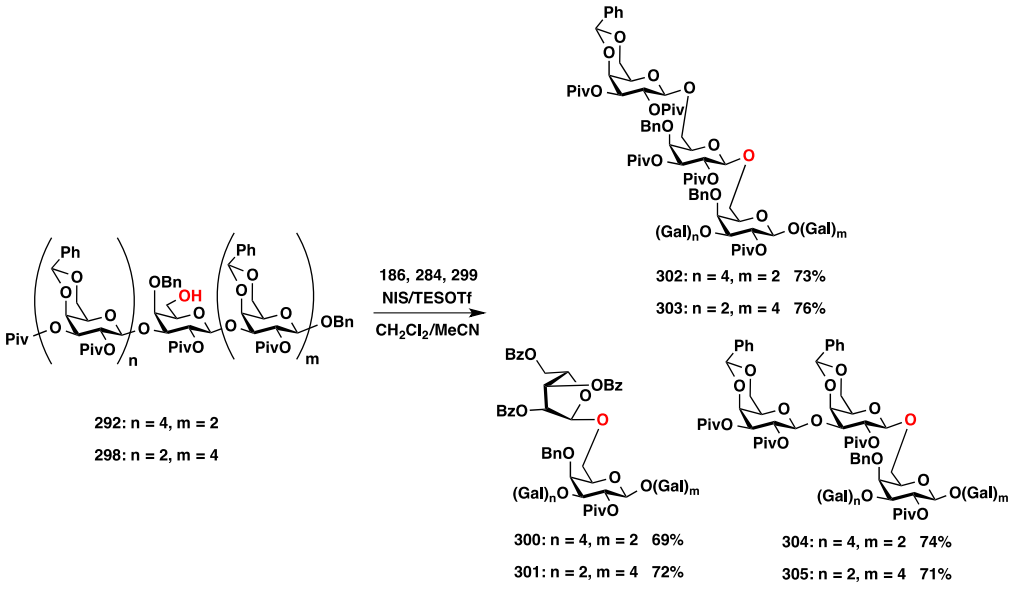
5.3.4 Introduction of branchings and global deprotection

Three different side chains were introduced on each heptasaccharide by glycosylation with the thioglycoside donors **186**, **299** and **284** shown in Scheme 86. Their synthesis has already been described in previous sections.



Scheme 86. Thioglycosides used for introduction of branchings.

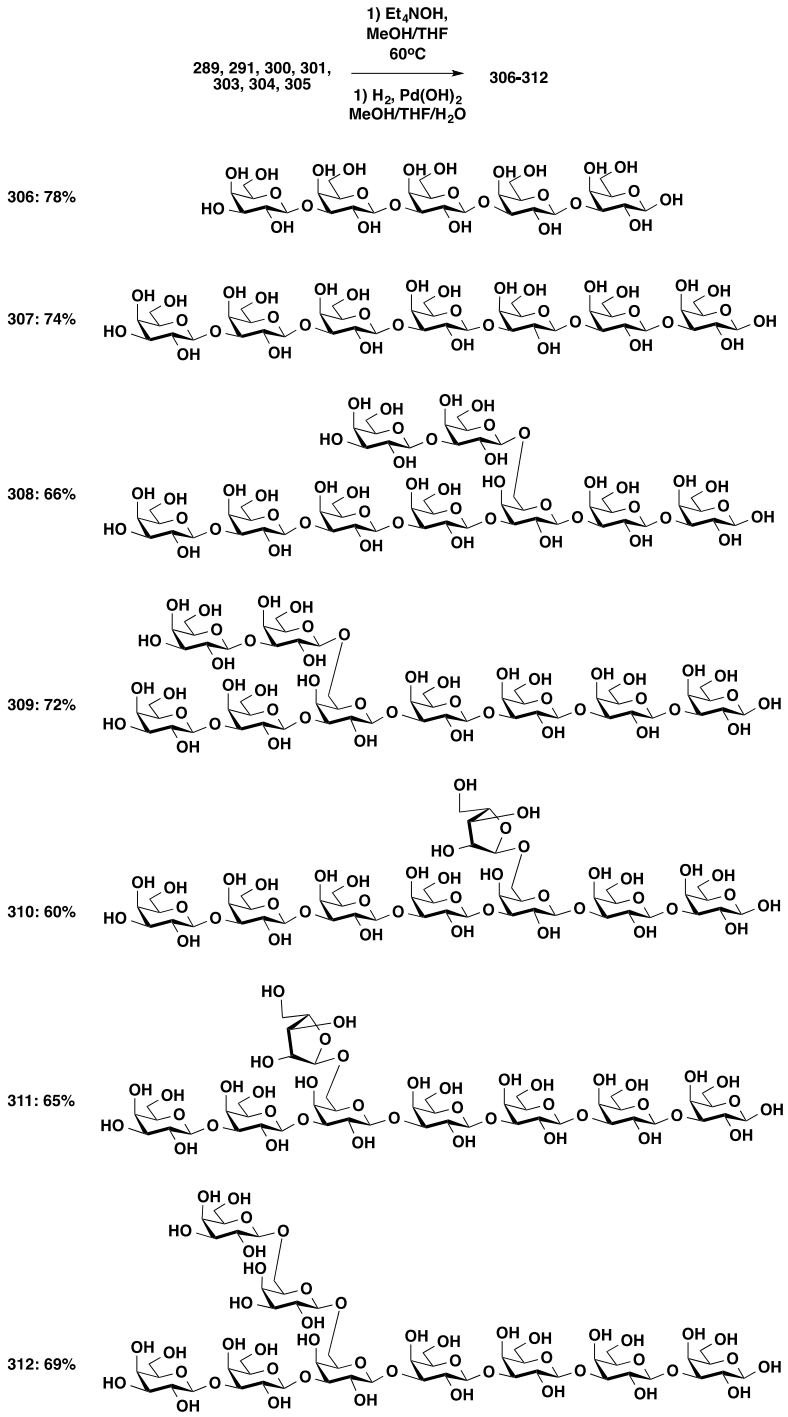
All of the glycosylations were promoted by NIS/TESOTf in a 1:1 mixture of CH_2Cl_2 and MeCN at -30 ºC (Scheme 87). The low temperature and use of MeCN was necessary to increase the stereoselectivity. The reactions were slow compared to the couplings to the 3-position and full conversion of the acceptor was not achieved even with 2 equiv. of donor. Just as for the branched β-(1→4)-linked galactans, the reactivity of the C6-*OH* seems to be reduced due to its position in the middle of the oligosaccharide chain. Nonetheless, the two octaasaccharides **300** and **301** and four nonasaccharides **302**-**305** were all isolated in yields above 70%. Unfortunately, compound **302** was lost prior to full characterization and needs to be resynthesized.



Scheme 87. Introduction of three different branchings.

Global deprotection of the linear penta- and heptasaccharide (**289** and **291**), two branched octasaccharides (**300** and **301**) and three nonasaccharides (**303**, **304** and **305**) was accomplished with the conditions described in section 4.9.2 (Scheme 88). Compared to the β-(1→4)-linked galactans, the deprotection of the pivaloyl group with Et_4NOH was faster and resulted in less by-products. This may be explained by the 1,2-trans diaxial relationship between β-(1→4)-linked sugars and neighboring hydrogen atoms, which makes them more susceptible to β-elimination. Unfortunately, the solubility of the partially protected (1→3)-linked galactans in common organic solvents is very low. This resulted in loss of material during purification and made the following hydrogenolysis over $Pd(OH)_2/C$ very slow (48 h). Even though the yields are still acceptable they could have been significantly higher if alternative conditions were found for the purification.

In conclusion, a strategy for linear and branched β-(1→3)-linked sugars has been developed and applied in the synthesis of a small library of AGP glycan fragments. The strategy makes it possible to introduce the branching point at different positions in the backbone. This could lead to interesting studies of various glycosyl hydrolases' ability to degrade branched sugars. The glycosylations of the heptasaccharide acceptors resulted in high yields and it is likely that larger and less reactive donors could also be used. An obvious choice would be to introduce β-(1→6)-linked tetra- and hexagalactans to make structures that mimic the AGP glycan to an even higher extent.



Scheme 88. Deprotection of β-(1→3)-oligosaccharid

6 Synthesis of β-(1→6)-D-galactan oligosaccharides

The final class of oligosaccharides that we were interested in were the β-(1→6)-linked galactans. As opposed to the other β-galactans, linear and branched (1→6)-linked galactans have been prepared via a wide range of strategies. The primary hydroxy group of the 6-position is much more reactive than both the 3- and 4-position. The glycosylation reactions are therefore generally more efficient and the protecting group manipulations are easier. However, the higher reactivity also exacerbates the stereoselectivity issue described in section 5. Thus, careful choice of protecting groups and reaction conditions is critical. Most of the published work describes synthesis of fragments AGP-glycan side chains. The references are compiled in Table 9.

Table 9. Published work on synthesis of β-(1→6)-linked galactans.

Synthetic oligosaccharide fragment	Reference
Trisaccharides	
α-L-Ara*f*-1→3-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Valdor & Mackie[260]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OSE *fully protected*	Ravindranathan *et al.*[261]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe *fully protected*	Kováč[262]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Kováč[263]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Ziegler *et al.*[264]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Srivastava *et al.*[265]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OCH_2CHOCH_2	Nashed & Glaudemans[266]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Kováč[267]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-$OC_4H_6pNO_2$	Ekborg *et al.*[268]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*	Bhattacharjee *et al.*[269]
Tetrasaccharides	
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-$O(CH_2)_3NH_2$	Liang *et al.*[270]
β-D-Gal*p*-(1→6)-[β-D-Gal*p*-(1→3)]-β-D-Gal*p*-(1→6)-D-Gal*p*	Ning *et al.*[271]
β-D-Gal*p*-(1→6)-[β-D-Gal*p*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-Ser *fully protected*	Du *et al.*[272]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-$O(CH_2)_3NH_2$	Fekete *et al.* [273]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p* *fully protected*	Yang *et al.*[274]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p* *fully protected*	Huang *et al.*[275]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-α-D-Gal*p*-OMe *fully protected*	Zhu & Kong[276]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-$O(CH_2)_{11}CH_3$	Du *et al.*[277]

Synthetic oligosaccharide fragment	Reference
[α-L-Ara*f*-1→2]-β-D-Gal*p*-(1→6)- β-D-Gal*p*-(1→6)-β-D-Gal*p*-$O(CH_2)_{11}CO_2Me$	Timmers *et al.*[278]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-$O(CH_2)_{11}CO_2Me$	Timmers *et al.* [278]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-$O(CH_2)_{11}CO_2Me$	Timmers *et al.* [278]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Ziegler *et al.*[279]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Nashed & Glaudemans[280]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OCH_2CHOCH_2	Nashed & Glaudemans[266]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Kováč[267]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe *fully protected*	Kováč[262]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OPr	Srivastava & Schuerch[281]
[α-L-Ara*f*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-D-Gal*p*	Pan *et al.*[282]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→3)]-D-Gal*p*	Pan *et al.*[282]
Pentasaccharides	
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-D-Gal*p* *fully protected*	Huang *et al.*[275]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→5)-α-L-Ara*f*-(1→2)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OM*p*	Zeng *et al.*[283]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-D-Gal*p*	Miura *et al.*[284]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6) -β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Kováč[267]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe *fully protected*	Kováč[262]
Hexasaccharides	
[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)- β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-$O(CH_2)_3NH_2$	Fekete *et al.* [273]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-*OMp*	Li & Kong [285]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-α-D-Gal*p*-*OMe*	Gu *et al.*[286]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-D-Gal*p*	Ning *et al.*[271]
β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe *fully protected*	Kováč[262]
Heptasaccharides	
β-D-Gal*p*-(1→3)-[{β-D-Gal*p*-(1→6)}$_4$-(1→6)]-β-D-Gal*p*-(1→3)-β-D-Gal*p*-OMp	Li & Kong[254]

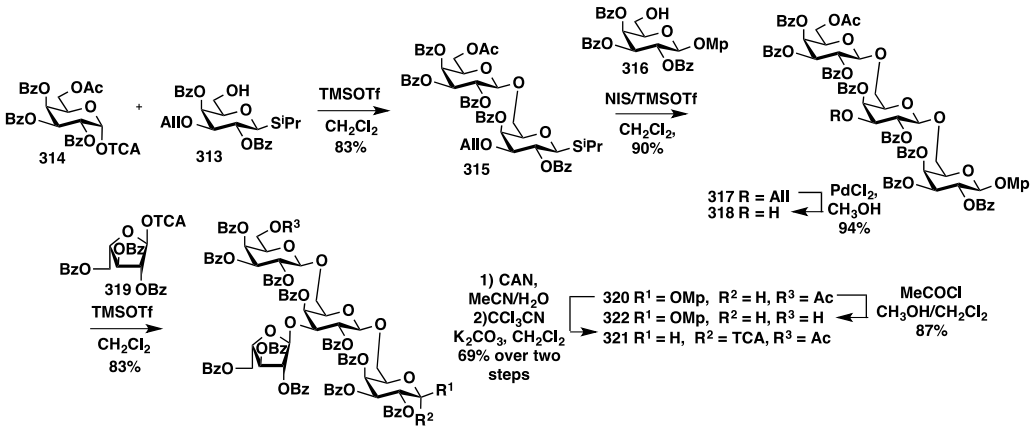
Synthetic oligosaccharide fragment	Reference
β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OMe	Ziegler *et al.*[279]
Octasaccharides	
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→5)-α-L-Ara*f*-(1→2)]-β-D-Gal*p*-(1→6)- β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→5)-α-L-Ara*f*-(1→2)]-β-D-Gal*p*-*OpMP*	Zeng *et al.*[283]
β-D-Gal*p*-(1→3)-[{β-D-Gal*p*-(1→6)}$_5$-(1→6)]-β-D-Gal*p*-(1→3)-D-Gal*p*-O*p*MP	Li & Kong [254]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-O*p*MP	Li & Kong [285]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-(1→6)-D-Gal*p*	Csávás *et al.*[287]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→5)-α-L-Ara*f*-(1→2)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→5)-α-L-Ara*f*-(1→2)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-*OpMP*	Li & Kong [288]
Nonasaccharides	
β-D-Gal*p*-(1→3)-[{β-D-Gal*p*-(1→6)}$_6$-(1→6)]-β-D-Gal*p*-(1→3)-D-Gal*p*-O*p*MP	Li & Kong [254]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→5)-α-L-Ara*f*-(1→2)]-β-D-Gal*p*-(1→6)-D-Gal*p*	Csávás *et al.*[287]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→5)-α-L-Ara*f*-(1→2)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-(1→6)-D-Gal*p*	Csávás *et al.*[287]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→5)-α-L-Ara*f*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-O*p*MP	Li & Kong [289]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→5)-α-L-Ara*f*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-O*p*MP	Li & Kong [289]
Decasaccharides and larger oligomers	
β-D-Gal*p*-(1→3)-[{β-D-Gal*p*-(1→6)}$_7$-(1→6)]-β-D-Gal*p*-(1→3)-D-Gal*p*-O*p*MP	Li & Kong [254]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-O*p*MP	Li & Kong[290]
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→2]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-1→3]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-O*p*MP	Li & Kong [285]

6.1 Previous studies of β-(1→6)-linked galactans

6.1.1 Synthesis of branched icosaose arabinogalactan by block synthesis

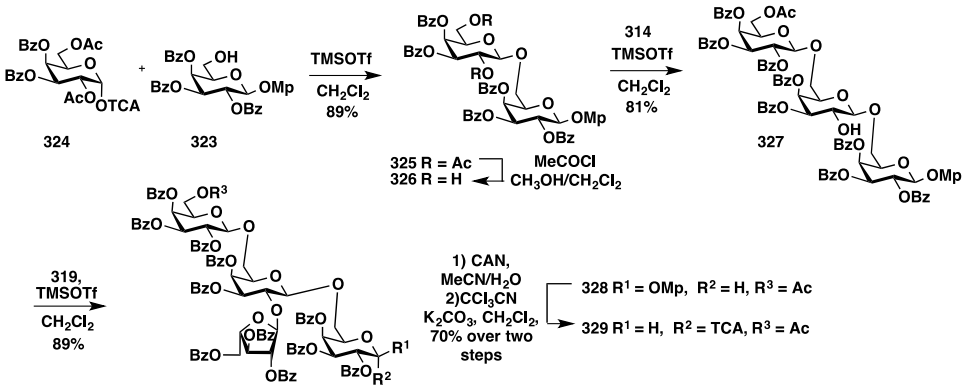
By means of a general synthetic strategy, Kong and co-workers have prepared a range of linear and branched arabinogalactans ranging from DP 4-20.[254,283,288–291] The largest structure is an icosaose consisting of a β-(1→6)-linked pentadecasaccharide backbone with arabinofuranose side chains attached at C-2 or C-3 of the middle galactose residue of each consecutive β-(1→6)-linked galactotriose unit. The strategy was based on synthesis block, which allowed for the consecutive couplings of two tetrasaccharide units. Acetyl groups were used as temporary protecting groups of the 6-position whereas allyl groups served as orthogonal protecting groups at the branching points.[285]

The C-3 branched tetrasaccharide building block was prepared starting from thioglycoside **313** (Scheme 89). Coupling to TCA donor **314** in a TMSOTf-catalyzed glycosylation reaction afforded disaccharide donor **315**. This was condensed with 4-methoxyphenyl acceptor **316** using NIS/TMSOTf as promoter to give trisaccharide **317** in an excellent yield. Subsequent, deallylation and coupling to the perbenzoylated TCA donor **319** gave the fully protected tetrasaccharide **320**. This could either be converted to donor **321** via oxidative cleavage of the *p*-methoxyphenyl group followed by trichloroacetimidate formation or turned into acceptor **322** by selective deacetylation under acidic conditions.



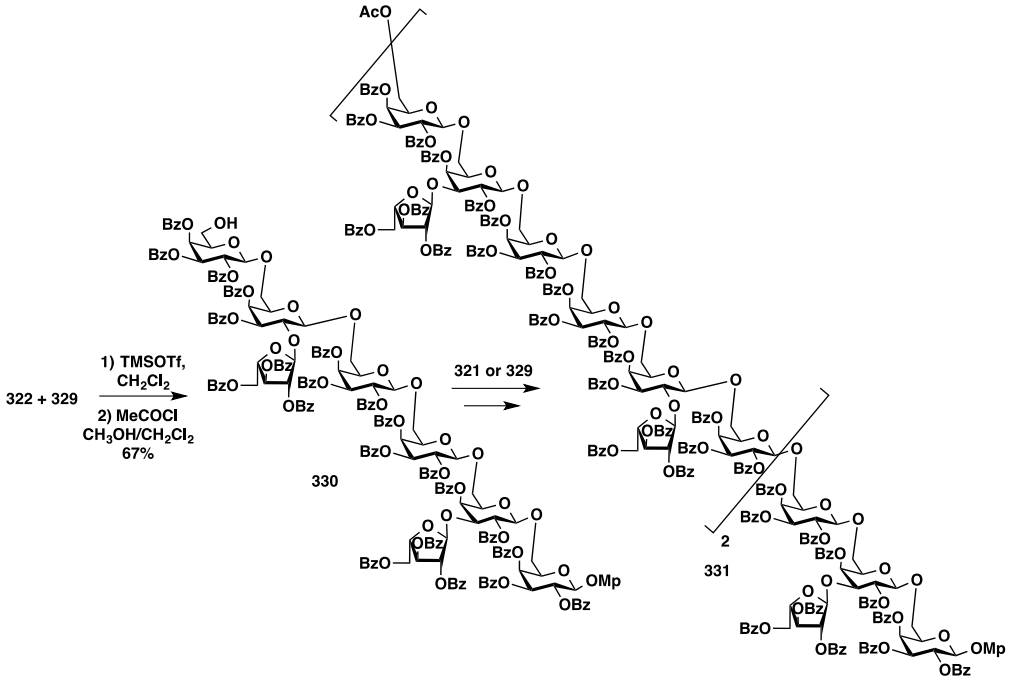
Scheme 89. Synthesis of 3-branched tetrasaccharide building block.

The C2'-branched tetrasaccharide was prepared by a similar method (Scheme 90). TMSOTf-catalyzed glycosylation of 4-methoxyphenyl acceptor **323** with diacetyl-protected donor **324** afforded disaccharide **325** in 89% yield. Deacetylation under acidic conditions gave the diol **326,** which after regioselective glycosylation of the 6-postion with donor **314** afforded trisaccharide **327**. It is remarkable that none of the (1→2)-linked trisaccharide was observed. Now the C2-*OH* was the only nucleophile and it was possible to couple **327** with TCA donor **319** to give tetrasaccharide **328**. Finally, oxidative cleavage of the methoxyphenyl group followed by trichloroacetimidation gave the tetrasaccharide donor **329**.



Scheme 90. Synthesis of 2-*O*-branched tetrasaccharide building block.

TMSOTf-catalyzed coupling of the two tetrasaccharides followed by selective deacetylation gave the octasaccharide acceptor **330** (Scheme 91). This sequence was repeated three times with either donor **321** or donor **329** to give the icosaose **331**. The yields of the glycosylations decrease with the growing size of the acceptor but remain over 65% for all coupling.



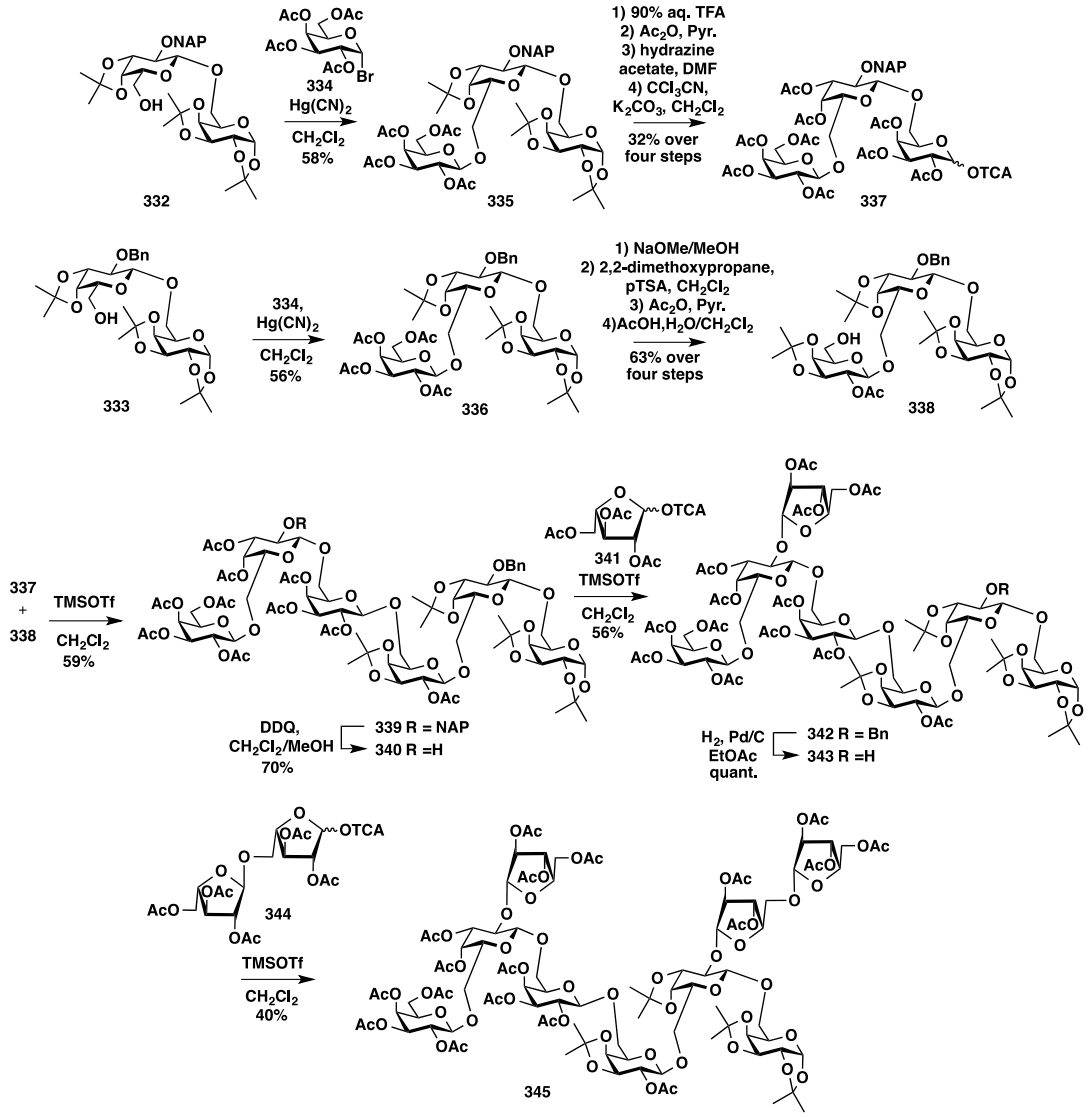
Scheme 91. Synthesis of 2- and 3-branched icosaose 331.[285]

6.1.2 Synthesis of arabinogalactan-type octa- and nonasaccharide

Lipták and co-workers reported the synthesis of double-branched octa- and nonasaccharides.[287] The key reaction in the strategy was the treatment of β-D-galactopyranosyl-(1→6)-galacto-pyranose with 2,2-dimethoxypropane in the presence of an acid catalyst. This made it possible to access disaccharide **332** and **333** in just three steps. The C2'-*OH* was protected with either a benzyl- or NAP-ether that served as acid and base stable orthogonal protective groups. Both can be removed by hydrogenolysis but the NAP group can also be cleaved under oxidative conditions with DDQ or CAN. The two disaccharides were coupled to glycosyl bromide **334** in a Hg(CN)-$_2$-catalyzed Helferich glycosylation to afford trisaccharides **335** and **336** in 58% and 56% yield, respectively (Scheme 92).[292] The NAP-protected

trisaccharide **335** was converted to the corresponding trichloroacetimidate donor **337** in four steps whereas protecting group manipulations on **336** gave acceptor **338**. TMSOTf-catalyzed coupling of the two trisaccharides gave the fully protected hexasaccharide **339** in 59% yield. The orthogonal protecting groups at the 2-positions made it possible to prepare all of the three oligosaccharides from this building block.

First, the NAP-ether was removed with DDQ to afford **340,** followed by glycosylation with the peracetylated TCA donor **341** to give heptasaccharide **342** in 56% yield. Next, hydrogenolysis liberated the C2'-*OH*, which was glycosylated with donor **344** to give nonasaccharide **345**. Global deprotection was accomplished in two steps by deacetylation under Zemplén conditions followed by mild hydrolysis of the isopropylidenes with TFA. The low yield in the final glycosylation results in a low overall yield (approx. 1%). It is nonetheless remarkable that molecules of this complexity can be made in just 13 steps for the longest linear sequence.



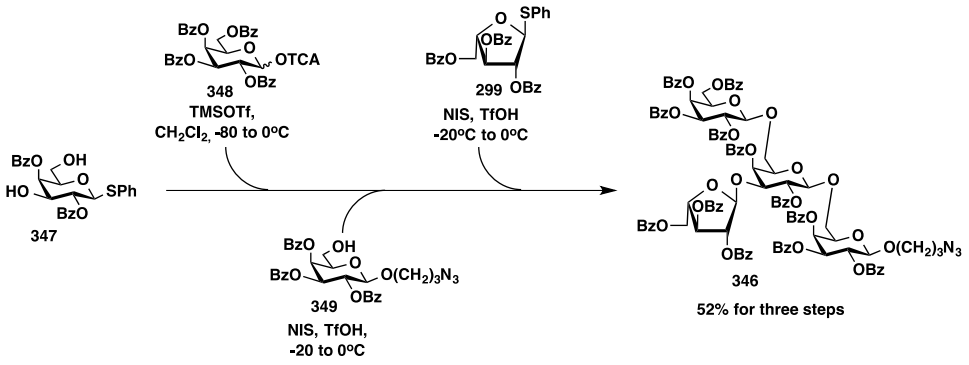
Scheme 92. Strategy for synthesis of C2-branched arabinogalactans.[287]

6.1.3 One-pot synthesis of arabinogalactan fragments

The two routes discussed so far required multiple protection/deprotection steps for elongation of the sugar chain, which makes them time consuming. One way to address this problem is to perform several glycosylation in a single vessel without intermediate purification also known as one-pot synthesis. This approach has received growing attention due to its efficiency in rapid preparation of oligosaccharides.

Recently, Yang and co-workers reported a one-pot synthesis of a (1→3)-branched β-(1→6)-linked tetrasaccharide **346** (Scheme 93).[270] The strategy relies on the reactivity difference of the primary and secondary hydroxy groups. Starting from the 3,6-dihydroxy thioglycoside **347**, it was possible to perform a regio- and chemoselective glycosylation of the primary alcohol with TCA donor **348**.

Next, another regioselective coupling of the resulting disaccharide with acceptor **349** gave the trisaccharide. Finally, the remaining secondary hydroxy group was glycosylated with thioglycoside **299** to give the perbenzoylated tetrasaccharide **346** in 52% yield for three steps. The entire sequence takes less than 5 h, which makes it an interesting alternative to existing methods. It should however be mentioned that only relatively small oligosaccharides have been made by one-pot strategies so far. The major reason being that all glycosylations must be very effective in order to avoid too many deletion sequences.

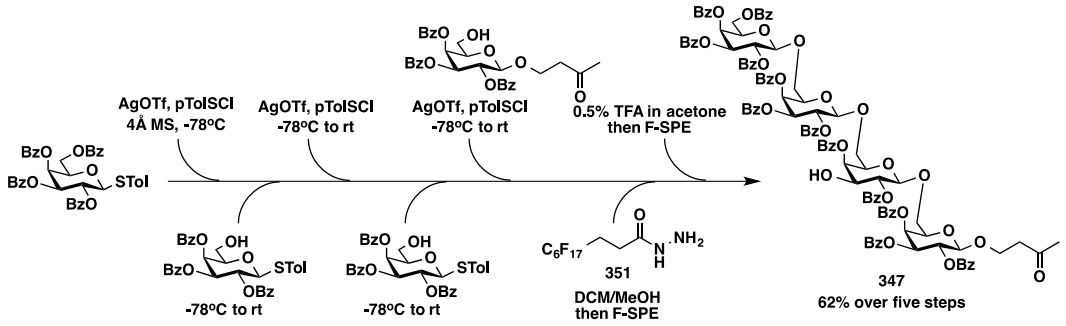


Scheme 93. One-pot four-component synthesis of 3,6-branched arabinogalactosyl glycoside 346.[270]

Another problem in one-pot synthesis is the purification of the final product. Due to the many manipulations done in a single step, this is often a challenging process that requires time- and solvent-consuming flash chromatography. Huang and co-workers developed a new methodology to solve this problem.[274] After the one-pot synthesis is done a fluorous tag is used to selectively "catch" the desired oligosaccharide. This makes it possible to purify the conjugate by a simple fluorous solid-phase extraction (F-SPE). Subsequently, the oligosaccharide is "released" from the fluorous tag that can be removed by a second F-SPE purification.

The methodology was applied in the one-pot synthesis of the linear β-(1→6)-linked tetragalactoside **347** (Scheme 94). The tetrasaccharide was made by sequential preactivation-based glycosylation of three thioglycoside donors using AgOTf/*p*TolSCl as promoter. After the glycosylations, the reaction mixture was treated with the fluorous hydrazide **351** under mild acidic conditions resulting in formation of corresponding hydrazone. This made it possible to remove all non-fluorous compounds by F-SPE.

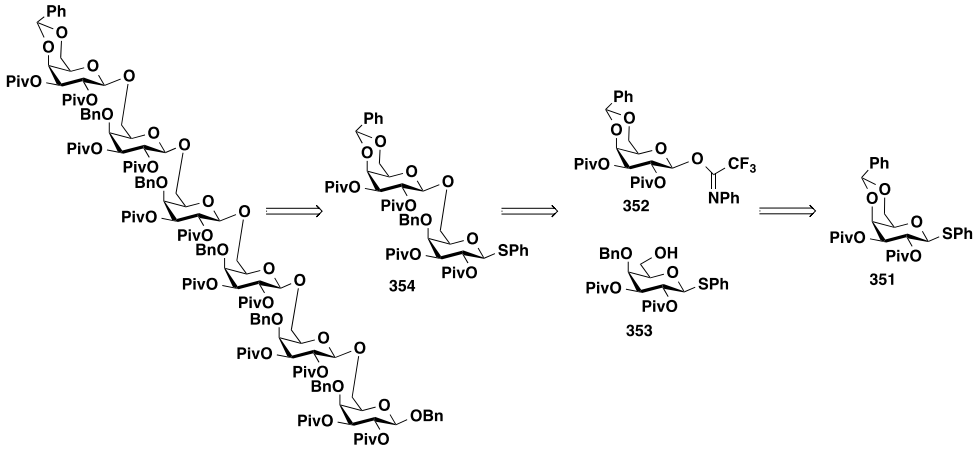
Finally, acidic hydrolysis of the hydrazone and another F-SPE column gave the pure tetrasaccharide **347** in 62% yield over five steps. The 4-hydroxy-2-butanone "handle", furthermore, has the advantage that it can be removed by a *retro*-Michael reaction under Zemplén conditions to produce the free sugar. The entire synthesis and purification took less than three hours.



Scheme 94. Synthesis of linear tetrasaccharide by a fluorous-assisted one-pot strategy.[274]

6.2 β-(1→6)-Linked linear tetra, hexa- and octagalactans

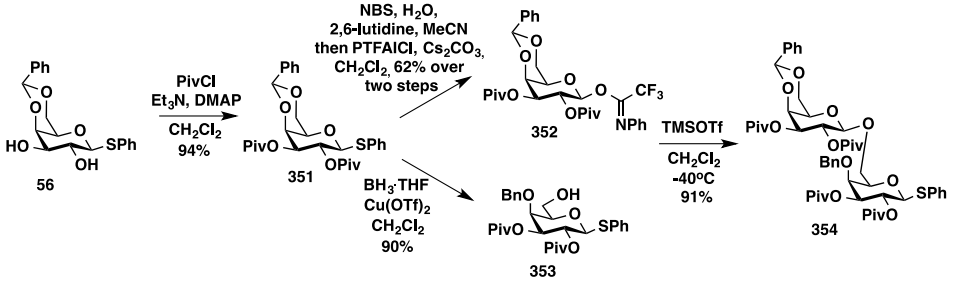
As described in the previous section, excellent methods already exist for synthesis of β-(1→6)-galactans and there is no point in re-inventing the wheel. Nevertheless, we were interested in studying if it would be possible to apply the same concept that had been used for the (1→3)- and (1→4)-linked galactans. A single monosaccharide building block **351** was converted to orthogonal donor **352** and acceptor **353** and coupled (Scheme 95). The resulting disaccharide **354** could be turned into an acceptor but was also used as donor in the consecutive glycosylations. In this way the synthesis was kept short and was easily scaled up. It was decided to use a thioglycoside building block, since aglycon transfer should not be a problem. Good results had previously been obtained in the regioselective opening of benzylidene acetals with borane-THF complex and copper(II) triflate.[196] A benzylidene acetal was therefore chosen as the temporary protecting group. The 2- and 3-positions were protected with pivaloyl esters to get anchimeric assistance while avoiding migration and orthoester formation.



Scheme 95. Retrosynthetic analysis of the synthesis of β-(1→6)-linked galactans.

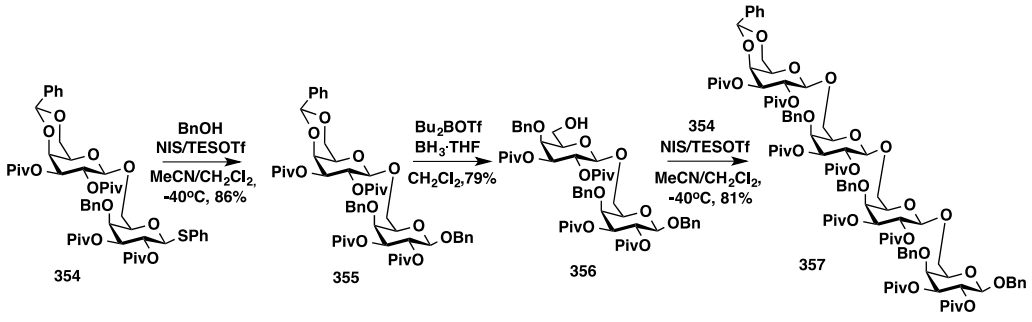
6.2.1 Synthesis of tetrasaccharide based on benzylidene protected donor

The synthesis of the disaccharide donor **354** is outlined in Scheme 96. Starting from the known thioglycoside **56**, the C2- and C3-*OH* was protected with pivaloyl esters to give **351**. Interestingly, only the 3-position was protected, if the reaction was carried out at 22 °C with 0.1 equiv. of DMAP. This is consistent with reports by Jiang and co-workers, who isolated the same compound after treatment with pivaloyl chloride and pyridine.[293] Complete protection was achieved when the reaction was heated to reflux and 0.5 equiv. DMAP was used. Thioglycoside **351** was hydrolyzed with NBS/H_2O/2,6-lutidine followed by treatment with PTFAICl and Cs_2CO_3 to give the corresponding PTFAI glycoside **352**.[207] Thioglycoside **351** was converted to acceptor **353** by regioselective opening of the benzylidene acetal with BH_3·THF and $Cu(OTf)_2$.[216] Coupling of PTFAI donor **352** and acceptor **353** by TMSOTf-promoted glycosylation afforded disaccharide **354** in 91% yield. It was critical to perform the reaction at low temperature since formation of the α-product was otherwise observed.



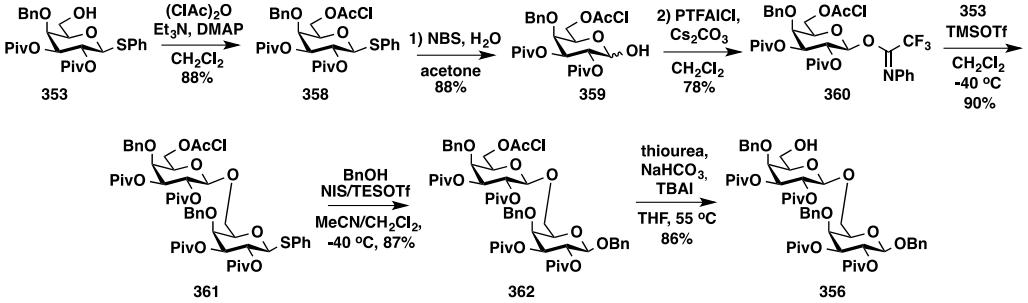
Scheme 96. Synthesis of disaccharide donor 354.

Thioglycoside **354** was converted to an acceptor in two steps (Scheme 97). First, the anomeric center was protected with a benzyl group by glycosylation of benzyl alcohol to give **355** in 86% yield. The following regioselective opening of the benzylidene acetal turned out to be problematic. The $Cu(OTf)_2/BH_3$·THF combination resulted in significant hydrolysis of the glycosidic linkage and **355** was isolated in only 35% yield. Similar results were obtained after treatment with $PhBCl_2/Et_3SiH$ at -78 ºC.[294]. The best method proved to be Bu_2BOTf/BH_3·THF, which afforded disaccharide acceptor **356** in 79% yield.[295,296] However, the reaction still gave rise to hydrolysis and the problem was believed to increase in the following benzylidene openings due to the increasing number of glycosidic linkages. It was therefore decided to change the strategy.



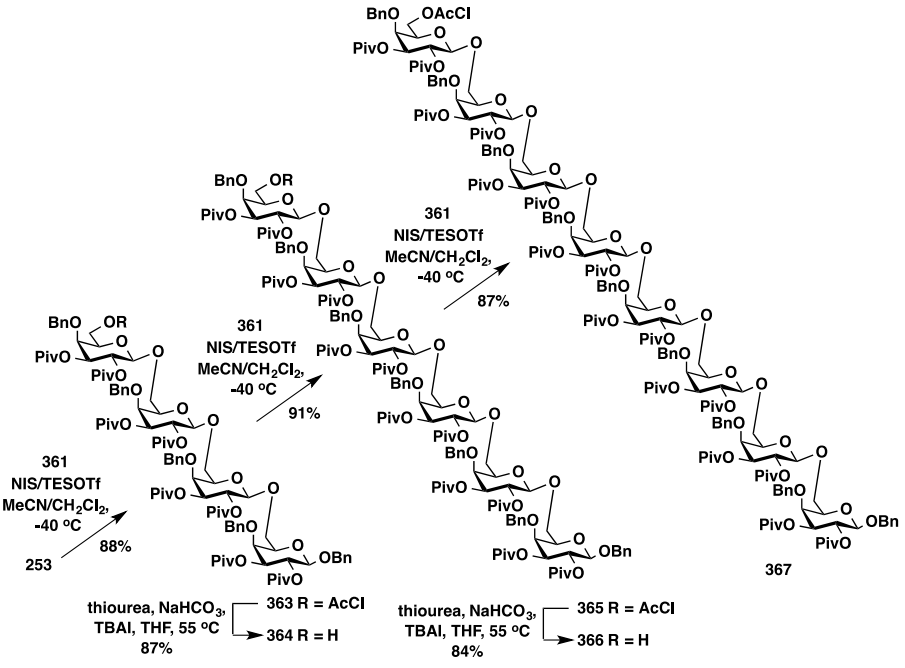
Scheme 97. Conversion of thioglycoside 354 into disaccharide acceptor 356.

The C6-*OH* of thioglycoside **353** was instead protected with a chloroacetyl group to give thioglycoside **358** (Scheme 98). Hydrolysis with NBS in wet acetone afforded hemiacetal **359**. In this case it was not necessary to add a base, which resulted in a faster reaction. The hemiacetal was converted to the PTFAI donor **360** by treatment with PTFAICl and Cs_2CO_3 and coupled to thioglycoside **353** in a TMSOTf-promoted glycosylation. The reaction was slow compared to the benzylidene acetal-protected PTFAI donor **352**, but disaccharide **361** was isolated in similar yield. The reducing end building block **356** could now be prepared without problems by NIS/TESOTf-mediated glycosylation of benzyl alcohol to give **362** followed by deprotection of the chloroacetyl with thiourea, $NaHCO_3$ and TBAI.



Scheme 98. Synthesis of chloroacetyl-protected disaccharide donor 361.

NIS/TESOTf-promoted glycosylation of disaccharide acceptor **363** with disaccharide donor **361** gave the tetrasaccharide **363** in excellent yield (Scheme 99). The chloroacetyl group was removed with thiourea, $NaHCO_3$ and TBAI to give acceptor **364** followed by a second NIS/TESOTf-promoted glycosylation with donor **361** to give the hexasaccharide **365**. A final deprotection and glycosylation afforded the fully protected octasaccharide **367**. The yield and reaction time were very similar in the three glycosylations. It is therefore likely that much longer oligosaccharides can be made with this protecting group combination.



Scheme 99. Synthesis of tetra-, hexa- and octasaccharide 363, 365 and 367.

In conclusion, we have shown that it is possible to use a general strategy for synthesis of β-(1→3), β-(1→4) and β-(1→6)-galactans. As expected, the glycosylations of the primary hydroxy group gave significantly higher yields compared to the 3- and 4-position and problems such as aglycon transfer and poor stereoselectivity were not observed. One of the advantages in this strategy is that the C4-*O*-benzyl blocks potential acyl migration. This is a problem in many of the published strategies since acyl groups have a tendency to migrate towards the 6-position under both acidic and basic conditions.[142] Branching could be easily introduced with the 3-*O*-NAP protected monosaccharide **204** and since no primary benzyl groups are present the selective deprotection should be straightforward. This was, however, outside the scope of this project. Likewise, deprotection of the β-(1→6)-linked oligosaccharides was not performed before the deadline.

7 Applications of synthetic D-galactan oligosaccharides

A major obstacle in the study of pectin's glycobiology is the lack of pure and structurally well-defined carbohydrates. The complexity of the degradation products and the micro heterogeneity of polysaccharides greatly complicate their isolation and characterization from natural sources. The oligosaccharides prepared throughout this work can therefore be used to get new, valuable information about the pectic structure, biosynthesis and degradation. The synthesis of the complex oligosaccharides was not completed until the end of the PhD and therefore only a limited number of substrates have been available for the collaborators. Nevertheless, some of the smaller oligosaccharides have already found application in three different studies. This section gives a short introduction to some of the results.

7.1 Pectin Biosynthesis: GALS1 in *Arabidopsis thaliana* is a β-1,4-Galactan β-1,4-Galactosyltransferase

The first application of the oligosaccharides was performed by H. Scheller and co-workers at Lawrence Berkeley National Laboratory, Berkeley, California. They were interested in studying the biosynthesis of pectin that involves a range of enzymes (e.g. glycosyl transferases), of which only a few have been identified.[297]

The investigation was based on recent finding of a new family of glycosyltranferases, GT92, which acts as β-(1→4)-galactosyltransferases in animals. The GT92 protein was reported from pigeons, where they catalyze the transfer of β-(1→4)-linked Gal onto β-(1→4)-linked Gal in *N*-glycan structures.[298] All plants that have had their genome sequenced contain members of the GT92 family but since plants do not have β-(1→4)-linked *N*-glycans, they are likely to have another role. Tension wood is known to be rich in β-(1→4)-galactan and it was therefore decided to study the function of three members of the GT92 family in *Arabidopsis thaliana.* The proteins were designated GALS1, GALS2 and GALS3. Loss-of-function mutants in the corresponding genes resulted in decreased β-(1→4)-galactan content, and overexpression of GALS1 resulted in plants with 50% higher β-(1→4)-galactan content. These results strongly suggest that GALS1 acts as β-(1→4)-synthase.

For further characterization of the galactosyltransferase activity, it was necessary to determine the substrate. It was not possible to isolate pure β-(1→4)-linked galactans from plant sources. Instead, galactotriose, -tetraose and –pentaose (**130**-**132**) synthesized by the strategy described in section 4.7 were studied as acceptors. The protein was heterologously expressed and incubated with the acceptor and ^{14}C-labeled uridine diphosphate galactose (UDP-[^{14}C]Gal). Purification and analysis by liquid scintillation counting showed substantial transfer of Gal onto the galactopentaose but not the other acceptors. The activity obtained with FLAG-GALS1 corresponds to more than 50 nmol Gal h^{-1} mg $protein^{-1}$ with 0.34 mM UDP-Gal (Figure 14A). The specific activity is substantially higher than what has been reported for other cell wall–related glycosyltransferases after heterologous expression. TLC analysis demonstrated a

ladder of products, with longer incubation times and higher UDP-Gal/acceptor ratios leading to increasingly large products (Figure 14B). Interestingly, TLC indicates that the incorporation speed was higher for the products than the pentaose acceptor. This suggests that the hexaose, heptaose and octaose may be even better substrates for the enzyme.

It is not clear if the GALS1 enzyme will add the first Gal residues onto the RG-I backbone, but it is unlikely due to the very different properties of the acceptor polysaccharide. Most likely, one or two as yet unidentified galactosyltransferases are required to initiate the β-(1→4)-galactan side chains. This is agreement with GALS1's lack of activity towards short acceptors. Further studies with the larger oligosaccharides discussed in section 4.10 will possibly give more insight to the enzyme specificity and potentially lead to activity for the GALS2 and GALS3 enzymes.

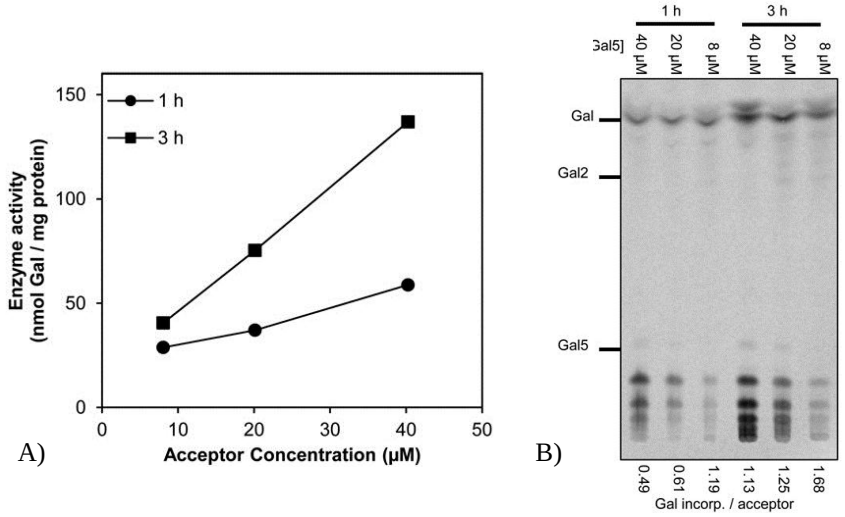


Figure 14. A) Activity of GALS1 as a function of acceptor concentration. B) TLC analysis showing the formation of the more polar hexa, hepta, octa and nonasaccharide products

7.2 Distinct substrate specificities of three glycoside hydrolase family 42 β-galactosidases from Bifidobacterium longum subsp. infantis ATCC 15697

Over the last decade, genome sequencing and homology modeling has resulted in discovery of several new glycosyl hydrolase families. However, insight into the specificity of individual enzymes with respect to substrate monosaccharide composition, glycosidic linkage, and degree of polymerization is lagging. Not only is enzyme isolation difficult but in many cases the studies are also precluded by a lack of well-defined substrates. The simple oligosaccharides β-(1→4)-galactotriose and -tetraose (section 4.7) and β-(1→6)-galactotetraose (see section 6.2) were therefore included in a study performed by A. Viborg at the Department of Systems Biology, DTU, Lyngby, Denmark.[299]

Viborg and co-workers were interested in studying glycoside hydrolase family 42 (GH42), which includes β-galactosidases catalyzing the release of galactose from the non-reducing end of different β-D-galactosides. Health-promoting probiotic bifidobacteria, which are important members of the human gastrointestinal tract microbiota, produce GH42 enzymes enabling utilization of β-galactosides exerting prebiotic effects.[299]

Kinetic analysis of natural and synthetic substrates resembling various milk and plant galactooligosaccharides made it possible to distinguish the three GH42 members, Bga42A, Bga42B and Bga42C, encoded by the probiotic *B. longum* subsp. infantis ATCC 15697. The results revealed the glycosyl residue at subsite +1 and its linkage to the terminal Gal at subsite -1 to be key specificity determinants. Bga42A thus prefers the β-(1→3)-galactosidic linkage from human milk oligosaccharides (HMOs) and other β-(1→3)- and β-(1→6)-galactosides with glucose or Gal situated at subsite +1. In contrast, Bga42B very efficiently hydrolyses (1→4)-galacto-syllactose (Galβ1→4Galβ1→4 Glc) as well as 4-galactobiose (Galβ1→4Gal) and 4-galactotriose (Galβ1→4Galβ1→Gal). The specificity of Bga42C resembles that of Bga42B, but the activity was one order of magnitude lower. Based on enzyme kinetics, gene organization and phylogenetic analyses, Bga42C is proposed to act in the metabolism of arabinogalactan-derived oligosaccharides. Overall, the data illustrate the metabolic adaptation of bifidobacteria to the β-galactoside-rich gut niche and emphasize the importance and diversity of β-galactoside metabolism in probiotic bifidobacteria.[299]

7.3 Determination of LM16-specificity by microarray screening

One of the main objectives in the project was to prepare a microarray with a range of defined pectic oligosaccharide fragments in collaboration with Willats and co-workers. Oligosaccharide fragments of the homogalacturonan- and rhamnogalactorunan backbone had previously been prepared and current work in the Clausen group also includes synthesis of arabinans.[300,301] Microarrays make it possible to assess hundreds or thousands of molecular interactions simultaneously using minimal amounts of analytes. Thus, the arrayed samples could be interrogated by a number of different glycan-binding proteins, ligands or enzymes including Gal-3 and monoclonal antibodies. The preliminary studies of the oligogalactans were performed on the unprotected oligosaccharides **42**-**45**.

The system developed by Willats and co-workers was based on probe capture where the oligosaccharides are immobilized on a surface and then exposed to probes in solution.[302,303] Binding of the probes to arrayed oligosaccharides is detected by means of a fluorescent or colorimetric tag, usually coupled to an antibody. This is analogous to antibody-capture enzyme-linked immunosorbent assays (ELISAs) and contrasts with most nucleotide microarrays and some protein microarrays in which the probes are immobilized and the substrates added in solution.[302]

The method relies on non-covalent immobilization on nitrocellulose membranes, which is advantageous since the samples can be spotted directly onto the membrane. Unfortunately, non-covalent immobilization is generally not effective for oligosaccharides of less than ten sugar residues. In order to overcome this, the oligosaccharides were coupled to bovine serum albumin (BSA).[302] The use of BSA as a carrier molecule has the advantage that BSA-based neoglycoproteins are a multifunctional resource that can be used not just for microarray production but also as immunogens and as components of other assays, for which immobilization is required. However, any coupling procedure that involves modification of

reducing ends is likely to interfere with the activity of reducing end-acting probes or enzymes, and this may be exacerbated by the large size of the BSA molecule.[304]

The conjugation of tetrasaccharide **42-45** to BSA was carried out by reductive amination between the sugars reducing end residue and the ε-amino functionality of lysine in BSA. The best results were obtained with a procedure by Knox and co-workers, where $NaCNBH_3$ is used as reducing agent in a borane/sulphate buffer.[305] The work-up was done by filtration through centrifugal filter with a cut-off of 10 kDA. This made it possible to remove unreacted sugar residues and the buffer leaving only the protein behind. Based on the starting material, 40-60% of the BSA-conjugate was recovered from the four experiments. The products were analyzed by Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight (MALDI-TOF), which indicated 7 to 12 sugar residues/BSA molecule.

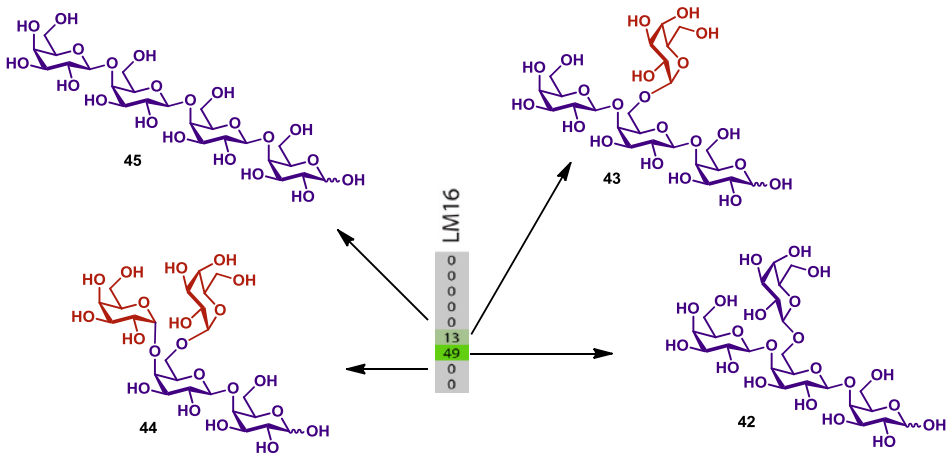


Figure 15. Binding of mAb LM16 to linear- and branched tetragalactoside-BSA conjugates.

Microarray printing and binding analysis was performed by Willats and co-workers. The branched oligosaccharides **42**, **43** and **44** are not known to occur on any plant cell wall polysaccharide and it was therefore surprising that mAb LM16 bound strongly to 6'-β-D-galactosyl-(1→4)-β-D-galacto-triose **42** (Figure 15). LM16 has previously been described to bind an epitope occurring on sugar beet RG-I that is generated by arabinofuranosidase treatment and is galactosidase labile.[306] Sugar beet arabinan side chains can in some cases be attached to RG-I backbones via short galactosyl motifs and it is possible that LM16 recognizes this structure once exposed by arabinofuranosidase.[306] It has been shown that such short galactan stubs can be substituted with ferulic acid at the C6 position but substitution with another sugar has not been reported[307]. LM16 does not bind to galactosyl residues per se since it does not bind to linear galactan, galactomannan or galactoxyloglucans. The strong binding of LM16 to both structure **42** and native sugar beet pectin therefore raises the intriguing possibility of a novel RG I epitope. It will be very interesting to test the affinity of LM16 and other mAbs for the larger oligosaccharides fragments.[304]

The results suggest that the microarray technology is a promising tool for studying protein-glycan interactions. It has not been possible to set up a rigid system for screening of Gal-3 affinity due to limited access to pure Gal-3. However, we hope that this issue will soon be solved so that the binding affinity of defined oligogalactans to Gal-3 can be tested in the near future.[304]

7.4 Co-crystallization of Gal-3 and β-(1→4)-pentagalactoside

As described in section 3.2, it has been hypothesized that the CRD of Gal-3 is able to accommodate a linear tetrasaccharide. If this is the case, oligosaccharides of four or more residues are likely to have higher binding affinity than *N*-acetyllactosamine (LacNAc), which has previously been used as scaffold for development of Gal-3 inhibitors. No crystal structures have been published of Gal-3 in complex with carbohydrates larger than disaccharides. Since RG-I fragments are believed to be ligands for Gal-3, it was decided to crystallize Gal-3 in complex with the linear pentasaccharide **132**. This could give valuable information about the binding site and guide us in the design of better ligands.

The protein crystallization and crystallography was performed in collaboration with the Nilsson group and SARomics Biostructures in Lund. They had previously solved high-resolution X-ray crystal structures of human Gal-3 in complex with a series of LacNAc-conjugates and, consequently, had a great expertise in Gal-3 expression and crystallization.

The co-crystallization turned out to be challenging. Lactose contaminants in the first protein sample occupied the binding site and thereby precluded co-crystallization with the ligand. However, use of a lactose-free batch of protein and a higher ligand concentration made it possible to obtain a crystal structure of Gal-3 in complex with pentasaccharide **132** at 1.4 Å resolution. A cartoon- and surface model of the structure is shown in Figure 16A-C. Contrary to expectations, Gal-3 only binds two of the five galactose residues. The remaining residues are too flexible to be observed. Moreover, the second residue appears to have a lower occupancy than the first one. Since the first residue has full occupancy and there is presumably no hydrolysis of the ligand, this means that the second residue has other conformations. Given that the binding site has really evolved to bind glucose in the second site, it is perhaps not surprising that galactose binds with lower affinity. Important interactions observed between the C3-*O* of glucose and Arg162/Glu184 seem to be lost, and a water molecule binds there instead (Figure 16D). Nonetheless, it is surprising that the pentasaccharide does not occupy subsite A and B.

The results suggest, that the general view of Gal-3's carbohydrate recognition domain as a multi-sugar binding site should be subject to revision. Even though the binding of the β-(1→4)-linked galactan seems to be poor it does not exclude it as a potential ligand of Gal-3. As described in section 3.2 Gal-3 is able to form oligomers and binding to several digalactan motifs could therefore result in a significantly higher total binding affinity.[308]

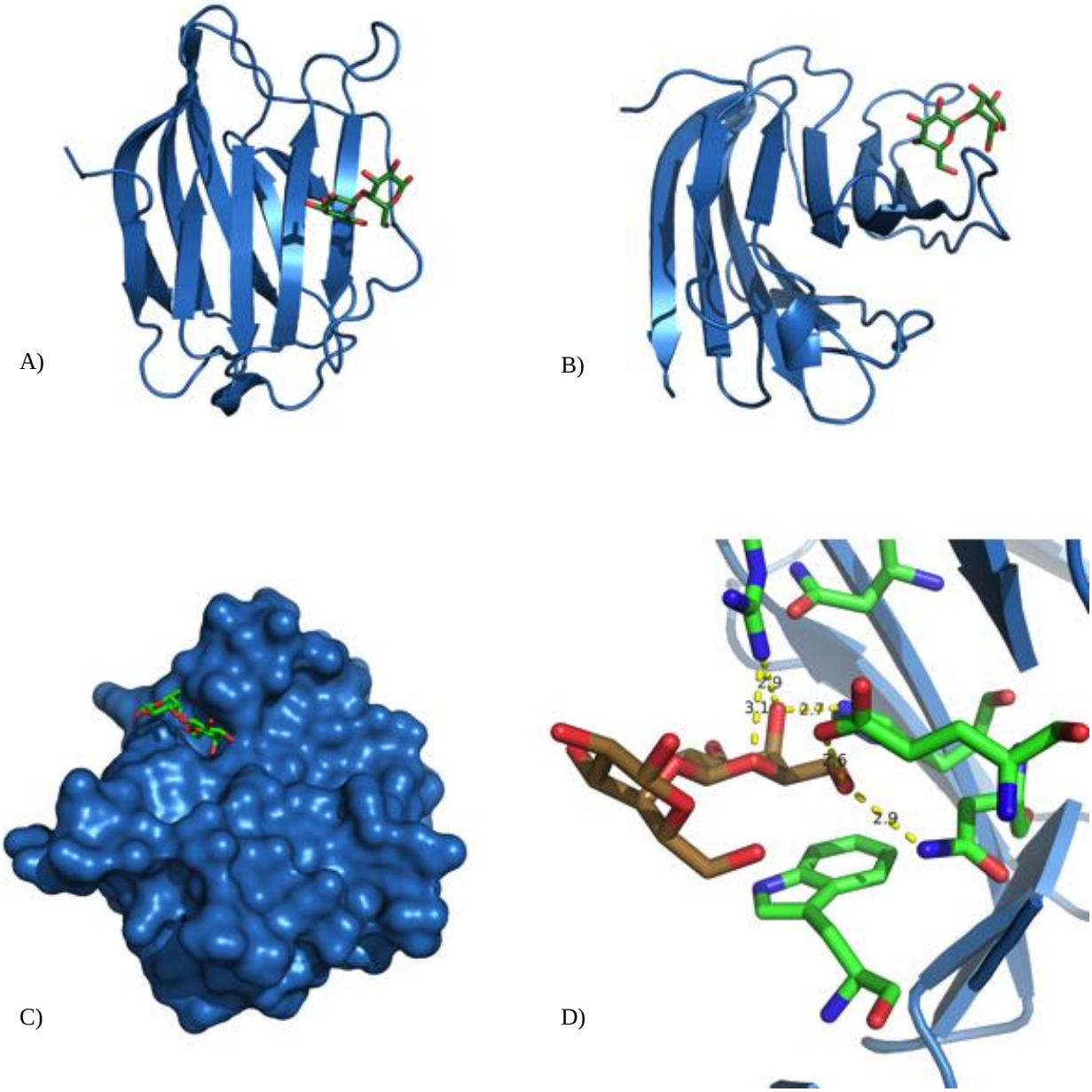


Figure 16. A) and B) Cartoon representations of Galectin-3 in complex with β-(1→4)-linked pentagalactoside 132 C) Surface model of Galectin-3 showing binding pocket D) Close-up of the binding pocket showing the polar connections to the ligand.

8 Tunicamycin analogues as glycosyltransferase inhibitors

8.1 Project background

Disease-causing microbes that have become resistant to drug therapy are an increasing public health problem. Until recently, research and development efforts have provided new drugs in time to treat bacteria that became resistant to older antibiotics. However, the development of new antimicrobial agents has slowed dramatically and we may face the prospect of a future, where we have far fewer options in the treatment of infectious diseases. This may lead to a scenario, where simple surgeries may be life threatening due to routine infections.

One of the reasons for the decline in new antibiotics is the challenge of developing new drug scaffolds. This requires huge libraries of compounds with great diversity and a reliable screening setup. A much simpler approach would be to alter a naturally occurring antibiotic and thereby change its activity or selectivity. In this way it may be possible to develop new, potent drugs with a minimum of resources. Tunicamycin was first isolated in 1971 by Takatsuki *et al*. from Streptomyces lysosuperificus following the screening of over 4000 Actinomycetes strains for antibiotic activity.[309] Its structure was subsequently solved and it emerged that Tunicamycin was present as a mixture of closely related nucleoside antibiotics (Figure 17).[310] The core structure of the Tunicamycin family members is highly unusual. It comprises a unique eleven-carbon dialdose termed tunicamine that resembles ribose and 6-deoxy-galactosamine residues linked tail-to-tail through a C-C bond. At one end of the pseudo disaccharide is an *N*-glycosidically linked uracil group and at the other an *N*-acetyl-D-glucosamine (GlcNAc) residue attached through a non-reducing α,β-1,1 glycosidic bond – also referred to as an α,β-trehalose linkage.[311] The diversity of the Tunicamycin family derives from the nature of the acyl chain attached to the core through the tunicamine nitrogen.[312]

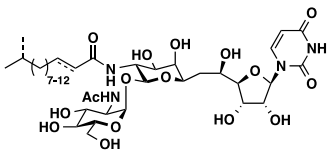


Figure 17. Structure of Tunicamycin.

The Tunicamycins act as non-hydrolysable analogues of UDP-GlcNAc, and together with their fatty acyl chains they most likely functions as bi-substrate transition-state mimics. This make them exhibit extraordinary properties as tightly binding and highly specific glycosyltransferase inhibitors. Their antibiotic activity arises from their ability to block the biosynthesis of peptidoglycan. They do so by inhibition of the membrane protein MraY, which is responsible for the formation of the key peptidoglycan precursor undecaprenyl-pyrophosphoryl-*N*-acetyl-muramoyl pentapeptide (lipid I) (Figure 18).[313] Even though Tunicamycins have great antibiotic properties, they have never been used clinically. This is due to cytotoxicity against mammalian cells associated with their inhibition of eukaryotic UDP-GlcNAc:dolichol-P GlcNAc-1-P transferase (GPT), which is involved in the first step of protein *N*-glycosylation.[314] By tailoring the terminal GlcNAc moiety of Tunicamycin to more closely resemble

the native muramic acid (MurNAc) substrate of MraY, a greater selectivity for MraY over GPT might be achieved. This has the potential to provide a novel therapeutic antibiotic with a mode of action orthogonal to those of existing drugs and thus helping to combat emerging antibiotic-resistance in bacteria. Based on the structure of the peptidoglycan precursor the compound shown in Figure 18 would be the best inhibitor and is therefore the main focus of this project. A broader range of Tunicamycin analogues was, however, also pursued, since this could give rise to compounds with other interesting properties. For example replacement of the GlcNAc residue with other carbohydrates could change the analogues specificity into targeting a range of physiologically important glycosyl transferase enzymes.

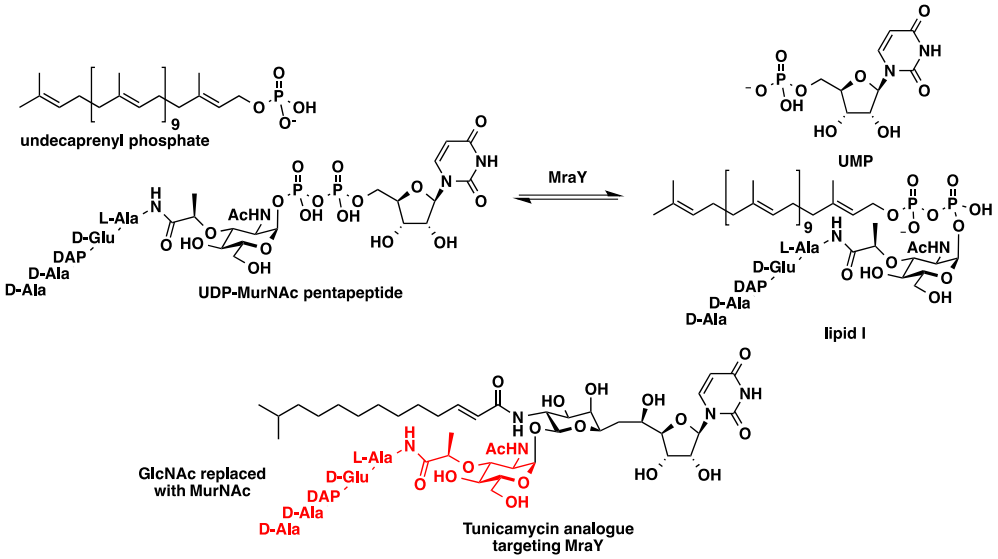
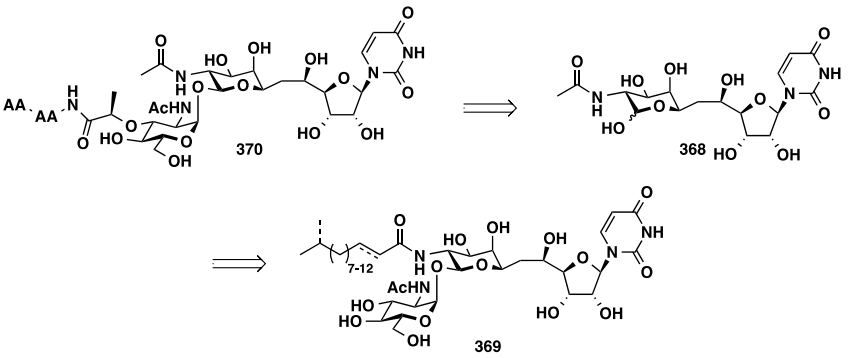


Figure 18. Lipid I biosynthesis and the target Tunicamycin analogue.

8.2 Synthetic strategy

The essential substrate in the synthesis of analogues is the tunicaminyl uracil **368** (Scheme 100). It possesses the core of the parent natural product and can be functionalized with a variety of subunits. A number of synthetic routes to tunicaminyl uracil derivatives have been developed, but they are all lengthy and result in low yields.[311,315,316,317] A far more economical route to this intermediate is through degradation of native Tunicamycins **369** followed by protection and glycosylation. It has previously been shown in the Davis group that tunicamycins can be isolated in preparative quantities in pure form from fermentation broths of *S. chartreusis*.[313] This is in contrast to other natural products, which are often produced by organisms that are extremely difficult to culture or grow very slowly. Acidic hydrolysis of the *N*-acyl chain and GlcNAc followed by acetylation and selective anomeric deprotection should give the glycosyl acceptor **368**. Finally, glycosylation, selective deprotection, peptide coupling and global deprotection should give the target compound **370**. As seen in Scheme 100, the *N*-acyl chain is not re-installed in order to simplify the synthesis. This may result in lowered permeability of the cell membrane resulting in lower activity.



Scheme 100. Retrosynthetic analysis of the target structure.

8.3 Preparative scale isolation of Tunicamycin

Preparative scale isolation of tunicamycins was based on a procedure described by Wyszyński but several factors were varied to improve the yield. The results are compiled in Table 10.[313] In the original procedure the *S. chartreusis* culture was grown for 6-8 days at 28 °C. However, it was shown that a growth period of eight days is essential. On the contrary, higher temperature, higher glucose concentration, or lower oxygen levels only stunted the bacterial growth.

Table 10. Preparative scale isolation of Tunicamycins.

Entry	Modification to the original procedure	Crude yield (mg)	Purity (%)	mg/L media
1	6 day growth	618	24	12.4
2	8 day growth	1080	38	34.2
3	Temperatures up to 42 °C during period	820	34	23.2
4	Additional glucose	1011	33	27.8
5	1.5L media/2 L conical flask	880	30	14.7
6	Same as entry 2 but 16 L culture	1408-1730	35-41	36.1-38

The tunicamycins are found both in the supernatant and inside the cells, but by taking advantage of their hydrophobicity, a rather short work-up allows high recovery. The tunicamycins were extracted from the supernatant using Amberlite XAD-16 resin, which has a high affinity for lipids. Liberation from the resin followed by precipitation from 1 M HCl gave rise to highly enriched samples. The mycelium cake was treated with 1 M HCl in order to break the cells and remove cellular debris and then extracted with MeOH. The combined tunicamycin extracts were finally purified by recrystallization. The purity was determined by high-pressure liquid chromatography (HPLC) using a standard curve based on a commercial tunicamycin sample (Figure 19).

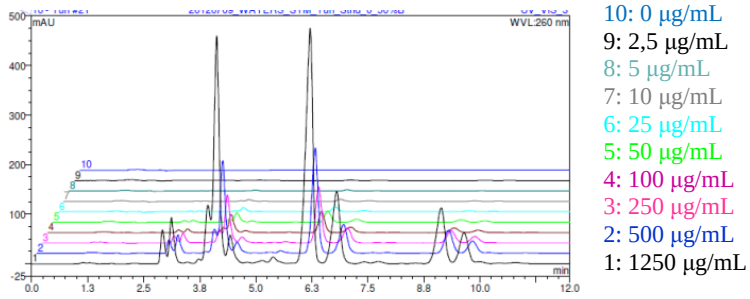
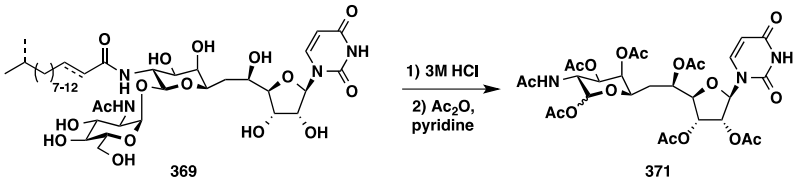


Figure 19. Example of HPLC chromatograms of a range of tunicamycin concentrations.

8.4 Degradation of tunicamycins

The degradation of tunicamycins was carried out according to a procedure by Myers *et al.*[315] They reported that a sample of tunicamycins could be heated to reflux in 3 M HCl followed by acetylation of the crude mixture to give heptaacetyl-tunicaminyl uracil in 30% yield. A similar method for cleaving of the tunicamycins' *N*-acyl and terminal GlcNAc moieties was described by Tamura, although no yields were reported.[318] As such, tunicamycins isolated from *S. chartreusis* cultures were refluxed in 3 M HCl, concentrated, and acetylated with Ac_2O in pyridine to give heptaacetyl-tunicaminyl uracil **371** as an α/β-mixture (Scheme 101). The yields ranged between 31% and 37%. Interestingly, the compound has a distinct red color when visualized with H_2SO_4-stain compared to the brown color of GlcNAc and other sugars.



Scheme 101. Degradation of tunicamycins.

The relatively low yield in this reaction makes it a bottleneck in the synthesis of tunicamycin analogues. The harsh conditions gave rise to a range of by-products and the reaction was hard to monitor. It has been reported that 2 M TFA at 120 °C results in cleaner degradation of polysaccharides.[319] After acetylation and purification these conditions resulted in a product with the same R_f in much higher yields (59%). However, NMR of the product did not match the product of the HCl treatment. This may be explained by opening of the uracil ring.

8.4.1 Selective deprotection of the anomeric acetyl group

The final step in the synthesis of the acceptor was selective deprotection of the anomeric acetyl group. To avoid wasting tunicaminyl uracil **371**, a series of test reactions were performed using peracetylated GlcNAc **372** as a model substrate. The synthesis of tetraacetate **372** and the results of the deprotection are shown in Table 11.

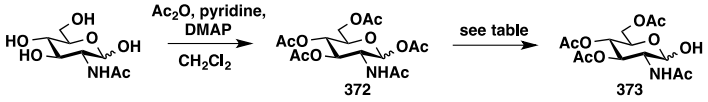
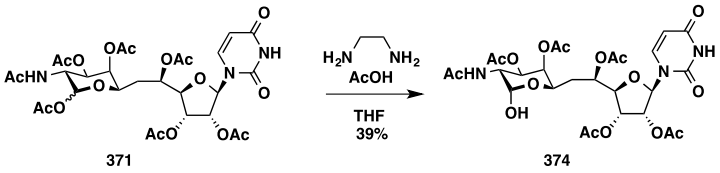


Table 11. Synthesis and anomeric deprotection of GlcNAc.

Entry	Reagents	Reaction time	Yield
1	Hydrazine acetate (55 °C)	4 h	75%
2	MeOH over 4 Å MS	2 h	82%
3	Ethylenediamine, AcOH	24 h	80%
4	Benzyl amine	12 h	64%

Hydrazine acetate,[320] MeOH over 4 Å MS,[321] and ethylenediamine acetate[322] all gave very similar results, whereas benzyl amine[323] was less attractive. MeOH over 4 Å MS was by far the fastest reaction (2 h), but also gave rise to substantial deacetylation of the 6-postion. It had previously been reported in the group that prolonged treatment of heptaacetyl-tunicaminyl uracil with hydrazine acetate had resulted in almost complete degradation. The milder conditions used in the deprotection with ethylenediamine therefore seemed more appealing. When the reaction was performed with heptaacetyl-tunicaminyl uracil as substrate, only 50% conversion was observed (Scheme 102). NMR analysis showed that almost only the β-anomer had reacted. The hexaacetate could be isolated in 39% yield together with 46% of the starting material.



Scheme 102. Selective anomeric deprotection of heptaacetyl tuncaminyl uracil.

The hexaacetate **374** exist as a single stereoisomer and judging from the coupling constant of H-1, it is the α-anomer (Figure 20). This may be problematic in the following glycosylations, since the glycosidic linkage has to be β,α-linked. The strong preference for the α-conformation is most likely attributed to the solvent polarity of $CDCl_3$. A more polar solvent such as MeCN is likely to favor the β-conformation.[324]

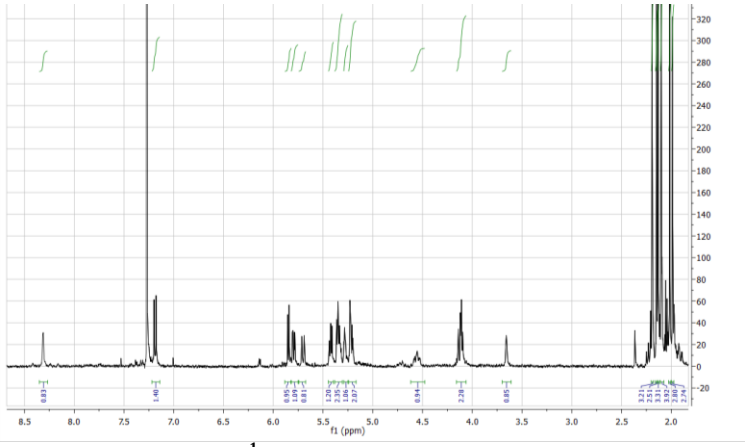


Figure 20. ^{1}H-NMR spectra of compound 374.

8.5 Synthesis of MurNac and Gal glycosyl donors

With the acceptor in hand a suitable donor had to be synthesized. As discussed in the introduction, the peptidoglycan layer in the bacterial cell wall is made up by linear chains of two alternating amino sugars, namely *N*-acetyl glucosamine and *N*-acetyl muramic acid (MurNAc).[325] Since the muramic acid residue is not found in mammalian cells as opposed to GlcNAc, it was hypothesized that exchanging the GlcNAc in tunicamycin for a MurNAc or MurNAc pentapeptide could result in tunicamycin analogues specific towards bacterial cells. We also wanted to introduce a simple carbohydrate to see which effects this would have on activity and specificity. This would furthermore make the glycosylation simpler compared to the rather complex MurNAc donor. D-Galactose was chosen and α- and β-selective donors were synthesized.

The glycosylation of hexaacetyl-tunicaminyl uracil is very challenging. Not only is the acceptor very electron-poor due to the many acetyl groups. The glycosidic linkage formed is also a trehalose bond, giving rise to four possible isomers. Hence, only two groups have managed to prepare it and only in low yields (21%) using a glycosyl chloride and glycosyl bromide as donors.[316] It is therefore crucial to choose the right set of protecting- and leaving groups.

Thioglycoside donors were chosen, since they are stable, often crystalline solids that can be activated under selective and mild conditions. Furthermore, thioglycosides can be converted into other glycosyl donors such as glycosyl halides and imidates, which is useful in case the coupling reaction proves to be prohibitively slow. Based on good results using *N*-phenyl trifluoroacetimidates for difficult couplings, it was decided to make the corresponding imidate in the D-galactose series. This would make it possible to compare thioglycosides and glycosyl imidates performance in the glycosylation of a model substrate.

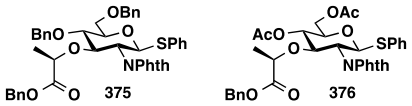


Figure 21. Target MurNAc donor.

The amino functionality was protected as a phthalimide (NPhth), since 2-acetylamino-2-deoxy sugars are known to be poor donors due to formation of a stable oxazoline.[142] The phthalimide also has the advantage that it gives rise to β-selective glycosylations due to neighboring group participation[142]. In order to avoid interference from the carboxylic acid, this was also protected with a benzyl group. The 4- and 6-position were protected with either acetyl- or benzyl groups. This gives rise to a disarmed and an armed donor. The target donors **375** and **376** are shown in Figure 21. The D-galactose donors were also protected with benzyl groups as permanent protecting groups and both a α-direting and β-directing set of donors (**33, 377, 378, 379**) were prepared (Figure 22).

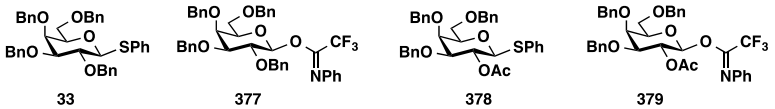
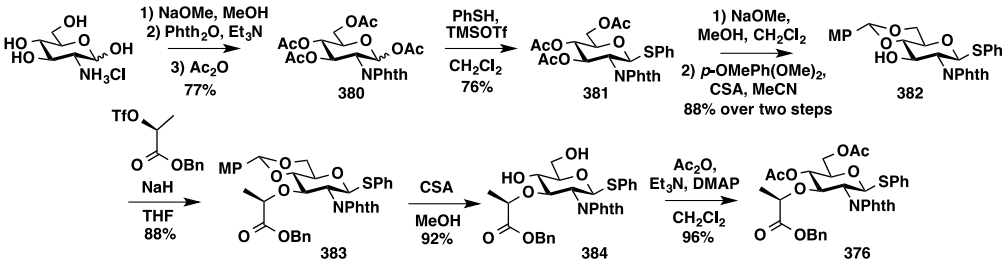


Figure 22. Target D-galactose donors.

8.5.1 β-Directing muramic acid donor

The synthesis of the MurNAc building block is shown in Scheme 103. Thioglycoside **382** was prepared according to work by Hernandez-Torres *et al*.[326] Commercially available glucosamine hydrochloride was neutralized with NaOMe and then treated with phthalic anhydride and Et_3N in a one-pot procedure to form the phthalamate intermediate. The crude product was acetylated with Ac_2O/pyridine, which also closed the phthalimide ring to give the tetraacetate **380** in 77% yield as an 8:1 mixture of anomers after recrystallization.



Scheme 103. First synthesis of the MurNAc donor.

The anomeric mixture of glycosyl tetraacetates **380** was most efficiently converted to thiophenyl glycoside **381** using PhSH and TMSOTf. The less expensive $BF_3{\cdot}OEt_2$ resulted in longer reaction times and partial decomposition. The acetyl groups were removed via transesterification under Zemplén conditions. Careful control of the temperature was important, since the reaction did not proceed at an appreciable rate under -20 °C and partial cleavage of the phthalimide was observed at temperatures above 0 °C. The crude product was treated with *p*-anisaldehyde dimethylacetal and a catalytic amount of CSA in refluxing MeCN to afford the 4-methoxybenzylidene protected carbohydrate **382**. Next, the lactic acid moiety was introduced via an alkylation. This proved difficult and optimization had to be done. The results are shown in Table 12.

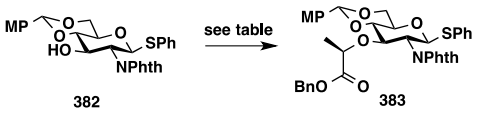
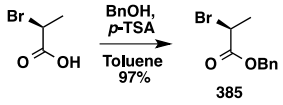


Table 12. Optimization of alkylation of compound 383.

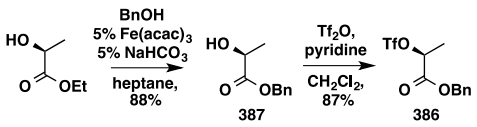
Entry	Electrophile	Equiv. of electrophile	Solvent	Temp. (°C)	Yield (%)
1	**385**	2	DMF	25	20
2	**385**	5	DMF	25	35
3	**385**	5	THF	25	42
4	**385**	5	THF	0	>10
5	**386**	5	DMF	25	>10
6	**386**	5	THF	0	86
7	**386**	2	THF	0	88

The lactyl side chain is usually introduced as the free carboxylic acid followed by protection (most commonly as the methyl ester).[327,328,329] In order to make the synthesis more convergent, the commercially available (*S*)-2-bromopropanoic acid was first esterified with benzyl alcohol to give **385** (Scheme 104).



Scheme 104. Synthesis of benzyl (*S*)-2-bromolactate.

Alkylation of thioglycoside **382** using **385** as electrophile and NaH as base gave rise to a range of by-products and muramic acid analogue **383** was only obtained in 35% yield. Changing reaction temperature, amount of reagent and solvent did not improve the yield to a great extent. The low yields were caused by competing transesterification and phthalimide opening. Furthermore, the undesired diastereoisomer could be formed if the reaction did not follow the S_N2 mechanism. It was postulated that a better electrophile could solve the problem. The corresponding triflate **386** was prepared in two steps from the cheap starting material ethyl L-lactate via a iron(III)acetylacetone-catalyzed ($Fe(acac)_3$) transesterification to give **387** followed by formation of the triflate **386** using Tf_2O in pyridine/CH_2Cl_2 (Scheme 105).[330,331] At first 2,6-lutidine was used, but it was later avoided due to problems in the purification. The first experiment with **386** as electrophile was done in DMF and once again gave poor results. However, it was found that excellent yield (entry 6) could be obtained in THF at 0 °C and that the amount of electrophile could be reduced to 2 equivalents (entry 7).

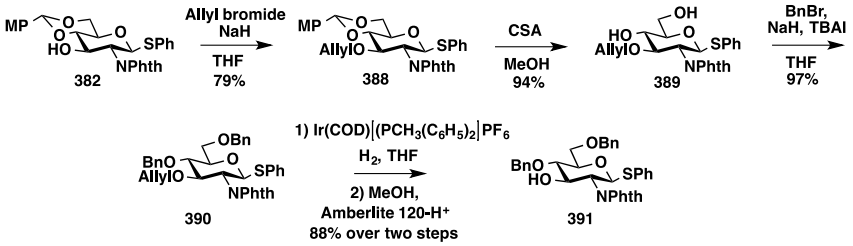


Scheme 105. Synthesis of benzyl (*S*)-2-triflatelactate 386.

Judging from the NMR, thioglycoside **383** was not a single compound but rather a 3:1 mixture of two compounds. It was first believed, that this was two diastereoisomers resulting from an S_N1 attack that were just inseparable. The acetal was hydrolyzed with MeOH/CSA in order to see, if they could be separated at this point. Interestingly, this gave the diol **384** in 92% yield as a single compound based on NMR. The 3:1 mixture is therefore most likely due to a rotamer system rather than two diastereoisomers. Acetylation of diol **384** with Ac_2O, Et_3N and DMAP afforded target donor **376** in 96% yield. The final benzylation on the other hand gave rise to problems. Under basic conditions the benzyl lactate was attacked by the C4-*OH* to form a cyclic intermediate, which render alkylation under basic conditions impossible. Instead, alkylation with BnBr, Ag_2O and KI was done.[332] This gave the product **375,** but only in 40% yield and with an inseparable by-product present.

Based on literature reports, cyclization could also be a problem after deprotection of the amine.[329] This would be necessary in order to prepare the azide. Hence, it was decided to modify the strategy to allow introduction of the lactate as the final step (Scheme 106). An allyl group was introduced at the 3-position using allyl bromide and NaH to give **388** in 79% yield. The acetal was hydrolyzed with MeOH/CSA to give the diol **389** in 94% yield followed by benzylation to give **390** in 97% yield. THF again turned out to

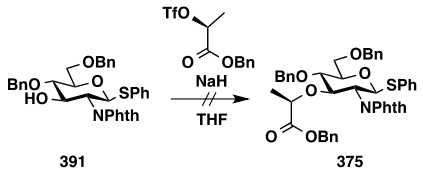
be the solvent of choice, since use of DMF resulted in almost complete opening and benzylation of the phthalimide.



Scheme 106. Synthesis of armed β-directing MurNAc donor.

The common reagent for allyl deprotection is $PdCl_2$, but this was avoided, since sulfur has been reported to poison palladium catalysts. Instead, a procedure using *n*-BuLi and Wilkinson's catalyst ($RhCl(PPh_3)_3$) was used to isomerize the allyl group.[301,333] The isomerization product was observed, however, the reaction did not go to completion, even when 20 mol% of the catalyst was used. Instead, the iridium catalyst, $Ir(COD)[PCH_3(C_6H_5)_2]PF_6$ and H_2, was used.[334] This resulted in complete isomerization with only 6 mol% catalyst after 2 h. The resulting 1-propenyl ether was cleaved with methanol in the presence of Amberlite-120 H^+ resin to give **391** in excellent yield.

The final alkylation was done using the optimal conditions developed in the synthesis of **383** (Scheme 107). Unfortunately, no reaction was observed at 0 °C and when the reaction mixture was heated to 22 °C several by-products were formed. Hence, the MurNAc donor **375** was only obtained in 21% yield with several inseparable impurities. The benzyl groups seem to be more bulky than the acetal, which makes the alkylation slow. The competing opening of the phthalimide therefore becomes the dominant pathway. In the future, the phthalimide should be substituted with a less base-labile alternative.



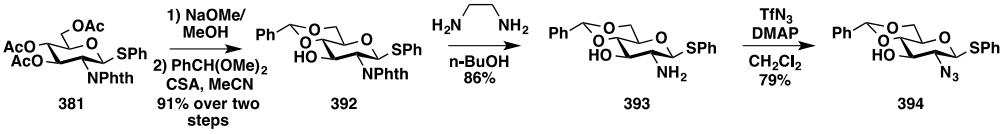
Scheme 107. Problems in the alkylation of the hindered 3-position.

8.5.2 α-Directing MurNAc donors

The UDP-MurNAc pentapeptide is α-linked. It was therefore decided to make a set of donors with a non-participating protecting group in the 2-position. An azide functionality was chosen, since it is stable towards most protecting group manipulations and glycosylations. Moreover, it can be cleaved under mild conditions by hydrogenolysis or reduction with phosphines.[335,336]

As opposed to the phthalimide protecting group, the azide is stable towards basic conditions. It was therefore decided to follow the same strategy as described in Scheme 106, where the lactate is introduced as the final step. The first part of the synthesis is shown in Scheme 108. The triol was protected by treatment with benzaldehyde dimethyl acetal and CSA to afford benzylidene acetal-protected thioglycoside **392**. Next, the phthalimide was deprotected with ethylenediamine to give the free amine **393**. This was selectively protected via diazotransfer with triflic azide and DMAP according to a

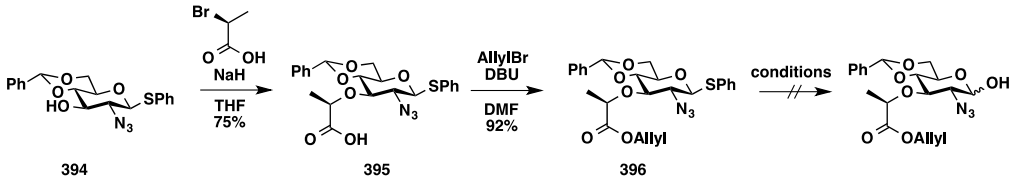
procedure developed by Konradsson and co-workers to afford the azide **394**.[337] An alternative procedure by Zhang and Ye was tested in an effort to reduce the amount of the toxic reagents NaN_3 and Tf_2O.[338] However, this resulted in lower yields and a troublesome purification.



Scheme 108. Introduction of azide protecting group.

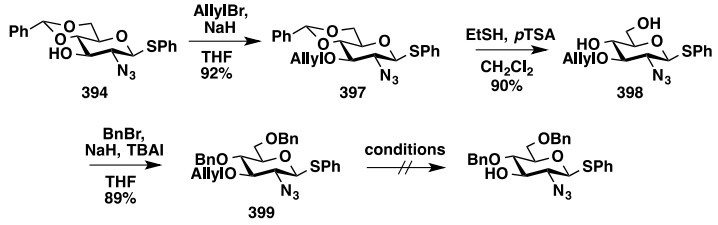
It is not possible to selectively remove benzyl ethers in the presence of an azide. This precluded the use of the triflate **386** for introduction of the lactate moiety. Moreover, the base-labile uracil ring in the target molecule rules out simple alkyl esters. It was therefore decided to protect the carboxylic acid with an allyl group. Compound **394** was treated with (*S*)-(−)-2-bromopropionic acid and NaH to give the free carboxyl acid **395** (Scheme 109). This was converted to the corresponding allyl ester **396** by treatment with allyl bromide and DBU.

The allyl ester turned out to be a poor choice of protecting group, since it precluded conversion of **396** to the corresponding PTFAI donor. Hydrolysis of the thioglycoside with NBS/H_2O or NIS/H_2O resulted in conversion of the alkene to a halohydrin. As an alternative, preactivation with Me_2S_2/Tf_2O, followed by hydrolysis was tried, but this only resulted in decomposition.



Scheme 109. Synthesis of thioglycoside 396 and failed attempt of hydrolysis.

Benzylidene acetals have been shown to significantly lower the reactivity of glycosyl donors due to torsional strain. It was therefore decided to replace the benzylidene acetal for two benzyl ethers (Scheme 110). The C3-*OH* was protected with an allyl group followed by hydrolysis of the benzylidene acetal with ethanethiol and *p*-TSA to give **398**. The use of ethanethiol resulted in significantly higher yields compared to other classic methods such as 60% aq. AcOH or 1,3-propandiol/p-TSA.[217] Benzylation of the diol **398** resulted in formation of thioglycoside **399** in an excellent yield.

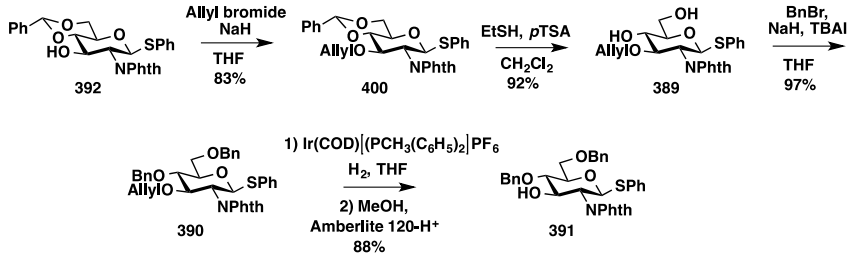


Scheme 110. Towards synthesis of armed α-directing MurNAc donor.

The two final steps were to removed the allyl ether and introduce a lactate moiety. However, no isomerization was observed when **399** was treated with $Ir(COD)[PCH_3(C_6H_5)_2]PF_6$ and H_2. Several other conditions were tried including *tert*-BuOK/DMSO,[339] $H_2Ru(PPh_3)_4$,[229] and $RhCl(PPh_3)_3$,[340] but they only

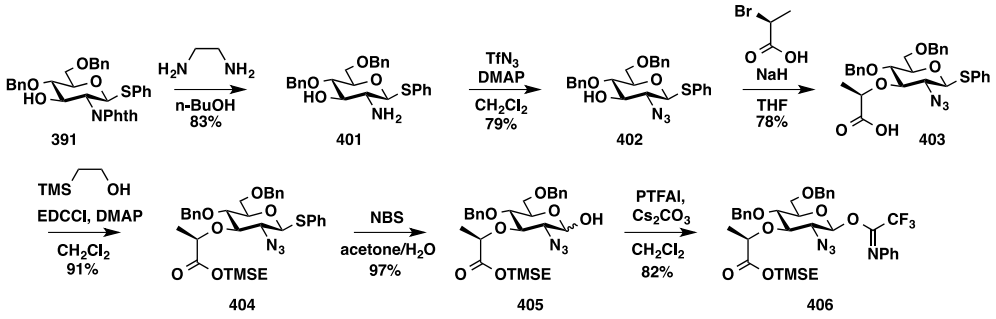
resulted in decomposition of the starting material or no reaction. It had been possible to remove allyl ethers in presence of a phthalimide group, but not an azide. This could indicate that concomitant reduction of the azide or coordination to the catalyst causes the problem. Instead, it was decided to introduce the azide as one of the final steps, after the allyl group had been removed. This is also advantageous since both the α- and β-directing donors can be made from one synthetic sequence (Scheme 111).

Starting from the thioglycoside **392**, the 3-position was protected by an allyl group to give the fully protected thioglycoside **400**. The benzylidene acetal was hydrolyzed with ethanethiol and *p*-TSA and the resulting diol **389** was benzylated to afford **390**. Finally, the allyl ether was cleaved via isomerization catalyzed by iridium complex followed by acidic hydrolysis to give **391**.



Scheme 111. Alternative synthesis of MurNAc building block.

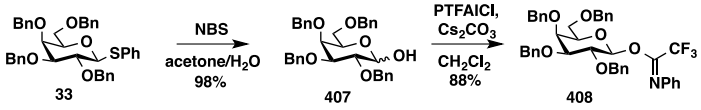
Deprotection of the phthalimide followed by diazotransfer afforded the azide **402** (Scheme 112). Next, the lactate moiety was introduced as the carboxylic acid by alkylation with (*S*)-(−)-2-bromopropionic acid and NaH to give **403**. As a consequence of the many problems with allyl ethers, it was decided to use a different protecting group. A range of protecting groups has been developed for carboxylic acids but the selection is limited by the many different functionalities in the final molecule. Thus, the protecting group should be orthogonal to acetyl groups, benzyl ethers, azides, alkenes and glycosylation conditions. The trimethylsilylethyl (TMSE) group was found to meet all these criteria, since it can be removed with a fluoride source such as TBAF or tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F) under neutral conditions.[341,342] The protecting group was introduced using with 2-trimethylsilylethanol, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCl) and DMAP to afford **404**. As opposed to the allyl ester this was easily converted to PTFAI donor **406** by hydrolysis with NBS/H_2O followed by treatment with PTFAICl and Cs_2CO_3.



Scheme 112. Final steps in the synthesis of an armed MurNAc donor.

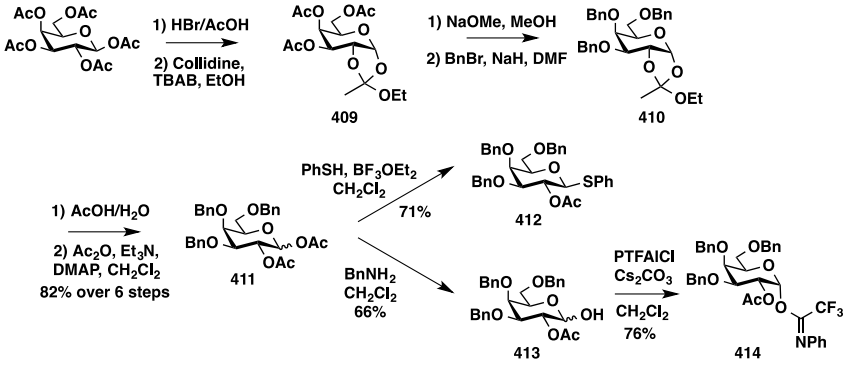
8.5.3 D-Galactose donors

Synthesis of the α-selective pair of galactose donors is shown in Scheme 113. The perbenzylated thioglycoside **33** was prepared according to the procedure described in section 4.3.[343] Thiogly-coside **33** could be converted into the corresponding *N*-phenyl trifluoroacetimidate over two steps.[344] Hydrolysis with NBS/H_2O afforded the lactol **407** and next the imidate functionality was introduced with PTFAICl in presence of Cs_2CO_3 to give the imidate **408.**



Scheme 113. α-Selective galactose donors.

The β-directing galactose donors had an acetyl group in the 2-position that provides anchimeric assistance. The rest of the hydroxyl-groups were protected with arming benzyl groups. The synthesis is outlined in and is based on literature procedures (Scheme 114).[345,346]



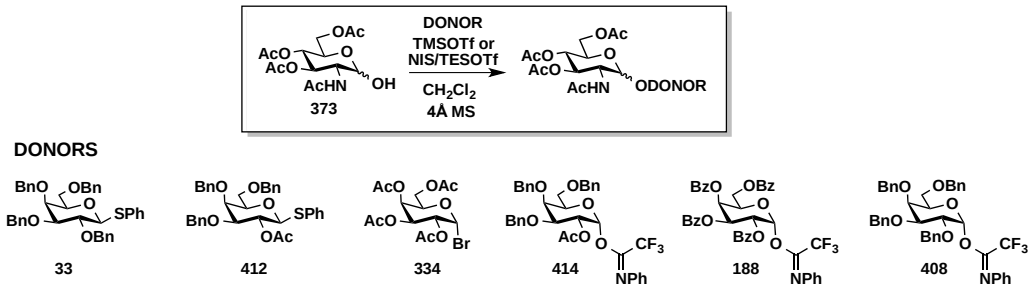
Scheme 114. β-Selective galactose donors.

Galactose pentaacetate was treated with 33% HBr/AcOH to give the glycosyl bromide which upon reflux in collidine in presence of TBAB and ethanol gave the ethyl orthoester **409**. The acetyl groups were exchanged with benzyl groups to afford **410** after which the orthoester was opened and acetylated to give **411** in 82% yield over six steps. The acetate **411** could be turned into both thioglycoside **412** in 71% yield by treatment with thiophenol and $BF_3{\cdot}OEt_2$ or into the free hemiacetal **413** in 66% yield via reaction with benzyl amine. This could be converted to PTFAI donor **414** by treatment with PTFAICl and Cs_2CO_3.

8.6 Glycosylation experiments

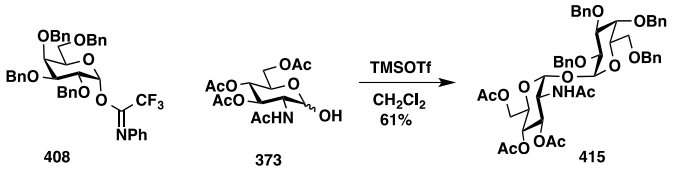
8.6.1 Test glycosylations to GlcNAc hemiacetal

The next step was to perform the final glycosylation. Since the amount of tunicaminyl uracil was limited, it was decided to screen different donors and reaction conditions against a test substrate (Scheme 115). The hemiacetal **373** was chosen due to its high similarity to the tunicaminyl uracil. Furthermore, it had the advantage that Dragendorff TLC stain could be used to selectively visualize any products containing a *N*-acetyl due to its preference for amides.



Scheme 115. Test glycosylations for synthesis of trehalose linkage.

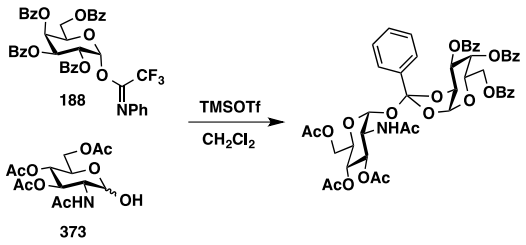
Glycosylation with thioglycoside **33** using NIS/TESOTf as promoter only resulted in slow degradation of the thioglycoside. The temperature was raised from -30 ºC to 0 ºC to increase the reactivity of the acceptor, but this just resulted in faster hydrolysis of the donor. Furthermore, a by-product was formed which appeared to be (1→1)-digalactan formed by glycosylation of the hydrolyzed donor. A similar outcome was obtained when the "super armed" thioglycoside **412** was used.[347] In this case, a second by-product appeared due to hydrolysis, migration of the acetyl, followed by glycosylation to give the (1→2)-linked digalactan. It was postulated that the high reactivity of the electron-rich donors **33** and **412** made them degrade, before the unreactive acceptor had a chance to react. A less reactive donor could therefore be a better match. However, AgOTf-promoted glycosylation with the electron-poor glycosyl bromide **334** once again only resulted in decomposition of the donor.



Scheme 116. Successful formation of the mixed trehalose 415.

PTFAI donors have previously been used for couplings to very unreactive acceptors. When the imidate **408** was used as donor with TMSOTf as promoter, the product **415** was formed in 25% yield (Scheme 116). Further optimization increased the yield to 61%. It was found to be crucial to add 4 Å MS and to conduct the reaction at 0 ºC. At lower temperatures no product was formed and the donor slowly degraded. The "super armed" imidate **414**, on the other hand, only resulted in by-product formation even with the optimized conditions. The conversion of the donor was much faster, which can be explained by rapid formation of the acetoxonium ion. Finally, the perbenzoylated imidate donor **188** was tested to see if lowered reactivity would be beneficial (Scheme 117). This did not result in the expected product, but

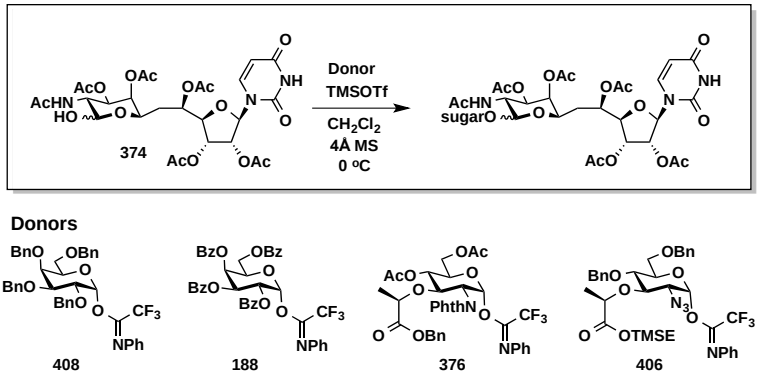
instead the orthoester was formed in 64% yield. This was still a promising result, since it should be possible to rearrange the orthoester into the product under acid conditions.



Scheme 117. Orthoester formation under coupling of 188 and 373.

8.6.2 Glycosylations to tunicaminyl uracil hemiacetal

Having shown that it was possible to glycosylate the unreactive hemiacetal **373**, we turned the focus towards couplings to the tunicaminyl acceptor **374**. Based on the results from the test experiments, it was decided to use PTFAI donors and to conduct the reactions at the optimized conditions used for acceptor **373**. Four different donors were chosen: An α- and β-directing galactose donor and an α- and β-directing muramic acid donor (Scheme 118).



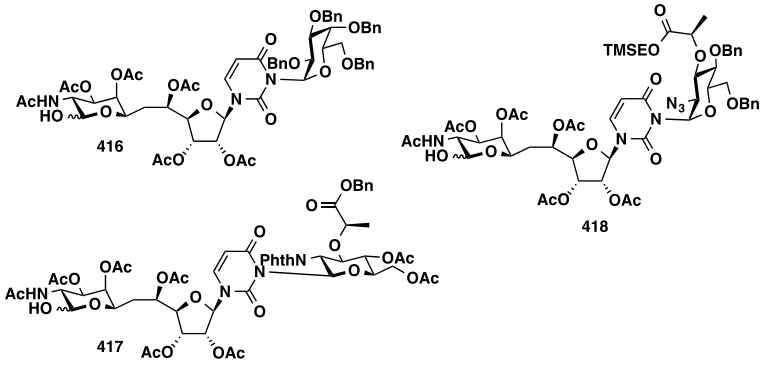
Scheme 118. Glycosylation of tunicaminyl uracil 374 with various donors.

Coupling with perbenzoylated imidate **188** with 0.3 equiv. TMSOTf to avoid orthoester formation only resulted in slow degradation of the donor. The amount of promoter was lowered to 0.1 equiv. in an attempt to form the orthoester, but the outcome was the same.

Glycosylation between imidate **405** and the tunicaminyl acceptor **374**, on the other hand, resulted in full conversion of the acceptor and formation of a product in 65% yield. Preliminary characterization by NMR and LC-MS showed that the compound had the correct mass and characteristic signals. It was therefore decided to perform the last two couplings. The β-directing muramic acid imidate **376** did also give rise to a single product, but the reaction was slower, and it was not possible to get full conversion of the acceptor. Nonetheless, the product could be isolated in 45% yield with 30% recovery of the acceptor. The difference in yield may be caused by the fact that donor **376** is less electron rich than donor **408**. This is consistent with the last coupling of imidate **406** and acceptor **374**, which was faster and gave the product in 59% yield.

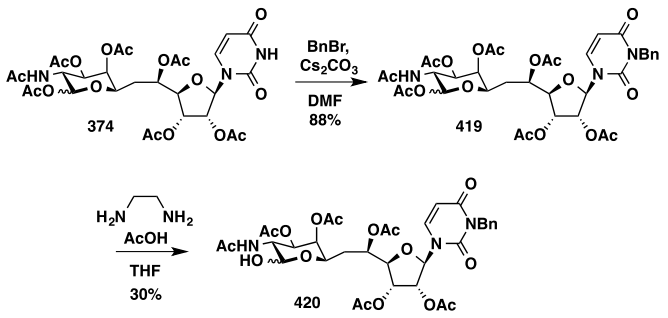
It was believed that global deprotection would give the target compounds. However, careful analysis by NMR showed that the anomeric signal of the muramic acid or galactose moiety was found unexpectedly

far downfield. HMBC correlations between the anomeric center and the uracil carbonyls confirmed that the glycosylation had taken place on the imide-nitrogen instead of the hemiacetal. This resulted in the three molecules **416-418** shown in Scheme 119 rather than the target molecules.



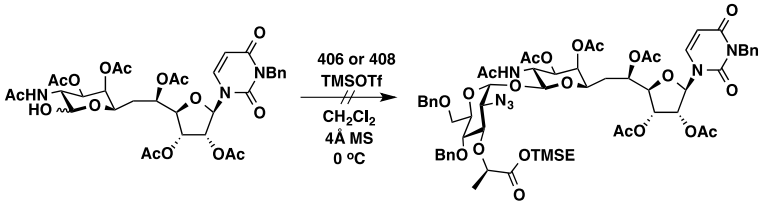
Scheme 119. The structure of the actual product after full assignment by NMR.

Couplings to imides have previously been reported as by-products in glycosylations promoted by NIS. However, the hydroxy groups are normally much stronger nucleophiles and it was therefore surprising that the imide gave rise to problems. The result shows that the hemiacetal must be very unreactive and that all other nucleophiles must be protected. Hence, it was decided to protect the imide with a benzyl group. Treatment of hexaacetyl tunicaminyl uracil **374** with benzyl bromide and Cs_2CO_3 gave the fully protected tunicaminyl **419** (Scheme 120). Next, the anomeric acetyl group was removed with ethylenediamine and acetic acid to give the acceptor **420**.



Scheme 120. Protection of the imide.

Glycosylation of acceptor **420** with the muramic acid donor **406** using the optimized conditions did not result in formation of the expected product (Scheme 121). The only conversion observed resulted from TMS-protection of the hemiacetal. Similar results were obtained when the galactose donor **408** was used. Due to time constraints no additional glycosylation experiments were performed.



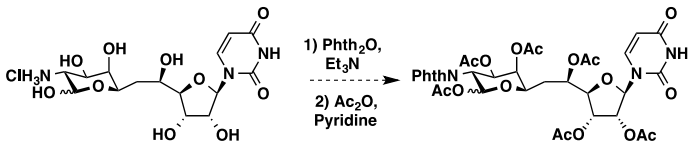
Scheme 121. Attempts to glycosylate the benzyl-protected tunicaminyl acceptor 420.

In conclusion, a novel synthetic route to the tunicaminyl uracil hemiacetal **374** has been developed. This gives access to a potential glycosyl acceptor in only three steps from tunicamycins isolated from *S. chartreusis* cultures. Due to the short route and the use of bacterial cultures, it would be possible to scale the synthesis to multi-gram quantities. This is in stark contrast to the published total syntheses, where analogues of **374** have only been prepared on milligram scale. The degradation and selective deacetylation are still major bottlenecks due to mediocre yields. Further optimization, such as degradation with milder acids, is therefore desirable.

A range of donors was prepared including α- and β-selective MurNAc and galactose donors. In the synthesis of MurNAc donors, the introduction of the lactate turned out to be very challenging. The secondary bromide was too unreactive resulting in concomitant transesterification and phthalimide opening. This problem was partially solved by using the corresponding triflate. However, it was still not possible to alkylate sterically hindered hydroxyl groups as in the case of **391**. In the future, a less base-labile amino protecting group should be chosen instead of a phthalimide.

A series of glycosylations of a model substrate made it possible to find the best donor match and glycosylation conditions before the final couplings. The hemiacetal **373** turned out to be very unreactive, but with *N*-phenyl trifluoroacetimidates it was possible to synthesize a novel α,α-linked mixed trehalose sugar **415**. PTFAI donors were therefore used for the final glycosylations. They all resulted in formation of a major product with the correct mass and characteristic signals. However, full characterization showed that the glycosylation had taken place on the uracil ring instead of the hemiacetal. The imide must be more nucleophilic than the lactol. It was therefore protected with a benzyl group in an attempt to solve the problem. Unfortunately, glycosylations of the acceptor **420** did not give rise to any product. More experiments are needed to see if different temperatures and/or promoter will give better results.

The major challenge is the low reactivity of the tunicaminyl acceptor. The many electron-withdrawing acetyl groups and steric hindrance from the second ring seems to make the lactol virtually unreactive. One way to address this would be to exchange the acetyl with benzyl ethers, which would make the ring more electron-rich. Alternatively, another amine protecting group should be used since this has a great effect due to its proximity to the anomeric center. This would furthermore allow late stage introduction of fatty acid chains, which have been shown to be important for binding. This could for example be done by phthalimide or azide protection of the tunicaminyl uracil after the degradation (Scheme 122).



Scheme 122. Possible strategies for protection of amine functionality of tunicaminyl uracil

9 Conclusion

The aim of the project was to develop reliable and efficient methods for synthesizing defined fragments of plant cell wall galactans and arabinogalactans. A general method for preparation of both linear and branched β-(1→4)-linked and β-(1→3)-linked D-galactosides were the major outcome of the project. The strategy utilizes a convergent block strategy where a disaccharide donor could be prepared from a single building block and used in the remaining glycosylations. This resulted in a significant reduction of the number of glycosylation reactions required. Furthermore, late stage regioselective deprotection made it possible to introduce branches on the backbone.

A broad range of routes towards a β-(1→4)-linked digalactoside donor was studied (chapter 4). As a result of the low reactivity of the C4-*OH* in galactose, aglycon transfer was observed when common thioglycoside acceptors were applied. The problem was solved either by applying hindered 2,6-dimethylthiophenyl acceptors or via use of the less nucleophilic aglycons -*O*-TBPDS and -*O*-*n*-pentenyl. A novel, mild procedure for hydrolysis of *n*-pentenyl glycosides, which reduces formation of halohydrin byproducts, was developed. This made it possible to obtain the corresponding PTFAI donors in high yields. The PTFAI donors were exceptional donors for glycosylation of pentenyl glycoside acceptors and gave access to fully protected pentenyl disaccharide donors.

Decreasing reactivity of the acceptors with growing degree of polymerization turned out to be a major obstacle to the synthesis of longer oligosaccharides. It was therefore crucial to increase the reactivity of the acceptor by using small, electron donating protecting groups for the neighboring hydroxy groups. The 3,6-*O*-benzyl protected disaccharide donor **170** made it possible to prepare a small library of oligogalactans including linear tetra-, penta-, hexa-, and heptasaccharides (**131**, **132**, **210** and **176**) and six (1→6)-branched hepta- or octasaccharides (**211**-**216**). The assembly of the oligosaccharides went smoothly with good to excellent yields and high selectivity for the desired β-linked products. This constitutes the first reported synthesis of branched β-(1→4)-linked galactans.

Potential inhibitors of the β-1→4-galactosyltransferase, GALS1 were prepared by late stage introduction of C4-*F*, C4-*OMe* or C4-*epimer* galactose residues. Meerwein's salt and Proton sponge® were used for methylation of D-galactose. This is the first application of this method in carbohydrate chemistry and it serves as a mild alternative to other known methods. The hindered fluorine analogue was prepared high yields by TBAF-mediated displacement of a C4-triflate.

The 3-position of galactose is significantly more reactive compared to the 4-position. Thus, aglycon transfer was not a problem and the more stable and readily available thioglycosides were used for the assembly of β-(1→3)-linked galactans. Due to significant migration of the 2-*O*-acyl group under basic conditions, a novel method for selective deacetylation of carbohydrates was developed, where the acetyl group is removed by treatment with the bulky reducing agents, L-selectride or superhydride. Using an orthogonally protected monosaccharide building block, it was possible to introduce branching at two

different positions in a heptasaccharide backbone. This resulted in five different β-(1→3)-linked octa- and nonasaccharides (**308**-**312**). Furthermore, the strategy gave access to the linear penta- and heptasaccharide (**306** and **307**), which have previously only been prepared as the methyl glycosides. Finally, a series of linear β-(1→6)-linked D-galactosides (**363**, **365**, and **367**) was prepared. The increased reactivity of the 6-position resulted in very high glycosylation yields and it is likely that even longer oligosaccharides can be prepared by the same strategy.

Proof of concept for the utility of the synthetic cell wall fragments was obtained by researchers at Lawrence Berkeley National Laboratory, Berkeley, California. They used compound **130**-**132** as substrates in the characterization of a novel β-1→4-galactosyltransferase from *Arabidopsis thaliana*, which is believed to take part in pectin biosynthesis. Researchers at DTU Systems Biology in Lyngby used some smaller oligosaccharides to study the substrate specificities of three β-galactosidases from Bifidobacterium. Moreover, researchers at University of Copenhagen were able to study the binding of oligosaccharides **42**-**45** with a novel microarray technology. This gave interesting new information about the epitope of antibody LM16, which had higher affinity for branched structures than linear. Finally, co-crystallization of pentasaccharide **132** with the important cancer biomarker Galectin-3 gave new insight to the size and specificity of the carbohydrate binding site. Further studies are currently being undertaken concerning the oligosaccharides' potential as Galectin-3 inhibitors in collaboration with University of Copenhagen and the German Cancer Research Center, Heidelberg, Germany.

In conclusion, the project has been very rewarding. Methods for synthesizing branched- and linear oligogalactosides have been developed and exemplified by the preparation of three small libraries of oligosaccharides. The work is a typical example of the challenges faced in oligosaccharide synthesis. Each position in the pyranose ring has different reactivity which is furthermore affected by the nature of the surrounding protecting groups. This makes it hard to predict the outcome of glycosylation reactions and often makes extensive method development necessary. A systematic analysis of acceptor conformation and reactivity could result in a better understanding of chemical glyco-sylation reactions.

The project has shown the value of synthetically prepared, well-defined oligosaccharides for various aspects of plant research. Hopefully, the larger oligosaccharides will give further insight to the structure and function of the plant cell wall in the future.

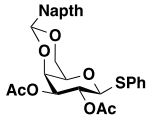
10 Experimental

10.1 General Considerations

Starting materials, reagents and solvents were purchased from commercial suppliers and have been used without further purification. All solvents are HPLC-grade. The dry solvents were obtained from Innovative Technology PS-MD-7 Pure-solv solvent purification system. All of the reactions were carried out in flame-dried glassware under inert atmosphere. Thin-layer chromatography (TLC) was performed on Merck Aluminium Sheets pre-coated with silica, C-60 F_{254} plates. Compounds were visualized by charring after dipping in CAM stain ($Ce(SO_4)_2$ (1.6 g) and $(NH_4)_6Mo_7O_{24}$ (4 g) in 10 % sulphuric acid (200 mL). Eluent systems are specified for each R_f-value, and ratios are given as volume ratios. Evaporation of solvents was performed with a VWR International Laborota 400 under reduced pressure (*in vacuo)* at temperatures ranging between 35-55°C. Trace solvent was removed by under reduced pressure by means of an oil pump. Flash chromatography was performed using Matrex 60 Å silica gel (35-70 µm) as the stationary phase by the general procedure developed by Still *et al*.[348] The eluent system is specified under the protocol for each synthesis. Eluent ratios are given as volume ratios. NMR-spectras were recorded on a Bruker Ascend 400, Varian Mercury 300 B, Bruker DQX 400 and Bruker AC 500 spectrometer. Chemical shifts (δ) are reported in ppm and coupling constants in Hz. Solvents were $CDCl_3$, CD_3OD, D_2O or d_6-DMSO and their resonances were used as internal standards. IR analysis was done on a Bruker Alpha-P FT-IR instrument where solid compound is applied directly onto the instrument. Optical rotation was measured on a Perkin Elmer Model 241 Polarimeter. Solvents used were either $CHCl_3$ or H_2O. Melting points were measured on a Stuart melting point SMP30 and reported in ° C uncorrected. UPLC/MS analysis was performed on a Waters AQUITY UPLC system equipped with PDA and SQD MS detector. Column: AQUITY UPLC BEH C18 1.7µm, 2.1 x 50mm. Column temp: 65 º C. Flowrate: 0.6 ml/min. Solvent A: 0.1% formic acid in water, Solvent B: 0.1% formic in MeCN. Gradient: 5% B to 100% B in 2.4 min, hold 0.1 min, total run time – 2.6 min. High-resolution LC-DAD-MS was performed in an Agilent 1100 system equipped with a photodiode array detector (DAD) and coupled to a LCT orthogonal time-of-flight mass spectrometer (Waters-Micromass, Manchester, UK) with Z-spray electrospray ionization (ESI) source and a LockSpray probe and controlled MassLynx 4.0 software. LC-MS calibration from *m/z* 100-900 was done with a PEG mixture. Standard separation involved a LUNA 2 column with a MeCN (50 ppm TFA) in water gradient starting from 15% to 100% over 25 minutes with a flow rate of 0.3 mL/min.

Most of the compounds have been characterized by NMR and/or HRMS. However, *N*-phenyl trifluoroacetimidates are generally not characterized due to low stability.

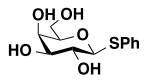
Phenyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-1-thio-β-D-galactopyranoside (22)



24 (12 g ; 29.23 mmol) was dissolved in CH_2Cl_2 (250 mL). Et_3N (12.2 mL; 87.7 mmol), DMAP (71 mg; 0.58 mmol) and acetic anhydride (6.9 mL; 73.1 mmol) were added to the solution and the reaction mixture was stirred until TLC revealed full conversion (2 h). The reaction was quenched with MeOH (5 mL), washed with water (2x200 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (CH_2Cl_2/MeOH 19:1) to afford 22 as a white crystalline powder. R_f 0.71 (1:1 EtOAc/Tol). Yield: 13.59 g (95%)

mp: 165.4 - 167 °C. $[\alpha]_D^{20}$= +36.0° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3059.39, 2974.36, 2906.11, 2863.98, 2803.27, 1751.73, 1243.25, 1216.57, 1097.35, 1031.81, 993.68. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 – 7.74 (m, 4H, Ar-*H*), 7.60 – 7.52 (m, 2H, Ar-*H*), 7.50 – 7.38 (m, 3H, Ar-*H*), 7.28 – 7.17 (m, 3H, Ar-*H*), 5.56 (s, 1H, CH^{Napth}), 5.31 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, H-2), 4.96 (dd, 1H, $J_{2,3}$ = 9.9, $J_{3,4}$ = 3.5 Hz, H-3), 4.66 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 4.36 (d, 1H, $J_{3,4}$ = 3.5 Hz, H-4), 4.36 (dd, 1H, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ = 1.7 Hz, H-6b), 4.02 (dd, 1H, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ =1.7 Hz, H-6a), 3.56 (t, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 1.7 Hz, H-5), 2.03 (s, 3H, CH_3), 1.96 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.96, 169.32, 135.05, 134.01, 133.83 (2C), 133.02, 131.52, 129.05, 128.62, 128.38, 128.30, 127.96, 126.63, 126.30, 126.11, 124.38, 101.62, 85.45, 73.80, 73.41, 69.99, 69.41, 67.03, 21.16 (2C, CO*C*H_3). **HRMS**: calc. $[M+NH_4]^+$: 512.1743 found $[M+ NH_4]^+$: 512.1755

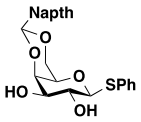
Phenyl 1-thio-β-D-galactopyranoside (23)[349]



A solution of galactose pentaacetate (25.0 g; 64.0 mmol), thiophenol (7.3 mL; 70.4 mmol) and BF_3·OEt_2 (7.9 mL; 64.0 mmol) in CH_2Cl_2 (200 mL) was stirred at 22 °C for 16 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. $NaHCO_3$ (300 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. Without further purification, the peracetylated thioglycoside was deacetylated. Na (1.03 g; 44.8 mmol) was dissolved in MeOH (100 mL) and the NaOMe/MeOH solution was slowly added to a solution of the peracetylated sugar in MeOH (100 mL). The reaction mixture was stirred at 22 °C until TLC showed full conversion (12 h). The reaction was quenched with Amberlite IR-120 H^+ (50 mL) and stirred for 1 h. The ion-exchange resin was filtered off, washed with MeOH and the filtrate was concentrated. The product was recrystallized from EtOAc to give **23** as colorless crystals. R_f 0.48 (1:1 EtOAc/Acetone). Yield (over two steps) 15.87 g (91%)

mp: 97-100 °C (litt.[350] 98-100 °C). $[\alpha]_D^{20}$= -53.4° (c 1.0, EtOH) (litt[350]-55°). **IR** (neat, cm^{-1}): 3500-3000, 2884.8, 1074.72, 1045.53, 1024.75. **^{1}H NMR** (300 MHz, DMSO) δ 7.42 (d, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 1H), 5.12 (d, *J* = 6.0 Hz, 1H), 4.87 (dd, *J* = 6.0, 3.1 Hz, 1H), 4.62 (t, *J* = 6.0 Hz, 1H), 4.56 (d, *J* = 9.3Hz, 1H), 4.47 (d, *J* = 3.1 Hz, 1H), 3.68 (s, 1H), 3.57 – 3.26 (m, 7H). **^{13}C NMR** (300 MHz, DMSO) δ 136.25, 129.80 (2C), 129.47 (2C), 126.72, 88.36, 79.81, 75.33, 69.86, 68.98, 61.20, 49.91. **HRMS**: calc. $[M+Na]^+$: 295.0616 found $[M+ Na]^+$: 295.0608

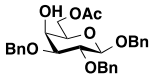
Phenyl 4,6-*O*-(2-naphthyl)methylene-1-thio-β-D-galactopyranoside (24)



To a solution of 2-naphthaldehyde (7.7 g, 49.3 mmol) and camphorsulphonic acid (255 mg, 1.1 mmol) in MeCN (200 mL) was added **23** (10 g, 36.5 mmol). The flask was equipped with a distillation unit and the mixture was heated to 95 °C for 1.5 h. During the period app. 100 mL of MeCN-MeOH was distilled off. The distillation unit was replaced with a condenser and the reaction mixture was heated to reflux until TLC showed completion (1 h). The reaction mixture was concentrated and purified by flash chromatography (19:1 CH_2Cl_2/MeOH) to afford **24** as a white crystalline powder. R_f 0.14 (1:1 EtOAc/toluene). Yield: 13.8 g (92%)

mp: 129.5 - 132 °C. $[\alpha]_D^{20}$= -21.3° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3600-3000, 3057.04, 2976.16, 2904.45, 2857.50, 1402.74, 1354.27, 1094.07, 1068.42, 1041.28. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 – 7.73 (m, 4H, Ar-*H*), 7.69 – 7.58 (m, 2H, Ar-*H*), 7.50 – 7.39 (m, 3H, Ar-*H*), 7.30 – 7.17 (m, 3H, Ar-*H*), 5.60 (s, 1H, -CH^{Napth}), 4.45 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 4.36 (dd, 1H, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.2 Hz, H-6b), 4.19 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-4), 4.01 (dd, 1H, *J* = 12.5, 1.2 Hz, H-6a), 3.71 – 3.61 (m, 2H, H-2, H-3), 3.51 (dd, 1H, $J_{5,6a}$ = 1.2, $J_{5,6a}$ = 1.5 Hz, H-5). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.20, 134.01, 133.82 (2C), 133.02, 131.12, 129.16 (2C), 128.54, 128.36, 127.97, 126.79, 126.50, 126.16, 124.28, 101.66, 87.15, 75.69, 73.87, 70.19, 69.52, 68.84. **HRMS**: calc. $[M+H]^+$: 411.1266 found $[M+ H]^+$: 411.1249

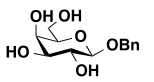
Benzyl 6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (25)[123]



The diol **29** (5 g; 11.2 mmol) was dissolved in CH_2Cl_2 (35 mL). Et_3N (2.3 mL; 16.8 mmol) and acetic anhydride (1.2 mL; 12.3 mmol) was added and the reaction mixture was stirred until TLC revealed full conversion (1-2h). The reaction was quenched by addition of MeOH, diluted with CH_2Cl_2 (50 mL) and washed with H_2O (50 mL). The organic phase was dried over $MgSO_4$ and concentrated to a white crystalline powder. The product was purified by flash chromatography (1:2 EtOAc/ Heptane) to give **25** as a white crystalline powder. R_f 0.4 (EtOAc/Heptane 1:1). Yield: 5.3g (97%)

mp: 97-100 °C (litt.[123] 99-103 °C). $[\alpha]_D^{20}$= -16.3° (c 1.0, $CHCl_3$) C (litt.[123] -17.7). **IR** (neat, cm^{-1}): 3500-3400, 3028.7, 2917.8, 1710.6, 1271.5, 1088.7. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 15H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.88 (d, *J* = 11.5 Hz, 1H), 4.71 – 4.56 (m, 4H), 4.37 (d, *J* = 7.8 Hz, 1H), 4.29 (dd, *J* = 6.3, 2.5 Hz, 2H), 3.86 (d, *J* = 3.4 Hz, 1H), 3.64 (dd, *J* = 9.4, 7.8 Hz, 1H), 3.51 (t, *J* = 6.7 Hz, 1H), 3.43 (dd, *J* = 9.4, 3.4 Hz, 1H), 2.03 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.07, 138.65, 137.95, 137.52, 128.76-127.91 (15C), 102.50, 80.59, 79.16, 75.50, 72.92, 72.05, 71.08, 66.94, 63.32, 21.19. **HRMS**: calc. $[M+ Na]^+$: 515.2046 found $[M+ Na]^+$: 515.2067

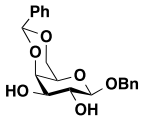
Benzyl β-D-galactopyranoside (26)[351]



A solution of galactose pentaacetate (25 g; 64 mmol), BnOH (12.0 mL; 116 mmol) and $BF_3{\cdot}OEt_2$ (10.0 mL; 79 mmol) in CH_2Cl_2 (200 mL) was stirred at 22 °C for 12 h. The mixture was diluted with CH_2Cl_2 (150 mL) and washed with sat. aq. $NaHCO_3$ (300 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. Without further purification the fully protected monosaccharide was deacetylated. Na (1.03 g; 44.8 mmol) was dissolved in MeOH (100 mL) and the NaOMe/MeOH solution was slowly added to a solution of the fully protected monosaccharide in MeOH (100 mL). The reaction was stirred at 22 °C until TLC showed full conversion (14 h), quenched with Amberlite IR-120 H^+ (50 mL) and stirred for 1 h. The ion-exchange resin was filtered off, washed with MeOH and the filtrate was concentrated. Purified by flash chromatography (acetone:EtOAc 1:1) to give **26** as a white colorless solid. R_f 0.15 (1:1 EtOAc/Acetone). Yield (over two steps): 14.20 g (81%)

mp: 96-98 °C (litt.[351] 100-101 °C). $[\alpha]_D^{20}$= -25.2° (c 1.0, $CHCl_3$) C (litt.[351] -27.2). **^{1}H NMR** (300 MHz, DMSO) δ 7.41 – 7.22 (m, 5H), 4.97 (d, *J* = 4.7 Hz, 1H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.68 (d, *J* = 5.6 Hz, 1H) 4.61 (1H, d, *J* = 5.8 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.35 (d, *J* = 4.7 Hz, 1H), 4.17 (d, *J* = 7.5 Hz, 1H), 3.64 (t, *J* = 4.7 Hz, 1H), 3.53 (ddd, 12.5, 5.8, 3.0 Hz, 1H), 3.38 – 3.30 (m, 4H). **^{13}C NMR** (75 MHz, DMSO) δ 138.85, 128.77, 128.26, 127.97, 103.39, 75.97, 74.10, 71.30, 70.07, 68.85, 61.16. **HRMS**: calc. $[M+NH_4]^+$: 288.1447 found $[M+ NH_4]^+$: 288.1453

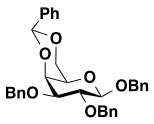
Benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside (27)[351]



To a solution of $PhCH(OMe)_2$ (7.7 mL, 50.0 mmol) and camphorsulphonic acid (258 mg, 1.1 mmol) in MeCN (200 mL) was added **26** (10 g, 37.0 mmol). The flask was equipped with a distillation unit and the mixture was heated to reflux for 2 h during which time approximately 100 mL of MeCN-MeOH was distilled off. The distillation unit was then replaced with a condenser and the reaction mixture was heated to reflux until TLC showed completion (1 h). The reaction mixture was concentrated and recrystallized from EtOAc to afford **27** as a white crystalline powder. R_f 0.56 (9:1 CH_2Cl_2/MeOH). Yield: 12.73 g (96%)

mp: 198-201 °C (litt.[351] 209-210 °C). $[\alpha]_D^{20}$= -61.8° (c 1.0, $CHCl_3$) (litt.[351] -62.4). **^{1}H NMR** (300 MHz, DMS) δ 7.50 – 7.23 (m, 10H), 5.55 (s, 1H), 5.08 (d, *J* = 4.3 Hz, 1H), 4.90 (d, *J* = 5.5 Hz, 1H), 4.82 (d, *J* = 12.3 Hz, 1H), 4.58 (d, *J* = 12.3 Hz, 1H), 4.31 (d, *J* = 6.4 Hz, 1H), 4.06 (s, 3H), 3.49 (s, 1H), 3.48 – 3.41 (m, 2H). **^{13}C NMR** (75 MHz, DMSO) δ 139.31, 138.74, 129.25, 128.80 (2C), 128.56 (2C), 128.24 (2C), 128.03, 126.93 (2C), 103.21, 100.42, 76.68, 72.56, 70.78, 70.33, 69.29, 66.69. **HRMS**: calc. $[M+ H]^+$: 359.1459 found $[M+ NH_4]^+$: 359.1498

Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-β-D-galactopyranoside (28)[351]

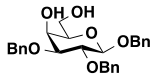


27 (10.0 g; 27.9 mmol) was dissolved in DMF (150 mL). NaH (5.1 g; of ~50% oil dispersion, 106.3 mmol) was added and the mixture was stirred until gas evolution ceased (10 min). The reaction mixture was cooled to 0 °C followed by addition of BnBr (10.0 mL; 17.41 84.3 mmol) and Bu_4NI (0.72 g; 2.0 mmol) and the solution was stirred at 22 °C overnight. Quenched with MeOH, diluted with CH_2Cl_2 (500 mL) and washed with H_2O (3x400 mL). The organic phase was dried over $MgSO_4$, concentrated and recrystallized from EtOAc to yield **28** as colorless crystals. R_f 0.59 (1:1 EtOAc/Heptane). Yield: 13.53 g (90%)

mp: 168-169 °C (litt. [351] 169.5-170.5 °C). $[\alpha]_D^{20}$= -4.1° (c 1.0, $CHCl_3$) (litt.[351] -2.3). **IR** (neat, cm^{-1}): 3064.58, 3027.05, 2886.78, 2861.33,1495.81, 1365.55, 1098.97, 1060.26, 1023.43. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.08 (m, 20H, $-CH_2^{Bn,a}$), 5.43 (s, 1H, $-CH^{benzylidene}$), 4.93 (d, *J* = 12.1 Hz, 1H, $-CH_2^{Bn,a}$), 4.87 (d, *J* = 10.8 Hz, 1H, $-CH_2^{Bn,b}$), 4.72 (d, *J* = 10.8 Hz, 1H, $-CH_2^{Bn,b}$), 4.68 (d, *J* = 4.7 Hz, 2H, $-CH_2^{Bn,c}$), 4.59 (d, *J* = 12.1 Hz, 1H, $-CH_2^{Bn,a}$), 4.43 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.26 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6a}$ = 1.5 Hz, 1H, H-6a), 4.04 (dd, $J_{3,4}$ = 3.7, $J_{4,5}$ = 1.0 Hz,

1H, H-4), 3.95 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$ = 1.8 Hz, 1H, H-6b), 3.85 (dd, $J_{2,3}$ = 9.7, $J_{1,2}$ = 7.7 Hz, 1H, H-2), 3.48 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.7 Hz, 1H, H-3), 3.24 (m, 1H, H-5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.80, 138.42, 137.84, 137.63, 128.97, 128.36 (4C), 128.26 (2C), 128.16 (2C), 128.11 (2C), 127.92 (2C), 127.77 (2C), 127.69, 127.68, 127.53, 126.52 (2C), 102.55, 101.36, 79.28, 78.50, 75.33, 73.99, 72.07, 70.91, 69.26, 66.46. **HRMS**: $[M+NH_4]^+$: calc. for $C_{34}H_{34}NaO_6$: 558.2314 found $[M+NH_4]^+$: 558.2307

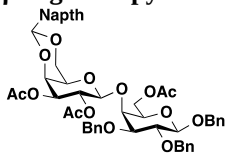
Benzyl 2,3-di-*O*-benzyl-β-D-galactopyranoside (29)[351]



28 (10 g; 18.6 mmol) was dissolved in CH_2Cl_2 (100 mL) and MeOH (100 mL). Propan-1,3-diol (6.7 mL; 92.82 mmol) and *p*-toluene sulphonic acid (80 mg; 0.46 mmol) was added and the reaction mixture was immersed in an oil bath and heated to reflux. After 72 hours the reaction mixture was cooled, diluted by 100 mL CH_2Cl_2, washed with 200 mL sat. aq. $NaHCO_3$, dried with $MgSO_4$ and concentrated. The product was recrystallized from EtOAc-heptane to afford **29** as a white crystalline solid. R_f 0.15 (1:1 EtOAc/Heptane). Yield: 7.70 g (92%)

mp: 115-116 °C (litt.[351] 116-117 °C). $[\alpha]_D^{20}$= -16.8° (c 1.0, $CHCl_3$) C (litt.[351] -17.0). **IR** (neat, cm^{-1}): 3500-3000, 3088.8, 3030.7, 2899.3, 1713.5, 1451.9, 1026.8. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.11 (m, 15H), 4.88 (d, *J* = 8.9 Hz, 1H), 4.89 (d, *J* = 8.9 Hz, 1H), 4.73 – 4.58 (m, 4H), 4.42 (d, *J* = 7.8 Hz, 1H), 3.91 (dd, *J* = 11.7, 6.8 Hz, 1H), 3.91 (dd, *J* = 3.5, 1.1 Hz, 1H), 3.75 (dd, *J* = 11.7, 4.5 Hz, 1H), 3.65 (dd, *J* = 9.4, 7.8 Hz, 1H), 3.44 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.38 (ddd, *J* = 6.8, 4.5, 1.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.68, 137.96, 137.67, 128.95 – 127.77 (15C), 103.02, 80.67, 79.12, 75.52, 74.22, 72.82, 71.51, 67.68, 62.72. **HRMS**: calc. $[M+NH_4]^+$: 468.2386 found $[M+NH_4]^+$: 468.2405

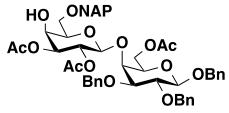
Benzyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranosyl-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (30)



A mixture of **25** (2.0 g; 4.01 mmol) and **22** (2.58 g; 5.21 mmol) was dried azeotropically with benzene (2x30 mL) and subjected to vacuum overnight. The mixture was dissolved in dry CH_2Cl_2 (25 mL) and dry MeCN (25 mL), cooled to -20 °C, followed by addition of NIS (1.20 g; 5.33 mmol) and TESOTf (212 mg; 0.80 mmol). The reaction mixture was stirred at -20 °C until TLC revealed full conversion of the donor (2 h). The solution was diluted with CH_2Cl_2 (150 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (5:1 toluene/EtOAc) to afford **30** as a white crystalline material. R_f 0.58 (1:2 EtOAc/toluene). Yield: 2.70 g (77%)

mp: 152.3-154.1 °C. $[\alpha]_D^{20}$= +47.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3062.68, 3030.40, 2868.79, 1737.93, 1222.87, 1057.46. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.88 – 7.72 (m, 4H, Ar-*H*), 7.56 (dd, 1H, *J* = 8.5, 1.6 Hz, Ar-*H*), 7.44 – 7.35 (m, 2H, Ar-*H*), 7.33 – 7.17 (m, 15H, Ar-*H*), 5.53 (s, 1H, CH^{Napth}), 5.33 (dd, 1H, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.8 Hz, H-2'), 4.90 (d, 1H, J_{CH2} = 2.0 Hz, 0.5xCH_2^{Bn}), 4.87 (d, 1H, J_{CH2} = 1.5 Hz, 0.5xCH_2^{Bn}), 4.85 (d, 1H, $J_{2,3}$ = 9.0 Hz, H-3'), 4.74 – 4.54 (m, 5H, CH_2^{Bn}, H-1'), 4.50 (dd, 1H, $J_{6a,6b}$ = 11.9, $J_{5,6b}$ = 4.5 Hz, H-6b), 4.33 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.30 – 4.13 (m, 2H, H-4', H-6b'), 4.03 – 3.91 (m, 2H, H-6a, H6a'), 3.70 – 3.62 (m, 1H, H-5'), 3.58 (dd, 1H, $J_{2,3}$ = 9.7, $J_{1,2}$ = 7.6 Hz, H-2), 3.47 (dd, 1H, $J_{5,6a}$ = 7.0, $J_{5,6b}$ = 4.5 Hz, H-5), 3.39 (dd, 1H, $J_{2,3}$ = 9.7, $J_{3,4}$ = 2.9 Hz, H-3), 3.29 (s, 1H, H-4), 1.98 (s, 6H, 2xCH_3^{Ac}), 1.82 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.23, 171.18, 169.64, 138.82, 138.52, 137.71, 135.16, 134.08, 133.10, 128.72-127.81 (15C), 126.58, 126.26, 126.19, 124.40, 102.47, 101.93, 101.73, 81.55, 79.49, 75.53, 74.64, 73.73, 73.53, 72.39, 72.16, 70.88, 69.18, 68.22, 66.38, 64.42, 21.26, 21.23, 21.11. **HRMS**: calc. $[M+NH_4]^+$: 894.3701 found $[M+NH_4]^+$: 894.3695

Benzyl 2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (31)

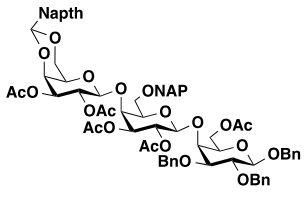


To a solution of **30** (2.6 g; 2.96 mmol) in dry THF (60 mL), $NaCNBH_3$ (3.73 g; 59.30 mmol) was added. The mixture was stirred at 22 °C and a 2M solution of HCl in dry ether was added drop wise until gas development ceased and the mixture remained acidic (pH 3-4). The reaction mixture was concentrated to 4 ml, diluted with CH_2Cl_2 (150 mL) and neutralized with sat. aq. $NaHCO_3$ (80 mL). The aqueous phase was extracted with CH_2Cl_2 (3x100 mL). The combined organic phases were washed with water (500 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (3:1 toluene/EtOAc) to afford **31** as a colorless crystalline powder. R_f 0.49 (1:2 EtOAc/toluene). Yield: 2.16 g (83%)

mp: 133.5-134.8 °C. $[\alpha]_D^{20}$= +46.4° (c 1.0, $CHCl_3$). **IR** (neat, cm^{-1}): 3600-3400, 3030.61, 2916.50, 2868.86, 1738.02, 1366.16, 1226.88, 1063.52. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 3H, Ar-*H*), 7.69 (s, 1H, Ar-*H*), 7.43 – 7.33 (m, 3H, Ar-*H*), 7.33 – 7.15 (m, 15H, Ar-*H*), 5.20 (dd, 1H, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.8 Hz, H-2'), 4.90 – 4.78 (m, 3H, H-1', CH_2^{Bn}), 4.67 – 4.51 (m, 7H, H-6b, 3xCH_2^{Bn}), 4.37 – 4.29 (m, 2H, H-1, H-6b'), 4.19 (dd, 1H, $J_{2,3}$ = 10.8, $J_{2,3}$ = 3.2 Hz, H-3'), 4.05 (d, 1H, *J* = 2.7 Hz, H-6a), 3.87 (d, 1H, *J* = 2.4 Hz, H-6a'), 3.68 (m, 2H, H-4', H-5'),

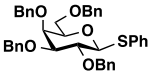
3.59 – 3.49 (m, 2H, H-2, H-4), 3.43 (dd, 1H, $J_{5,6a}$ = 6.7, $J_{5,6b}$ = 5.0 Hz, H-5), 3.34 (dd, 1H, $J_{2,3}$ = 9.7, $J_{3,4}$ = 2.9 Hz, H-3), 2.01 (s, 3H, CH_3^{Ac}), 1.91 (s, 3H, CH_3^{Ac}), 1.78 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.04 170.64, 169.89, 138.76, 138.33, 137.66, 135.46, 133.45, 133.26, 128.66 (2C), 128.57 (2C), 128.52 (3C), 128.28 (2C), 128.23 (2C), 128.12, 128.04, 127.93 (2C), 127.85 (2C), 126.85, 126.42, 126.23, 125.91, 102.48, 102.15, 81.39, 79.45, 75.53, 74.56, 74.10, 73.61, 73.57, 73.33, 72.17, 70.88, 69.70, 69.46, 68.03, 64.36, 21.19, 21.12, 21.00. **HRMS**: calc. $[M+NH_4]^+$: 896.3858 found $[M+ NH_4]^+$: 896.3824

Benzyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranosyl)-(1→4)-(2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (32)



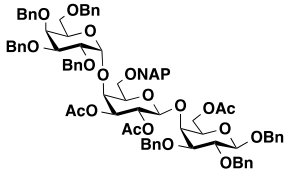
A mixture of **31** (1.9 g; 2.16 mmol) and **22** (1.50 g; 3.02 mmol) was dried azeotropically with benzene (2x30 mL) and subjected to vacuum overnight. The mixture was dissolved in dry CH_2Cl_2 (20 mL) and dry MeCN (20 mL), cooled to -20 °C, followed by addition of NIS (0.69 g; 3.09 mmol) and TESOTf (114 mg; 0.43 mmol). The reaction mixture was stirred at -20 °C until TLC revealed full conversion of the donor (3 h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (3:1 toluene/EtOAc) to afford **31** as a white crystalline material R_f 0.41 (2:1 toluene/EtOAc). Yield: 2.21 g (81%)
mp: 87.4 – 88.3 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -18.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3062.10, 3030.30, 2919.45, 2865.48, 1744.70, 1368.26, 1241.72, 1222.54, 1060.61. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 (s, 1H, Ar-*H*), 7.88 – 7.78 (m, 3H, Ar-*H*), 7.71 – 7.57 (m, 4H, Ar-*H*), 7.51 (d, *J* = 6.7 Hz, 1H, Ar-*H*), 7.47 – 7.41 (m, 2H, Ar-*H*), 7.35 – 7.17 (m, 18H, Ar-*H*), 5.60 (s, 1H, CH^{Napth}), 5.33 (dd, 1H, $J_{2,3}$ = 10.5, $J_{1,2}$ = 7.9 Hz, H-2''), 4.92 (m, 5H, H-1'', H-2', H-3'', CH_2^{Bn}), 4.75 – 4.51 (m, 8H, H-1', H-6b, 3xCH_2^{Bn}), 4.38 – 4.15 (m, 5H, H-1, H-3', H-4'', H-6b', H-6b''), 4.06 (d, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 3.97 – 3.76 (m, 3H, H-4', H-6a', H6a''), 3.62 – 3.45 (m, 3H, H-2, H-5', H-5''), 3.46 – 3.38 (m, 1H, H-5), 3.36 (s, 1H, H-4), 3.33 (dd, 1H, $J_{2,3}$ = 9.8, $J_{3,4}$ = 2.9 Hz, H-3), 2.14 (s, 3H, CH_3^{Ac}), 2.04 (s, 3H, CH_3^{Ac}), 2.02 (s, 3H, CH_3^{Ac}), 1.84 (s, 3H, CH_3^{Ac}), 1.81 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.89, 170.762, 170.16, 169.52, 169.33, 138.49, 138.14, 137.42, 135.80, 135.07, 133.73, 133.13, 132.78, 128.93, 128.41-125.62 (m, 29C), 102.13, 101.13, 100.98, 81.27, 79.13, 75.09, 73.47, 73.29, 73.11, 72.47, 71.92, 71.77, 70.50, 69.81, 68.95, 68.45, 66.26, 63.80

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (33)[352]



23 (3.0 g; 11.0 mmol) was dissolved in DMF (40 mL) and cooled to 0 °C. NaH (2.53 g of ~50% oil dispersion, 52.80 mmol) was added and the mixture was stirred until gas evolution ceased (20 min). BnBr (6.28 mL; 52.80 mmol) was added and the reaction was stirred at 22 °C overnight. Quenched with MeOH, diluted with CH_2Cl_2 (150 mL) and washed with H_2O (3x400 mL). The organic phase was dried over $MgSO_4$, concentrated and purified by flash chromatography (Heptane:EtOAc 9:1) to yield **33** as colorless crystals. R_f 0.6 (EtOAc/Heptane 1:3). Yield: 6.01 g (87%)
mp: 69-71 °C (lit. 70-71 °C). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= +15.1° (c 1.0, $CHCl_3$) (lit. +16.5). **IR** (neat, cm^{-1}): 3060.01, 3029.96, 2916.62, 2883.94, 2863.99, 1452.95, 1369.33, 1080.33, 1049.58, 1014.86. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 – 7.45 (m, 2H), 7.35 – 7.14 (m, 20H), 7.14 – 7.05 (m, 3H), 4.89 (d, *J* = 11.5 Hz, 1H), 4.74 – 4.62 (m, 3H), 4.56 (d, *J* = 9.5 Hz, 1H), 4.54 – 4.48 (m, 2H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.34 (d, *J* = 11.7 Hz, 1H), 3.90 (d, *J* = 2.7 Hz, 1H), 3.86 (t, *J* = 9.5 Hz, 1H), 3.55 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.98, 138.54, 138.48, 138.09, 134.37, 131.73-127.27 (25C), 87.95, 84.41, 77.52 (2C), 75.89, 74.69, 73.82 (2C), 72.96, 68.99. **HRMS**: calc. $[M+ Na]^+$: 655.2495 found $[M+ Na]^+$: 655.2498

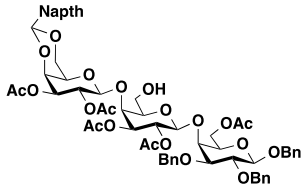
Benzyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl-(1→4)-(2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (34)



A mixture of **31** (1.2 g; 1.37 mmol) and **33** (1.21 g; 1.91 mmol) was dried azeotropically with benzene (2x30 mL) and subjected to vacuum overnight. The mixture was dissolved in dry CH_2Cl_2 (10 mL) and dry Et_2O (10 mL), cooled to -20 °C, followed by addition of NIS (0.44 g; 1.95 mmol) and TESOTf (72 mg; 0.27 mmol). The reaction mixture was stirred at -20 °C until TLC revealed full conversion of the donor (4 h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (80 mL) and sat. aq. $NaHCO_3$ (80 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (4:1 toluene/EtOAc) to afford **34** as a white crystalline material R_f 0.62 (2:1 toluene/EtOAc). Yield: 1.61 g (84%)
mp: 54.2 – 55.1 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -27.2° (c 1. 0, $CHCl_3$). **IR** (neat, cm^{-1}): 3062.57, 3030.41, 2925.39, 2866.92, 1742.01, 1365.91, 1236.91, 1065.61. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75 – 7.64 (m, 3H, Ar-*H*), 7.47 (s, 1H, Ar-*H*), 7.37 (m,

4H, Ar-*H*), 7.32 – 7.09 (m, 34H, Ar-*H*), 5.21 (dd, 1H, $J_{2,3}$ = 10.6, $J_{1,2}$ = 7.7 Hz, H-2'), 4.95 – 4.72 (m, 8H, 4xCH_2^{Bn}), 4.65 – 4.45 (m, 7H, H-1', H-6b, 2.5xCH_2^{Bn}), 4.39 – 4.17 (m, 8H, H-1, H-1'', H-3', H-6b', H-6b'', 0.5xCH_2^{Bn}), 4.08 (m, 3H, H-4'', H-6a, H-6a''), 3.97 (dd, 1H, $J_{2,3}$ = 9.5, $J_{3,4}$ = 3.3 Hz, H-3), 3.81 (m, 2H, H-3'', H-4'), 3.56 (m, 3H, H-2, H-5', H-5''), 3.47 – 3.28 (m, 4H, H-2'', H-6a', H-4, H-5), 1.85 (s, 3H, CH_3^{Ac}), 1.79 (s, 3H, CH_3^{Ac}), 1.74 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (75 MHz, $CDCl_3$) 170.78 (2C), 169.51, 139.10, 138.94, 138.80, 138.25, 138.10, 137.60, 135.56, 133.32, 133.10, 128.46-127.84 (m, 38C), 127.55, 126.54, 126.22, 126.01, 125.79, 102.52 (2C), 100.35(1C), 81.26, 79.51, 79.03, 75.47, 75.12, 74.43, 74.19, 73.73, 73.57, 73.40, 73.12, 72.70, 72.05, 70.94, 69.88, 69.59, 68.22, 67.63, 63.87, 20.89 (2C), 20.74.

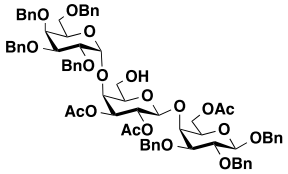
Benzyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranosyl)-(1→4)-(2,3-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (35)



To a solution of **32** (1.1 g; 0.87 mmol) in CH_2Cl_2 (8 mL) and MeOH (2 mL), DDQ (0.27 g; 1.18 mmol) and three drops of water were added and the reaction was stirred at 22 °C. After complete conversion (2 h), the mixture was concentrated and the residue was purified by flash chromatography (19:1 CH_2Cl_2/MeOH followed by another column with the eluent system 3:1 toluene/EtOAc). R_f 0.31 (2:1 toluene/EtOAc). Yield: 0.77 g (79%)

mp: 114.3 – 115.4 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= 31.5° (c 1.0, $CHCl_3$). **IR** (neat, cm^{-1}): 3600-3400, 3063.06, 3030.43, 2869.65, 1742.52, 1367.26, 1220.37, 1055.46. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 – 7.74 (m, 4H, Ar-*H*), 7.56 (m, 1H, Ar-*H*), 7.46 – 7.39 (m, 2H, Ar-*H*), 7.34 – 7.16 (m, 15H, Ar-*H*), 5.57 (s, 1H, CH^{Napth}), 5.31 (dd, 1H, $J_{2,3}$ = 10.5, $J_{3,4}$ = 7.9 Hz, H-2''), 5.08 – 4.77 (m, 5H, H-1'', H-3'', 1.5xCH_2^{Bn}), 4.69 (d, 1H, $J_{6a,6b}$ = 11.3 Hz, H-6b), 4.63 – 4.49 (m, 5H, H-1', H-2', 1.5xCH_2^{Bn}), 4.40 – 4.26 (m, 3H, H-1, H-4'', H-6b''), 4.21 – 4.11 (m, 2H, H-3', H-6b'), 4.03 (d, 1H, $J_{6a,6b}$ = 11.3 Hz, H-6a), 3.86 (d, 1H, J = 2.6 Hz, H-6a'), 3.82 – 3.67 (m, 2H, H-4', H-6a''), 3.58 – 3.46 (m, 3H, H-2, H-4, H-5,), 3.42 (t, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 5.8 Hz, H-5'), 3.36 (dd, 1H, $J_{2,3}$ = 9.7, $J_{3,4}$ = 2.9 Hz, H-3), 3.18 (t, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 7.3 Hz, H-5''), 2.12 (s, 3H, CH_3^{Ac}), 2.05 (s, 3H, CH_3^{Ac}), 2.02 (s, 3H, CH_3^{Ac}), 2.00 (s, 3H, CH_3^{Ac}), 1.80 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.97, 170.83, 170.24, 169.351 (2C), 138.47, 138.13, 137.37, 134.61, 133.75, 132.74, 128.34-127.47 (m, 18C), 126.30, 125.96, 125.77, 123.82, 102.22, 101.56 (2C), 101.36, 81.09, 79.15, 75.16, 74.51, 73.81 (2C), 73.26, 73.14, 72.56, 71.74, 71.48, 70.64, 69.46, 68.63 (2C), 66.50, 63.81, 60.36, 20.83-20.59 (5C)

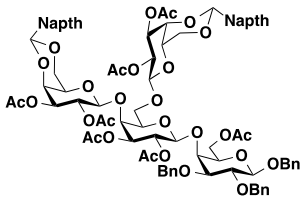
Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→4)-(2,3-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (36)



To a solution of **34** (0.92 g; 0.66 mmol) in CH_2Cl_2 (8 mL) and methanol (2 mL), DDQ (0.18 g; 0.79 mmol) and three drops of water were added and the reaction was stirred at 22 °C. After complete conversion (2 h) the mixture was concentrated and the residue was purified by flash chromatography (19:1 CH_2Cl_2/MeOH followed by another column with the eluent system 4:1 toluene/EtOAc). R_f 0.47 (2:1 toluene/EtOAc). Yield: 0.72 g (87%).

mp: 61.2 – 63.5 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -15.7° (c 1.0, $CHCl_3$). **IR** (neat**,** cm^{-1}): 3600-3400, 3063.13, 3030.31, 2917.56, 2868.89, 1746.19, 1365.82, 1221.71,1052.50. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.12 (m, 35H, Ar-*H*), 5.16 (dd, 1H, $J_{2,3}$ = 10.7, $J_{1,2}$ = 7.7 Hz, H-2'), 4.93 – 4.70 (m, 7H, 3.5xCH_2^{Bn}), 4.70 – 4.46 (m, 7H, 3.5xCH_2^{Bn}), 4.43 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1'), 4.39 – 4.30 (m, 2H, H-1, H-1''), 4.27 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-4', H-6b), 4.26 (d, 1H, $J_{6a,6b}$ = 6.1, H-6b), 4.21 (dd, 1H, $J_{2,3}$ = 9.3, $J_{3,4}$ = 3.6 Hz, H-3'), 4.08 (s, 1H, H-6b''), 4.02 (s, 1H, H-6a), 3.98 (dd, 2H, J = 6.2, 2.6 Hz, H-4'', H-5''), 3.77 (d, 1H, J = 2.5 Hz, H-6a''), 3.70 – 3.29 (m, 9H, H-2, H-2'', H-3, H-3'', H-4, H-5, H-5', H-6a', H-6b'), 1.99 (s, 3H, CH_3^{Ac}), 1.85 (s, 3H, CH_3^{Ac}), 1.76 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.78, 170.61, 169.15, 138.75, 138.52, 138.42, 138.21, 138.03, 137.48, 137.36, 128.21-127.42 (m, 45), 102.44 (2C), 101.26, 81.01, 79.22, 78.76, 75.65, 75.29, 74.96, 74.68, 74.56, 74.40, 73.32, 72.78, 72.20, 71.56, 70.83, 69.61, 69.28, 67.93, 63.53, 60.13, 20.85-20.69 (3C)

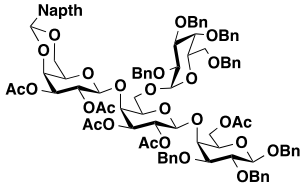
Benzyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranosyl-(1→4)-[2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranosyl-(1→6)]-(2,3-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (37)



A mixture of **35** (450 mg; 0.40 mmol) and **22** (277 mg; 0.56 mmol) was dried azeotropically with benzene (2 x 5 mL) and subjected to vacuum overnight. The mixture was dissolved in dry CH_2Cl_2 (2.5 mL) and dry MeCN (2.5 mL), cooled to -20 °C, followed by addition of NIS (130 mg; 0.58 mmol) and TESOTf (21 mg; 0.08 mmol). The reaction mixture was stirred at -20 °C until TLC revealed full conversion of the donor (2 h). The solution was diluted with CH_2Cl_2 (40 mL) and washed with sat. aq. NaS_2O_3 (40 mL) and sat. aq. $NaHCO_3$ (40 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (3:1 toluene/EtOAc) to afford a white crystalline material. R_f 0.25 (2:1 toluene/EtOAc). Yield: 452 mg (75%)

mp: 143.4 – 144.2 °C. $[\alpha]_D^{20}$= -42.5° (c 1.0, $CHCl_3$). **IR** (neat**,** cm^{-1}): 3062.41, 3030.38, 2867.75, 1742.18, 1367.70, 1242.11, 1220.49, 1061.20. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.00 – 7.67 (m, 9H, Ar-*H*), 7.59 (dd, 1H, *J* = 8.4, 1.5 Hz, Ar-*H*), 7.51 – 7.14 (m, 19H, Ar-*H*), 5.51 (s, 1H, CH^{Napth}), 5.40 (s, 1H, CH^{Napth}), 5.28 (m, 2H, H-2'', Gal-1,6 H-2), 5.05 – 4.52 (m, 11H, H-1'', Gal-1,6 H-1, H-2', H-3'', Gal-1,6 H-3, 3xCH_2^{Bn}), 4.44 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.40 – 3.90 (m, 11H, H-3', H-4'', Gal-1,6 H-4, H-6a, H-6a', H-6a'', Gal-1,6 H-6a, H-6b, H-6b', H-6b'', H-4'), 3.84 (dd, 1H, $J_{6a,6b}$ = 12.0, $J_{5,6b}$ = 7.9 Hz, Gal-1,6 H-6b), 3.51 (m, 6H, H-2, H-4, H-5, H-5', H-5'', Gal-1,6 H-5), 3.36 (dd, 1H, $J_{2,3}$ = 9.7, $J_{3,4}$ = 2.8 Hz, H-3), 3.12 (s, 1H, H-4), 2.12 (s, 3H, CH_3^{Ac}), 2.09 (s, 3H, CH_3^{Ac}), 2.02 (s, 3H, CH_3^{Ac}), 2.00 (s, 3H, CH_3^{Ac}), 1.95 (s, 3H, CH_3^{Ac}), 1.87 (s, 3H, CH_3^{Ac}), 1.82 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.09 (2C), 170.66, 170.44, 169.67, 169.54, 169.23, 138.74, 138.39, 137.65, 135.49, 135.19, 133.93, 133.76, 132.98, 128.53-127.633 (m, 14C), 126.60, 126.33, 126.05, 125.80, 124.35, 124.17, 102.22, 101.49, 101.30 (2C), 101.04 (2C), 81.48, 79.44, 75.25, 73.78, 73.39, 72.44, 72.06, 71.87, 70.66, 69.77, 69.57, 69.11, 68.84, 66.36, 66.24, 65.28, 21.17-20.85 (7C).

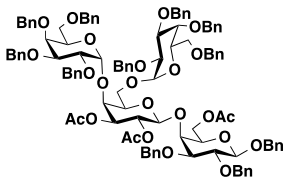
Benzyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranosyl)-(1→4)-[2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→6)]-(2,3-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (38)



A mixture of **35** (450 mg; 0.40 mmol) and **33** (355 mg; 0.56 mmol) was dried azeotropically with benzene (2 x 5 mL) and subjected to vacuum overnight. The mixture was dissolved in dry CH_2Cl_2 (2.5 mL) and dry Et_2O (2.5 mL), cooled to -20 °C, followed by addition of NIS (130 mg; 0.58 mmol) and TESOTf (21 mg; 0.08 mmol). The reaction mixture was stirred at -20 °C until TLC revealed full conversion of the donor (4 h). The solution was diluted with CH_2Cl_2 (40 mL) and washed with sat. aq. NaS_2O_3 (40 mL) and sat. aq. $NaHCO_3$ (40 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (4:1 toluene/EtOAc) to afford a white crystalline material. R_f 0.44 (2:1 toluene/EtOAc). Yield: 514 mg (78%)

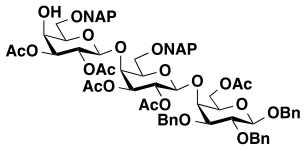
mp: 85.8 – 86.4 °C. $[\alpha]_D^{20}$= 31.2° (c 1.0, $CHCl_3$). **IR** (neat, cm^{-1}): 3062.96, 3030.63, 2868.58, 1746.69, 1367.42, 1220.78, 1058.26. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.88 – 7.65 (m, 4H, Ar-*H*), 7.54 (dd, 1H, *J* = 8.5, 1.6 Hz, Ar-*H*), 7.42 – 7.05 (m, 37H, Ar-*H*), 5.48 (s, 1H, -CH^{Napth}), 5.27 (dd, 1H, *J* = 10.5, 7.9 Hz, H-2''), 5.03 (dd, 1H, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.7 Hz, H-2'), 4.93 – 4.74 (m, 7H, H-1'', 3xCH_2^{Bn}), 4.70 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1'), 4.63 – 4.39 (m, 9H, H-1, H-3'', H-6b, 3xCH_2^{Bn}), 4.37 – 4.03 (m, 8H, Gal-1,6 H-1, H-3', H-4'', H-6a, H-6b'', Gal-1,6 H-6b, CH_2^{Bn}), 4.00 – 3.65 (m, 9H, H-2, Gal-1,6 H-2, Gal-1,6 H-3, H-4', Gal-1,6 H-4, Gal-1,6 H-5, H-6a', H-6a''), 3.61 (t, 1H, $J_{5,6a}$ = $J_{5,6b}$ =5.4 Hz, H-5''), 3.55 – 3.33 (m, 4H, H-4, H-5, H-5', Gal-1,6 H-6a), 3.28 (dd, H1, $J_{2,3}$ = 9.8, $J_{3,4}$ = 2.8 Hz, H-3), 2.12 (s, 3H, CH_3^{Ac}), 2.07 (s, 3H, CH_3^{Ac}), 2.00 (s, 3H, CH_3^{Ac}), 1.90 (s, 3H, CH_3^{Ac}), 1.79 (s, 3H, CH_3^{Ac}), 1.60 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.078 (2C), 170.38, 169.56 (2C), 139.24, 138.96, 138.79, 138.44, 138.22, 137.69, 135.15, 133.90, 132.97, 128.41-127.53 (m, 39C), 126.35, 126.04, 125.91, 124.28, 102.22, 101.40 (3C), 98.58, 81.45, 79.40, 75.29, 74.90, 73.84, 73.49, 73.24, 72.58, 72.28, 72.02, 70.62, 69.97, 69.39, 69.00, 68.74, 67.43, 66.49, 64.36, 21.06-20.86 (m, 5C)

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→4)-[2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→6)]-(2,3-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (39)



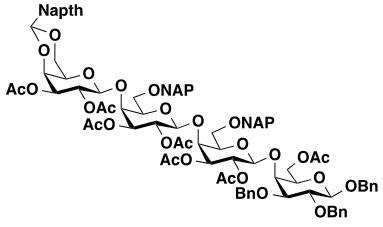
A mixture of **36** (310 mg; 0.25 mmol) and **33** (218 mg; 0.34 mmol) was dried azeotropically with benzene (2 x 5 mL) and subjected to vacuum overnight. The mixture was dissolved in dry CH_2Cl_2 (2.5 mL) and dry Et_2O (2.5 mL), cooled to -20 °C, followed by addition of NIS (79 mg; 0.35 mmol) and TESOTf (13 mg; 0.05 mmol). The reaction mixture was stirred at -20 °C until TLC revealed full conversion of the donor (2 h). The solution was diluted with CH_2Cl_2 (40 mL) and washed with sat. aq. NaS_2O_3 (40 mL) and sat. aq. $NaHCO_3$ (40 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (4:1 toluene/EtOAc) to afford a white crystalline material. R_f 0.55 (2:1 toluene/EtOAc) Based on ^{1}H NMR and ^{13}C NMR the product is a mixture of the α- and β-product and is therefore deprotected prior to characterization. Separated mass: 355 mg (81%)
mp: 44.7-45.9 °C. **IR** (neat, cm^{-1}): 3062.83, 3029.99, 2919.27, 2868.25, 1750.43, 1453.96, 1365.76, 1237.76, 1094.02, 1054.77. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 6.90 (m, 55H, Ar-*H*), 5.19 (dd, 1H, *J* = 10.7, 7.7 Hz, H-2'), 5.00 – 3.21 (m, 49H, H-1, H-1', H-1'', Gal-1,6 H-1, H-2, H-2'', Gal-1,6 H-2, H-3, H-3', H-3'', Gal-1,6 H-3, H-4, H-4', H-4'', Gal-1,6 H-4, H-5, H-5', H-5'', Gal-1,6 H-5, H-6a, H-6a', H-6a'', Gal-1,6 H-6a, H-6b, H-6b', H-6b'', Gal-1,6 H-6b, 11xCH_2^{Bn}), 1.90 (s, 3H, CH_3^{Ac}), 1.86 (s, 3H, CH_3^{Ac}), 1.72 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.67 (2C), 169.53, 139.27, 139.03, 138.86, 138.68, 138.25, 138.14, 137.61, 128.44-127.21 (m, 59C), 102.60, 102.43, 99.97, 98.73, 81.22, 79.53, 78.86, 76.20, 75.47, 75.12, 74.85, 73.62, 73.52, 73.33, 72.94, 72.73, 72.41, 72.03, 70.89, 69.92, 69.54, 69.12, 68.28, 63.88, 21.07, 20.77, 20.67.

Benzyl 2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1→4)-(2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (40)



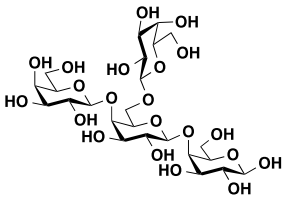
To a solution of **32** (1.0 g; 0.79 mmol) in dry THF (20 mL), $NaCNBH_3$ (1.0 g; 15.81 mmol) was added. The mixture was stirred at 22 °C and a 2M solution of HCl in dry ether was added drop wise until gas development ceased and the mixture remained acidic (pH 3-4). The mixture was concentrated to 2 ml, diluted with CH_2Cl_2 (50 ml) and the mixture was neutralized with sat. aq. $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic phases were washed with water (200 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (4:1 toluene/EtOAc) to afford a colorless crystalline powder. **40** was used for the following reaction without characterization. R_f 0.35 (2:1 toluene/EtOAc)
Yield: 290 mg (74%)

Benzyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranosyl-(1→4)-(2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl)-(1→4)-(2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (41)



A mixture of **40** (760 mg; 0.60 mmol) and **22** (416 mg; 0.84 mmol) was dried azeotropically with benzene (2 x 5 mL) and subjected to vacuum overnight. The mixture was dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -20 °C, followed by addition of NIS (196 mg; 0.87 mmol) and TESOTf (32 mg; 0.12 mmol). The reaction mixture was stirred at -20 °C until TLC revealed full conversion of the donor (2 h). The solution was diluted with CH_2Cl_2 (40 mL) and washed with sat. aq. NaS_2O_3 (40 mL) and sat. aq. $NaHCO_3$ (40 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (4:1 toluene/EtOAc) to afford a white crystalline material. **41** was deprotected prior to characterization. R_f 0.44 (1:1 toluene/EtOAc)
Mass: 749 mg (76%)

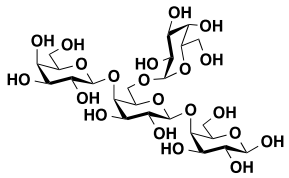
β-D-galactopyranosyl-(1→4)-[β-D-galactopyranosyl-(1→6)]-β-D-galactopyranosyl-(1→4)-D-galactopyranose (42)



37 (465 mg; 0.28 mmol) was dissolved in MeOH (6 mL) and THF (2 mL) and 6 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until full conversion was observed by TLC (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield colorless crystals. The product was next dissolved in MeOH (6 mL), THF (2 mL) and AcOH (0.5 mL). 10% Pd/C (223 mg; 0.18 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred for 2 h, and then water (2 mL) was added. The reaction was stirred until TLC indicated full conversion (72 h), filtered through celite, and concentrated to give a white solid. R_f 0.72 (3:1 MeOH/H_2O). Yield: 92 mg (79%).

^{1}H NMR (400 MHz, D_2O) δ 5.21 (d, $J_{1,2}$ = 3.8 Hz, 1H, H-1^{1}α), 4.60 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1β), 4.59 (d, J = 8.0 Hz, 1H, H-1α), 4.55 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1β), 4.52 (d, $J_{1,2}$ = 7.8 Hz, 2H, H-1α, H-1β), 4.39 (d, $J_{1,2}$ = 8.0, 2H, H-1α, H-1β), 4.20 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4^{1}a), 4.14 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4α, H-4β), 4.12 (d, $J_{3,4}$ = 3.3 Hz, 3H, H-4α, 2xH-4β), 4.10 – 4.02 (m, 3H, H-4α, H-4β, H-6α), 3.99 – 3.41 (m, 39H). **^{13}C NMR** (75 MHz, D_2O) δ 107.46, 106.99, 106.28, 101.11, 99.11, 95.06, 82.47, 81.55, 80.41, 80.20, 77.99, 77.84, 77.26, 76.51, 76.01, 75.75, 75.49, 75.09, 74.72, 74.43, 74.21, 73.62, 72.83, 72.44, 72.23, 71.92, 71.66, 71.41, 70.96, 69.83, 63.87 **HRMS**: calc. $[M+H]^+$: 667.2297 found $[M+ H]^+$: 667.2267

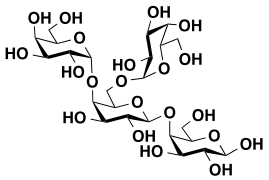
β-D-galactopyranosyl-(1→4)-[α-D-galactopyranosyl-(1→6)]-β-D-galactopyranosyl-(1→4)-D-galactopyranose (43)



38 (323 mg; 0.21 mmol) was dissolved in MeOH (6 mL) and THF (2 mL) and 5 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until full conversion was observed by TLC (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (9:1 EtOAc/MeOH) to yield colorless crystals. The product was next dissolved in MeOH (6 mL), THF (2 mL) and AcOH (0.5 mL). 10% Pd/C (132 mg; 0.18 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred for 2 h, then water (2 mL) was added. The reaction was stirred until TLC indicated full conversion (72 h), filtered through celite, and concentrated to give a white solid. R_f 0.68 (3:1 MeOH/H_2O)
Yield: 67 mg (81%)

^{1}H NMR (400 MHz, D_2O) δ 5.30 (d, $J_{1,2}$ = 3.8 Hz, 1H, H-1^{1}α), 5.03 (d, $J_{1,2}$ = 3.5 Hz, 2H, H-1α,α, H-1α,β), 4.71 – 4.56 (m, 4H, 4xH-1), 4.48 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.32 – 4.11 (m, 4H, 4xH-4), 4.04 – 3.52 (m, 40H). **^{13}C NMR** (75 MHz, D_2O) δ 106.85, 106.62, 106.06, 98.88, 81.24, 80.26, 79.94, 77.61, 76.67, 76.27, 75.76, 75.26, 74.77, 74.22, 73.97, 73.24, 72.64, 72.21, 71.34, 71.14, 63.47, 63.16 **HRMS**: calc. $[M+H]^+$: 667.2297 found $[M+ H]^+$: 667.2275.

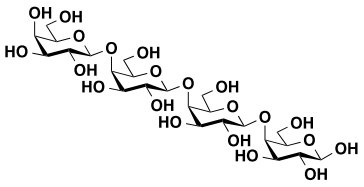
α-D-galactopyranosyl-(1→4)-[α-D-galactopyranosyl)-(1→6)]-β-D-galactopyranosyl-(1→4)-D-galactopyranose (44)



39 (200 mg; 0.11 mmol) was dissolved in MeOH (6 mL), THF (2 mL) and AcOH (0.5 mL). 10% Pd/C (223 mg; 0.18 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred for 2 h, then water (2 mL) was added. The reaction was stirred until TLC indicated full conversion (48 h), filtered through celite, and concentrated to give a white solid. The product was next dissolved in MeOH (6 mL) and THF (2 mL) and 6 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until full conversion was observed by TLC (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (2:1 toluene/EtOAc) to yield colorless crystals. R_f 0.31 (1:1 toluene/EtOAc). Yield 269 mg (90%).

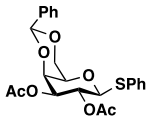
^{1}H NMR (400 MHz, D_2O) δ 5.22 (d, $J_{1,2}$ = 3.9 Hz, 1H, H-1^{1}α), 4.92 (d, $J_{1,2}$ = 3.8 Hz, 4H, H-1α,α, H-1α,β, H-1α,α, H-1α,β), 4.55 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1β), 4.49 (d, J = 7.8 Hz, 1H, H-1α), 4.40 – 4.30 (m, 8H, 8xH-4), 4.21 – 3.42 (m, 40H). **^{13}C NMR** (75 MHz, D_2O) δ 107.69, 107.43, 106.58, 105.95, 102.89, 101.40, 99.08, 95.03, 84.49, 82.71, 81.83, 81.30, 79.59, 79.42, 77.86, 77.33, 76.76, 76.33, 76.04, 75.41, 75.06, 74.80, 74.31, 73.76, 73.37, 72.91, 72.248, 72.10, 71.87, 71.72, 71.46, 70.89, 68.66, 66.06, 64.09, 63.81, 63.22 **HRMS**: calc. $[M+Na]^+$: 689.2117 found $[M+ Na]^+$: 689.2095

β-D-galactopyranosyl-(1→4)-(β-D-galactopyranosyl)-(1→4)-(β-D-galactopyranosyl)-(1→4)-D-galactopyranose (45)



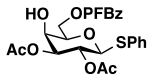
41(260 mg; 0.16 mmol) was dissolved in MeOH (6 mL) and THF (2 mL) and 5 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until full conversion was observed by TLC (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (4:1 EtOAc/MeOH) to yield colorless crystals. The product was next dissolved in MeOH (6 mL), THF (2 mL) and AcOH (0.5 mL). 10% Pd/C (223 mg; 0.18 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred for 2 h, then water (2 mL) was added. The reaction was stirred until TLC indicated full conversion (48 h), filtered through celite, and concentrated to give a white solid. R_f 0.74 (3:1 MeOH/H_2O). Yield: 72 mg (83%).
^{1}H NMR (400 MHz, D_2O) δ 5.17 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1α), 4.58 – 4.47 (m, 7H, 7xH-1), 4.13 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 4.08 (m, 7H, 7xH-4), 4.03 (dd, *J* = 7.2, 5.7 Hz, 1H, H-5), 3.89 – 3.42 (m, 39H). **^{13}C NMR** (101 MHz, D_2O) δ 104.38, 104.34, 104.29, 104.24, 96.35, 92.27, 78.80, 77.83, 77.55, 77.51, 77.07, 75.11, 74.47, 74.41, 74.27, 73.33, 73.28, 73.24, 73.19, 72.70, 72.19, 71.85, 71.79, 71.75, 71.32, 69.81, 69.66, 68.77, 68.57, 60.95, 60.85, 60.69, 60.67, 60.50. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{42}NaO_{21}$ 689.2116 Found 689.2111.

Phenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (54)[353]



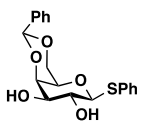
56 (7 g; 19.3mmol) was dissolved in CH_2Cl_2 (150 mL). Et_3N (8.1 mL; 58.0 mmol), DMAP (0.05 g; 0.39 mmol) and acetic anhydride (4.6 mL; 48.4 mmol) was added to the solution and the reaction mixture was stirred until TLC revealed full conversion (1.5 h). The reaction was quenched with MeOH (5 mL), washed with water (2x100 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (CH_2Cl_2/MeOH 19:1) to afford **54** as a white crystalline powder R_f 0.71 (19:1 CH_2Cl_2/MeOH). Yield: 8.5 g (98%).
mp: 158-160 °C. $[\alpha]_D^{20}$= +12.3° (c 1.0, $CDCl_3$) (litt.[137] + 5.8). **IR** (neat**,** cm^{-1}): 3031.90, 2886.39, 1729.88, 1243.25, 1046.47, 995.65, 933.67. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 – 7.50 (m, 2H), 7.36 – 7.14 (m, 8H), 5.40 (s, 1H), 5.28 (t, *J* = 9.8 Hz, 1H), 4.93 (dd, *J* = 9.8, 3.4 Hz, 1H), 4.64 (d, *J* = 9.8 Hz, 1H), 4.31 (dd, *J* = 12.5, 1.6 Hz, 2H), 4.30 (d, *J* = 3.4 Hz, 1H), 3.96 (dd, *J* = 12.5, 1.6 Hz, 1H), 3.53 (d, *J* = 1.6 Hz, 1H), 2.02 (s, 3H), 1.96 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.95, 169.31, 137.68, 133.82 (2C), 131.47, 129.39, 129.03 (2C), 128.39 (2C), 128.34, 126.75 (2C), 101.34, 85.37, 73.65, 73.41, 69.93, 69.29, 66.96, 21.15 (2C). **HRMS**: calc. $[M+ NH_4]^+$: 462.1587 found $[M+ NH_4]^+$: 462.1566

Phenyl 2,3-di-*O*-acetyl-6-*O*-(2,3,4,5,6-pentafluorobenzoyl)-1-thio-β-D-galactopyranoside (55)



57 (280 mg; 0.79 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. 2,3,4,5,6-pentafluorobenzoyl chloride (0.11 mL; 0.81 mmol) and Et_3N (0.16 mL; 1.18 mmol) was added and the reaction was stirred at 0 °C for 1½ h. The reaction mixture was quenched with MeOH, diluted with 35 mL CH_2Cl_2 and washed with H_2O (40 mL). The organic phase was dried over $MgSO_4$, concentrated and purified by flash chromatography (1:1 EtOAc/Heptane) to afford **55** as a white crystalline powder. R_f 0.71 (3:1 EtOAc/Heptane). Yield: 375 mg (87%)
mp: 160-161 °C. $[\alpha]_D^{20}$= +9.9° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3600-3400, 3063.14, 2964.84, 1740.89, 1736.41, 1732.71, 1494.50, 1222.64, 1054.20. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 2H), 7.26 – 7.13 (m, 3H), 5.22 (t, *J* = 9.9 Hz, 1H), 4.96 (dd, *J* = 9.9, 3.2 Hz, 1H), 4.67 (d, *J* = 9.9 Hz, 1H), 4.61 (dd, *J* = 11.6, 7.3 Hz, 1H), 4.49 (dd, *J* = 11.6, 5.0 Hz, 1H), 4.08 (dd, *J* = 4.6, 3.2 Hz, 1H), 3.86 (ddd, *J* = 7.3, 5.0, 4.6 Hz, 1H), 2.03 (s, 3H), 2.03 (s, 3H).. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.27, 169.87, 158.87, 132.68 (2C), 132.57, 129.08 (2C), 128.30, 86.77, 75.90, 74.31, 67.63 (2C), 65.10, 21.05 (2C). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -137.69 – (-137.91) (m), -147.97 (tt, *J* = 21.0, 4.9 Hz), -160.32 – (-160.79) (m). **HRMS**: calc. $[M+ NH_4]^+$: 568.1065 found $[M+ NH_4]^+$: 568.1071

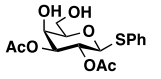
Phenyl 4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (56)[354]



To a solution of $PhCH(OMe)_2$ (7.6 mL, 49.3 mmol) and camphor sulphonic acid (255 mg, 1.1 mmol) in MeCN (200 mL) was added **23** (10 g, 36.5 mmol). The flask was equipped with a distillation unit and the mixture was heated to reflux for 1.5 h. During this period app. 100 mL of MeCN-MeOH was distilled off. The distillation unit was replaced with a condenser and the reaction mixture was heated to reflux until TLC showed full conversion (1 h). The reaction mixture was concentrated and purified by flash chromatography (CH_2Cl_2/MeOH 19:1) to afford **56** as a white crystalline powder. R_f 0.25 (CH_2Cl_2/MeOH 19:1) Yield: 13.1 g (99%)
mp: 148-150 °C (litt. [184] 149-151 °C). $[\alpha]_D^{20}$= -27.2° (c 1.0, $CDCl_3$) (litt. [184] -24). **IR** (neat, cm^{-1}): 3500-3100, 3070.9, 2916.85, 2873.10, 1096.39, 1066.36, 1039.24. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 – 7.65 (m, 2H), 7.45 –

7.23 (m, 8H), 5.51 (s, 1H), 4.51 (d, *J* = 8.0 Hz, 1H), 4.38 (d, *J* = 12.5 Hz, 1H), 4.21 (d, *J* = 1.3 Hz, 1H), 4.03 (d, *J* = 12.5 Hz, 1H), 3.76 – 3.63 (m, 2H), 3.56 (s, 1H), 2.30 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.82, 133.88 (2C), 131.03, 129.58, 129.15 (2C), 128.48 (2C), 128.39, 126.75 (2C), 101.58, 87.14, 75.59, 73.95, 70.22, 69.48, 68.92. **HRMS**: calc. $[M+ NH_4]^+$: 378.1375 found $[M+ NH_4]^+$: 378.1362.

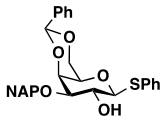
Phenyl 2,3-di-*O*-acetyl-1-thio-β-D-galactopyranoside (57)[137]



54 (1.5g; 3.37mmol) was dissolved in CH_2Cl_2 (30 mL) and MeOH (30 mL). Propan-1,3- diol (1.22 mL; 16.83 mmol) and *p*-toluenesulphonic acid (14 mg; 0.084 mmol) was added and the reaction mixture was heated to reflux. After 12 hours the reaction mixture was allowed to cool, diluted by CH_2Cl_2 (100 mL), washed with sat. aq. $NaHCO_3$ (200 mL), dried over $MgSO_4$ and concentrated to afford a white crystalline solid. The product was purified by flash chromatography (19:1 CH_2Cl_2/MeOH) to give **57** as a colorless crystalline material. R_f 0.63 (9:1 CH_2Cl_2/MeOH). Yield: 0.98 g (82%).

mp: 166.3-167.5 °C. $[\alpha]_D^{20}$= +13.7° (c 1.0, $CDCl_3$) (litt.[355] +13.3). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H), 7.30 – 7.21 (m, 3H), 5.26 (t, *J* = 9.9 Hz, 1H), 4.92 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.68 (d, *J* = 9.9 Hz, 1H), 4.12 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.90 (dd, *J* = 12.0, 5.8 Hz, 1H), 3.80 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.58 (ddd, *J* = 5.5, 4.3, 0.9 Hz, 1H), 2.02 (s, 3H), 2.02 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.48, 169.91, 132.37 (2C), 129.28 (2C), 129.20, 128.26, 86.62, 78.09, 74.65, 68.58, 67.84, 62.85, 21.13, 21.11. **HRMS**: calc. $[M+ NH_4]^+$: 374.1274 found $[M+ NH_4]^+$: 374.1282.

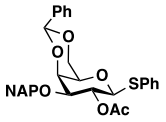
Phenyl 4,6-*O*-benzylidene-3-*O*-(2-naphthyl)methyl-1-thio-β-D-galactopyranoside (58)



Di-*n*-butyl tin oxide (4.48g; 19.42 mmol) was added to a solution of compound **56** (5.00 g, 13.87 mmol) in dry toluene (130 mL) and stirred under refluxing temperature for 12 h. The temperature was adjusted to 75-80 °C, and then *n*-Bu_4NI (7.69 g, 20.81 mmol) and naphthylmethyl bromide (4.6 g, 20.81 mmol) were added in one portion; stirring was maintained at this temperature for 24 h. The mixture was concentrated and purified by flash chromatography (4:1 Tol/EtOAc) to give **58** as white crystals. R_f 0.60 (2:1 Tol/EtOAc). Yield: 4.72 g (68%).

mp: 181.3 – 182.4 °C. $[\alpha]_D^{20}$= -18.0° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3500-3100, 3053.72, 2981.81, 2871.51, 1071.98, 1044.72, 995.03, 734.37. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 – 7.63 (m, 6H), 7.63 – 7.53 (m, 2H), 7.48 – 7.23 (m, 9H), 7.23 – 7.09 (m, 4H), 5.32 (s, 1H), 4.80 (s, 2H), 4.74 (s, 2H), 4.42 (d, *J* = 9.5 Hz, 1H), 4.24 (dd, *J* = 12.4, 1.5 Hz, 1H), 4.05 (d, *J* = 3.3 Hz, 1H), 3.91 (t, *J* = 9.5, 1H), 3.84 (dd, *J* = 12.4, 1.5 Hz, 2H), 3.46 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.30 (d, *J* = 1.1 Hz, 1H), 2.46 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.05, 135.70, 134.01 (2C), 130.86, 129.31-125.41 (18C), 101.40, 87.29, 80.41, 73.60, 72.07, 70.28, 67.49, 65.68. **HRMS**: calc. $[M+ NH_4]^+$: 518.2001 found $[M+ NH_4]^+$: 518.1995

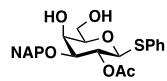
Phenyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2-naphthyl)methyl-1-thio-β-D-galactopyranoside (59)



58 (4.2 g ; 8.39 mmol) was dissolved in CH_2Cl_2 (30 mL). Et_3N (2.0 mL; 14.68 mmol), DMAP (20 mg; 0.17 mmol) and acetic anhydride (1.2 mL; 12.6 mmol) was added to the solution and the reaction mixture was stirred until TLC revealed full conversion (2 h). The reaction was quenched with MeOH (2 mL), washed with water (2x30 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (2:1 toluene/EtOAc) to afford **59** as a white crystalline powder. R_f 0.67 (1:2 EtOAc/toluene). Yield: 4.19 g (92%)

mp: 190.4 – 191.8 °C. $[\alpha]_D^{20}$= -14.3° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3059.50, 2991.18, 2969.61, 2874.91, 1736.20, 1368.60, 1232.25, 1052.34. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 – 7.62 (m, 4H), 7.56 – 7.48 (m, 2H), 7.44 – 7.11 (m, 11H), 5.35 (s, 1H), 5.28 (t, *J* = 9.7 Hz, 1H), 4.74 (d, *J* = 12.9 Hz, 1H), 4.68 (d, *J* = 12.9 Hz, 1H), 4.53 (d, *J* = 9.7 Hz, 1H), 4.24 (dd, *J* = 12.4, 1.5 Hz, 1H), 4.11 (d, *J* = 3.4 Hz, 1H), 3.87 (dd, *J* = 12.4, 1.5 Hz, 1H), 3.57 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.32 (t, *J* = 1.5 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.44, 137.83, 135.67, 133.63 (2C), 133.34, 133.25, 131.95, 129.30-125.83 (15C), 101.53, 85.58, 78.70, 73.42, 71.52, 70.19, 69.46, 68.56, 21.37. **HRMS**: calc. $[M+ NH_4]^+$: 560.2107 found $[M+ NH_4]^+$: 560.2105.

Phenyl 2-*O*-acetyl-3-*O*-(2-naphthyl)methyl-1-thio-β-D-galactopyranoside (60)

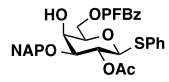


59 (500 mg; 0.92 mmol) was dissolved in CH_2Cl_2 (15 mL) and MeOH (15 mL). Propan-1,3- diol (0.33 mL; 4.61 mmol) and *p*-toluenesulphonic acid (4 mg; 0.023 mmol) was added and the reaction mixture was heated to reflux. After 14 hours the reaction mixture was allowed to cool, diluted with CH_2Cl_2 (50 mL), washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (19:1 CH_2Cl_2/MeOH) resulting in **60** as a white crystalline solid. R_f 0.15 (1:1 EtOAc/Heptane). Yield: 390 mg (93%)

mp: 138.1 – 138.6 °C. $[\alpha]_D^{20}$= 11.5° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}) 3600-3100, 3056.93, 2932.17, 2879.93, 1742.58, 1369.11, 1229.72, 1048.29. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 – 7.69 (m, 3H), 7.63 (s, 1H), 7.49 – 7.28 (m, 5H), 7.27 – 7.12 (m, 3H), 5.18 (dd, *J* = 10.5, 9.5 Hz, 1H), 4.76 (d, *J* = 12.4 Hz, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.52 (d, *J*

= 10.5 Hz, 1H), 4.06 (d, *J* = 3.1 Hz, 1H), 3.97 – 3.83 (m, 1H), 3.81 – 3.64 (m, 1H), 3.50 (dd, *J* = 9.5, 3.1 Hz, 1H), 3.44 (t, *J* = 5.8 Hz, 1H), 1.97 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.88, 134.83, 133.33 (2C), 132.10 (2C), 129.16 (2C), 128.70, 128.09, 127.97 (2C), 127.94, 127.02, 126.63, 126.48, 125.81, 86.59, 79.56, 78.54, 71.82, 69.21, 66.93, 62.65, 21.30. **HRMS**: calc. $[M+NH_4]^+$: 472.1794 found $[M+ NH_4]^+$: 472.1804.

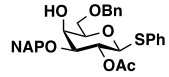
Phenyl 2-*O*-acetyl-3-*O*-(2-naphthyl)methyl-6-*O*-(2,3,4,5,6-pentafluorobenzoyl)-1-thio-β-D-galactopyranoside (61)



60 (350 mg; 0.77 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. 2,3,4,5,6-pentafluorobenzoyl chloride (0.11 mL; 0.79 mmol) and Et_3N (0.16 mL; 1.16 mmol) was added and the reaction was stirred at 0 °C for 1½ h. The reaction mixture was quenched with MeOH, diluted with CH_2Cl_2 (35 mL) and washed with water (40 mL). The organic phase was dried over $MgSO_4$, concentrated and purified by flash chromatography (3:1 Tol/EtOAc) to afford **61** as a white crystalline powder. R_f 0.72 (2:1 Tol/EtOAc). Yield: 460 mg (93%)

mp: 174 – 175.3 °C. $[\alpha]_D^{20}$= +9.4° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3545.59, 3069.09, 2976.76, 2884.34, 1737.78, 1524.10, 1495.93, 1220.96, 1094.86. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 – 7.67 (m, 3H), 7.63 (s, 1H), 7.44 – 7.27 (m, 5H), 7.18 – 7.07 (m, 3H), 5.19 (t, *J* =9.6 Hz 1H), 4.76 (d, *J* = 12.4 Hz, 1H), 4.63 (d, *J* = 12.4 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 9.6 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.02 (d, 3.3 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.53 (dd, *J* = 9.3, 3.3 Hz, 1H), 1.98 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.89, 158.90, 134.70, 133.35, 133.32, 133.30, 132.28 (2C), 128.97 (2C), 128.77, 128.06, 127.96 (2C), 127.06, 126.67, 126.54, 125.76, 86.83, 79.26, 75.84, 72.15, 68.99, 66.60, 65.71, 21.29. **^{19}F NMR** (282 MHz, cdcl$_3$) δ -136.99 – -138.72 (m), -148.23 (tt, *J* = 20.9, 4.8 Hz), -159.81 – -161.54 (m). **HRMS**: calc. $[M+NH_4]^+$: 666.1585 found $[M+ NH_4]^+$: 666.1586

Phenyl 2-*O*-acetyl-6-*O*-benzyl-3-*O*-(2-naphthyl)methyl-1-thio-β-D-galactopyranoside (62)

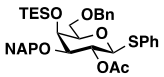


To a solution of **59** (1.5 g; 2.76 mmol) in dry THF (45 mL), $NaCNBH_3$ (2.61 g; 41.46 mmol) was added. The mixture was stirred at 22 °C and a 2M solution of HCl in dry ether was added drop wise until gas development ceased and the mixture remained acidic (pH 3-4). The mixture was concentrated to 2 ml, diluted with CH_2Cl_2 (150 ml) and the mixture was neutralized with sat. aq. $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic phases were washed with water (500 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (2:1 toluene/EtOAc) to afford **62** a colorless crystalline powder. R_f 0.39 (1:2 EtOAc/toluene). Yield: 1.31 g (87%).

mp: 141.3 – 142.2 °C. $[\alpha]_D^{20}$= +3.9° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3565.71, 3055.31, 2868.77, 1736.40, 1362.21, 1230.57, 1065.77. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 – 7.69 (m, 3H), 7.64 (s, 1H), 7.45 – 7.37 (m, 4H), 7.32 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.29 – 7.11 (m, 8H), 5.19 (t, *J* = 9.7 Hz, 1H), 4.77 (d, *J* = 12.3 Hz, 1H), 4.60 (d, *J* = 12.3 Hz, 1H), 4.51 (d, *J* = 9.7 Hz, 3H), 4.49 (s, 2H), 4.08 (s, 1H), 3.72 (dd, *J* = 5.9, 2.8 Hz, 2H), 3.56 (t, *J* = 5.9, 1H), 3.48 (dd, *J* = 9.7, 3.2 Hz, 1H), 2.51 (s, 1H), 1.96 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.83, 138.15, 134.93, 133.34, 133.32 (3C), 132.17-125.83 (17C), 86.67, 79.68, 77.60, 73.96, 71.74, 69.47, 69.20, 66.58, 21.32.

HRMS: calc. $[M+ NH_4]^+$: 562.2264 found $[M+ NH_4]^+$: 562.2277

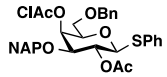
Phenyl 2-*O*-acetyl-6-*O*-benzyl-4-*O*-triethylsilyl-3-*O*-(2-naphthyl)methyl-1-thio-β-D-galactopyranoside (63)



62 (650 mg; 1.19 mmol) was dissolved in DMF (10 mL) and cooled to 0 °C. To the solution were added triethylsilyl chloride (0.30 mL; 1.79 mmol) and imidazole (162 mg; 2.39 mmol). The reaction mixture was stirred at 0 °C in 1h and then at 22 °C for 12h. The mixture was diluted with Et_2O (100 mL) and washed with water (4 x 25 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (5:1 toluene/EtOAc). R_f 0.69 (1:2 EtOAc/Tol)
Yield: 708 mg (99%).

mp: 89.3 – 91.2 °C. $[\alpha]_D^{20}$= -8.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3060.03, 2953.41, 2874.51, 1747.77, 1227.91, 1070.90, 906.55, 725.83. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 3H), 7.78 (s, 1H), 7.64 – 7.26 (m, 13H), 5.45 (t, *J* = 9.7 Hz, 1H), 4.89 (d, *J* = 12.2 Hz, 1H), 4.69 (d, *J* = 12.2 Hz, 1H), 4.64 (d, *J* = 9.7 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 2H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 2.5 Hz, 1H), 3.83 – 3.65 (m, 3H), 3.51 (dd, *J* = 9.6, 2.5 Hz, 1H), 2.03 (s, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.65 (q, *J* = 8.0, 3.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.66, 138.16, 135.56, 133.51, 133.46, 133.25, 132.28 (2C), 128.97-125.95 (15C), 86.44, 81.41, 78.41, 73.98, 72.97, 69.48, 69.20 , 68.51 , 21.39, 7.26 (3C), 5.49 (3C). **HRMS**: calc. $[M+ NH_4]^+$: 676.3128 found $[M+ NH_4]^+$: 676.3141

Phenyl 2-*O*-acetyl-6-*O*-benzyl-4-*O*-chloroacetyl-3-*O*-(2-naphthyl)methyl-1-thio-β-D-galactopyranoside (64)

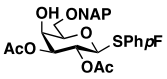


156 (470 mg; 0.86 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. $(ClAc)_2O$ (251 mg; 1.47 mmol), Et_3N (0.21 mL; 1.51 mmol) and DMAP (4 mg; 0.03 mmol) was added and the reaction was stirred at 0 °C for 2 h. The reaction mixture was concentrated and purified by flash chromatography (4:1 Tol/EtOAc) to afford a white crystalline powder. R_f 0.76 (1:2 EtOAc/Tol). Yield: 487 mg (91%).

mp: 113.6 – 116-1 °C. $[\alpha]_D^{20}$= -6.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3058.34, 2869.99, 1747.58, 1227.39, 1169.72, 1094.82, 1060.35. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 – 7.69 (m, 3H), 7.63 (s, 1H), 7.45 – 7.35 (m, 4H), 7.34 – 7.12 (m, 9H), 5.66 (d, *J* = 3.2 Hz, 1H), 5.04 (t, *J* = 9.8 Hz, 1H), 4.77 (d, *J* = 12.6 Hz, 1H), 4.52 (d, *J* = 9.8 Hz, 1H), 4.50 (d, *J* = 12.6 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.04 (d, *J* = 15.1 Hz, 1H), 3.91 (d, *J* = 15.1 Hz, 1H), 3.72 (t, *J* = 6.6 Hz, 1H), 3.61 – 3.49 (m, 2H), 3.45 (dd, *J* = 9.8, 3.2 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.63, 167.16, 137.52, 134.82, 133.33, 133.30, 133.01, 132.50 (2C), 129.06 (2C), 128.76 (2C), 128.47, 128.43 (2C), 128.28, 128.09 (2C), 127.93, 127.28, 126.50, 126.36, 126.12, 86.89, 77.42, 75.87, 73.97, 71.56, 68.97, 68.40, 67.60, 41.05, 21.23.

HRMS: calc. $[M+Na]^+$: 643.1534 found $[M+ Na]^+$: 643.1553

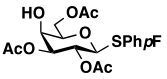
4-fluorophenyl 2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-1-thio-β-D-galactopyranoside (65)



To a solution of **69** (1.0 g; 1.95 mmol) in dry THF (20 mL), $NaCNBH_3$ (2.45 g; 39.02 mmol) was added. The mixture was stirred at 22 °C and a 2M solution of HCl in dry ether was added drop wise until gas development ceased and the mixture remained acidic (pH 3-4). The mixture was concentrated to 2 ml, diluted with CH_2Cl_2 (50 ml) and the mixture was neutralized with sat. aq. $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic phases were washed with water (200 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (4:1 toluene/EtOAc) to afford a colorless crystalline powder. R_f 0.48 (1:2 EtOAc/toluene). Yield: 843 mg (84%).

mp: 148.7 – 151.1 °C. $[\alpha]_D^{20}$= +6.8° (c 1.0, $CDCl_3$) **IR** (neat, cm^{-1}) 3577.97, 3061.31, 2959.52, 2911.52, 2869.03, 1747.80, 1490.32, 1367.87, 1234.70, 1216.60, 1052.55. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 – 7.79 (m, 4H), 7.76 (s, 1H), 7.56 – 7.45 (m, 4H), 6.92 (t, *J* = 8.7 Hz, 2H), 5.26 (t, *J* = 9.7 Hz, 1H), 4.97 (dd, *J* = 9.7, 3.0 Hz, 1H), 4.73 (s, 2H), 4.60 (d, *J* = 9.7 Hz, 1H), 4.19 (d, *J* = 3.0 Hz, 1H), 3.82 (dd, *J* = 5.0, 2.0 Hz, 2H), 3.73 (dd, *J* = 5.0, 2.0 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 170.26, 169.58, 135.89 (2), 135.73 (2), 135.04, 133.35, 128.51, 128.02, 127.86, 126.79, 126.40, 126.23(2C), 125.72, 116.30, 115.86, 86.20, 76.52, 74.62, 74.07, 69.66, 68.38, 67.71, 20.99 (2C). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -112.99. **HRMS**: calc. $[M+Na]^+$: 537.1360 found $[M+ Na]^+$: 537.1360

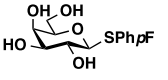
4-fluorophenyl 2,3,6-tri-*O*-acetyl-1-thio-β-D-galactopyranoside (66)



70 (1.3 g; 3.62 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. acetic anhydride (0.38 mL; 3.98 mmol) and Et_3N (0.76 mL; 5.43 mmol) was added and the reaction was stirred at 0 °C for 3 h. The reaction mixture was quenched with MeOH, diluted with CH_2Cl_2 (100 mL) and washed with water (100 mL). The organic phase was dried over $MgSO_4$, concentrated and purified by flash chromatography (4:1 toluene/EtOAc) to afford a white crystalline powder. R_f 0.51 (1:2 EtOAc/toluene). Yield: 1.07 g (71%)

mp: 190 - 191 °C. $[\alpha]_D^{20}$= +39.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3600-3400, 3077.36, 2939.18, 2881.31, 1732.78, 1726.81, 1490.09, 1366.38, 1215.13, 1037.66. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.7, 5.3 Hz, 2H), 6.95 (t, *J* = 8.7 Hz, 2H), 5.14 (t, *J* = 9.9 Hz, 1H), 4.91 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.52 (d, *J* = 9.9 Hz, 1H), 4.24 (d, *J* = 6.4 Hz, 2H), 3.99 (s, 1H), 3.70 (td, *J* = 6.4, 0.9 Hz, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.07, 170.31, 169.76, 136.03, 135.92, 126.83 (2C), 116.33, 116.04, 86.29, 76.08, 74.39, 67.57, 67.43, 62.77, 21.09, 21.06 (2C). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.11. **HRMS**: calc. $[M+NH_4]^+$: 434.1285 found $[M+ NH_4]^+$: 434.1299.

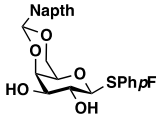
4-fluorophenyl 1-thio-β-D-galactopyranoside (67)[356]



A solution of galactose pentaacetate (20.0 g; 51.24 mmol), 4-fluorothiophenol (6.6 mL; 61.48 mmol) and $BF_3{\cdot}OEt_2$ (7.8 mL; 61.48 mmol) in CH_2Cl_2 (200 mL) was stirred at 22 °C for 24 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. $NaHCO_3$ (300 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. Without further purification it was deacetylated. Na (1.03 g; 44.8 mmol) was dissolved in MeOH (100 mL) and the NaOMe/MeOH solution was slowly added to a solution of 157 in MeOH (100 mL). The reaction mixture was stirred at 22 °C until TLC showed full conversion (12 h). The reaction was quenched with Amberlite IR-120 H^+ (50 mL) and stirred for 1 h. The ion-exchange resin was filtered off, washed with MeOH and the filtrate was concentrated. The product was recrystallized from EtOAc to give **67** as colorless crystals. R_f 0.32 (3:2 Heptane/EtOAc). Yield (over two steps) 12.18 g (83%)

mp: 140.6 – 141.7 °C. $[\alpha]_D^{20}$= -51.2° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3600-3100, 3061.53, 2885.85, 2865.08, 1491.75, 1073.19, 1037.98, 980.84. **^{1}H NMR** (300 MHz, D_2O) δ 7.42 (dd, *J* = 8.9, 5.3 Hz, 2H), 6.97 (t, *J* = 8.9 Hz, 2H), 4.50 (d, *J* = 9.5 Hz, 1H), 3.80 (d, *J* = 2.8 Hz, 1H), 3.67 – 3.32 (m, 5H). **^{13}C NMR** (75 MHz, D_2O) δ 134.36, 134.25, 127.56, 127.51, 116.41, 116.12, 88.65, 79.08, 74.07, 69.25, 68.76, 61.03. **^{19}F NMR** (282 MHz, D_2O) δ -114.68 (ddd, *J* = 14.1, 9.5, 4.8 Hz). **HRMS**: calc. $[M+NH_4]^+$: 308.0968 found $[M+ NH_4]^+$: 308.0957.

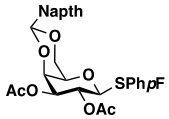
4-fluorophenyl 4,6-*O*-(2-naphthyl)methylene-1-thio-β-D-galactopyranoside (68)



To a solution of 2-naphthaldehyde (6.54 g, 41.85 mmol) and camphorsulphonic acid (216 mg, 0.93 mmol) in MeCN (200 mL) was added **67** (9.0 g, 31.0 mmol). The flask was equipped with a distillation unit and the mixture was heated to 95 °C for 1.5 h. During the period app. 100 mL of MeCN-MeOH was distilled off. The distillation unit was replaced with a condenser and the reaction mixture was heated to reflux until TLC showed completion (1 h). The reaction mixture was concentrated and purified by flash chromatography (19:1 CH_2Cl_2/MeOH) to afford **68** as a white crystalline powder. R_f 0.18 (1:1 EtOAc/toluene). Yield: 12.5 g (94%)

mp: 153.5 – 154.3 °C. $[\alpha]_D^{20}$= -13.9° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3600-3100, 3060.82, 2861.77, 1489.72, 1098.55, 1069.52, 1046.65. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (m, 4H), 7.63 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.44 (dd, *J* = 6.2, 3.2 Hz, 2H), 7.34 (d, *J* = 9.9 Hz, 1H), 6.94 (t, *J* = 8.8 Hz, 2H), 5.58 (s, 1H), 4.39 (d, *J* = 9.0 Hz, 1H), 4.33 (dd, *J* = 12.5, 1.6 Hz, 1H), 4.17 (d, *J* = 3.1 Hz, 1H), 4.00 (dd, *J* = 12.5, 1.6 Hz, 1H), 3.63 (dd, *J* = 9.0, 3.1 Hz, 1H), 3.56 (t, *J* = 9.0 Hz, 1H), 3.49 (t, *J* = 1.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 136.84, 136.73, 135.10, 134.04, 132.99, 128.50, 128.41, 126.87, 126.59, 124.13, 116.41, 116.13, 101.68, 86.82, 75.62, 73.92, 70.17, 69.50, 68.78. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -112.90 (s). **HRMS**: calc. $[M+H]^+$: 429.1172 found $[M+ H]^+$: 429.1193

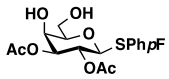
4-fluorophenyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-1-thio-β-D-galactopyranoside (69)



68 (10.0 g; 23.34 mmol) was dissolved in CH_2Cl_2 (150 mL). Et_3N (9.7mL; 70.02 mmol), DMAP (57 mg; 0.47 mmol) and acetic anhydride (5.5 mL; 58.35 mmol) was added to the solution and the reaction mixture was stirred until TLC revealed full conversion (3 h). The reaction was quenched with MeOH (10 mL), washed with water (2x200 mL), dried over $MgSO_4$ and concentrated. The product was recrystallized with EtOAc/Heptane to afford **69** as a white crystalline powder R_f 0.73 (1:1 EtOAc/toluene). Yield: 11.15 g (93%).

mp: 156.5 – 157.4 °C. $[\alpha]_D^{20}$= -12.4° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3064.79, 2901.98, 2863.27, 2845.97, 1750.90, 1244.26, 1216.43, 1098.16, 1037.73, 995.08. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.8 Hz, 4H), 7.65 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.51 (dd, *J* = 6.3, 3.2 Hz, 2H), 7.36 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.97 (t, *J* = 8.6 Hz, 2H), 5.61 (s, 1H), 5.29 (t, *J* = 9.9 Hz, 1H), 5.01 (dd, *J* = 9.9, 3.4 Hz, 1H), 4.63 (d, *J* = 9.9 Hz, 1H), 4.40 (dd, *J* = 12.4, 1.5 Hz, 2H), 4.41 (d, *J* = 3.4 Hz, 1H)., 4.07 (dd, *J* = 12.4, 1.5 Hz, 1H), 3.62 (d, *J* = 1.5 Hz, 1H), 2.11 (s, 3H), 2.02 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.94, 169.33, 137.27, 137.16, 134.95, 134.05, 132.97, 128.56, 128.36, 126.69, 126.38, 124.20, 116.24, 115.95, 101.63, 84.68, 73.70, 73.37, 69.94, 69.39, 66.86, 21.18, 21.14. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -112.89 (s). **HRMS**: calc. $[M+NH_4]^+$: 530.1649 found $[M+ NH_4]^+$: 530.1642

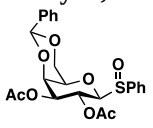
4-fluorophenyl 2,3-di-*O*-acetyl-1-thio-β-D-galactopyranoside (70)



69 (3 g; 6.05 mmol) was dissolved in CH_2Cl_2 (50 mL) and MeOH (50 mL). Propan-1,3-diol (2.2 mL; 30.27 mmol) and *p*-toluenesulphonic acid (26 mg; 0.15 mmol) was added and the reaction mixture was heated to reflux. After 10 h the reaction mixture was allowed to cool, diluted with CH_2Cl_2 (50 mL), washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated to afford a white crystalline solid. The product was purified by flash chromatography (19:1 CH_2Cl_2/MeOH). R_f 0.44 (9:1 CH_2Cl_2/MeOH). Yield: 1.96 g (86%)

mp: 109.4 – 110.7 °C. $[\alpha]_D^{20}$= +6.4° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3500-3100, 3068.15, 2932.95, 2897.06, 1740.80, 1490.07, 1368.35, 1222.86, 1044.28. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.05 – 6.98 (t, *J* = 8.9 Hz, 2H), 5.25 (t, *J* = 9.9 Hz, 1H), 4.97 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.63 (d, *J* = 9.9 Hz, 1H), 4.17 (dd, *J* = 3.1, 1.0 Hz, 1H), 3.91 (ddd, *J* = 11.9, 5.5, 4.4 Hz, 2H), 3.63 (ddd, *J* = 5.5, 4.4, 1.0 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.44, 169.88, 135.74, 135.63, 126.96, 126.99, 116.47, 116.18, 86.49, 78.02, 74.62, 68.55, 67.74, 62.82, 21.11 (2C). ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.10 (s). **HRMS**: calc. $[M+NH_4]^+$: 392.1180 found $[M+ NH_4]^+$: 392.1186

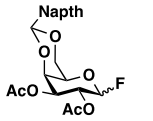
Phenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranosyl sulfoxide (71)[357]



54 (1.0 g, 2.24 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to -78 °C. The solution was treated drop wise with a solution of 3-chloroperbenzoic acid (0.78 g, 4.50 mmol) in CH_2Cl_2 (5 mL). After 15 min at this temperature, the mixture was poured into sat. aq. $NaHCO_3$ (200 mL). The organic layer was separated, washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$, and concentrated. This resulted in a syrup which was purified by flash chromatography (toluene/EtOAc, 1:1) to give **71** as a colorless powder. R_f 0.14, 0.24 (1:1 EtOAc/Tol). Yield: 787 mg (76%)

mp: 89.3-91.3 °C. $[\alpha]_D^{20}$= -47.2° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3600-3100, 3060.13, 2987.07, 2866.11, 1726.19, 1236.39, 1217.94, 1087.57, 1050.58, 1025.55, 993.99. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.05 – 7.66 (m, 2H), 7.53 – 7.43 (m, 2H), 7.36 – 7.07 (m, 4H), 6.99 – 6.90 (m, 2H), 5.30 (t, *J* = 9.9 Hz, 1H), 5.24 (s, 1H), 4.94 (dd, *J* = 9.9, 3.3 Hz, 1H), 4.51 (d, *J* = 9.9 Hz, 1H), 4.22 (d, *J* = 3.3 Hz, 1H), 4.18 (dd, *J* = 12.6, 1.6 Hz, 1H), 3.84 (dd, *J* = 12.6, 1.6 Hz, 1H), 3.51 (d, *J* = 1.6 Hz, 1H), 2.05 (s, 3H), 1.96 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.36, 170.77(1C), 137.36(1C), 132.00(1C), 129.51, 128.94 (2C), 128.30 (2C), 127.28 (2C), 126.73 (2C), 101.36, 92.65, 77.72, 77.30, 76.87, 73.10, 72.82, 70.19, 68.57, 65.20, 21.08 (2C).

Phenyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-D-galactopyranosyl fluoride (72)



22 (1.5 g; 3.03 mmol) was dried azeotropically with benzene (2x10 mL) and subjected to vacuum for 2h. It was then dissolved in CH_2Cl_2 (10 mL) and cooled to -15 °C. The stirred solution was treated with DAST (0.73 g; 4.45 mmol) and allowed to stir for 2 min before NBS (0.70 g, 3.94 mmol) was added. After 1h the reaction mixture heated to 22 °C and was monitored by TLC until full conversion was observed (2h). The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with sat. aq. $NaHCO_3$ (6 mL) and brine (6 mL). Finally the organic phase was dried over $MgSO_4$ and concentrated. The oily product so was subjected to flash column chromatography (2:1 heptane/EtOAc) to afford the two diastereoisomers **72a** and **72b**. R_f(**72a**) 0.49 (1:2 EtOAc/Tol), R_f(**72b**) 0.29 (1:2 EtOAc/Tol). Yield (total of diastereoisomers): 419 mg (77%)

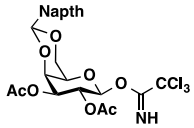
α-glycosyl fluoride (72a)

mp: 191.3-192.6 °C. $[\alpha]_D^{20}$= 102.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3063.51, 2971.58, 2906.60, 1755.99, 1738.21, 1370.53, 1238.96, 1221.96, 1095.80, 1040.72, 976.45. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.85 – 7.74 (m, 3H), 7.53 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.46 – 7.39 (m, 2H), 5.87 (dd, *J* = 53.9, 1.9 Hz, 1H), 5.62 (s, 1H), 5.34 (qd, *J* = 10.9, 2.4 Hz, 2H), 5.30 (d, *J* = 1.9 Hz, 1H), 4.53 (d, *J* = 2.4 Hz, 1H), 4.31 (dd, *J* = 12.7, 1.6 Hz, 1H), 4.06 (dd, *J* = 12.7, 1.6 Hz, 1H), 3.97 (t, *J* = 1.6 Hz, 1H), 2.05 (s, 3H), 2.05 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.83, 170.34, 134.77, 133.97, 133.07, 128.66, 128.40, 127.93, 126.71, 126.40, 125.91, 123.94, 105.46 (d, *J* = 225.9 Hz, 1C), 101.37, 73.58, 68.95, 68.17, 67.64 (d, *J* = 24 Hz, 1C), 64.69 (d, *J* = 2.4 Hz, 1C), 21.19, 20.95. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -150.09 (dd, *J* = 53.5, 23.2 Hz). **HRMS**: calc. $[M+H]^+$: 405.1349 found $[M+H]^+$: 405.1368

β-glycosyl fluoride (72b)

mp: 183.4 – 183.8 °C. $[\alpha]_D^{20}$= 121.2° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3063.51, 2971.58, 2906.60, 1755.99, 1738.21, 1370.53, 1238.96, 1221.96, 1095.80, 1040.72, 976.45. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.85 – 7.75 (m, 3H), 7.57 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.47 – 7.38 (m, 2H), 5.61 (s, 1H), 5.47 (ddd, *J* = 12.1, 10.4, 7.2 Hz, 1H), 5.24 (dd, *J* = 52.6, 7.2 Hz, 1H), 4.94 (ddd, *J* = 10.4, 3.4, 1.0 Hz, 1H), 4.40 (d, *J* = 3.4 Hz, 1H), 4.37 (dd, *J* = 12.6, 1.6 Hz, 1H), 4.08 (dt, *J* = 12.7, 1.7 Hz, 1H), 3.62 (s, 1H), 2.04 (s, 3H), 2.02 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.90, 169.42, 134.75, 134.02, 133.04, 128.67, 128.41, 127.95, 126.71, 126.37, 126.11, 124.14, 107.65 (d, *J* = 217.2 Hz, 1C), 101.64, 72.99, 71.27 (d, *J* = 10.9 Hz, 1C), 69.12, 68.80, 66.94 (d, *J* = 4.9 Hz, 1C), 21.09, 20.97. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -142.25 (dd, *J* = 52.6, 12.1 Hz). **HRMS**: calc. $[M+H]^+$: 405.1349 found $[M+H]^+$: 405.1331

2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-α-D-galactopyranosyl trichloroacetimidate (74)

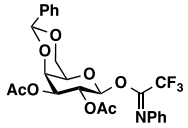


22 (490 mg; 1.22 mmol) was dried under vacuum for 12h and dissolved in anhydrous CH_2Cl_2 (50 mL). CCl_3CN (0.49 mL; 4.87 mmol) was added followed by DBU (20 μL; 0.13 mmol). The reaction was stirred for 1 h, concentrated and purified by flash chromatography (4:1 Tol/EtOAc) to afford only the α-trichloroacetimidate as a white powder. R_f 0.55 (1:1:0.005 EtOAc/heptane/Et_3N). Yield: 570 mg (85%)

mp: 183.3 – 184.8 °C. $[\alpha]_D^{20}$= +148° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3352.98, 3062.60, 2956.30, 2917.99, 2870.05, 1743.18, 1669.09, 1371.45, 1235.55, 1218.17, 1075.35, 1053.86, 1032.68 **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.91 (s, 1H), 7.86 – 7.69 (m, 3H), 7.55 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.47 – 7.37 (m, 2H), 6.67 (d, *J* = 3.4 Hz, 1H), 5.62 (s, 1H), 5.52 (dd, *J* = 10.8, 3.4 Hz, 1H), 5.36 (dd, *J* = 10.8, 3.4 Hz, 1H), 4.58 (d, *J* = 3.4 Hz, 1H), 4.31 (dd, *J* = 12.7, 1.5 Hz, 1H), 4.04 (dd, *J* = 12.7, 1.7 Hz, 1H), 3.98 (dd, *J* = 1.7, 1.5 Hz, 1H), 2.04 (s, 3H), 1.96 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.95, 170.17, 161.16, 134.90, 133.98, 133.08, 128.67, 128.39, 127.93, 126.67, 126.36, 125.97, 124.04, 101.44, 94.73, 73.65, 69.11, 68.79, 67.21, 64.94, 21.27, 20.83.

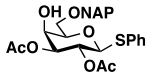
HRMS: hydrolyzed on column

2,3-di-*O*-acetyl-4,6-*O*-benzylidene-D-galactopyranose *N*-phenyl trifluoroacetimidate (74)



22 (420 mg; 1.19 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) at 0 °C. PTFAICl (495 mg; 2.38 mmol) and Cs_2CO_3 (777 mg; 2.38 mmol). The reaction mixture was stirred for 6 h at 22 °C after which it was filtered through a plug of celite, concentrated and purified by flash chromatography (9:1 Tol/EtOAc) to afford **75** as a white foam. The product was used directly in the following glycosylation reaction without characterization to avoid degradation. R_f 0.43 (9:1 Tol/EtOAc)). Yield: 474 mg (76%)

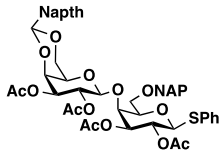
Phenyl 2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-1-thio-β-D-galactopyranoside (76)



To a solution of **22** (2.0 g; 4.04 mmol) in dry THF (30 mL), $NaCNBH_3$ (5.1 g; 80.88 mmol) was added. The mixture was stirred at 22 °C and a 2M solution of HCl in dry ether was added drop wise until gas development ceased and the mixture remained acidic (pH 3-4). The reaction mixture was concentrated to 5 ml, diluted with CH_2Cl_2 (100 ml) and neutralized with sat. aq. $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3x100 ml). The combined organic phases were washed with water (400 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (2:1 Tol/EtOAc) to afford **76** as colorless crystalline powder. R_f 0.39 (1:2 EtOAc/Tol). Yield: 1.70 g (85%)

mp: 68.3 – 71.5 °C. $[\alpha]_D^{20}$= +5.5° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3500-3000, 3058.70, 2945.74, 2916.68, 2820.42, 1741.63, 1725.79, 1367.73, 1242.88, 1218.38, 1033.12. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 – 7.64 (m, 4H), 7.54 – 7.32 (m, 5H), 7.27 – 7.13 (m, 3H), 5.26 (t, *J* = 9.9 Hz, 1H), 4.92 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.67 (s, 2H), 4.65 (d, *J* = 9.9 Hz, 1H), 4.14 (d, *J* = 3.1 Hz, 1H), 3.80 – 3.65 (m, 3H), 2.01 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.45, 169.78, 135.18, 133.43, 133.27, 132.82 (2C), 132.61, 129.17 (2C), 128.58, 128.19, 128.14, 127.94, 126.88, 126.44, 126.27, 125.87, 86.59, 77.27, 74.71, 74.13, 69.74, 68.49, 67.86, 21.17, 21.12. **HRMS:** calc. $[M+Na]^+$: 519.1454 found $[M+ Na]^+$: 519.1445

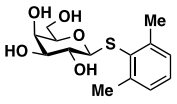
Phenyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-(2-naphthyl)methyl-1-thio-β-D-galactopyranoside (77)



A mixture of **72b** (270 mg; 0.54 mmol) and **76** (330 mg; 0.81 mmol) was dried azeotropically with benzene (2 x 10 mL) and subjected to vacuum overnight. The mixture was dissolved in dry CH_2Cl_2 (12 mL) and freshly activated 4Å molecular sieves (250 mg) were added. The slurry was cooled to -15 °C, followed by addition of $BF_3{\cdot}OEt_2$ (8 drops (~39 mg); 0.27 mmol). The reaction mixture was stirred at -15 °C for 1h and then at 5 °C for 3h. The reaction mixture was filtered through celite, diluted with CH_2Cl_2 (40 mL) and washed with sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (2:1 Tol/EtOAc) to afford **77** as a colorless crystalline material. R_f 0.18 (2:1 Tol/EtOAc). Yield: 201 mg (42%)

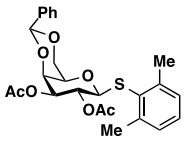
mp: 89.5–91.8 °C. $[\alpha]_D^{20}$= -8.3° (c 1.0, $CDCl_3$). **^{1}H NMR** (300 MHz, $cdcl_3$) δ 8.15 – 6.99 (m, 19H), 5.67 (s, 1H), 5.43 (dd, *J* = 10.4, 7.9 Hz, 1H), 5.20 (t, *J* = 9.9 Hz, 1H), 5.07 – 4.97 (m, 2H), 4.76 (s, 1H), 4.71 (d, *J* = 10.0 Hz, 1H), 4.62 (d, *J* = 7.9 Hz, 1H), 4.39 (d, *J* = 3.6 Hz, 1H), 4.32 (d, *J* = 2.9 Hz, 1H), 4.14 (d, *J* = 12.3 Hz, 1H), 3.99 (d, *J* = 8.1 Hz, 1H), 3.96 (d, *J* = 8.2 Hz, H), 3.85 – 3.74 (m, 2H), 3.45 (s, 1H), 2.13 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.06, 170.23, 169.57, 169.34, 135.87, 135.22, 133.94, 133.31, 132.96 (2C), 131.99 (2C), 129.08-125.77 (m, 18C), 124.19, 101.49 (2C), 86.47, 74.662, 73.47, 73.30, 71.98, 69.10, 68.92, 68.65, 68.03, 66.35, 20.99-20.71(4C). **HRMS**: calc. $[M+NH_4]^+$: 898.3109 found $[M+ NH_4]^+$: 898.3082

2,6-dimethylphenyl 1-thio-β-D-galactopyranoside (78)[163]



A solution of galactose pentaacetate (25.0 g; 64.0 mmol), 2,6-dimethylbenzenethiol (11.1 mL; 83.3 mmol) and $BF_3{\cdot}OEt_2$ (8.7 mL; 70.5 mmol) in CH_2Cl_2 (300 mL) was stirred at 22 °C for 16 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. $NaHCO_3$ (300 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. Without further purification the peracetylated thioglycoside was deacetylated. Na (1.03 g; 44.8 mmol) was dissolved in MeOH (200 mL) and the NaOMe/MeOH solution was slowly added to a solution of the thioglycoside in MeOH (200 mL). The reaction mixture was stirred at 22 °C until TLC showed full conversion (12 h). The reaction was quenched with Amberlite IR-120 H^+ (50 mL) and stirred for 1 h. The ion-exchange resin was filtered off, washed with MeOH and the filtrate was concentrated. The product was recrystallized from EtOAc to give **78** as colorless crystals. R_f 0.53 (1:1 EtOAc/Acetone). Yield (over two steps) 7.4 g (69%)

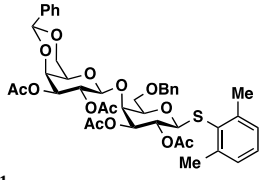
2,6-dimethylphenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (79)[163]



To a solution of $PhCH(OMe)_2$ (5.1 mL, 33.3 mmol) and camphor sulphonic acid (172 mg, 0.7 mmol) in MeCN (150 mL) was added **78** (7.4 g, 24.6 mmol). The flask was equipped with a distillation unit and the mixture was heated to reflux for 2 h. During this period app. 100 mL of MeCN-MeOH was distilled off. The distillation unit was replaced with a condenser and the reaction mixture was heated to reflux until TLC showed completion (1 h). The reaction mixture was concentrated. The crude was dissolved in CH_2Cl_2 (150 mL). Et_3N (10.4 mL; 74.8 mmol), DMAP (138 mg; 1.1 mmol) and acetic anhydride (6.4 mL; 67.9 mmol) was added to the solution and the reaction mixture was stirred until TLC revealed full conversion (2 h). The reaction was quenched with MeOH (10 mL), washed with water (2x200 mL), dried over $MgSO_4$ and concentrated. R_f 0.70 (2:1 EtOAc/toluene). Yield (over two steps): 10.4 g (94%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.39 (m, 2H, Ar-H), 7.37 – 7.23 (m, 3H, Ar-H), 7.14 – 6.97 (m, 3H, Ar-H), 5.40 (t, $J_{1,2} = J_{2,3} = 10.0$ Hz, 1H, H-2), 4.88 (dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.6$ Hz, 1H, H-3), 4.40 (d, $J_{1,2} = 10.0$ Hz, 1H, H-1), 4.27 (dd, $J_{3,4} = 3.6$, $J_{4,5} = 1.1$ Hz, 1H, H-4), 4.10 (dd, $J_{6a,6b} = 12.4$, $J_{5,6a} = 1.5$ Hz, 1H, H-6a), 3.87 (dd, $J_{6a,6b} = 12.4$, $J_{5,6b} = 1.8$ Hz, 1H, H-6b), 3.25 (m, 1H, H-5), 2.50 (s, 6H, CH_3^{dSPh}), 2.06 (s, 3H, CH_3^{Ac}), 2.00 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (101 MHz, CDCl3) δ 170.84, 169.57, 144.41, 137.72, 131.52-126.54 (10C), 101.12, 88.61, 73.61, 73.22, 69.47, 69.28, 67.92, 22.60(2C), 21.04, 20.98. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{28}O_7S$: 495.1453; Found 495.1456.

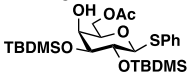
2,6-dimethylphenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-1-thio-β-D-galactopyranoside (80)



To a 10 mL flame-dried flask was added **79b** (200 mg, 0.42 mmol) and **75** (286 mg, 0.55 mmol). The mixture was co-evaporated with toluene (2x5 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (5 mL) and cooled to -30 °C. TMSOTf (10 mg; 0.04 mmol) was added and the reaction mixture was stirred at -30 °C for 1h. Et_3N (0.5 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography. Yield: 177 mg (52%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H, Ar-H), 7.34 (m, 2H, Ar-H), 7.21 – 7.10 (m, 6H, Ar-H), 7.10 – 6.97 (m, 3H, Ar-H), 5.41 (s, 1H, $CH^{benzylidene}$), 5.34 (dd, $J_{2,3} = 10.4$, $J_{1,2} = 7.9$ Hz, 1H, H-2'), 5.12 (dd, J = 9.8 Hz, $J_{1,2} = 10.2$, 1H, H-2), 4.89 (dd, $J_{2,3} = 10.5$, $J_{3,4} = 3.6$ Hz, 1H, H-3'), 4.85 (dd, $J_{2,3} = 9.8$, $J_{3,4} = 3.1$ Hz, 1H, H-3), 4.49 (d, $J_{1,2} = 7.9$ Hz, 1H, H-1'), 4.45 (d, $J_{CH2} = 11.9$ Hz, 1H, 0.5xCH_2), 4.38 (d, $J_{CH2} = 11.9$ Hz, 1H, 0.5xCH_2), 4.30 (d, J = 10.2 Hz, 1H, H-1), 4.26 (d, $J_{3,4} = 3.6$ Hz, 1H, H-4'), 4.13 (dd, $J_{3,4} = 3.1$, $J_{4,5} = 1.0$ Hz, 1H, H-4), 4.01 (dd, $J_{6a,6b} = 12.5$, $J_{5,6a} = 1.6$ Hz, 1H, J-6a,), 3.87 (dd, $J_{6a,6b} = 12.5$, $J_{5,6b} = 1.7$ Hz, 1H, H-6b'), 3.78 (dd, $J_{6a,6b} = 9.8$, $J_{5,6a} = 6.1$ Hz, 1H, H-6a), 3.55 (dd, $J_{6a,6b} = 9.8$, $J_{5,6b} = 5.4$ Hz, 1H, H-6b), 3.51 – 3.42 (m, 1H, H-5), 3.33 (t, $J_{5,6a} = J_{5,6b} = 1.3$ Hz, 1H, H-5'), 2.46 (s, 6H, 2xCH_3^{dSPh}), 2.13 (s, 3H, CH_3^{Ac}), 2.03 (s, 3H, CH_3^{Ac}), 2.02 (s, 6H, 2xCH_3^{Ac}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.12, 170.26, 169.67, 169.44, 144.25, 138.49, 137.81, 131.74, 129.28, 129.23, 128.37, 128.37, 128.34, 128.33, 127.61, 127.61, 127.48, 126.60, 126.59, 101.67, 101.26, 88.81, 77.39, 74.80, 73.60, 73.38, 73.33, 72.11, 69.21, 68.97, 68.79, 68.65, 66.38, 22.69, 22.69, 21.10, 20.97, 20.96, 20.87. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{42}H_{48}NaO_{14}S$: 831.2663; Found 831.2668.

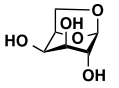
Phenyl 6-*O*-acetyl-2,3-di-*O*-(*tert*-butyldimethylsilyl)-1-thio-β-D-glucopyranoside (81, 82, 83)



To a solution of 3,4-dimethoxybenzaldehyde (1.65 g, 9.9 mmol) and camphor sulphonic acid (51 mg, 0.22 mmol) in MeCN (100 mL) was added **56** (2.0 g, 7.34 mmol). The flask was equipped with a distillation unit and the mixture was heated to reflux for 2 h. During this period approx. 50 mL of MeCN-MeOH was distilled off. The distillation unit was replaced with a condenser and the reaction mixture was heated to reflux until TLC showed completion (1 h). The reaction mixture was concentrated, re-dissolved in toluene and filtered through a plug of silica to afford **81**. To a solution of the crude acetal and DMAP (100 mg) in pyridine (15 mL) was slowly added TBSOTf (6.7 mL, 29.38 mmol) at 0 °C. The mixture was heated to 60 °C. After 14 h the reaction was quenched with MeOH, diluted with EtOAc, and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated to give an yellow oil. The crude oil was dissolved in MeOH (50 mL) followed by addition of PPTS (0.18 g; 0.73 mmol). The reaction was stirred at 22 °C until TLC showed full conversion (4h). The solution was concentrated and co-evaporated with toluene (50 mL) purified by flash chromatography (9:1 Tol/EtOAc) to give **82** as a colorless solid (2.6 g; 71% over three steps). The diol was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. Et_3N (0.76 mL; 7.79 mmol) and Ac_2O (0.38 mL; 5.71 mmol) were added and the reaction was stirred at 5 °C for 10 h. The

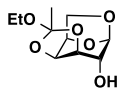
reaction was quenched with MeOH (0.5 mL), diluted with CH_2Cl_2 (50 mL) and washed with H_2O (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (19:1 Tol/EtOAc) to give **83**. Yield 2.54 g (91%). R_f 0.28 (19:1 Tol/EtOAc)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 2H, Ar-H), 7.16 – 7.00 (m, 3H, Ar-H), 4.37 (d, $J_{1,2}$ = 8.6 Hz, 1H, H-1), 4.26 – 4.12 (m, 2H, H-6), 3.68 (dd, $J_{3,4}$ = 3.2, $J_{4,5}$ = 1.4 Hz, 1H, H-4), 3.67 (t, $J_{1,2}$= $J_{2,3}$ = 8.6 Hz, 1H, H-2), 3.53 (ddd, $J_{5,6a}$ = 7.7, $J_{5,6b}$ = 4.8, $J_{4,5}$ = 1.4 Hz, 1H, H-5), 3.49 (dd, $J_{2,3}$ = 8.1, $J_{3,4}$ = 3.2 Hz, 1H, H-3), 1.88 (s, 3H, CH_3^{Ac}), 0.78 (s, 18H, CH_3^{TBDMS}), 0.09 (s, 3H, CH_3^{TBDMS}), 0.00 (s, 3H, CH_3^{TBDMS}), -0.03 (s, 3H, CH_3^{TBDMS}), -0.05 (s, 3H, CH_3^{TBDMS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.90, 135.52, 131.43(2C), 128.83(2C), 127.25, 90.15, 77.28, 75.58, 71.31, 70.17, 63.84, 26.48(3C), 26.44(3C), 20.97, 18.45, 18.35, -2.03, -3.21, -3.36, -3.95. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for **:** $C_{26}H_{46}NaO_6SSi_2$ 565.2451; Found 565.2453.

1,6-anhydro-β-D-galactopyranoside (84, 85)[358]



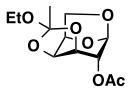
A solution of galactose pentaacetate (25.0 g; 64.0 mmol), thiophenol (7.3 mL; 70.4 mmol) and $BF_3{\cdot}OEt_2$ (7.9 mL; 64.0 mmol) in CH_2Cl_2 (200 mL) was stirred at 22 °C for 16 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. $NaHCO_3$ (300 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. Without further purification phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-**D**-galactopyranoside (**84**) (35 g) was added a solution of sodium hydroxide (53 g) in water (1 L). After the sugar was fully dissolved, the reaction mixture was heated to reflux for 12 h. The solution was cooled and 12 M HCl (100 ml) was slowly added. 3 M HCl was then added slowly in portions until pH 3 was observed. The solution was concentrated to ~200 mL and washed with EtOAc (2 x 200 mL). The aqueous phase was evaporated to dryness and the residue was extracted with 1:1 DCM/MeOH (600 mL) using a Soxhlet extractor for 6-12 h. The mixture was finally concentrated to give a yellowish solid, which was purified by flash chromatography (9:1 DCM/MeOH) to afford **85**. Yield: 7.78 g (75%). R_f 0.38 (DCM/MeOH 6:1).
mp. 220-222 °C, $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$= -21.3° (c 1.1, H_2O) **^{1}H NMR** (300 MHz, D_2O); δ 5.28 (s, 1H), 4.38 (t, J = 4.7 Hz, 1H), 4.19 (d, J = 7.7 Hz, 1H), 3.93 (t, J = 4.3 Hz, 1H), 3.84 – 3.78 (m, 1H), 3.70 – 3.65 (m, 1H), 3.57 – 3.49 (m, 1H). **^{13}C NMR** (75 MHz, D_2O) δ 100.73, 74.37, 71.33, 70.22, 64.32, 63.61. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_6H_{10}NaO_5$ 185.0426; Found 185.0423.

1,6-anhydro-3,4-*O*-(1-ethoxyethylidene)-β-D-galactopyranoside (86)



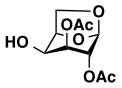
85 (7.7 g; 47.5 mmol) was added to a mixture of triethyl orthoacetate (40 mL) and MeCN (40 mL). To the mixture was added *p*-toluene sulphonic acid monohydrate (90 mg; 0.475 mmol), a condenser was installed and the reaction mixture was heated to 60 °C on an oil bath. The reaction was monitored by TLC until full conversion of the starting material was observed (approx. 24 h). The reaction was quenched with Et_3N (4 ml), and the solution was poured into ice-water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The compound was purified by flash chromatography (2:1 Tol/EtOAc). Yield: 9.70 g (88%) R_f 0.28 (2:1Tol/EtOAc).
$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$= -3.4° (c 0.5, $CDCl_3$) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.37 (t, J = 1.2 Hz, 1H), 4.54-4.50(m, 2H), 4.36 – 4.27 (m, 1H), 3.96 (d, J = 7.7 Hz, 1H), 3.87 (dd, J = 8.4, 1.2 Hz, 1H), 3.64 – 3.57 (m, 1H), 3.52 (qd, J = 7.1, 0.8 Hz, 2H), 1.63 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ 120.44, 101.36, 76.09, 71.90, 69.80, 63.88, 58.68, 54.58, 19.80, 14.61. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{10}H_{16}NaO_6$ 255.0845; Found 255.0848.

2-*O*-acetyl-1,6-anhydro-3,4-*O*-(1-ethoxyethylidene)-β-D-galactopyranoside (87)[169]



Compound **86** (10 g; 43.1 mmol) was dissolved in CH_2Cl_2 (200 mL). Et_3N (10.5 mL; 75.4 mmol), DMAP (53 mg; 0.43 mmol) and acetic anhydride (6.1 mL; 64.6 mmol) was added to the solution and the reaction mixture was stirred for 3 hours. The reaction mixture was quenched with MeOH (5 mL), washed with water (200 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (Tol/EtOAc 2:1) to afford the product as a white crystalline powder. R_f 0.27 (4:1 Toluene/EtOAc) Yield: 11.1 g (94%)
mp.: 60 °C, $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$= -25.7° (c 1.0, $CDCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.38 (s, 1H), 4.91 (d, J = 0.7 Hz, 1H), 4.62-4.50 (m, 2H), 4.24 (d, J = 6.9 Hz, 1H), 4.00 (d, J = 7.7 Hz, 1H), 3.63 (ddd, J = 7.7, 4.9, 1.2 Hz, 1H), 3.54 (qd, J = 7.0, 0.7 Hz, 2H), 2.13 (s, 3H), 1.66 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.72, 120.81, 99.09, 73.69, 72.07, 70.99, 69.62, 63.54, 59.36, 21.11, 19.92, 15.63. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{12}H_{18}NaO_7$ 297.0950; Found 297.0945

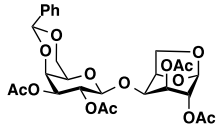
2,3-di-*O*-acetyl-1,6-anhydro-β-D-galactopyranoside (88)[359]



To **87** (6.48 g; 23.6 mmol) was added a 4:1 H_2O/AcOH mixture (90 mL) and the reaction was stirred for 30 min. The solution was concentrated and co-evaporated with toluene (3x100 mL) and heptane (100 mL). This resulted in a white crystalline material that did not need further purification. R_f 0.20 (2:1 Tol/EtOAc). Yield: 5.67 g (97 %)

mp.: 105-110 °C (litt.108-112 °C), $[\alpha]_D^{20}$= +6.5° (c 1.0, $CDCl_3$) (+1.2 °, c 1.6, $CDCl_3$)
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (t, J = 1.4 Hz, 1H), 5.06 (dq, J = 5.5, 1.4 Hz, 1H), 4.76 (t, J = 1.5 Hz, 1H), 4.42 (dd, J = 4.7, J=0.9 Hz, 1H), 4.25 (d, J = 7.6 Hz, 1H), 4.20 (t, J = 5.5 Hz, 1H), 3.68 (ddd, J = 7.5, 5.1, 0.9 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.57, 169.69, 98.81, 74.18, 71.18, 70.19, 64.75, 64.04, 21.17, 21.04. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{10}H_{14}NaO_7$ 269.0637; Found 269.0632.

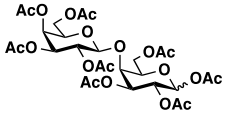
2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-1,6-anhydro-β-D-galactopyranoside (89)



A mixture of acceptor **88** (209 mg; 0.845 mmol) and donor **54** (501 mg; 1.12 mmol) was dried azeotropically with toluene (2x10 mL) and left under vacuum over night. The mixture was dissolved in dry CH_2Cl_2 (10 mL) and dry MeCN (10 mL) and cooled to -30 °C on an acetone/dry ice bath. Then NIS (260 mg; 1.2 mmol) and TESOTf (20 µL; 0.087 mmol) were added and the reaction mixture was stirred at -30 °C until TLC showed full conversion of the acceptor (30 min). The solution was diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. NaS_2O_3 (15 mL) and sat. aq. $NaHCO_3$ (15 mL), dried over $MgSO_4$ and concentrated. The yellow crystalline product was purified by flash chromatography (2:1 toluene/EtOAc) to yield a white crystalline solid. R_f 0.14 (2:1 Toluene/EtOAc). Yield: 420 mg (85 %)

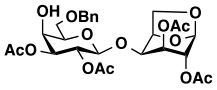
mp. 90 °C. $[\alpha]_D^{20}$= +47.8 °(c 1.0, $CHCl_3$), **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10 – 6.98 (m, 5H), 5.51 (d, J = 6.9 Hz, 1H), 5.37 (t, J = 1.5 Hz, 1H), 5.35 – 5.25 (m, 2H), 4.90 (dd, J = 10.4, 3.7 Hz, 1H), 4.76 (dd, J = 10.0, 5.5 Hz, 1H), 4.70 (t, J = 1.6 Hz, 1H), 4.62 (d, J = 7.9 Hz, 1H), 4.41 (t, J = 5.1 Hz, 1H), 4.38 (d, J = 3.7 Hz, 1H), 4.29 (dd, J = 12.5, 1.4 Hz, 1H), 4.14 – 3.98 (m, 2H), 3.78 – 3.66 (m, 1H), 3.54 (d, J = 1.0 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.94, 170.14, 169.83, 169.52, 129.37, 129.26, 128.57, 128.45, 126.40, 125.52, 102.40, 101.05, 98.76, 74.51, 73.24, 72.69, 72.06, 71.94, 69.08, 68.25, 67.30, 66.70, 54.66, 22.92, 21.14, 21.05, 20.98. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{27}H_{32}NaO_{14}$ 603.1690; Found 603.1691.

Acetyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-di-*O*-acetyl-D-galactopyranoside (90)[360]



$Sc(OTf)_3$ (2 mg; 0.004 mmol) was added to a solution of **89** (500 mg, 0.86 mol) in Ac_2O (5 mL) and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of MeOH. The reaction mixture was concentrated and the product was purified by silica gel chromatography (4:1 Tol/EtOAc) to afford **90**. Yield: 555 mg (95%). The NMR correlates with literature data.[360]

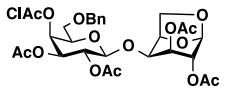
2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-1,6-anhydro-β-D-galactopyranoside (91)



To a solution of the disaccharide **89** (0.99 g; 1.71 mmol) in dry THF (30 mL) was added $NaCNBH_3$ (1.61 g; 25.6 mmol). The mixture was stirred at 22 °C, and a 2M solution of HCl in dry ether was added drop-wise until gas development ceased. The mixture was concentrated to approximately 5 mL and then diluted with CH_2Cl_2 (100 mL). The mixture was neutralized with sat. aq. $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3x30 mL) and the combined organic phases were washed with water (100 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography (3:2 Tol/EtOAc) to yield a white crystalline solid. R_f 0.31 (3:2 toluene/EtOAc). Yield: 777 mg (78%)

Mp. 69 °C, $[\alpha]_D^{20}$= +7.88° (c 0.7, $CDCl_3$) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 – 7.21 (m, 5H, Ar-H), 5.37 (d, J = 1.4 Hz, 1H), 5.33 – 5.27 (m, 1H), 5.21 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.9 Hz, 1H, H-2'), 4.89 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.2 Hz, 1H, H-3), 4.74 – 4.65 (m, 2H), 4.62 – 4.47 (m, 3H), 4.38 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1'), 4.14 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4), 4.02 (t, J = 4.7 Hz, 1H), 3.80 – 3.61 (m, 5H), 2.10 (s, 3H, CH_3^{Ac}), 2.08 (s, 3H, CH_3^{Ac}), 2.06 (s, 3H, CH_3^{Ac}), 2.05 (s, 3H, CH_3^{Ac}) **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.30, 170.02(2C), 169.54, 129.25-128.02(6C), 102.69, 98.73, 74.45, 73.92, 73.46, 73.33, 72.94, 71.94, 69.13, 68.76, 67.91, 67.17, 64.84, 21.07-20.87(m, 4C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{27}H_{34}NaO_{14}$ 605.1846; Found 605.1844.

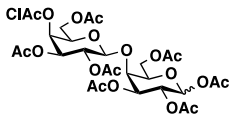
2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-chloroacetyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-1,6-anhydro-β-D-galactopyranoside (92)



Compound **91** (1.3 g; 2.2 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C. $(ClAc)_2O$ (0.65 g; 3.8 mmol), Et_3N (0.54 mL; 3.9 mmol) and DMAP (5 mg; 0.4 mmol) was added and the reaction was stirred at 0 °C for 3 h. The reaction mixture was concentrated and purified by flash chromatography (9:1 Tol/EtOAc) to afford **92** as a white crystalline powder. Yield 1.42 g (98%)

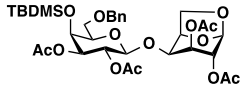
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 5H, Ar-H), 5.43 (dd, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.2 Hz, 1H, H-4'), 5.31 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 5.23 (dd, $J_{3,4}$ = 5.0, $J_{2,3}$ = 1.5 Hz, 1H, H-3), 4.99 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 7.6 Hz, 1H, H-2'), 4.92 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.3 Hz, 1H, H-3'), 4.62 (dd, $J_{1,2}$ = $J_{2,3}$ = 1.5 Hz, 1H, H-2), 4.59 – 4.54 (m, 1H, H-5), 4.50 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1'), 4.46 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.35 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.30 (dd, $J_{6a,6b}$ = 7.6, $J_{5,6a}$ = 0.8 Hz, 1H, H-6a), 3.99 (d, J_{CH2} = 14.8 Hz, 1H, 0.5xCH_2^{AcCl}), 3.94 (td, $J_{3,4}$ = 5.0, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.87 (d, J_{CH2} = 14.8 Hz, 1H, 0.5xCH_2^{AcCl}), 3.81 (ddd, $J_{5,6b}$ = 7.1, $J_{5,6a}$ = 5.9, $J_{4,5}$ = 1.2 Hz, 1H, H-5'), 3.63 (dd, $J_{6a,6b}$ = 7.6, $J_{5,6b}$ = 5.2, 1H, H-6b), 3.45 (dd, $J_{6a,6b}$ = 9.2, $J_{5,6b}$ = 5.9 Hz, 1H, H-6a'), 3.37 (dd, $J_{6a,6b}$ = 9.2, $J_{5,6b}$ =7.1 Hz, 1H, H-6b'), 2.04 (s, 3H, CH_3^{Ac}), 2.00 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}), 1.91 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (101 MHz, CDCl3) δ 170.02, 169.87(2C), 169.40, 166.91, 137.30, 128.70(2C), 128.23, 128.19(2C), 102.50, 98.67, 74.31, 73.64, 72.98, 71.95, 71.82, 70.75, 69.28, 68.30, 67.04, 66.84, 64.67, 40.66, 20.95(2C), 20.80, 20.64. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{29}H_{36}ClNaO_{15}$ 682.1640; Found 682.1641.

Acetyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-di-*O*-acetyl-D-galactopyranoside (93)



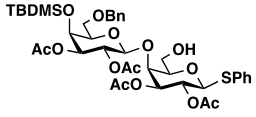
$Sc(OTf)_3$ (1.8 mg; 0.004 mmol) was added to a solution of **92** (478 mg, 0.72 mol) in Ac_2O (5 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of MeOH. The reaction mixture was concentrated and the product was purified by silica gel chromatography (4:1 Tol/EtOAc) to afford **90**. Yield: 470 mg (91%).

2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-1,6-anhydro-β-D-galactopyranoside (96)



Compound **91** (1 g; 1.72 mmol) was dissolved in pyridine (8 mL), and DMAP (100 mg) was added. The reaction mixture was stirred 0 °C, and *tert*-butyldimethylsilyl trifluoromethanesulphonate (0.68 g; 2.57 mmol) was added slowly. The reaction was heated to 50 °C and stirred over night. After cooling to 0 °C, the reaction was quenched by addition of MeOH. The mixture was diluted with EtOAc, washed with water, HCl (1 M), sat. aq. $NaHCO_3$ and brine. The organic phase was concentrated and purified by flash chromatography (4:1 Tol/EtOAc) to give **96** as a colorless glassy solid (1.1 g, 92%).

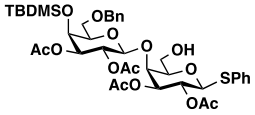
Phenyl 2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-β-D-galactopyranoside (97)



The disaccharide **96** (1.0 g; 1.43 mmol) was mixed with (phenylthio) trimethylsilane (0.95 mL; 5.02 mmol) and ZnI_2 (801 mg; 2.51 mmol) in $C_2H_4Cl_2$ (30 mL) and stirred at 22 °C for 8 h. The mixture was then diluted with Et_2O (200 mL) and washed with 1 M HCl (100 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated. Purified by flash chromatography (2:1 Tol/EtOAc) to give **97** as a yellow crystalline material. Yield: 671 mg (58%)

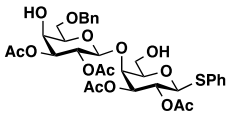
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 6.98 (m, 5H, Ar-H), 5.20 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2'), 5.04 (t, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, 1H, H-2), 4.92 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.85 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 2.7 Hz, 1H, H-3'), 4.63 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.50 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1'), 4.28 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 3.99 – 3.85 (m, 1H, H-6a), 3.91 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-4'), 3.81 – 3.60 (m, 5H, 2xH-5, 1.5xH-6,), 2.02 (s, 3H, CH_3^{Ac}), 1.98 (s, 6H, 2xCH_3^{Ac}), 1.95 (s, 3H, CH_3^{Ac}), 0.85 (s, 9H, 3xCH_3^{TBDMS}), 0.00 (s, 3H, CH_3^{TBDMS}), -0.07 (s, 3H, CH_3^{TBDMS}). **^{13}C NMR** (101 MHz, CDCl3) δ 171.13, 170.56, 169.91, 169.52, 132.53, 131.81(2C), 129.19(2C), 127.94, 102.05, 86.15, 76.64, 75.14, 74.25, 73.81, 73.41, 69.09, 68.59, 67.68, 63.11, 59.76, 25.93(3C), 21.36, 21.26, 20.98, 20.69, 18.41, -4.20, -4.48. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{39}H_{54}NaO_{14}SSi$ 829.2901; Found 829.2899.

Phenyl 2,3-di-O-acetyl-6-O-benzyl-4-O-(tert-butyldimethylsilyl)-β-d-galactopyranosyl-(1→4)-2,3,6-tri-O-acetyl-1-thio-β-d-galactopyranoside (98)



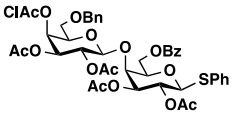
The disaccharide 97 (200 mg; 0.25 mmol) was dissolved in CH2Cl2 (10 mL). Et3N (55 μL; 0.40 mmol), DMAP (1 mg; 0.005 mmol) and Ac2O (35 μL; 0.37 mmol) were added and the reaction mixture was stirred at 22 °C until TLC revealed full conversion (2 h). The reaction was quenched with MeOH (0.5 mL), diluted with CH_2Cl_2 (50 mL), washed with water (2x25 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (2:1 Tol/EtOAc). Yield: 206 mg (98%)

Phenyl 2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-β-D-galactopyranoside (99)



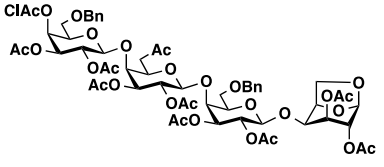
The disaccharide **91** (490 mg; 0.841 mmol) was mixed with (phenylthio) trimethylsilane (0.7 mL; 3.7 mmol) and ZnI_2 (678 mg; 2.12 mmol) in $C_2H_4Cl_2$ (10 mL) and stirred at 22 °C for 14 h. The mixture was diluted with Et_2O (100 mL) and washed with 1 M HCl (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated. Purified by flash chromatography (3:2 Tol/EtOAc). R_f 0.32 (1:1 Tol/EtOAc). Yield: 243 mg (41 %)
Mp. 85 °C, $[\alpha]_D^{20}$= -3.96 ° (c 0.5, $CDCl_3$) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 – 6.90 (m, 10H), 5.29 – 5.15 (m, 2H), 5.03 (t, $J_{1,2}$ = $J_{2,3}$ = 9.8 Hz, 1H, H-2), 4.91 (dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 3.2 Hz, 1H, H-3), 4.84 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 2.9 Hz, 1H, H-3), 4.57 (dd, J = 10.9, 6.0 Hz, 2H), 4.43 – 4.29 (m, 2H), 4.18 (d, $J_{3,4}$ = 2.9 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.78 – 3.44 (m, 4H), 2.03 (s, 3H, CH_3^{Ac}), 2.01 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}), 1.97 (s, 3H, CH_3^{Ac}) **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.48, 170.30, 169.87, 169.40, 137.23-128.02(12C), 102.69, 86.28-59.25(12C), 21.10, 21.06, 21.01, 20.69. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{33}H_{40}NaO_{14}S$ 71520365; Found 715.2031.

Phenyl 2,3-di-*O*-acetyl-6-*O*-benzyl-4-O-chloroacetyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-O-benzoyl-1-thio-β-D-galactopyranoside (100)



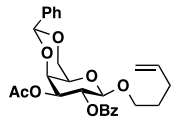
To a solution of **99** (205 mg; 0.296 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added BzCl (0.04 mL; 0.311 mmol) and Et_3N (0.06 mL; 0.444 mmol) and the reaction was stirred for 10h at 5 °C. The reaction mixture was quenched with MeOH (1 mL), diluted with CH_2Cl_2 (100 mL), and washed with H_2O (60 mL). The water phase was washed with CH_2Cl_2 (60 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated yielding a syrupy residue. The crude product was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Chloroacetic anhydride (76 mg; 0.45 mmol), Et_3N (78 μL; 0.55 mmol) and DMAP (5 mg; 0.045 mmol) was added and the reaction was stirred at 22 °C for 8 h. The reaction was quenched with MeOH (0.5 mL) and concentrated. The product was purified by flash chromatography (3:1 Tol/EtOAc). R_f 0.40 (2:1 Tol/EtOAc). Yield over two steps: 193 mg (75 %).
Mp. 76 °C, $[\alpha]_D^{20}$= -8.0 °(c 0.5, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.27 – 6.74 (m, 15H), 5.42 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4'), 5.20 – 5.02 (m, 2H), 5.02 – 4.82 (m, 2H), 4.61 (d, J = 10.0 Hz, 1H), 4.53 (dd, J = 11.9, 4.6 Hz, 1H), 4.47 – 4.29 (m, 3H), 4.26 – 4.10 (m, 2H), 4.00 (d, J_{CH2} = 15.1 Hz, 1H), 3.93 – 3.79 (m, 2H), 3.70 (d, J = 6.6 Hz, 1H), 3.38 – 3.19 (m, 2H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.93 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.41, 170.30, 169.64, 169.47, 167.14, 166.31, 137.47-127.95(18C), 102.07, 86.76, 75.93-66.95(11C), 40.81, 21.04, 21.03, 20.85, 20.78. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{42}H_{46}ClNaO_{16}S$ 896.2093; Found 896,2088.

2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-chloroacetyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3-O-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-*O*-acetyl-1,6-anhydro-β-D-galactopyranoside (101)



A mixture of acceptor **91** (40 mg; 0.069 mmol) and donor **100** (50 mg; 0.057 mmol) was dried azeotropically with toluene (2x2 mL) and subjected to vacuum over night. The mixture was then dissolved in dry CH_2Cl_2 (1 mL) and dry MeCN (1 mL) and cooled to -30 °C. NIS (13 mg; 0.059 mmol) and one drop of TESOTf was added and the mixture was stirred at -30 °C until TLC showed full conversion of the donor 1 h. The solution was diluted with CH_2Cl_2 (15 mL) and washed with 10 mL of sat. aq. NaS_2O_3 and 10 mL of sat. aq. $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated, yielding a syrupy residue. The product was purified by flash chromatography (3:2 Tol/EtOAc). R_f 0.24 (1:1 Tol/EtOAc). Yield: 31 mg (41 %)
Mp.: 95 °C, $[\alpha]_D^{20}$= -6.6 °(c 1.0, CHCl3) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.13 – 6.74 (m, 15H), 5.42 (d, J = 3.0 Hz, 1H), 5.35 – 3.10 (m, 33H), 2.06 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H) **^{13}C NMR** (50 MHz, $CDCl_3$) δ 170.24-166.01(m, 10 C), 138.14-128.07(m, 18C), 102.19(1C), 101.93(1C), 101.64(1C), 98.60(1C), 74.14-63.53(m, 22C), 40.62(1C), 20.93-20.81(8C)

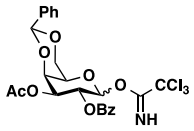
Pent-4-enyl 3-*O*-acetyl-2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside (103)



110 (4.6 g; 12.15 mmol) was dissolved in pyridine (80 mL). DMAP (45 mg; 0.36 mmol) and benzoyl chloride (2.11 mL; 18.23 mmol) was added to the solution and the reaction mixture was stirred at 22 °C for 12 h. The reaction was quenched with MeOH (2 mL), concentrated and purified by flash chromatography (9:1 Tol/EtOAc) to afford **103** as a white crystalline solid. Yield 5.4 g (92%). R_f 0.31 (9:1 Tol/EtOAc).

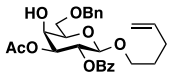
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.88 (m, 2H, Ar-H^{Bz}), 7.60 – 7.22 (m, 8H, Ar-H), 5.64 – 5.48 (m, 1H, -*CH*=CH_2), 5.59 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2), 5.46 (s, 1H, $CH^{benzylidene}$), 5.10 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.6 Hz, 1H, H-3), 4.77 – 4.67 (m, 2H, -CH=*CH*$_2$), 4.56 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.34 (dd, $J_{3,4}$ = 3.6, $J_{4,5}$ = 1.5 Hz, 1H, H-4), 4.28 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 1.5 Hz, 1H, H-6a), 4.02 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6b}$ = 1.5 Hz, 1H, H-6b), 3.86 (dt, *J* = 9.5, 6.0 Hz, 1H, -$OCH_2^{pentenyl}$), 3.49 (t, $J_{5,6a}$ = $J_{5,6b}$ = 1.5 Hz, 1H, H-5), 3.41 (ddd, *J* = 9.6, 7.4, 6.1 Hz, 1H, -$OCH_2^{pentenyl}$), 1.91 (s, 3H, CH_3^{Ac}), 1.91 (s, 2H, -$CH_2^{pentenyl}$), 1.64 – 1.40 (m, 2H,-$CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.96, 165.20, 138.05, 137.62, 133.23, 129.87, 129.80(2C), 129.16, 128.51(2C), 128.27(2C), 126.51(2C), 114.78, 101.34, 101.14, 73.70, 72.05, 69.30, 69.07, 68.84, 66.52, 29.92, 28.62, 20.97. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{27}H_{30}NaO_8$, 505.1838; Found 505.1840.

3-*O*-acetyl-2-O-benzyl-4,6-*O*-benzylidene-α-D-galactopyranosyl trichloroacetimidate (104)



Compound **103** (3.53 g; 7.32 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0 °C. Br_2 (1.29 g; 8.05 mmol) was added drop-wise and the resulting reaction mixture was stirred at 0 °C for 2 h. The reaction mixture poured into a solution of TBAB (4.72 g; 14.63 mmol), H_2O (1.32 g; 73.16 mmol) and Et_3N (0.51 mL; 3.66 mmol) in MeCN (100 mL). The reaction mixture was heated to 55 °C and stirred for 4 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with water (200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (2:1 Tol/EtOAc) to give **111**. Yield: 2.55 g. Small impurities from TBAB are present in the compound. Compound **111** was applied directly in the following step. **111** (2.55 g; 6.15 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. DBU (0.10 mL; 0.68 mmol) was added followed by trichloroacetonitrile (1.78 g; 12.31 mmol). The reaction was tirred at 0 °C for 3h. It was then filtered, concentrated and purified by flash chromatography (9:1) to give **104** as an α/β-mixture.
Yield: 2.86 g (70%) over two steps

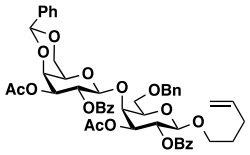
Pent-4-enyl 3-*O*-acetyl-2-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranoside (105)



$NaCNBH_3$ (3.44 g; 54.75 mmol) was added to a solution of **103** (1.76 g; 3.65 mmol) in dry THF (30 mL). The mixture was stirred at 22 °C while HCl in Et_2O (2M) was added drop wise until gas development ceased and the mixture remained acidic (pH 3-4). The reaction mixture was concentrated to app. 10 ml, diluted with CH_2Cl_2 (100 mL) and neutralized with sat. aq. $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were washed with water (100 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (4:1 Tol/EtOAc) to afford **105** as a colorless crystalline powder. Yield: 1.38 g (78%) R_f 0.38 (4:1 Tol/EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.84 (m, 2H, Ar-H^{Bz}), 7.58 – 7.15 (m, 8H, Ar-H^{Bz}), 5.64 – 5.51 (m, 1H, -*CH*=CH_2), 5.47 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.9 Hz, 1H, H-2), 5.07 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.1 Hz, 1H, H-3), 4.79 – 4.64 (m, 2H, -CH=*CH*$_2$), 4.55 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.51 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.51 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.14 (dd, $J_{4,OH}$ = 4.7, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 3.83 (dt, *J* = 9.7, 6.1 Hz, 1H, -$OCH_2^{pentenyl}$), 3.78 – 3.67 (m, 3H, H-5, H-6), 3.42 (ddd, *J* = 9.7, 7.2, 6.1 Hz, 1H, -$OCH_2^{pentenyl}$), 2.59 (d, *J* = 4.5 Hz, 1H, 4-OH), 1.94 (s, 3H, CH_3^{Ac}), 1.93 – 1.81 (m, 2H, $CH_2^{pentenyl}$), 1.62 – 1.44 (m, 2H, $CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.44, 165.37, 138.01(2C), 137.72, 133.31, 129.87(2C), 128.66(2C), 128.56(2C), 128.06, 127.93(2C), 114.91, 101.72, 73.96, 73.48, 73.35, 70.05, 69.30, 68.40, 29.94, 28.71, 21.01. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{27}H_{32}NaO_8$, 507.1995; Found 507.1998.

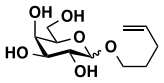
Pent-4-enyl 3-*O*-acetyl-2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-3-*O*-acetyl-2-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranoside (106)



To a 50 mL flame-dried flask was added **105** (1.45 g, 2.99 mmol) and **112** (2.28 g, 3.89 mmol). The mixture was co-evaporated with toluene (2x30 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (20 mL) and cooled to -40 °C. TESOTf (43 mg; 0.30 mmol) was added and the reaction mixture was stirred at -20 °C for 4h. Et_3N (0.5 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (9:1 Tol/EtOAc) to give **106**. Yield: 5.13 g (82%) R_f 0.29 (9:1 Tol/EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.90 (m, 2H, Ar-H^{Bz}), 7.92 – 7.69 (m, 2H, Ar-H^{Bz}), 7.63 – 6.96 (m, 16H, Ar-H), 5.58 – 5.53 (m, 1H, -*CH*=CH_2) 5.55 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 7.6 Hz, 1H, H-2), 5.45 (s, 1H, $CH^{benzylidene}$), 5.22 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2), 5.17 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.5 Hz, 1H, H-3), 5.08 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.1 Hz, 1H, H-3), 4.75 – 4.64 (m, 2H, -CH=*CH_2*), 4.71 (d, $J_{1,2}$ = 7.8 Hz, 1H), 4.53 (s, 2H, CH_2^{Bn}), 4.45 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.29 (d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 4.19 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 4.07 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6a}$=1.6 Hz, 1H, H-6a), 3.92-3.90 (m, 2H, H-6b, H-6a), 3.76 (dt, J = 9.7, 6.1 Hz, 1H, -$OCH_2^{pentenyl}$), 3.72 – 3.65 (m, 2H, H-6b, H-5), 3.42 (dd, $J_{5,6a}$ = $J_{5,6b}$ =1.3 Hz, 1H, H-5), 3.35 (ddd, J = 9.7, 7.2, 6.2 Hz, 1H, -$OCH_2^{pentenyl}$), 1.94 (s, 3H, CH_3^{Ac}), 1.90 – 1.75 (m, 2H, $CH_2^{pentenyl}$), 1.64 (s, 3H, CH_3^{Ac}), 1.54 – 1.36 (m, 2H, $CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.11, 170.43, 165.32, 164.24, 138.51, 138.21, 137.82, 132.97, 132.82, 130.23, 130.15(2C), 129.95, 129.66(2C), 129.32, 128.43(2C), 128.39(3C), 128.24(2C), 127.79(2C), 127.58, 126.64(2C), 114.66, 101.71, 101.40, 101.29, 74.07, 73.90, 73.57, 73.45, 73.23, 71.85, 70.06, 70.03, 69.10, 68.68, 68.57, 66.37, 29.93, 28.62, 21.05, 20.60. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{49}H_{52}NaO_{15,}$ 903.3204; Found 903.3204.

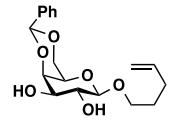
Pent-4-enyl β-D-galactopyranoside (108)[349]



To a solution of galactose pentaacetate (35 g; 89.7 mmol) and pent-4-en-1-ol (20 mL, 194 mmol) in CH_2Cl_2 (250 mL) was added $BF_3{\cdot}OEt_2$ (14 mL, 110 mmol). The mixture was stirred at 22 °C under an atmosphere of nitrogen for 10 h, and then diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. $NaHCO_3$ (350 mL). The organic layer was dried over $MgSO_4$ and concentrated. The syrupy residue was dissolved in 0.04 M NaOMe in MeOH (300 mL) and stirred for 4 h. The mixture was quenched with Amberlite IR-120 (H^+) (15 mL) and stirred for an additional 30 min. The resin was removed by filtration and the filtrate concentrated and purified by flash chromatography (6:1 CH_2Cl_2/MeOH) to give 17.5 g of a greasy solid. Recrystallization from EtOAc afforded **108** (12.5 g, 56%) as white crystals. R_f 0.30 (6:1 CH_2Cl_2/MeOH)

mp 88-90 °C (EtOAc). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= –10.0 (c 1.6, H_2O). (lit. –9.02 (c 1.23, H_2O). **^{1}H NMR** (D_2O, 300 MHz) δ 5.82 (m, 1H), 5.01 (d, *J* = 17.4 Hz, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 4.30 (d, *J* = 8.0 Hz, 1H), 3.87-3.82 (m, 2H), 3.72-3.51 (m, 5H), 3.42 (t, *J* = 8.9 Hz, 1H), 2.07 (m, 2H), 1.65 (m, 2H). **^{13}C NMR** (D_2O, 75 MHz) δ 139.1, 115.0, 103.0, 75.3, 73.1, 71.0, 70.1, 68.9, 61.1, 29.6, 28.3

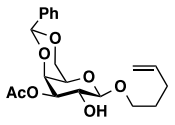
Pent-4-enyl 4,6-*O*-benzylidene-β-D-galactopyranoside (109)[361]



To a solution of $PhCH(OMe)_2$ (33 mL, 220 mmol) and CSA (450 mg) in $CHCl_3$ (980 mL) was added **108** (38.5 g, 155 mmol). The flask was equipped with a distillation unit and the mixture heated at reflux for 1.5 h during which time about 250 mL of a $CHCl_3$-MeOH mixture distilled off. The reaction mixture was quenched with Et_3N (0.7 mL) and concentrated to a solid which was recrystal-lized from EtOAc to give **109** (51.7 g, 99%). R_f 0.53 (EtOAc).

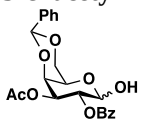
Mp. 158-160 °C (EtOAc). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -36.5 (c 1.5, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 300 MHz) 7.49 (m, 2H, Ar-H), 7.35 (m, 3H, Ar-H), 5.81 (m, 1H, CH=*CH_2*), 5.54 (s, 1H, $CH^{benzylidene}$), 5.04 (dq, J_{trans} = 17.1, J_{CH2} =1.7 Hz, 1H, CH=*CH_2*), 4.97 (dq, J_{cis} = 10.4, J_{CH2} =1.7 Hz, 1H, CH=*CH_2*), 4.32 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$= 1.5 Hz, 1H, H-6a), 4.26 (d, $J_{1,2}$ = 7.3 Hz, 1H, H-1), 4.20 (dd, $J_{3,4}$ = 3.6, $J_{4,5}$ =1.5 Hz, 1H), 4.07 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$= 1.5 Hz 1.9 Hz, 1H, H-6b), 3.98 (dt, *J* = 9.7, 6.6 Hz, 1H, -OCH_2), 3.74 (dd, $J_{2,3}$ = 9.6, $J_{1,2}$ = 7.3 Hz, 1H, H-2), 3.69 (dd, $J_{2,3}$ = 9.6, $J_{3,4}$ = 3.6 Hz, 1H), 3.52 (dt, *J* = 9.4, *J* = 7.0 Hz, 1H, -OCH_2), 3.46 (m, 1H, H-5), 2.24-2.06 (m, 4H), 1.76 (m, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz) 138.4, 137.8, 129.4, 128.4 (2C), 126.7 (2C), 115.1, 103.1, 101.6, 75.7, 73.0, 72.0, 69.6, 69.4, 66.9, 30.4, 28.9. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{18}H_{24}NaO_6$ 359.1471; Found 359.1464.

Pent-4-enyl 3-*O*-acetyl-4,6-*O*-benzylidene-β-D-galactopyranoside (110)



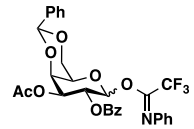
Di-*n*-butyl tin oxide (7.77 g; 31.21 mmol) was added to a solution of compound **109** (10.0 g, 29.73 mmol) in dry toluene (300 mL) and stirred under refluxing temperature for 12 h while water was removed with a Dean-Stark apparatus. The reaction mixture was cooled to 0 °C, and freshly activated 4Å MS (10g) were added. After 30 min acetyl chloride (2.18 mL, 30.62 mmol) was added drop-wise and the reaction mixture was stirred at 0 °C for 1h. The reaction was quenched by addition of MeOH, filtered through a pad of celite and concentrated. The crude product was purified by flash chromatography (2:1 Tol/EtOAc) to give **110** as white crystals. R_f 0.23 (2:1 Tol/EtOAc). Yield: 9.91 g (88%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.36 (m, 2H, Ar-H), 7.35 – 7.23 (m, 3H, Ar-H), 5.75 (ddt, J_{trans} = 16.9, J_{cis}=10.2, J_{CH2}=6.7 Hz, 1H, -*CH*=CH_2), 5.42 (s, 1H, $CH^{benzylidene}$), 4.96 (dq, J_{trans} = 17.2, J_{gem} = 1.7 Hz, 1H, *CH*$_2$=CH_{trans}), 4.90 (dq, J_{cis} = 10.2, J_{gem} = 1.7 Hz, 1H, *CH*$_2$=CH_{cis}), 4.78 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.7 Hz, 1H, H-3), 4.31 (d, $J_{3,4}$ = 3.7, 1H, H-4), 4.26 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.24 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 1.4 Hz, 1H, H-6a), 3.98 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6b}$ = 1.8 Hz, 1H, H-6b), 3.95 – 3.87 (m, 2H, -$OCH_2^{pentenyl}$, H-2), 3.46 (dt, *J* = 9.5, 6.9 Hz, 1H, -$OCH_2^{pentenyl}$), 3.41 (m, 1H, H-5), 2.16 – 2.07 (m, 2H, $CH_2^{pentenyl}$), 2.06 (s, 3H, CH_3^{Ac}), 1.76 – 1.61 (m, 2H, $CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.16, 138.24, 137.76, 129.06, 128.22(2C), 126.36(2C), 115.04, 103.13, 101.02, 73.84, 73.50, 69.50, 69.15, 68.60, 66.55, 30.30, 28.68, 21.19. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{20}H_{26}NaO_7$ 401.1576; Found 401.1579.

3-*O*-acetyl-2-*O*-benzoyl-4,6-*O*-benzylidene-D-galactopyranose (111)



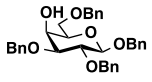
110 (3.5 g; 7.32 mmol) was dissolved in CH_2Cl_2 (30 mL) and the solution was cooled to 0 °C. Br_2 (1.29 g; 8.05 mmol) was added drop wise to the solution until the solution remained red. The reaction mixture was transferred to a flask containing a solution of TBAB (4.7 g; 14.65 mmol) and H_2O (1.3 g; 73.20 mmol) in MeCN (50 mL). The reaction mixture was heated to 55 °C and stirred at this temperature for 4 h. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (2x100 mL). The combined organic phases were dried over $MgSO_4$, concentrated and purified by flash chromatography (4:1 Tol/EtOAc) to afford **111**. Yield: 2.48 g (82%)

3-*O*-acetyl-2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (112)



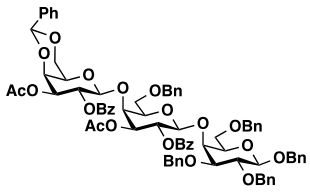
112 (2 g; 4.82 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C. Cs_2CO_3 (3.1 g; 9.65 mmol) and PTFAICl (2.0 g; 9.65 mmol) were added. The ice bath was removed and the reaction mixture was stirred at 22 °C for 14 h. The reaction mixture was filtered through a plug of celite, concentrated and purified by flash chromatography (9:1) to afford **112** Yield: 2.3 g (81%)

Benzyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (113)[362]



To **28** (5 g; 9.28 mmol) was added DIBAL-H (27.84 mL, 27.84 mmol) in CH_2Cl_2 (1 M) drop wise at 0 °C, and the reaction mixture was stirred for 1.5 h. The reaction mixture was diluted by $CHCl_3$, and quenched by addition of MeOH at 0 °C. The mixture was poured into 10% aq. KOH (50 mL) and was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The product **113** was isolated by flash chromatography (9:1 Tol/EtOAc). R_f 0.27 (9:1 Tol/EtOAc)
$[\alpha]_D^{20}$ = -14.2° (c 1.0, $CDCl_3$) **IR(**neat**):** 3474.44, 3087.73, 3062.46, 3030.10, 2913.33, 2868.67, 1496.31, 1453.67, 1364.03, 1209.14, 1094.25, 1071.25, 735.70, 696.81. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.12 (m, 20H, Ar-H), 4.89 (d, *J* = 12.0 Hz, 1H, -$CH_2^{Bn,a}$), 4.84 (d, *J* = 10.9 Hz, 1H, -$CH_2^{Bn,b}$), 4.66 (d, *J* = 10.9 Hz, 1H, -$CH_2^{Bn,b}$), 4.63 (s, 2H, -$CH_2^{Bn,c}$), 4.58 (d, *J* = 12.0 Hz, 1H, -$CH_2^{Bn,a}$), 4.53 (s, 2H, -$CH_2^{Bn,d}$), 4.39 (d, *J* = 7.7 Hz, 1H, H-1), 3.94 (dd, $J_{3,4}$ = 3.4, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.80 – 3.60 (m, 3H, H-2, H-6a, H-6b), 3.49 (td, $J_{5,6a}$ = $J_{5,6b}$ = 5.9, $J_{4,5}$ = 1.1 Hz, 1H, H-5), 3.41 (dd, $J_{2,3}$ = 9.4, $J_{3,4}$ = 3.4 Hz, 1H, H-3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.54, 138.03, 137.89, 137.51, 128.50 (2C), 128.48 (2C), 128.38 (2C), 128.33 (2C), 128.31 (2C), 128.18 (2C), 127.96 (2C), 127.93, 127.87 (2C), 127.81 (3C), 127.72, 127.64, 102.58, 80.66, 79.00, 75.28, 73.76, 73.26, 72.49, 70.93, 69.26, 66.95. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{36}O_6Na$: 563.2410; Found 563.2415.

Benzyl 3-*O*-acetyl-2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-3-*O*-acetyl-2-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (114)

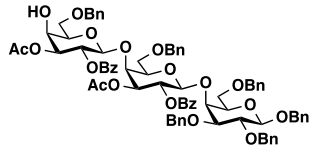


A mixture of **113** (300 mg; 0.55 mmol) and **106** (635 mg; 0.72 mmol) was dried azeotropically with toluene (2x10 mL) and subjected to vacuum over night. The mixture was then dissolved in dry CH_2Cl_2 (2.5 mL) and dry MeCN (2.5 mL) and cooled to -30 °C. NIS (165 mg; 0.74 mmol) and TESOTf (29 mg; 0.11 mmol) was added and the mixture was stirred at -30 °C until TLC showed full conversion of the donor (1 h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over

$MgSO_4$, filtered and concentrated, yielding a syrupy residue. The product was purified by flash chromatography (9:1 Tol/EtOAc). Yield: 529 mg (79 %) R_f 0.26 (9:1 TOl/EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.91 (m, 2H, Ar-H^{Bz}), 7.76 (s, 2H, Ar-H^{Bz}), 7.61 – 6.75 (m, 36H, Ar-H), 5.58 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.8 Hz, 1H, H-2), 5.49 (s, 1H, $H^{benzylidene}$),5.24 – 5.13 (m, 1H, H-2, H-3), 5.08 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.0 Hz, 1H, H-3) 4.89 (d, $J_{1,2}$ = 7.8 Hz, 1H), 4.77 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.76 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.57 – 4.40 (m, 7H, 3.5xCH_2^{Bn}), 4.35 (d, J_{CH2} = 12.1 Hz, 1H, 0.5xCH_2^{Bn}), 4.34 (d, $J_{3,4}$ = 3.7 Hz, 1H, H-1),4.24 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 4.22 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 4.21 (d, J_{CH2} = 10.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.09 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.6 Hz, 1H, H-6a), 3.99 – 3.91 (m, 2H, H-6b, H-4), 3.83 (dd, $J_{6a,6b}$ = 9.4, $J_{5,6a}$ = 6.6 Hz, 1H, H-6a), 3.67 (dd, $J_{6a,6b}$ = 10.1, $J_{5,6b}$ = 5.7 Hz, 1H), 3.64 – 3.53 (m, 3H, H-4, H-6), 3.59 (s, 1H, H-5), 3.46 (dd, $J_{6a,6b}$ = 9.4, $J_{5,6b}$ = 5.2 Hz, 1H, H-6b), 3.43 (s, 1H, H-5), 3.37 (t, $J_{5,6a}$ = $J_{5,6b}$ = 5.8 Hz, 1H, H-5), 3.28 – 3.14 (m, 3H, H-2, H-3, H-6a), 1.98 (s, 3H, CH_3^{Ac}), 1.72 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.12, 170.39, 165.66, 164.21, 138.85, 138.72, 138.59, 138.57, 138.01, 137.84, 132.90, 132.66, 130.25-126.47(40C), 102.42, 101.67, 101.45, 101.13, 81.65, 79.45, 74.75, 73.77, 73.71, 73.68, 73.44, 73.32, 73.30, 73.19, 72.01, 70.51, 70.41, 70.02, 69.70, 68.85, 68.75, 66.57, 21.07, 20.75. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{20}H_{26}NaO_7$ 1357.4984; Found 1357.4984.

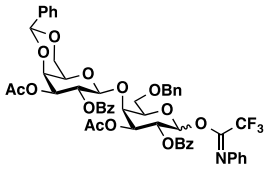
Benzyl 3-*O*-acetyl-2-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3-*O*-acetyl-2-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (115)



$NaCNBH_3$ (705 mg; 11.2 mmol) was added to a solution of **114** (500 mg; 0.37 mmol) in dry THF (15 mL). The mixture was stirred at 22 °C while HCl in Et_2O (2M) was added drop wise until gas development ceased and the mixture remained acidic (pH 3-4). The reaction mixture was concentrated to approx. 5 ml, diluted with CH_2Cl_2 (50 mL) and neutralized with sat. aq. $NaHCO_3$ (50 mL). The combined aqueous phase was extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were washed with water (100 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (6:1 Tol/EtOAc) to afford **115** as a colorless crystalline powder. Yield: 389 mg (78%) R_f 0.30 (6:1 Tol/EtOAc)

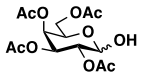
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 7.97 (m, 2H, Ar-H^{Bz}), 7.91 – 7.70 (m, 2H, Ar-H^{Bz}), 7.44 – 7.01 (m, 36H, Ar-H), 5.48 (dd, $J_{2,3}$ = 9.5, $J_{1,2}$ = 7.4 Hz, 1H, H-1), 5.28 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 5.13 (dd, $J_{2,3}$ = 9.5, $J_{3,4}$ = 3.5 Hz, 1H), 5.07 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.89 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.77 (d, J_{CH2} = 12.3 Hz, 1H, 0.5xCH_2^{Bn}), 4.74 (d, $J_{1,2}$ = 7.4 Hz, 1H, H-1), 4.55 – 4.31 (m, 9H, 4.5xCH_2^{Bn}), 4.25 – 4.11 (m, 4H, H-1^1, 2xH-4, 0.5xCH_2^{Bn}), 3.94 (d, $J_{3,4}$ = 2.2 Hz, 1H, H-4), 3.79 – 3.45 (m, 9H, 0.5xCH_2^{Bn}, 2xH-5, 3xH-6), 3.37 (t, $J_{5,6a}$ = $J_{5,6b}$ = 5.8 Hz, 1H, H-5), 3.24 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 2.6 Hz, 1H, H-3^1), 3.19 (dd, $J_{2,3}$ = 9.7, $J_{1,2}$ = 7.1 Hz, 1H, H-2^1), 2.67 (d, $J_{4,OH}$ = 4.9 Hz, 1H, OH), 2.01 (s, 3H, CH_3^{Ac}), 1.66 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (101 MHz, CDCl3) δ 170.53, 170.45, 165.75, 164.38, 138.87, 138.82, 138.56, 138.45, 137.97, 137.62, 133.01, 132.73, 130.17-127.40(40C), 102.39, 101.73, 101.54, 81.61, 79.49, 74.76, 74.24, 73.84, 73.69, 73.68, 73.60, 73.42, 73.33, 73.33, 73.31, 73.10, 70.59, 70.40, 70.38, 69.70, 69.26, 69.10, 67.80, 21.04, 20.65. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{78}H_{80}NaO_{20}$ 1359.51406; Found 1359.51406.

3-*O*-acetyl-2-*O*-benzoyl-4,6-*O*-benzylidene-D-galactopyranose (116)



106 (1.2 g; 1.36 mmol) was dissolved in CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C. Br_2 (0.26 g; 1.63 mmol) was added drop wise to the solution until the solution remained red. The reaction mixture was transferred to a flask containing a solution of TBAB (0.88 g; 2.72 mmol) and H_2O (0.37 g; 20.43 mmol) in MeCN (30 mL). The reaction mixture was heated to 55 °C and stirred at this temperature for 4 h. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (2x100 mL). The combined organic phases were dried over $MgSO_4$, concentrated and filtered through a plug of silica. The resulting yellow oil was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Cs_2CO_3 (0.89 g; 2.72 mmol) and PTFAICl (0.56 g; 2.72 mmol) were added. The ice bath was removed and the reaction mixture was stirred at 22 °C for 14 h. The reaction mixture was filtered through a plug of celite, concentrated and purified by flash chromatography (9:1) to afford **111** Yield: 508 mg (38%)

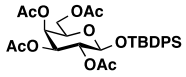
2,3,4,6-O-tetraacetyl-D-galactopyranose (117)[363]



Galactose pentaacetate (70.0 g, 179.36 mmol) was dissolved in anhydrous DMF (300 mL) at 55°C, hydrazine acetate (18.5 g, 200.91 mmol) was added and the mixture was stirred at 55°C for 20 min. After cooling, 50% sat. aq. $NaHCO_3$ (1000 mL) was added and the suspension was extracted with EtOAc (4 x 200 mL). The combined organic phase was washed with sat. aq. $NaHCO_3$ (400 mL) and H_2O (400 mL), evaporated on celite and purified by dry column vacuum chromatography (4.5 x 5.5 cm) on silica gel eluting with a gradient of 0-100% EtOAc in hexane (v/v) to give the hemiacetal **117**. Yield 57.7 g (92%) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.50 (d, $J_{1,2}$ = 3.6 Hz, 1H, H-1α), 5.47 (d, $J_{2,3}$ =10.7 Hz, $J_{1,2}$ =3.6 Hz, 1H, H-2), 5.40 (d, $J_{3,4}$ =3.3 Hz,1H, H-4),5.15 (dd, $J_{2,3}$ =10.7 Hz, $J_{3,4}$ =3.3Hz, 1H, H-3), 4.48 (t, $J_{5,6a}$ = 6.6 Hz, 1H, H-5), 4.38 (s, 1H, -OH), 4.11 (dd, $J_{5,6b}$ = 1.8 Hz, 1H, Gal H-6b), 4.09 (m, 1H, H-6a), 2.15 (s, 3H, CH_3^{Ac}), 2.10 (s, 3H, CH_3^{Ac}), 2.05 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.5, 170.4, 170.2, 170.0, 90.5, 68.4, 68.2, 67.2, 65.9, 61.7, 20.7, 20.54, 20.54, 20.54.

***tert*-butyldiphenylsilyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (118a)**

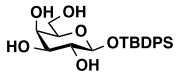


117 (55.0 g; 157.9 mmol) was dissolved in DMF (250 mL) and cooled to 0 °C. To the solution were added *tert*-butyl diphenylsilyl chloride (51.3 mL; 197.4 mmol) and imidazole (26.9 g; 394.8 mmol). The reaction mixture was stirred at 0 °C in 1h and then at 22 °C for 18h. The mixture was diluted with Et_2O (500 mL) and washed with water (4 x 500 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (9:1 Tol/EtOAc) to give **118a** as a white solid. R_f 0.65 (2:1 Tol/EtOAc). Yield: 85.3 g (92%).

$[\alpha]_D^{20}$= 2.1° (c 1.0, $CDCl_3$) **IR** (neat, cm^{-1}): 3073.45, 3048.95, 2958.82, 2934.48, 2892.20, 2859.91, 1749.51, 1473.24, 1428.33, 1368.22, 1219.93, 1180.92, 1159.52, 1113.61, 1080.42, 1056.83, 813.78

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 2H, Ar-H), 7.59 – 7.53 (m, 2H, Ar-H), 7.41 – 7.25 (m, 6H, Ar-H), 5.29 – 5.19 (m, 2H, H-3, H-4), 4.79 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.5 Hz, 1H, H-3), 4.55 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 3.93 (m, 2H, H-6a, H-6b), 3.55 (dt, $J_{5,6a}$ = $J_{5,6b}$ = 6.6, $J_{4,5}$ = 1.2 Hz, 1H, H-5), 2.10 (s, 3H, CH_3^{Ac}), 1.89 (s, 3H, CH_3^{Ac}), 1.88 – 1.85 (m, 6H, 2xCH_3^{Ac}), 1.00 (s, 9H, 3xCH_3^{TBDPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.49, 170.45, 170.30, 169.61, 136.03 (2C), 135.81 (2C), 132.77, 132.76, 130.10, 130.06, 127.78 (2C), 127.60 (2C), 96.14, 71.07, 70.82, 70.74, 67.37, 61.50, 26.76 (3C), 20.94, 20.87, 20.71 (2C), 19.21. **HRMS** (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{30}H_{38}NaO_{10}Si$ 609.2132; Found 609.2101.

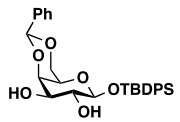
***tert*-butyldiphenylsilyl β-D-galactopyranoside (118)**



To a solution of **118a** (80.0 g; 136.35 mmol) in MeOH (200 mL) at -20 °C was added a freshly prepared 0.02M NaOMe solution in methanol (200 mL). The reaction mixture was stirred at -20 °C for 12h, quenched with Amberlite 120-H^+ ion-exchange resin, filtered and concentrated. The residue was purified by flash chromatography (1:1 Tol/EtOAc) to give **118** as an oil. R_f 0.06 (2:1 Tol/EtOAc). Yield: 50.7 g (79%)

$[\alpha]_D^{20}$= 12.9° (c 1.0, $CDCl_3$) **IR** (neat, cm^{-1}): 3384.00, 3072.66, 3049.46, 2955.08, 2931.95, 2892.28, 2858.60, 1472.39, 1427.48, 1392.47, 1363.05, 1172.10, 1112.17, 1074.35, 909.86, 823.43 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (m, 4H, Ar-H), 7.41 – 7.20 (m, 6H, Ar-H), 4.37 (d, $J_{1,2}$ = 7.4 Hz, 1H, H-1), 4.17 (d, $J_{3,OH}$ = 5.6 Hz, 1H, 3-OH), 3.85 (d, $J_{4,OH}$ = 4.5 Hz, 1H, 4-OH), 3.79 – 3.72 (m, 1H, H-4), 3.62 (ddd, $J_{2,3}$ = 9.4, $J_{1,2}$ = 7.4, $J_{2,OH}$ = 3.4 Hz, 1H, H-2), 3.56 – 3.40 (m, 3H, H-6a, H-6b, 2-OH), 3.31 (ddd, $J_{2,3}$ = 9.4, $J_{3,OH}$ = 5.6, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 3.01 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.0 Hz, 1H), 2.43 – 2.34 (m, 1H, 6-OH), 0.99 (s, 9H, 3xCH_3^{TBDPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.85 (2C), 135.80 (2C), 133.36, 132.92, 129.97, 129.94, 127.73 (2C), 127.55 (2C), 97.98, 74.19, 73.44, 73.38, 69.03, 61.53, 26.89 (3C), 19.18.

***tert*-butyldiphenylsilyl 4,6-*O*-benzylidene-β-D-galactopyranoside (119a)**

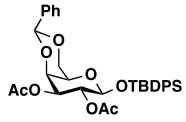


To a solution of $PhCH(OMe)_2$ (15 mL, 96.76 mmol) and camphorsulphonic acid (500 mg, 2.15 mmol) in MeCN (500 mL) was added **118** (30 g, 71.67 mmol). The flask was equipped with a distillation unit and the mixture was heated to reflux for 1h. In this period approximately 200 mL of MeCN-MeOH was distilled off. The distillation unit was then replaced with a condenser and the reaction mixture was heated to reflux until TLC showed completion (2h). The reaction mixture was concentrated and the product was purified by flash chromatography (4:1 Tol/EtOAc) to afford **119a** as a white crystalline powder. R_f 0.10 (9:1 Tol/EtOAc). Yield: 25.5 g (70%).

$[\alpha]_D^{20}$= -23.5° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3424.80, 3070.70, 3048.23, 2958.52, 2931.20, 2892.56, 2857.98, 1472.60, 1458.97, 1427.57, 1400.27, 1364.62, 1213.19, 1168.51, 1088.75, 1049.80, 997.59, 907.80, 822.55, 803.59. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 2H, Ar-H), 7.68 – 7.63 (m, 2H, Ar-H), 7.47 – 7.40 (m, 2H, Ar-H), 7.39

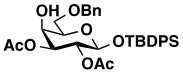
– 7.24 (m, 9H, Ar-H), 5.40 (s, 1H, $CH^{benzylidene}$), 4.40 (d, $J_{1,2}$ = 7.4 Hz, 1H, H-1), 3.99 (dd, $J_{3,4}$ = 3.9, $J_{4,5}$ = 1.1 Hz, 1H, H-4), 3.96 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6a}$ =1.5 Hz, 1H, H-6a), 3.81 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$ = 1.9 Hz, 1H, H-6b), 3.74 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 7.4 Hz, 1H, H-2), 3.51 – 3.39 (m, 1H, H-3), 2.63 – 2.31 (m, 2H, 2xOH), 1.05 (s, 9H, $3xCH_3^{TBDPS}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.79, 136.02 (2C), 135.78 (2C), 133.33, 133.31, 129.81, 129.72, 129.28, 128.32 (2C), 127.62 (2C), 127.40 (2C), 126.47 (2C), 101.30, 97.60, 75.29, 73.86, 72.58, 68.95, 66.46, 27.01, 19.34 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{34}NaO_6Si$ 529.2022; Found 529.2017.

tert-butyldiphenylsilyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-galactopyranoside (119)



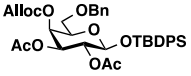
119a (20 g ; 39.47 mmol) was dissolved in CH_2Cl_2 (400 mL). Et_3N (16.5 mL; 118.42 mmol), DMAP (96 mg; 0.79 mmol) and acetic anhydride (9.31 mL; 98.69 mmol) was added to the solution and the reaction mixture was stirred until TLC revealed full conversion (3 h). The reaction was quenched with MeOH (10 mL), diluted with DCM (200 mL), washed with water (2x200 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (15:1 Tol/EtOAc). R_f 0.44 (9:1 Tol/EtOAc). Yield: 21.89 g (94%)
$[\alpha]_D^{20}$ = 40.0° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3071.67, 3047.62, 2959.11, 2932.86, 2893.38, 2858.91, 1745.50, 1459.30, 1428.07, 1404.12, 1368.68, 1242.29, 1221.57, 1174.02, 1096.33, 1063.57, 1044.37, 1004.22, 917.75, 823.00, 802.10, 738.23, 700.78. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.65 (m, 2H, H^{TBDPS}), 7.63 – 7.55 (m, 2H, H^{TBDPS}), 7.53 – 7.43 (m, 2H, H^{TBDPS}), 7.42 – 7.21 (m, 9H, H^{TBDPS}, Ar-H), 5.43 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 7.6 Hz, 1H, H-2), 5.36 (s, 1H, $-CH^{benzylidene}$), 4.72 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.7 Hz, 1H, H-3), 4.57 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1), 4.18 (dd, $J_{3,4}$ = 3.8, $J_{4,5}$ = 1.1 Hz, 1H, H-4), 3.97 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6a}$ = 1.5 Hz, 1H, H-6a), 3.82 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$ =1.8 Hz, 1H), 3.05 (m, 1H, H-5), 1.97 (s, 3H, $-CH_3^{Ac}$), 1.91 (s, 3H, $-CH_3^{Ac}$), 1.01 (s, 9H, $3xCH_3^{TBDPS}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.87, 169.34, 137.73, 136.07 (2C), 135.77 (2C), 133.10, 132.97, 129.82, 129.76, 129.10, 128.24 (2C), 127.55 (2C), 127.37 (2C), 126.48 (2C), 101.01, 95.93, 73.39, 72.09, 70.59, 68.76, 66.19, 26.74 (3C), 20.93, 20.91, 19.16. **HRMS** (ESI-TOF) m/z:$[M + Na]^+$ Calcd for $C_{33}H_{38}NaO_8Si$: 613.2234; Found 613.2244.

tert-butyldiphenylsilyl 2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranoside (120)



$NaCNBH_3$ (5.4 g; 86.33 mmol) and 3Å MS (3 g) were added to a solution of **119** (6.0 g; 10.15 mmol) in dry THF (100 mL). The mixture was stirred at 22 °C while TfOH (7.7 mL; 87.35 mmol) was added drop wise until gas development ceased and the mixture remained acidic (pH 3-4). The reaction mixture was concentrated to app. 10 ml, diluted with CH_2Cl_2 (200 mL) and neutralized with sat. aq. $NaHCO_3$ (200 mL). The aqueous phase was extracted with CH_2Cl_2 (3x100 mL). The combined organic phases were washed with water (500 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (8:1 Tol/EtOAc) to afford **120** as a colorless crystalline powder. R_f 0.13 (9:1 Tol/EtOAc). Yield: 4.8 (79%)
$[\alpha]_D^{20}$ = 6.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3469.06, 3071.41, 2932.65, 2858.98, 1748.28, 1453.65, 1367.94, 1243.32, 1223.88, 1178.04, 1112.32, 1060.21. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H, Ar-H), 7.60 – 7.54 (m, 2H, Ar-H), 7.38 – 7.10 (m, 11H, Ar-H), 5.31 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.7 Hz, 1H, H-2), 4.71 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.2 Hz, 1H, H-3), 4.54 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.40 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 4.35 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 3.98 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4), 3.56 (dd, $J_{6a,6b}$ = 10.2, $J_{5,6a}$ =5.4 Hz, 1H, H-6a), 3.48 (dd, $J_{6a,6b}$ = 10.2, $J_{5,6b}$ =5.0 Hz, 1H, H-6b), 3.29 (dd, $J_{5,6a}$ = 5.4, $J_{5,6b}$ = 5.0 Hz, 1H, H-5), 2.00 (s, 3H, CH_3^{Ac}), 1.87 (s, 3H, CH_3^{Ac}), 0.99 (s, 9H, $3xCH_3^{TBDPS}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.46, 169.73, 137.74, 136.10 (2C), 135.91 (2C), 133.01, 132.86, 130.02, 129.94, 128.55 (2C), 127.91, 127.80 (2C), 127.72 (2C), 127.54 (2C), 96.29, 73.88, 73.60, 73.09, 71.43, 69.28, 68.38, 26.78 (3C), 21.03, 20.93, 19.19. **HRMS** (ESI-TOF) m/z: $[M + NH_4]_+$ Calcd for $C_{33}H_{36}NaO_8$ 583.2308 Found 583.2303

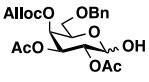
tert-butyldiphenylsilyl 2,3-di-*O*-acetyl-4-*O*-allyloxycarbonyl-6-*O*-benzyl-β-D-galactopyranoside (121)



TMEDA (1.21 mL; 8.1 mmol) and allyl chloroformate (1.57 mL; 14.8 mmol) were added to a solution of **120** (8.0 g; 13.5 mmol) in anhydrous CH_2Cl_2 (135 mL) at 0 °C. After 1h the mixture was diluted with CH_2Cl_2 (150 mL), washed with water (300 mL), dried over $MgSO_4$ and concentrated. The product **121** was purified by flash chromatography (19:1 Tol/EtOAc). R_f 0.47 (9:1 Tol/EtOAc). Yield: 8.3 g (91%)
$[\alpha]_D^{20}$ = -7.2° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}):3072.10, 3033.21, 2933.81, 2859.80, 1752.16, 1428.03, 1367.05, 1273.67, 1258.93, 1226.53, 1179.40, 1112.13, 1079.58, 1060.21. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 – 7.48 (m, 4H, Ar-H), 7.40 – 7.07 (m, 11H, Ar-H), 5.86 (ddt, J_{trans} = 17.2, J_{cis} = 10.5, J_{CH2} = 5.7 Hz, 1H, -C*H*=CH_2), 5.29 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 7.7 Hz, 1H, H-2), 5.32 (dd, J_{trans} = 17.2, J_{gem} = 1.5 Hz, 1H, trans-CH_2=CH-), 5.21 (dd, J = 10.5, 1.3 Hz, 1H, cis-CH_2=CH-), 5.12 (dd, $J_{3,4}$ = 3.4, $J_{4,5}$ = 0.9 Hz, 1H, H-4), 4.81 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 4.61 –

4.54 (m, 1H, 0.5xCH_2^{Alloc}), 4.57 – 4.46 (m, 1H, 0.5xCH_2^{Alloc}), 4.51 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.33 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.28 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 3.48 – 3.42 (m, 2H, H-5, H-6a), 3.39 – 3.32 (m, 1H, H-6b), 1.90 (s, 3H, -CH_3^{Ac}), 1.86 (s, 3H, -CH_3^{Ac}), 0.98 (s, 9H, -3xCH_3^{TBDPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.33, 169.54, 154.87, 137.82, 136.13 (2C), 135.90 (2C), 132.83, 132.75, 131.48, 130.06, 129.97, 128.49 (2C), 127.83, 127.81 (2C), 127.75 (2C), 127.54 (2C), 119.18, 96.15, 73.67, 71.98, 71.82, 71.32, 70.99, 68.91, 67.66, 26.76 (3C), 20.96, 20.82, 19.20. **HRMS** (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{37}H_{48}NO_{10}Si$ 694.3048 Found 694.3044

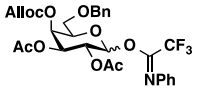
2,3-di-*O*-acetyl-4-*O*-allyloxycarbonyl-6-*O*-benzyl-D-galactopyranose (122a)



To a solution of **121** (7.8 g; 11.5 mmol) in THF (100 mL) was added AcOH (3.3 ml; 28.81 mmol) and TBAF (1M in THF; 25.4 mL; 25.4 mmol). The reaction mixture was stirred at 22 °C until TLC showed full conversion (8 h). The reaction mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash chromatography (4:1 Tol/EtOAc) to give **122a** as a white crystalline solid. R_f 0.42 (2:1 Tol /EtOAc). Yield: 4.6g (91%)

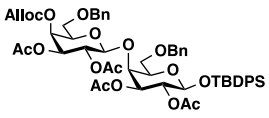
$[\alpha]_D^{20}$= -5.9° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3072.05, 3052.10, 3031.28, 2934.27, 2860.02, 1752.87, 1472.98, 1454.24, 1428.02, 1367.20, 1274.26,1259.02, 1227.33, 1179.31, 1112.52, 1079.65, 1060.18, 998.37, 955.10. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.12 (m, 10H, Ar-H), 5.92 – 5.77 (m, 2H, C*H*=CH_2α, C*H*=CH_2β), 5.42 (d, $J_{3,4}$ = 3.6 Hz, 1H, H-1α), 5.35 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4β), 5.33 – 5.07 (m, 8H, CH_2=CHα, CH_2=CHβ, H-2α, H-2β, H-3β, H-4α), 5.12 (dd, $J_{2,3}$ = 10.8, $J_{1,2}$ = 3.6 Hz, 1H, H-3α), 4.63 – 4.30 (m, 6H, H-1β, CH_2^{Bn}, CH_2^{AcCl}, H-5α), 3.86 – 3.76 (m, 1H, H-5β), 3.67 – 3.37 (m, 4H, H-6α, H-6β), 2.10 (s, 3H, CH_3^{Ac}β), 2.02 (s, 3H, CH_3^{Ac}β), 2.01 (s, 3H, CH_3^{Ac}α), 1.94 (s, 1H), 1.93 (s, 3H, CH_3^{Ac}α). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.28, 170.40, 170.20, 170.18, 154.82, 154.73, 137.59, 137.55, 131.42, 131.37, 128.60, 128.01, 127.97, 119.18, 119.11, 96.13, 90.72, 73.76, 73.68, 72.90, 72.26, 71.59, 71.30, 70.68, 68.97, 68.89, 68.41, 68.37, 67.67, 67.57, 67.35, 31.07, 20.96, 20.88, 20.79. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{26}NaO_{10}$ 461.1424 Found 461.1425.

2,3-*O*-diacetyl-4-*O*-allyloxycarbonyl-6-*O*-benzyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (122)



122a (4.4 g; 10.03 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. Cs_2CO_3 (6.5 g; 20.07 mmol) was added followed by *N*-phenyl trifluoroacetimidoyl chloride (4.2 g; 20.07 mmol). The ice bath was removed and the reaction mixture was stirred at 22 °C until TLC showed full conversion (8 h). The reaction mixture was filtered through a plug of celite, concentrated and purified by flash chromatography (9:1) to afford **122** as a white crystalline product. R_f 0.51 (9:1 Tol/EtOAc). Yield: 4.64 g (76%)

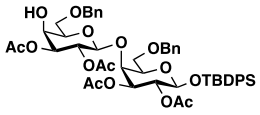
***tert*-butyldiphenylsilyl 2,3-di-*O*-acetyl-4-*O*-allyloxycarbonyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranoside (123)**



To a 250 mL flame-dried flask was added **120** (3.66 g, 6.17 mmol) and the **122** (5.46 g, 8.95 mmol). The mixture was co-evaporated with toluene (2x100 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (100 mL) and cooled to -40 °C. TMSOTf (0.23 mL; 1.54 mmol) was added and the reaction mixture was stirred at -40 °C for 4h. Et_3N (2 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (9:1 Tol/EtOAc) to give **123**. R_f 0.17 (9:1 Tol/EtOAc) Yield: 5.13 g (82%)

$[\alpha]_D^{20}$= -6.2° (c 1.0, $CDCl_3$) **IR** (neat, cm^{-1}):3070.55, 3030.83, 2933.04, 2859.78, 1747.93, 1427.83, 1367.61, 1219.07, 1175.33, 1104.45, 1063.84, 911.40 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.9, 1.4 Hz, 2H, Ar-H), 7.55 (dd, *J* = 7.9, 1.2 Hz, 2H, Ar-H), 7.40 – 7.00 (m, 16H, Ar-H), 5.88 (ddd, J_{trans} = 16.2, J_{cis} = 10.9, J_{CH2} = 5.7 Hz, 1H, C*H*=CH_2), 5.33 (dd, J_{trans} = 17.2, J_{CH2} = 1.3 Hz, 1H, CH_2=CH_{trans}), 5.26 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 7.9 Hz, 1H, H-2^2), 5.23 (dd, J_{cis} = 10.5, J_{CH2} = 1.1 Hz, 1H, CH_2=CH_{cis}), 5.21 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4^2), 5.11 (dd, $J_{2,3}$ = 10.3, $J_{2,3}$ = 7.6 Hz, 1H, H-2^1), 4.94 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.4 Hz, 1H, H-3^2), 4.71 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.1 Hz, 1H, H-3^1), 4.48 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1^1), 4.41 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^2), 4.34 – 4.21 (m, 4H), 3.95 (d, *J* = 3.1 Hz, 1H, H-4^1), 3.65 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.7 Hz, 1H, H-5^2), 3.60 (dd, $J_{6a,6b}$ = 10.2, $J_{5,6a}$ =5.2 Hz, 1H, H-6^1), 3.46 – 3.29 (m, 4H, H-5^1, 1.5xH-6), 2.15 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}), 1.95 (s, 3H, CH_3^{Ac}), 1.83 (s, 3H, CH_3^{Ac}), 0.98 (s, 9H, 3xCH_3^{TBDPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.45, 170.27, 169.76, 169.54, 154.84, 138.54, 137.61, 136.15 (2C), 135.90 (2C), 132.99, 132.91, 131.44, 129.90, 129.84, 128.56 (2C), 128.36 (2C), 127.94, 127.74 (2C), 127.68 (2C), 127.52, 119.26, 101.74, 95.87, 73.98, 73.65, 73.60, 73.39, 71.81, 71.67, 71.32, 71.28, 69.38, 68.94, 68.89, 67.27, 26.78 (3C), 20.93, 20.91, 20.85, 20.81, 19.18. **HRMS** (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{54}H_{64}NaO_{17}Si$ 1035.3811; Found 1035.3830.

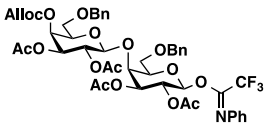
***tert*-butyldiphenylsilyl 2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranoside (124)**



To a solution of **123** (2.0 g; 1.97 mmol) in THF (100 mL) at 0 °C was added morpholine (208 mg; 1.21 mmol), PPh_3 (818 mg; 1.58 mmol) and $Pd(OAc)_2$ (22 mg; 0.10 mmol). The solution was stirred at 22 °C for 2 h and then concentrated. The product was purified by flash chromatography (3:1 Tol/EtOAc) to give **124** as a white crystal-line solid. R_f 0.45 (2:1 Tol/EtOAc). Yield: 1.6 g (87%)

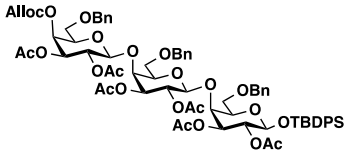
$[\alpha]_D^{20}$= -5.3° (c 1.0, $CDCl_3$) **IR** (neat, cm^{-1}):3486.42, 3031.65, 2932.77, 2859.46, 1746.03, 1367.54, 1242.00, 1220.52, 1104.60, 1054.24. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.9, 1.3 Hz, 2H, Ar-H), 7.55 (dd, *J* = 8.0, 1.2 Hz, 2H, Ar-H), 7.35 – 7.03 (m, 16H), 5.27 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 7.9 Hz, 1H, H-2^2), 5.13 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.6 Hz, 1H, H-2^1), 4.85 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.1 Hz, 1H, H-3^2), 4.71 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.1 Hz, 1H, H-3^1), 4.49 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1^1), 4.41 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^2), 4.35 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.31 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 4.25 (s, 2H, CH_2^{Bn}), 4.06 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4^2), 3.99 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4^1), 3.64 (dd, $J_{6a,6b}$ = 10.2, $J_{5,6a}$ = 5.2 Hz, 1H, H-6a), 3.60 (dd, $J_{6a,6b}$ = 8.8, $J_{5,6a}$ = 5.1 Hz, 1H), 3.53 – 3.39 (m, 3H, H-6b, H-6b, H-5), 3.34 (t, $J_{5,6a}$ = $J_{5,6b}$ = 5.6 Hz, 1H, H-5), 2.14 (s, 3H, CH_3^{Ac}), 2.05 (s, 3H, CH_3^{Ac}), 2.00 (s, 3H, CH_3^{Ac}), 1.84 (s, 3H, CH_3^{Ac}), 0.97 (s, 9H, 3xCH_3^{TBDPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.51, 170.35, 170.01, 169.52, 138.52, 137.56, 136.14 (2C), 135.89 (2C), 132.97, 132.93, 129.90, 129.83, 128.62 (2C), 128.36 (2C), 128.03, 127.73 (2C), 127.67 (2C), 127.53, 127.50 (4C), 101.83, 95.89, 73.99, 73.78, 73.69, 73.60, 73.50, 73.35, 72.95, 71.64, 69.42, 69.34, 69.01, 67.88, 26.77 (3C), 21.06, 20.94, 20.91, 20.81, 19.18. **HRMS** (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{50}H_{64}NO_{15}Si$ 946.4045 Found 946.4039

(2,3-di-*O*-acetyl-4-*O*-allyloxycarbonyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (125)



In a plastic container, compound **123** (2.1 g; 2.07 mmol) was dissolved in THF (20 mL) and the solution was cooled to 0 °C. HF·pyridine complex (5 mL) was added slowly while the temperature was maintained below 5 °C. The reaction was slowly heated to 22 °C and stirred at this temperature for 10 h. The solution was poured into sat. aq. $NaHCO_3$ (200 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified with a plug of silica to give a syrupy residue. Without further purification the hemiacetal was dissolved in CH_2Cl_2 (25 mL). Cs_2CO_3 (1.4 g; 4.14 mmol) was added followed by *N*-phenyl trifluoroacetimidoyl chloride (0.86 g; 4.14 mmol). The ice bath was removed and the reaction mixture was stirred at 22 °C until TLC showed full conversion (6 h). The reaction mixture was filtered through a plug of celite, concentrated and purified by flash chromatography (9:1) to afford **125** as a white crystalline product. Yield 1.33 g (68% over two steps).

***tert*-butyldiphenylsilyl 2,3-di-*O*-acetyl-4-*O*-allyloxycarbonyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)- 2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranoside (126)**

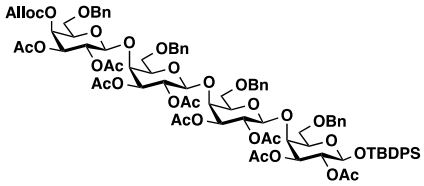


To a 50 mL flame-dried flask was added **124** (800 mg, 0.86 mmol) and **122** (709 mg, 1.16 mmol). The mixture was co-evaporated with toluene (2x25 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (20 mL) and cooled to -30 °C. TMSOTf (48 mg; 0.22 mmol) was added and the reaction mixture was stirred at -30 °C for 1h. Et_3N (0.5 mL) was added and the reaction mixture was concentrated. The crude compound **126** was purified by flash chromatography (3:1 Tol/EtOAc) to give **126.** R_f 0.44 (2:1 Tol/EtOAc). Yield: 928 g (80%).

$[\alpha]_D^{20}$= -22.5° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}):3030.77, 2933.30, 2860.01, 1747.84, 1367.65, 1218.43, 1095.87, 1058.26. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 2H, Ar-H), 7.58 – 7.50 (m, 2H, Ar-H), 7.39 – 6.97 (m, 21H), 5.85 (ddd, J_{trans} = 17.2, J_{cis} =10.9, J_{CH2} = 5.3 Hz, 1H, C*H*=CH_2), 5.31 (dd, J_{trans} = 17.2, J_{CH2} = 1.2 Hz, 1H, CH_2=CH_{trans}), 5.28 – 5.23 (m, 2H, H-2, H-4^3), 5.21 (dd, J_{cis} = 10.8, J_{CH2} = 0.5 Hz, 1H, CH_2=CH_{cis}), 5.12 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.5 Hz, 1H, H-2), 5.06 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.8 Hz, 1H, H-2), 4.98 (dd, $J_{2,3}$ = 10.6, $J_{3,4}$ = 3.3 Hz, 1H, H-3), 4.85 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 2.8 Hz, 1H, H-3), 4.71 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.59 (dd, J_{CH2} = 13.0, $J_{CH=CH2}$ = 5.8 Hz, 1H, CH_2^{Alloc}), 4.55 – 4.50 (m, 2H, CH_2^{Alloc}), 4.48 (d, $J_{1,2}$ = 7.9 Hz, 2H, H-1^1, H-1), 4.39 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.36 – 4.19 (m, 6H, 3xCH_2^{Bn}), 4.05 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 3.95 (d, $J_{3,4}$ = 2.8 Hz, 1H, H-4), 3.68 (t, *J* = 6.7 Hz, 1H, H-5), 3.64 – 3.26 (m, 8H, 2xH-5, 3xH-6), 2.19 (s, 3H, CH_3^{Ac}), 2.13 (s, 3H, CH_3^{Ac}), 2.04 (s, 3H, CH_3^{Ac}), 1.97 (s, 3H, CH_3^{Ac}), 1.96 (s, 3H, CH_3^{Ac}), 1.83 (s, 3H, CH_3^{Ac}), 0.98 (s, 9H, 3xCH_3^{TBDPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.41, 170.32, 170.16, 169.83, 169.80, 169.61, 154.84, 138.77, 138.33, 137.58, 136.16 (2C), 135.88 (2C), 133.11, 132.94, 131.38, 129.84, 129.82, 128.57 (2C), 128.46 (2C), 128.30 (2C), 127.96, 127.88 (2C), 127.74 (2C), 127.65 (2C), 127.49 (2C), 127.44 (2C), 127.37, 119.35, 101.50, 101.08, 95.76, 73.77, 73.61 (2C),

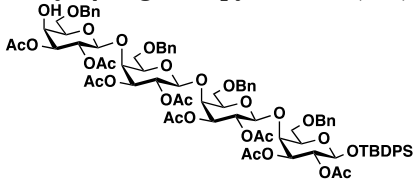
73.57 (2C), 73.50 (2C), 73.32 (2C), 73.17 (2C), 71.85, 71.77, 71.33, 71.14, 69.63, 69.51, 68.97 (2C), 68.82, 67.20, 26.80 (3C), 20.97, 20.90 (2C), 20.87, 20.84, 20.75, 19.19.

***tert*-butyldiphenylsilyl 2,3-di-*O*-acetyl-4-*O*-allyloxycarbonyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3- di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranoside (127)**



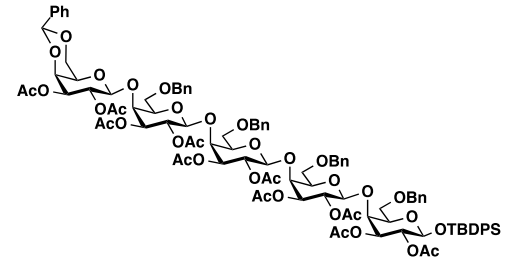
To a 50 mL flame-dried flask was added **124** (1.0 g, 1.08 mmol) and **125** (1.37 g, 1.45 mmol). The mixture was co-evaporated with toluene (2x25 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (25 mL) and cooled to -30 °C. TMSOTf (59 mg; 0.27 mmol) was added and the reaction mixture was stirred at -30 °C for 2 h. Et_3N (0.5 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (4:1 Tol/EtOAc) to give compound **127**. R_f 0.45 (2:1 Tol/EtOAc). Yield: 1.43 g (85%)
$[\alpha]_D^{20}$= 11.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}):3031.51, 2934.00, 2860.72, 1747.88, 1367.93, 1218.36, 1174.03, 1095.54, 1057.94. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (m, 2H, Ar-H), 7.59 – 7.50 (m, 2H, Ar-H), 7.39 – 7.07 (m, 26H, Ar-H), 5.83 (ddd, J_{trans} = 17.2, J_{cis} = 10.9, J_{CH2} = 5.3 Hz, 1H, C*H*=CH_2), 5.29 (dd, J_{trans} = 17.2, J_{CH2} = 1.4 Hz, 1H), 5.26 – 5.21 (m, 2H, H-4, H-2), 5.20 (dd, J_{cis} = 10.5, J_{CH2} = 1.1 Hz, 1H), 5.15 – 5.08 (m, 2H, H-2, H-2), 5.05 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.8 Hz, 1H, H-2), 4.97 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.4 Hz, 1H, H-3) 4.87 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.2 Hz, 1H, H-3), 4.86 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.70 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.1 Hz, 1H), 4.61 – 4.50 (m, 2H, CH_2^{Alloc}), 4.51 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.48 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1[1]), 4.44 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.41 – 4.15 (m, 9H, H-1, 4xCH_2^{Bn}), 4.08 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 4.07 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4), 3.93 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4), 3.72 – 3.52 (m, 4H, H-5, 1.5xH-6), 3.52 – 3.28 (m, 8H, 3xH-5, 2.5xH-6), 2.17 (s, 3H, CH_3^{Ac}), 2.12 (s, 3H, CH_3^{Ac}), 2.11 (s, 3H, CH_3^{Ac}), 2.05 (s, 3H, CH_3^{Ac}), 2.00 (s, 3H, CH_3^{Ac}), 1.97 (s, 3H, CH_3^{Ac}), 1.93 (s, 3H, CH_3^{Ac}), 1.82 (s, 3H, CH_3^{Ac}), 0.98 (s, 9H, CH_3^{TBDPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.40, 170.33, 170.19 (2C), 169.89, 169.83, 169.60, 169.58, 154.85, 138.85, 138.61, 138.36, 137.59, 136.17 (2C), 135.89 (2C), 133.11, 132.94, 131.39, 129.84, 129.79-127.35 (24C), 119.28, 101.71, 101.26, 100.61, 95.77, 73.90, 73.66, 73.61 (4C), 73.56 (2C), 73.50, 73.45 (2C), 73.39 (2C), 73.33 (2C), 71.95, 71.82 (2C), 71.31, 71.10, 69.71, 69.62, 69.57, 69.11, 68.95 (2C), 68.75, 67.18, 26.81 (3C), 20.99, 20.96, 20.91 (2C), 20.86, 20.84, 20.81, 20.76, 19.20.

***tert*-butyl diphenylsilyl 2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)- 2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl -β-D-galactopyranoside (128)**



To a solution of **127** (1.4 g; 0.83 mmol) in THF (50 mL) at 0 °C was added morpholine (87 mg; 1.0 mmol), PPh_3 (344 mg; 1.31 mmol) and $Pd(OAc)_2$ (9 mg; 0.04 mmol). The solution was stirred at 22 °C for 2 h and then concentrated. The product was purified by flash chromatography (2:1 Tol/EtOAc) to give **128** as a white crystalline solid. R_f 0.24 (2:1 Tol/EtOAc). Yield: 1.17 g (88%)

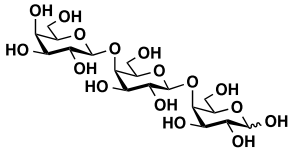
***tert*-butyl diphenylsilyl 2,3-*O*-diacetyl-4,6-*O*-benzylidene-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)- 2,3-*O*-diacetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)- 2,3-*O*-diacetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-*O*-diacetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3-*O*-diacetyl-6-*O*-benzyl -β-D-galactopyranoside (129)**



To a 10 mL flame-dried flask was added **128** (474 mg, 0.30 mmol) and **54** (197 mg, 0.44 mmol). The mixture was dried azeotropically with toluene (2x5 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (2.5 mL) and MeCN (2.5 mL), cooled to -30 °C, followed by addition of NIS (103 mg; 0.46 mmol) and TMSOTf (8 mg; 0.03 mmol). The reaction mixture was stirred at -20 °C until TLC revealed full conversion of the donor (3h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (2:1 toluene/EtOAc) to afford **129** as a white powder. R_f 0.17 (2:1 Tol/EtOAc). Yield: 396 mg (69%)
$[\alpha]_D^{20}$= 3.3° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}):3032.49, 2933.74, 2860.33, 1750.36, 1368.78, 1242.17, 1220.25, 1097.88, 1057.48. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 2H, Ar-H), 7.55 (m, 2H, Ar-H), 7.45 (m, 2H, Ar-H), 7.39 – 7.08 (m, 29H), 5.44 (s, 1H, $CH^{benzylidene}$), 5.35 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2[5]), 5.15 – 5.02 (m,

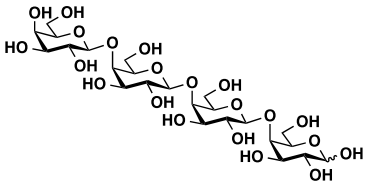
4H, 4xH-2), 4.92 – 4.81 (m, 4H, 4xH-3), 4.70 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.0 Hz, 1H, H-3[5]), 4.50 – 4.41 (m, 4H, 4xH-1), 4.39 – 4.24 (m, 9H, H-1, 4xCH_2^{Bn}), 4.16 (d, $J_{3,4}$ = 2.9 Hz, 1H, H-4), 4.09 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-4), 4.04 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4), 4.03 (d, $J_{6a,6b}$ = 11.3 Hz, 1H, H-6a), 3.92 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-4), 3.89 (d, $J_{6a,6b}$ = 11.3 Hz, 1H, H-6b), 3.72 (dd, $J_{6a,6b}$ = 9.3, $J_{5,6a}$ = 6.9 Hz, 1H, H-6a), 3.66 – 3.26 (m, 13H, H-4, 5xH-5, 3.5xH-6), 2.16 (s, 3H, CH_3^{Ac}), 2.11 (s, 3H, CH_3^{Ac}), 2.11 (s, 3H, CH_3^{Ac}), 2.04 (s, 3H, CH_3^{Ac}), 2.03 (s, 6H, 2xCH_3^{Ac}), 2.015 (s, 3H, CH_3^{Ac}), 2.01 (s, 3H, CH_3^{Ac}), 1.97 (s, 3H, CH_3^{Ac}), 1.81 (s, 3H, CH_3^{Ac}), 0.98 (s, 9H, 3xCH_3).. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.94, 170.33, 170.14, 170.09, 170.07, 169.80, 169.77, 169.53, 169.48, 169.36, 138.72, 138.55, 138.30, 138.27, 137.69, 136.07 (2C), 135.80 (2C), 133.00, 132.86, 129.72, 129.67, 129.04-126.25 (29C), 101.65, 101.16, 100.95, 100.82, 100.78, 95.66, 73.87, 73.67, 73.56, 73.45, 73.36, 73.29, 73.10, 73.00, 72.51, 72.00, 71.87, 71.70, 69.74, 69.54, 69.45, 69.19, 68.81, 68.59, 68.30, 66.37, 26.70 (3C), 20.95, 20.86 (3C), 20.80 (2C), 20.74, 20.70, 20.65 (2C), 19.08.

β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranose (130)



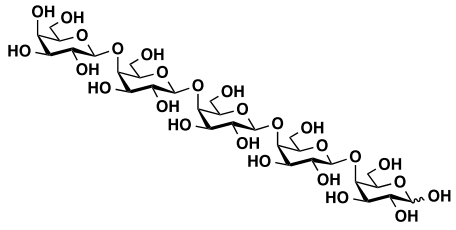
In a plastic container, compound **126** (900 mg; 0.67 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0 °C followed by slow addition of HF·pyridine complex (2 mL) while maintaining a temperature below 5 °C. The reaction was slowly heated to 22 °C and stirred at this temperature for 10 h. The solution was poured into sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (4:1 Tol/EtOAc). The product was dissolved in MeOH (12 mL) and THF (4 mL) and 10 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until full conversion was observed by TLC (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield colorless crystals. The product was next dissolved in MeOH (4 mL), THF (1 mL). 10% Pd/C (46 mg; 0.07 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred for 2 h, and then water (1 mL) was added. The reaction was stirred for 12 h, filtered through celite, and concentrated to give a white solid. Yield: 252 mg (75%)
^{1}H NMR (400 MHz, D_2O) δ 5.27 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1[1]α), 4.64 (d, $J_{1,2}$ = 8.0 Hz, 2H, H-1α, H-1β), 4.61 (d, $J_{1,2}$ = 7.9 Hz, 2H, H-1α, H-1β), 4.60 (d, $J_{1,2}$ = 7.6 Hz, H-1β), 4.23 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4[1]α), 4.17 (m, 5H, 5xH-4), 4.13 (dd, J = 7.2, 5.6 Hz, 1H), 3.99 – 3.53 (m, 29H). **^{13}C NMR** (101 MHz, D_2O) δ 104.39, 104.35, 104.24, 96.35, 92.27, 78.77, 77.80, 77.09, 77.07, 75.11, 74.40, 74.28, 73.25, 73.21, 72.70, 72.18, 71.84, 71.79, 71.33, 69.83, 69.67, 68.77, 68.58, 60.94, 60.87, 60.69, 60.50. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{32}NaO_{16}$ 527.1588 Found 527.1587

β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranose (131)



In a plastic container, compound **127** (600 mg; 0.36 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0 °C followed by slow addition of HF·pyridine complex (2 mL) while maintaining a temperature below 5 °C. The reaction was slowly heated to 22 °C and stirred at this temperature for 10 h. The solution was poured into sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (4:1 Tol/EtOAc). The product was dissolved in MeOH (8 mL) and THF (2 mL) and 8 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until full conversion was observed by TLC (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield colorless crystals. The product was next dissolved in MeOH (4 mL), THF (1 mL). 10% Pd/C (25 mg; 0.04 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred for 2 h, and then water (1 mL) was added. The reaction was stirred 12 h, filtered through celite, and concentrated to give a white solid. Yield: 165 mg (70%)
^{1}H NMR (400 MHz, D_2O) δ 5.17 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1α), 4.58 – 4.47 (m, 7H, 7xH-1), 4.13 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 4.08 (m, 7H, 7xH-4), 4.03 (dd, J = 7.2, 5.7 Hz, 1H, H-5), 3.89 – 3.42 (m, 39H). **^{13}C NMR** (101 MHz, D_2O) δ 104.38, 104.34, 104.29, 104.24, 96.35, 92.27, 78.80, 77.83, 77.55, 77.51, 77.07, 75.11, 74.47, 74.41, 74.27, 73.33, 73.28, 73.24, 73.19, 72.70, 72.19, 71.85, 71.79, 71.75, 71.32, 69.81, 69.66, 68.77, 68.57, 60.95, 60.85, 60.69, 60.67, 60.50. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{42}NaO_{21}$ 689.2116 Found 689.2111

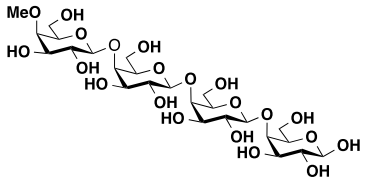
β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranose (132)



In a plastic container, compound **127** (400 mg; 0.36 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0 °C followed by slow addition of HF·pyridine complex (2 mL) while maintaining a temperature below 5 °C. The reaction was slowly heated to 22 °C and stirred at this temperature for 10 h. The solution was poured into sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (4:1 Tol/EtOAc). The product was dissolved in MeOH (4 mL) and THF (1 mL) and 4 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until full conversion was observed by TLC (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield colorless crystals. The product was dissolved in MeOH (4 mL), THF (1 mL). 10% Pd/C (25 mg; 0.04 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred for 2 h, and then water (1 mL) was added. The reaction was stirred for 12 h, filtered through celite, and concentrated to give a white solid. Yield: 117 mg (68%)

^{1}H NMR (400 MHz, D_2O) δ 5.18 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1α), 4.58 – 4.48 (m, 14H, H-1^{1}β-H-1^{5}β, H-1^{2}α-H-1^{5}α), 4.14 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 4.08 (m, 12H, 9xH-4), 4.04 (t, J = 6.5 Hz, 1H, H-5α), 3.90 – 3.43 (m, 49H). **^{13}C NMR** (101 MHz, D_2O) δ 104.34, 104.30, 104.24, 96.35, 92.27, 78.80, 77.82, 77.56, 77.53, 77.07, 75.12, 74.48, 74.46, 74.41, 74.28, 73.27, 73.24, 73.19, 72.71, 72.19, 71.80, 71.75, 71.32, 69.82, 69.66, 68.78, 68.58, 60.95, 60.86, 60.67, 60.50. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{52}NaO_{26}$ 851.2645Found 851.2642

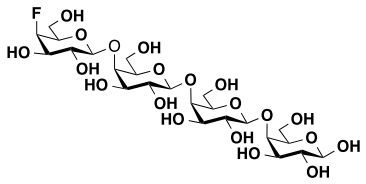
4-*O*-methyl-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranose (133)



159 (640 mg; 0.35 mmol) was dissolved in MeOH (10 mL) and THF (5 mL) and 10 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until full conversion was observed by TLC (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (2:1 Toluene/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (10 mL), THF (2 mL). 20% $Pd(OH)_2$/C (122 mg; 0.17 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 24h and then filtered through celite, and concentrated to give a white solid. Purified by reverse phase chromatography to give **133** as a white solid. Yield: 211 mg (89%)

^{1}H NMR (400 MHz, D_2O) δ 5.18 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1a), 4.55 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1b), 4.54 (d, $J_{1,2}$ = 7.7 Hz, 2H), 4.52 (d, $J_{1,2}$ = 8.3 Hz, 2H), 4.47 (d, $J_{1,2}$ = 7.9 Hz, 2H), 4.42 (d, $J_{1,2}$ = 7.9 Hz, 1H), 4.21 – 3.99 (m, 4H), 3.92 – 3.43 (m, 25H), 3.42 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, D_2O) δ 104.38, 104.34, 104.29, 104.16, 103.20, 96.35, 92.27, 78.99, 78.80, 77.83, 77.63, 77.57, 77.53, 77.08, 77.01, 75.24, 74.46, 74.42, 74.27, 74.23, 73.33, 73.29, 73.24, 73.20, 73.11, 72.19, 71.85, 71.79, 71.74, 71.59, 71.19, 70.46, 70.13, 69.81, 69.66, 69.39, 68.77, 62.44, 61.37, 60.85, 60.76, 60.69, 60.67, 60.49, 60.49, 60.47, 52.75. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{44}NaO_{21}$: 703.2273; Found 703.2268.

4-deoxy-4-fluoro-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranose (134)

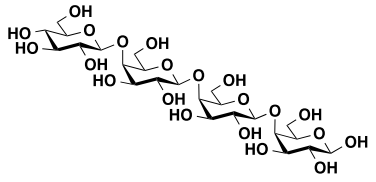


160 (550 mg; 0.30 mmol) was dissolved in MeOH (10 mL) and THF (5 mL) and 10 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until full conversion was observed by TLC (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (2:1 Toluene/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (10 mL), THF (2 mL). 20% $Pd(OH)_2$/C (105 mg; 0.15 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 24h and then filtered through celite, and concentrated to give a white solid. Purified by reverse phase chromatography to give **134** as a white solid. Yield: 165 mg (82%)

^{1}H NMR (400 MHz, D_2O) δ 5.28 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1a), 4.90 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-4^F), 4.72 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1b), 4.64 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1), 4.64 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1), 4.61 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1),

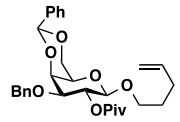
4.23 (d, *J* = 3.1 Hz, 1H), 4.21 – 4.16 (m, 9H), 4.13 (t, *J* = 6.4 Hz, 1H), 3.95 (dd, *J* = 10.3, 3.0 Hz, 1H), 3.90 (d, *J* = 3.8 Hz, 1H), 3.88 – 3.62 (m, 55H), 3.57 (dd, *J* = 10.0, 7.8 Hz, 2H). **^{13}C NMR** (101 MHz, D_2O) δ 102.93, 102.89, 102.83, 102.39, 94.89, 90.81, 88.85, 87.08, 77.35, 76.38, 76.09, 76.06, 75.96, 73.04, 72.99, 72.82, 72.27, 72.10, 71.84, 71.78, 70.73, 70.40, 70.34, 70.25, 70.12, 69.94, 69.84, 68.36, 68.21, 67.32, 59.40, 59.32, 59.21, 59.20, 58.34, 58.29, 57.10. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{41}FNaO_{20}$: 691.2073; Found 691.2068.

β-D-glucopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranose (135)



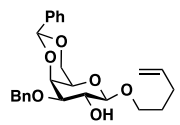
161 (615 mg; 0.32 mmol) was dissolved in MeOH (10 mL) and THF (5 mL) and 10 drops of freshly prepared 1M NaOMe in MeOH was added. The reaction mixture was stirred at 22 °C until TLC showed full conversion (24 hours). The reaction was quenched with Amberlite IR-120 (H^+), filtered and concentrated. The product was purified by flash chromatography (2:1 Toluene/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (10 mL), THF (2 mL). 20% $Pd(OH)_2/C$ (111 mg; 0.15 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 24h and then filtered through celite, and concentrated to give a white solid. Purified by reverse phase chromatography to give **135** as a white solid. Yield: 184 mg (87%).
^{1}H NMR (400 MHz, D_2O) δ 5.27 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1^{1}α), 4.67 (d, $J_{1,2}$ = 7.9 Hz, 2H, H-1α, H-1β), 4.64 (d, $J_{1,2}$ = 7.8 Hz, 4H, 2xH-1α, 2xH-1β), 4.61 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1β), 4.23 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4^{1}α), 4.17 (m, 7H, 7xH-4), 4.13 (t, *J* = 6.6 Hz, 1H), 4.00 – 3.30 (m, 39H). **^{13}C NMR** (101 MHz, D_2O) δ 104.39, 104.35, 104.28, 103.64, 96.35, 92.27, 78.81, 77.84, 77.51, 77.48, 77.23, 75.81, 75.67, 74.45, 74.28, 73.54, 73.31, 73.26, 73.24, 73.15, 72.19, 71.86, 71.80, 71.74, 69.82, 69.67, 69.52, 68.78, 60.86, 60.70, 60.66. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{42}NaO_{21}$: 689.2116; Found 689.2111.

Pent-4-enyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (136)



140 (10 g; 23.44 mmol) was dissolved in CH_2Cl_2 (150 mL). Et_3N (5.7 mL; 41.0 mmol), DMAP (1.43 g; 11.7 mmol) and pivaloyl chloride (4.3 mL; 35.2 mmol) was added to the solution and the reaction mixture was heated to 45 °C for 4 h. The reaction mixture was cooled to 0 °C, quenched with MeOH (10 mL), washed with water (2x150 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (15:1 Tol/EtOAc) to afford **136** as a white crystalline powder. R_f 0.40 (9:1 Tol/EtOAc). Yield 11.04 g (92%)
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= 30.0° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3066.29, 3032.92, 2973.51, 2934.24, 2907.31, 2871.73, 1732.08, 1479.12, 1454.26, 1397.47, 1367.41, 1279.10, 1175.00, 1145.56, 1103.67, 1081.36, 1061.30, 1027.14, 1002.40, 910.86, 734.44, 697.85 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (m, 2H, Ar-H), 7.35 – 7.13 (m, 8H, Ar-H), 5.71 (ddt, J_{trans} = 16.9, J_{cis} =10.2, J_{CH2} = 6.6 Hz, 1H, -C*H*=CH_2), 5.39 (s, 1H, $CH^{benzylidene}$), 5.32 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 8.0 Hz, 1H, H-2), 4.92 (ddd, J_{trans} = 17.1, J_{CH2} = 3.5, J_{gem} =1.6 Hz, 1H, CH_2=CH^{trans}), 4.86 (ddt, J_{cis} = 10.2, J_{CH2} = 2.1, J_{gem} =1.6 Hz, 1H, CH_2=CH^{cis}), 4.60 (d, J_{CH2} = 12.6 Hz, 1H, 0.5xCH_2^{Bn}), 4.57 (d, J_{CH2} = 12.6 Hz, 1H, 0.5xCH_2^{Bn}), 4.37 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.23 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6a}$ =1.4 Hz, 1H, H-6a), 4.05 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 3.95 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$ =1.7 Hz, 1H), 3.82 (dt, J_{CH2} = 9.4, $J_{CH=CH2}$ = 6.6 Hz, 1H, -$OCH_2^{pentenyl}$), 3.56 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.1 Hz, 1H, H-3), 3.38 (dt, J_{CH2} = 9.4, $J_{CH=CH2}$ =6.6 Hz, 1H, -$OCH_2^{pentenyl}$), 3.28 (m, 1H, H-5), 2.09 – 1.93 (m, 2H, $CH_2^{pentenyl}$), 1.68 – 1.45 (m, 2H, $CH_2^{pentenyl}$), 1.15 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.93, 138.35, 138.20, 137.80, 129.04, 128.46 (2C), 128.24 (2C), 127.86, 127.73 (2C), 126.56 (2C), 114.82, 101.36, 101.21, 77.67, 73.49, 71.37, 69.93, 69.32, 68.50, 66.69, 38.93, 30.23, 28.91, 27.36 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{38}O_7Na$: 533.2515; Found 533.2516.

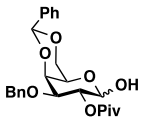
Pent-4-enyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (140)



To a solution of **109** (18.5 g, 55.0 mmol) in toluene (400 mL) was added Bu_2SnO (20.5 g, 82.50 mmol). The flask was fitted with a Dean-Stark apparatus and the mixture was stirred under reflux for 12 h. The reaction mixture was cooled to 22 °C and CsF (16.7 g, 110.00 mmol) and BnBr (19.6 mL, 165.00 mmol) were added. The reaction mixture was stirred at reflux for 24 h, and then cooled to 22 °C, diluted with EtOAc, and quenched with sat. aq. $NaHCO_3$. The water phase was extracted with EtOAc (2x300 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (9:1 Tol/EtOAc) to give **140**. R_f 0.19 (9:1 Tol/EtOAc). Yield: 18.5 g (79%).
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= 18.7° (c 1.0, $CDCl_3$), **IR**(neat): 3449.34, 3059.64, 3030.08, 2958.09, 2924.67, 2869.46, 1496.29, 1454.07, 1440.48, 1362.53, 1247.35, 1168.81, 1100.66, 1082.24, 1045.84, 1027.47, 994.84, 859.11, 831.63, 746.56, 697.69. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 2H, Ar-H), 7.38 – 7.16 (m, 8H, Ar-H), 5.74 (ddt, J_{trans} = 16.9, , J_{cis} = 10.1, J_{CH2} = 6.6 Hz, 1H, -C*H*=CH_2), 5.38 (s, 1H, -$CH^{benzylidene}$), 4.95 (dt, J_{trans} = 17.1, J_{gem} =1.8 Hz, 1H, -CH_2=CH_{cis}),

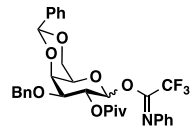
4.89 (ddd, J_{cis} = 9.9, J_{CH2} = 3.2, J_{gem} = 1.8 Hz, 1H, -CH_2=CH_{cis}), 4.68 (s, 2H, -CH_2^{Bn}), 4.22 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$= 1.6 Hz, 1H, H-6a), 4.20 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.04 (dd, $J_{3,4}$ = 3.6, $J_{4,5}$ = 1.1 Hz, 1H, H-4), 3.96 – 3.83 (m, 3H, -$OCH_2^{pentenyl}$, H-6b, H-2), 3.49 – 3.38 (m, 2H, -$OCH_2^{pentenyl}$, H-3), 3.26 (m, 1H, H-5), 2.17 – 1.98 (m, 2H, -$CH_2^{pentenyl}$), 1.75 – 1.61 (m, 2H, -$CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.32, 138.24, 137.87, 129.00, 128.54 (2C), 128.20 (2C), 127.95 (2C), 127.93, 126.48 (2C), 114.95, 103.05, 101.21, 79.21, 73.32, 71.61, 70.17, 69.39, 69.22, 66.75, 30.30, 28.74. **HRMS** (ESI-TOF) m/z:[M + Na]$^+$ Calcd for $C_{25}H_{30}O_6Na$: 449.1940; Found 567.1948.

4,6-*O*-benzylidene-3-*O*-benzyl-2-*O*-pivaloyl-D-galactopyranose (141a)



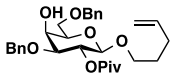
136 (12.0 g; 22.4 mmol) was dissolved in acetone (180 mL) and water (20 mL). NBS (16.0 g; 89.8 mmol) and 2,6-lutidine (13.0 mL; 112.2 mmol) were added and the reaction was stirred at 50 °C until TLC showed full conversion (3h). The solution was diluted with CH_2Cl_2 (400 mL) and washed with sat. aq. NaS_2O_3 (200 mL) and sat. aq. $NaHCO_3$ (200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (4:1 Tol/EtOAc) to afford **141a** as a 3:5 α/β mixture. R_f 0.44 (2:1 Tol/EtOAc) . Yield: 8.0 g (81%)
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= 75.0° (c 1.0, $CDCl_3$) **IR** (neat, cm^{-1}):3429.32, 3033.96, 2906.34, 1725.45, 1601.00, 1581.49, 1479.42, 1398.30, 1363.72, 1283.48, 1168.13, 1098.74, 1082.09, 1026.87, 997.43 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.16 (m, 20H, Ar-H), 5.51 (d, $J_{1,2}$ = 3.6 Hz, 1H, H-1α), 5.41 (s, 1H, $CH^{benzylidene}$β), 5.39 (s, 1H, $CH^{benzylidene}$α), 5.19 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 3.6 Hz, 1H, H-2α), 5.13 (dd, $J_{2,3}$ = 10.0, $J_{1,2}$ = 8.1 Hz, 1H, H-2β), 4.68 (d, J_{CH2} = 12.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.61 (m, 1H, 0.5xCH_2^{Bn}), 4.60 (d, J_{CH2} = 12.1 Hz, 2H, CH_2^{Bn}), 4.50 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1β), 4.25 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 1.4 Hz, 1H, H-6aβ), 4.13 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.4 Hz, 1H, H-6aα), 4.09 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4α), 4.06 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4β), 4.01 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.1 Hz, 1H, H-3α), 3.97 – 3.88 (m, 2H, H-6bα, H-6bβ), 3.79 (s, 1H, H-5α), 3.58 (dd, $J_{2,3}$ = 10.1, $J_{3,4}$ = 3.6 Hz, 1H, H-3β), 3.33 (d, $J_{5,6a}$ = 0.9 Hz, 1H, , H-5β), 1.16 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.47, 178.06, 157.22, 138.50, 137.92, 137.85, 137.64, 129.14, 129.07, 128.97, 128.53, 128.45, 128.33, 128.27, 128.24, 128.03, 127.81, 127.77, 127.71, 126.44, 126.37, 120.96, 101.08, 101.02, 96.48, 91.00, 76.96, 74.49, 73.39, 73.35, 72.96, 72.01, 71.69, 70.48, 69.55, 69.29, 66.96, 62.43, 39.08, 38.89, 27.27, 27.22. **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{25}H_{30}NaO_7$ 465.1889 Found 465.1893

4,6-O-benzylidene-3-O-chloroacetyl-2-O-pivaloyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (141)



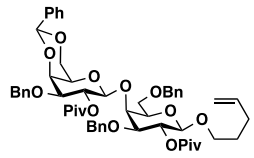
141a (8 g; 18.3 mmol) was dissolved in DCM (100 mL) and cooled to 0 °C. Cs_2CO_3 (11.9 g; 36.7 mmol) was added followed by *N*-phenyl trifluoroacetimidoyl chloride (7.6 g; 36.7 mmol). The ice bath was removed and the reaction mixture was stirred until TLC showed full conversion (12 h). It was then filtered, concentrated and purified by flash chromatography (20/1 Tol/EtOAc) to give a white crystalline product. Yield: 8.8 g (79%)

Pent-4-enyl 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranoside (142)



Trifluoroacetic acid (11.8 mL, 154 mmol) was added drop wise to a solution of **136** (10.4 g, 20.31 mmol) and triethylsilane (24.5 mL, 153.3 mmol) in CH_2Cl_2 (75 mL) at 0 °C. When the addition was complete (10 min), the reaction was warmed to 22 °C and stirred for 3 hr. The mixture was diluted with ethyl acetate and washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (4:1 Tol/EtOAc) to afford **142**. R_f 0.65 (2:1 Tol/EtOAc). Yield: 9.0 g (86%)
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -0.9° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3468.65, 3064.96, 3030.82, 2972.43, 2932.64, 2872.00, 1731.35, 1479.41, 1454.20, 1368.34, 1278.83, 1176.44, 1154.93, 1136.93, 1096.12, 1069.27, 911.64, 737.68, 698.36. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.16 (m, 10H, Ar-H), 5.70 (ddt, J_{trans} = 16.9, J_{cis} = 10.2, J_{CH2} = 6.6 Hz, 1H, -CH=CH_2), 5.14 (dd, J = 9.8, 8.0 Hz, 1H, H-2), 4.91 (dq, J_{trans} = 17.2, J_{gem} = 1.7 Hz, 1H, CH_2=CH_{trans}), 4.86 (ddd, J_{cis} = 10.0, J_{CH2} = 3.3, J_{gem} = 1.7 Hz, 1H, CH_2=CH_{cis}), 4.58 (d, J = 12.0 Hz, 1H, CH_2^a), 4.52 (s, 2H, CH_2^b), 4.49 (d, J = 12.0 Hz, 1H, CH_2^a), 4.28 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 3.98 (dd, $J_{3,4}$ = 3.4, $J_{4,5}$ = 1.1 Hz, 1H, H-4), 3.82 – 3.70 (m, 2H, -$OCH_2^{pentenyl}$, H-6a), 3.67 (dd, $J_{6a,6b}$ = 9.9, $J_{5,6b}$ = 6.0 Hz, 1H, H-6b), 3.53 (td, $J_{5,6a}$ = $J_{5,6b}$ = 6.0, $J_{4,5}$ = 1.1 Hz, 1H, H-5), 3.46 (dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 3.37 (dt, J_{gem} = 9.6, $J_{CH2pent}$ = 6.8 Hz, 1H, -$CH_2^{pentenyl}$), 2.09 – 1.91 (m, 2H, -$CH_2^{pentenyl}$), 1.66 – 1.46 (m, 2H, -$CH_2^{pentenyl}$) 1.13 (s, 9H, 3x$CH_3^{pivaloyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.94, 138.12, 137.98, 137.32, 128.51 (2C), 128.44 (2C), 128.00, 127.81 (2C), 127.78, 127.66 (2C), 114.75, 101.29, 79.03, 73.74, 73.47, 71.67, 70.48, 69.01, 68.83, 66.25, 38.80, 30.05, 28.81, 27.20 (3C). **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{30}H_{40}O_7Na$: 535.2672; Found 535.2688.

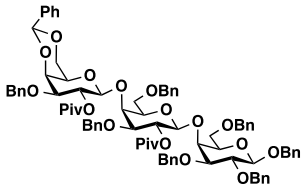
Pent-4-enyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranoside (143)



To a 250 mL flame-dried flask was added **142** (5 g, 9.75 mmol) and the **141** (8.4 g, 13.7 mmol). The mixture was co-evaporated with toluene (2x100 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (100 mL) and cooled to -40 °C. TMSOTf (0.15 mL; 1.0 mmol) was added and the reaction mixture was stirred at -40 °C for 2h. Et_3N (1 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (12:1 Tol/EtOAc) to give **143**. R_f 0.37 (9:1 Tol/EtOAc). Yield: 6.0 g (81%)

$[\alpha]_D^{20}$= 21.4° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3067.69, 3036.01, 2949.02, 2877.10, 1725.57, 1602.02, 1451.44, 1373.43, 1314.59, 1269.67, 1179.07, 1092.28, 1069.92, 1026.97, 999.28, 914.33. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.37 (m, 2H), 7.37 – 7.07 (m, 18H), 5.70 (ddt, J_{trans} = 16.9, J_{cis} =10.2, J_{CH2} = 6.6 Hz, 1H, -C*H*=CH_2), 5.31 (s, 1H, -$CH^{benzylidene}$), 5.26 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 7.9 Hz, 1H, H-2'), 5.11 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.8 Hz, 1H, H-2), 4.97 (d, *J* = 7.9 Hz, 1H, H-1'), 4.91 (dq, J_{trans} = 17.1, J_{CH2} = 1.7 Hz, 1H, CH_2=CH_{trans}), 4.86 (dt, J_{cis} = 10.3, J_{CH2} = 1.6 Hz, 1H, CH_2=CH_{cis}), 4.62 – 4.44 (m, 6H, 3xCH_2^{Bn}), 4.42 (dd, $J_{3,4}$ = 2.8, $J_{4,5}$ = 1.1 Hz, 1H, H-4), 4.27 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 3.97 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6a}$ = 1.6 Hz, 1H, H-6a'), 3.89 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4'), 3.81 – 3.66 (m, 3H, H-6b', H-6a 0.5x$OCH_2^{pentenyl}$), 3.61 (dd, $J_{6a,6b}$ = 9.9, $J_{5,6b}$ = 5.6 Hz, 1H, H-6b), 3.55 – 3.43 (m, 3H, H-3, H-3', H-5), 3.33 (dt, J_{CH2} = 9.6, J_{CH2} = 6.6 Hz, 1H, 0.5x$OCH_2^{pentenyl}$), 2.89 – 2.79 (m, 1H, H-5'), 1.98 (m, 2H, -$CH_2^{pentenyl}$), 1.53 (m, 2H, -$CH_2^{pentenyl}$), 1.19 (s, 9H, 3xCH_3^{Piv}), 1.11 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.31, 176.85, 138.60, 138.40, 138.32, 138.11, 137.93, 129.42-126.32 (15C), 114.72, 101.52, 101.03, 99.10, 81.07, 77.61, 74.09, 73.92, 73.63, 72.23, 71.61, 70.98, 70.62, 69.39, 68.91, 68.46, 68.20, 66.60, 38.99, 38.88, 30.19, 29.01, 27.46 (3C), 27.31 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{55}H_{68}NaO_{13}$ 959.4558; Found 959.4551.

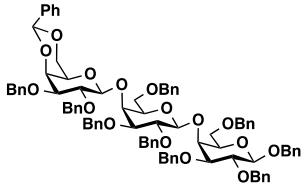
Benzyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (144)



To a 25 mL flame-dried flask was added acceptor **113** (400 mg, 0.74 mmol) and the donor **143** (901 mg, 0.96 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (10 mL) and cooled to -30 °C, followed by addition of NIS (221 mg; 0.98 mmol) and TMSOTf (33 mg; 0.15 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (12:1 Tol/EtOAc) to afford **144** as a white crystalline material. R_f 0.36 (9:1 Tol/EtOAc). Yield: 885 mg (86%)

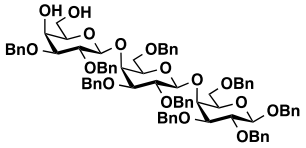
$[\alpha]_D^{20}$= 2.5° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3447.32, 3087.92, 2970.89, 2870.33, 1737.68, 1496.74, 1479.31, 1454.22, 1365.17, 1278.22, 1154.61, 1090.21, 1073.58, 1055.80. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.05 (m, 40H), 5.33 (s, 1H, -$CH^{benzylidene}$), 5.30 (dd, $J_{2,3}$ = 10.1, $J_{2,3}$ = 7.8 Hz, 1H, H-$2^{2/3}$), 5.08 (dd, $J_{2,3}$ = 10.1, $J_{2,3}$ = 7.9 Hz, 1H, H-$2^{2/3}$), 4.92 (d, *J* = 7.9 Hz, 1H, H-$1^{2/3}$), 4.90 – 4.81 (m, 2H, -CH_2^{Bn}), 4.80 (d, *J* = 7.8 Hz, 1H, H-$1^{2/3}$), 4.66 – 4.43 (m, 11H, 5.5xCH_2^{Bn}), 4.40 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-$4^{2/3}$), 4.33 (d, *J* = 7.8 Hz, 1H, H-1^1), 4.31 (d, *J* = 12.0 Hz, 1H, 0.5x-CH_2^{Bn}), 4.08 (d, $J_{3,4}$ = 2.5 Hz, 1H, H-4^1), 4.01 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 1.5 Hz, 1H, H-$6a^1$), 3.89 (d, $J_{3,4}$ = 3.6 Hz, 1H, H-$4^{2/3}$), 3.74 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 1.8 Hz, 1H, H-$6b^1$), 3.71 – 3.56 (m, 4H, H-2^1, H-$6a^{2/3}$, H-$6^{2/3}$), 3.47 – 3.29 (m, 3H, H-$3^{2/3}$, H-$3^{2/3}$, H-$5^{2/3}$, H-$5^{2/3}$, H-$6a^{2/3}$), 2.82 (m, 1H, H-5^1), 1.24 (s, 9H, 3xCH_3^{Piv}), 1.08 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.13, 176.64, 138.82, 138.69, 138.60, 138.53, 138.20, 138.10, 137.89 (2C), 128.80-126.28 (45C), 102.61, 100.80, 100.51, 99.24, 81.92, 81.40, 79.44, 77.63, 77.25, 75.08, 73.98, 73.71, 73.58, 73.46, 72.87, 72.19, 71.54, 71.37, 70.77, 70.51, 70.29, 70.12, 68.92, 68.85, 67.66, 66.48, 38.95, 38.75, 27.54, 27.37. **HRMS** (ESI-TOF) m/z:$[M + Na]^+$ Calcd for $C_{84}H_{94}NaO_{18}$: 1413.6338; Found 1413.6356.

Benzyl 4,6-*O*-benzylidene-2,3-*O*-dibenzyl-β-D-galactopyranosyl-(1→4)- 2,3,6-*O*-tribenzyl-β-D-galactopyranosyl-(1→4)- 2,3,6-*O*-tribenzyl-β-D-galactopyranoside (146)



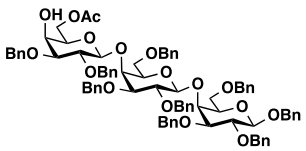
To a solution of **144** (6.4 g; 4.58 mmol) in DMSO (40 mL) was added KOH (5.1 g; 91.6 mmol) and the reaction mixture was stirred at 22 °C for 16 h. The solution was poured into sat. aq. NH_4Cl (300 mL) and extracted with CH_2Cl_2 (3x100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude compound **145** was dissolved in DMF (50 mL) and cooled to 0 °C. NaH (60% oil dispension; 730 mg; 18.31 mmol) was added and the reaction mixture was stirred at 0 °C until gas development ceased. Next BnBr (1.9 mL; 16.02 mmol) and TBAI (169 mg; 0.46 mmol) were added and the reaction mixture was stirred at 22 °C for 12h. The reaction mixture was quenched with MeOH, diluted with CH_2Cl_2 (500 mL) and washed with NH_4Cl (400 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (14:1 Tol/EtOAc) to give **146** as a white crystalline powder. R_f 0.36 (9:1 Tol/EtOAc). Yield: 5.2 g (82%)
$[\alpha]_D^{20}$ = 4.0° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3454.35, 3087.60, 2919.41, 1701.05, 1604.54, 1585.34, 1496.44, 1453.61, 1396.15, 1362.75, 1308.61, 1207.48, 1154.03, 1098.98, 1071.83. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.41 (m, 4H, Ar-H), 7.36 – 7.00 (m, 46H, Ar-H, H^{Bn}), 5.44 (s, 1H, -$CH^{benzylidene}$), 5.03 (d, J_{CH2} = 10.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.95 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-$1^{2/3}$), 4.89 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.85 (d, $J_{1,2}$ = 7.0 Hz, 1H, H-$1^{2/3}$), 4.84 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.79 – 4.50 (m, 12H, 6xCH_2^{Bn}), 4.46 – 4.30 (m, 3H, H-1^1, CH_2^{Bn}), 4.27 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-$4^{1/2/3}$), 4.24 (d, J_{CH2} = 10.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.18 (d, J = 2.8 Hz, 1H, H-$4^{1/2/3}$), 4.10 (d, J = 12.1 Hz, 1H, H-6a$^{1/2/3}$), 4.01 (d, J = 3.7 Hz, 1H, H-$4^{1/2/3}$), 3.87 (dd, J = 12.4, 1.7 Hz, 1H, H-6b$^{1/2/3}$), 3.81 – 3.36 (m, 6H, H-2^1-H-2^3, H-3^1 -H-3^3, H-5^1-H-5^3, H-$6^{1/2/3}$, H-$6^{1/2/3}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.15, 138.99 (2C), 138.81, 138.73, 138.59, 138.57, 138.28 (2C), 137.84, 128.92-126.49 (50C), 102.89, 102.81, 102.39, 101.20, 81.88, 81.83, 80.33, 80.02, 78.87, 78.83, 75.31, 74.91, 74.83, 74.37, 74.03, 73.73, 73.53, 73.36, 72.98, 72.76, 72.30, 71.02, 70.89, 70.31, 70.26, 69.19, 69.06, 66.24. **HRMS** (ESI-TOF) m/z:$[M + Na]^+$ Calcd for $C_{88}H_{90}NaO_{16}$: 1425.6127; Found 1425.6151.

Benzyl 2,3-di-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)- 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (147)



146 (6.2 g; 4.4 mmol) was dissolved in CH_2Cl_2 (100 mL). To the solution was added EtSH (1.6 mL; 22.1 mmol) and *p*-TSA (84 mg; 0.44 mmol) and the reaction mixture was stirred at 22 °C for 4 h. The reaction was quenched with Et_3N (2 mL) and concentrated. The product **147** was purified by flash chromatography (3:1 Tol/EtOAc). R_f 0.4 (2:1 Tol/EtOAc). Yield 5.4 g (94%)
$[\alpha]_D^{20}$ = 2.0° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3442.71, 3087.68, 3062.40, 3029.77, 2918.61, 2867.53, 1496.39, 1453.57, 1362.63, 1096.13, 1069.22, 735.98, 697.01. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 6.76 (m, 35H), 5.06 (d, J_{CH2} = 10.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.89 (d, J_{CH2} = 11.5 Hz, 2H, CH_2^{Bn}), 4.81 (d, J = 7.6 Hz, 1H, H-$1^{2/3}$), 4.74 (d, J = 7.7 Hz, 1H, H-$1^{2/3}$), 4.72 – 4.28 (m, 7H, H-1^1, 7.5xCH_2^{Bn}), 4.15 (d, J = 2.8 Hz, 1H, H-$4^{2/3}$), 4.11 (d, J = 2.9 Hz, 1H, H-$4^{2/3}$), 3.94 (dd, $J_{6a,6b}$ = 9.7, $J_{5,6a}$ =7.3 Hz, 1H, H-6a$^{1/2/3}$), 3.85 (dd, $J_{6a,6b}$ = 11.8, $J_{5,6a}$ =7.8 Hz, H-6a$^{1/2/3}$), 3.82 (d, J = 3.7 Hz, 1H, H-$4^{2/3}$), 3.76 - 3.24 (m, 6H, H-2^1-H-2^3, H-3^1 - H-3^3, H-5^1-H-5^3, H-$6^{1/2/3}$, H-$6^{1/2/3}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.01, 138.73 (2C), 138.70, 138.58, 138.38, 138.03, 137.97, 137.72, 128.51-127.35 (45), 103.44, 103.02, 102.81, 81.81, 81.33, 80.32, 80.20, 79.97, 79.00, 75.30, 74.98, 74.81, 74.21, 73.94, 73.66, 73.41, 73.02, 72.97, 72.78, 72.22, 72.09, 71.28, 70.98, 70.21, 68.56, 67.68, 62.41. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{81}H_{86}NaO_{16}$: 1337.5814; Found 1337.5828.

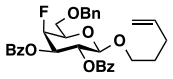
Benzyl 6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranosyl-(1→4)- 2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)- 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (148)



147 (5.8 g; 4.41 mmol) was dissolved in DCM (44 mL) and cooled to 0 °C. Et_3N (1.23 mL; 8.82 mmol) and acetic anhydride (0.66 mL; 6.6 mmol) was added and the reaction mixture was stirred until TLC revealed full conversion (36 h). The reaction was quenched with MeOH (2 mL), diluted with CH_2Cl_2 (50 mL), washed with water (2x100 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography to afford the product as a white crystalline powder. Yield: 5.3 g (88%)
$[\alpha]_D^{20}$ = 4.6° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 6.93 (m, 45H, Ar-H), 4.99 (d, J_{CH2} = 10.8 Hz, 1H, CH_2^{Bn}), 4.95 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.89 (d, J_{CH2} = 12.1 Hz, 1H, CH_2^{Bn}), 4.89 (d, J_{CH2} = 10.8 Hz, 1H, CH_2^{Bn}), 4.84 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 4.74 – 4.27 (m, 16H, H-1, 7.5xCH_2^{Bn}), 4.26 (dd, $J_{6a,6b}$ = 11.3, $J_{5,6b}$ = 5.7 Hz, 1H, H-6a^3), 4.21 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 4.20 (dd, $J_{6a,6b}$ = 11.3, $J_{5,6b}$ = 5.3 Hz, 1H, H-6b^3), 4.17 (d, $J_{3,4}$ = 2.0 Hz, 1H, H-4), 3.83 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4), 3.78 – 3.36 (m, 13H, 3xH-2, 3xH-3, 3xH-5, H-6^1, H-6^2), 1.95 (s, 3H, CH_3^{Ac}).

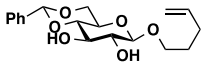
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.86, 139.16, 138.87, 138.81, 138.64, 138.59, 138.53, 138.46, 138.06, 137.88, 130.22-127.26 (45C), 103.11, 102.87, 102.34, 82.02, 81.88, 80.17, 80.12, 79.03, 77.36, 75.40, 74.99, 74.22, 73.70, 73.68, 73.62, 73.16, 73.10, 72.83, 71.85, 71.54, 71.00, 70.82, 70.65, 70.05, 67.11, 63.28, 21.02. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{83}H_{88}NaO_{17}$ 1379.5919; Found 1379.5922.

Pent-4-enyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-4-deoxy-4-fluoro-β-D-glucopyranoside (149)



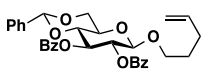
Trifluoromethanesulfonic anhydride (2.46 mL; 14.63 mmol) was added dropwise to a solution of **152** (4 g; 7.31 mmol) in dry CH_2Cl_2 and dry pyridine (1.37mL) at -15 °C, and stirred for 15 min before the reaction mixture was allowed to reach 22 °C and stirred for one hour. The reaction mixture was then concentrated *in vacuo* and cooled on ice as tetrabutylammonium fluoride (TBAF, 1 M in THF, 73.2 mL) was added drop wise. The mixture was stirred at 22 °C for 3 h, diluted with CH_2Cl_2 (100 mL) and washed with 1M HCl (3x50 mL). The combined aqueous phases were washed once with CH_2Cl_2 (100 mL) and the combined organic phases were washed with sat. aq. $NaHCO_3$ (2x50 mL), H_2O (50 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography. (Heptane/EtOAc 2:1) to give **149** as a yellow syrup. R_f 0.58 (9:1 Tol/EtOAc). Yield 3.4 g (85%)
$[\alpha]_D^{20}$ = 52.0° (c 1.0, $CDCl_3$) **IR**(neat, cm^{-1}): 3065.54, 3033.26, 2938.88, 2875.27, 1726.24, 1640.67, 1601.97, 1584.63, 1493.68, 1451.99, 1314.64, 1276.22, 1177.62, 1106.20, 1070.51, 1028.16, 709.86 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.79 (m, 4H, H^{Bz}), 7.54 – 7.35 (m, 2H, H^{Bz}), 7.37 – 7.18 (m, 9H, H^{Bz}, H^{Bn}), 5.66 (dd, J = 10.5, 7.9 Hz, 1H, H-2), 5.57 (ddt, J_{trans} = 17.1, J_{cis} =10.6, J_{CH2} =6.7 Hz, 1H, -C*H*=CH_2), 5.28 (ddd, $J_{3,F}$ = 27.4, $J_{2,3}$ = 10.5, $J_{3,4}$ = 2.7 Hz, 1H, H-3), 5.03 (dd, $J_{4,F}$ = 50.1, $J_{3,4}$ = 2.7 Hz, 1H, H-4), 4.77-4.73 (m, 2H, CH_2=$CH_{trans,}$ CH_2=CH_{cis}), 4.62 (dd, $J_{1,2}$ = 7.9, 0.9 Hz, 1H, H-1), 4.52 (s, 2H, -CH_2^{Bn}), 3.96 – 3.77 (m, 2H, -$OCH_2^{pentenyl}$, H-5), 3.76 – 3.62 (m, 2H, H-6a, H-6b), 3.45 (ddd, J = 9.7, 7.2, 6.2 Hz, 1H, -$OCH_2^{pentenyl}$), 2.01 – 1.76 (m, 2H, , -$CH_2^{pentenyl}$), 1.72 – 1.35 (m, 2H, , -$CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.03, 165.27, 137.94, 137.76, 133.63, 133.27, 130.10 (2C), 129.83 (2C), 129.63, 129.01, 128.62 (2C), 128.58 (2C), 128.53 (2C), 128.47 (2C), 128.02, 127.90 (2C), 114.95, 101.38, 87.30 (0.5C), 85.45 (0.5C), 73.85, 72.65 (0.25C), 72.56 (0.25C), 72.46 (0.25C), 72.38 (0.25C), 69.58, 69.37, 67.60 (0.5C), 67.55 (0.5C), 29.92, 28.69. **HRMS** (ESI-TOF) m/z:$[M + Na]^+$ Calcd for $C_{32}H_{33}FNaO_7$: 571.2108; Found 571.2111.

Pent-4-enyl 4,6-*O*-benzylidene-β-D-glucopyranoside (150)[221]



To a solution of $PhCH(OMe)_2$ (4.2 mL, 27.2 mmol) and camphorsulphonic acid (140 mg, 0.6 mmol) in MeCN (150 mL) was added pent-4-enyl β-D-glucopyranoside (5 g, 20.15 mmol). The flask was equipped with a distillation unit and the mixture was heated to reflux for 2 h during which time approximately 75 mL of MeCN-MeOH was distilled off. The distillation unit was replaced with a condenser and the reaction mixture was heated to reflux until TLC showed completion (2.5h). The reaction mixture was concentrated and the product was purified by flash chromatography (2:1 Tol/EtOAc) to afford **150** as an oil. R_f 0.31 (2:1 Tol/EtOAc). Yield: 6.5 g (98%)
$[\alpha]_D^{20}$ = -33.1° (c 1.0, $CDCl_3$) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.37 (m, 2H, Ar-H), 7.29 (m, 3H, Ar-H), 5.74 (ddt, J_{trans} = 16.9, J_{cis} = 10.2, J_{CH2} = 6.6 Hz, 1H), 5.44 (s, 1H, -$CH^{benzylidene}$), 4.97 (dd, J_{trans} = 17.2, J_{gem} = 1.8 Hz, 1H, -CH_2=CH_{trans}), 4.92 (dd, J_{cis} = 10.2, J_{gem} = 1.8 Hz, 1H, -CH_2=CH_{cis}), 4.29 (dd, $J_{1,2}$ = 7.7, 1.1 Hz, 1H, H-1), 4.25 (dd, $J_{6a,6b}$ = 10.8, $J_{5,6a}$ = 5.3 Hz, 1H, H-6a), 3.87 – 3.79 (m, 1H, -$OCH_2^{pentenyl}$), 3.75 – 3.64 (m, 2H, H-6b, H-3), 3.56 – 3.27 (m, 4H, H-2, H-4, H-5, -$OCH_2^{pentenyl}$), 3.10 – 2.93 (m, 1H, -OH), 2.88 – 2.73 (m, 1H, -OH), 2.13 – 2.02 (m, 2H, -$CH_2^{pentenyl}$), 1.75 – 1.62 (m, 2H, -$CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.97, 136.97, 129.28, 128.35 (2C), 126.30 (2C), 115.07, 103.18, 101.91, 80.58, 74.55, 73.11, 69.87, 68.68, 66.38, 30.12, 28.72. **HRMS** (ESI-TOF) m/z: [M + H]+ Calcd for $C_{18}H_{25}O_6$ 337.1651 Found 337.1659

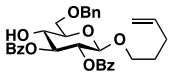
Pent-4-enyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-β-D-glucopyranoside (151)



150 (3.0 g; 8.92 mmol) was dissolved in CH_2Cl_2 (50 mL). Et_3N (4.3 mL; 31.21 mmol), DMAP (11 mg; 0.09 mmol) and benzoyl chloride (3.1 mL; 26.76 mmol) was added to the solution and the reaction mixture was stirred until TLC revealed full conversion (3 h). The reaction was quenched with MeOH (5 mL), diluted with CH_2Cl_2 (100 mL), washed with water (2x100 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (Tol/EtOAc 19:1) to afford **151** as an oil. R_f 0.57 (9:1 Tol/EtOAc). Yield 4.4 g (89%)
$[\alpha]_D^{20}$ = -5.0° (c 1.0, $CDCl_3$) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (m, 4H, Ar-H), 7.55 – 7.10 (m, 11H, Ar-H), 5.71 (t, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, 1H, H-3), 5.56 (ddt, J_{trans} = 17.0, J_{cis} = 10.4, J_{CH2} = 6.6 Hz, 1H), 5.47 (s, 1H, $CH^{benzylidene}$), 5.40 (dd, $J_{2,3}$ = 9.5, $J_{1,2}$ = 7.8 Hz, 1H, H-2), 4.76 (m, 2H, CH_2=CH-), 4.71 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.36 (dd, $J_{4,5}$ = 10.5, $J_{5,6}$ = 4.9 Hz, 1H, H-5), 3.90 – 3.79 (m, 3H, H-4, 0.5x$OCH_2^{pentenyl}$, H-6a), 3.62 (td, $J_{6a,6b}$ = 9.7, $J_{5,6b}$ = 4.9 Hz, 1H, H-6b), 3.46 (dt, J_{CH2} = 9.7, J_{CH2} = 6.7 Hz, 1H, 0.5x$OCH_2^{pentenyl}$), 2.08-1.72 (m, 2H, $CH_2^{pentenyl}$), 1.72 – 1.30 (m, 2H, $CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.65, 165.20, 137.71, 136.81, 133.19, 133.10, 129.83 (2C), 129.77

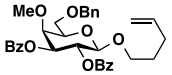
(2C), 129.44, 129.37, 129.04, 128.37 (2C), 128.31 (2C), 128.21 (2C), 126.13 (2C), 114.92, 101.79, 101.48, 78.88, 72.53, 72.12, 69.68, 68.71, 66.63, 29.77, 28.60. **HRMS** (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{32}H_{32}NaO_8$ 567.1995; Found 567.1996.

Pent-4-enyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-β-D-glucopyranoside (152)



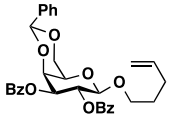
Trifluoroacetic acid (3.7 mL, 48.96 mmol) was added drop wise to a solution of **151** (5 g, 9.79 mmol) and triethylsilane (7.8 mL, 48.96 mmol) in CH_2Cl_2 (100 mL) at 0 °C. When the addition was complete (10 min), the reaction was warmed to 22 °C and stirred for 2 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc) to afford **152**. R_f 0.28 (9:1 Tol/EtOAc). Yield: 3.72 g (74%)
$[\alpha]_D^{20}$= 45.9° (c 1.0, $CDCl_3$) **IR** (neat, cm^{-1}): 3489.05, 3065.46, 3032.96, 2939.13, 2871.25, 1728.28, 1451.65, 1315.18, 1276.66, 1177.56, 1096.00, 1068.93, 1027.24, 709.90 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (m, 4H, Ar-H), 7.50 – 7.37 (m, 2H, Ar-H), 7.35 – 7.24 (m, 9H, Ar-H), 5.58 (ddt, J_{trans} = 17.1, J_{cis} = 10.7, J_{CH2} = 6.7 Hz, 1H, C*H*=CH_2), 5.43 – 5.28 (m, 2H, H-2, H-3), 4.77 (s, 1H, CH_2=CH), 4.74 (m, 1H, CH_2=CH), 4.60 (d, $J_{1,2}$ = 7.3 Hz, 1H, H-1), 4.58 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 4.53 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 3.89 (dt, $J_{3,4}$ = $J_{4,5}$ = 9.3, $J_{4,OH}$ = 3.2 Hz, 1H, H-4), 3.94 – 3.75 (m, 3H, 0.5x$OCH_2^{pentenyl}$, H-6a, H-6b), 3.62 (dt, $J_{4,5}$ = $J_{5,6a}$ = 9.3, $J_{5,6b}$ =4.6 Hz, 1H, H-5), 3.44 (dt, J_{CH2} = 9.7, J_{CH2} = 6.7 Hz, 1H, 0.5x$OCH_2^{pentenyl}$), 3.19 (d, $J_{4,OH}$ = 3.3 Hz, 1H, -OH), 2.02 – 1.78 (m, 2H, -$CH_2^{pentenyl}$), 1.66 – 1.44 (m, 2H, -$CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.23, 165.26, 137.84, 137.67, 133.42, 133.12, 129.98 (2C), 129.72 (2C), 129.50, 129.07, 128.50 (2C), 128.40 (2C), 128.33 (2C), 127.88, 127.78 (2C), 114.82, 101.07, 76.68, 74.58, 73.82, 71.51, 71.20, 70.12, 69.29, 29.82, 28.60.

Pent-4-enyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*O*-methyl-β-D-galactopyranoside (153)



To a solution of **155** (2.0 g, 3.67 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added Proton Sponge (7.9 g, 36.72 mmol) and Me_3OBF_4 (7.0 g, 36.72 mmol). The reaction mixture was warmed to 22 °C and stirred for 6 h. The reaction mixture was concentrated and quenched with sat. aq. NH_4Cl (50 mL). The reaction mixture was diluted with Et_2O (100 mL), and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with 1N aq. HCl solution (100 mL), sat. aq. $NaHCO_3$ (80 mL), H_2O (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (19:1 Tol/EtOAc) to afford the methyl ether **153** as a white crystalline material. R_f 0.50 (9:1 Tol/EtOAc). Yield: 1.7 g (84 %)
$[\alpha]_D^{20}$= 25.8° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3065.11, 2934.57, 2871.06, 1726.80, 1640.62, 1601.97, 1584.48, 1493.98, 1451.80, 1314.38, 1277.24, 1177.38, 1107.81, 1071.77, 1028.09.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 7.63 (m, 4H, Ar-H), 7.53 – 7.08 (m, 11H, Ar-H), 5.67 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 7.9 Hz, 1H, H-2), 5.63 – 5.51 (m, 1H, C*H*=CH_2), 5.25 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.76 (t, J_{gem} = 1.2 Hz, 1H, CH_2=CH), 4.74 – 4.70 (m, 1H, CH_2=CH), 4.56 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.54 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.48 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 3.87 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 3.86 – 3.75 (m, 2H, H-5, -$OCH_2^{pentenyl}$), 3.71 (dd, $J_{6a,6b}$ = 9.0, $J_{5,6a}$ =7.3 Hz, 1H, H-6a), 3.64 (dd, $J_{6a,6b}$ = 9.0, $J_{5,6b}$ = 5.7 Hz, 1H), 3.48 – 3.40 (m, 1H, -$OCH_2^{pentenyl}$), 3.39 (s, 3H, CH_3^{OMe}), 1.97 – 1.81 (m, 2H, $CH_2^{pentenyl}$), 1.63 – 1.42 (m, 2H, $CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.15, 165.41, 138.12, 137.98, 133.50, 133.08, 130.00 (2C), 129.92, 129.79 (2C), 129.27, 128.62 (2C), 128.60 (2C), 128.40 (2C), 127.96 (2C), 114.81, 101.48, 76.45, 74.96, 73.74, 73.53, 70.29, 69.09, 68.20, 61.50, 29.96, 28.71. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{33}FNaO_7$: 583.2308; Found 583.2312.

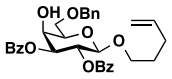
Pent-4-enyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene -β-D-galactopyranoside (154)



109 (4 g ; 11.90 mmol) was dissolved in CH_2Cl_2 (100 mL). Et_3N (5.0 mL; 35.70 mmol), DMAP (9 mg; 0.39 mmol) and benzoyl chloride (3.5 mL; 29.75 mmol) was added to the solution and the reaction mixture was stirred until TLC revealed full conversion (3 h). The reaction was quenched with MeOH (10 mL), washed with water (2x100 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (Tol/EtOAc 19:1) to afford **154** as a white crystalline powder. R_f 0.44 (9:1 Tol/EtOAc). Yield 6.0 g (94%)
$[\alpha]_D^{20}$= 105.9° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3068.38, 3035.61, 2939.64, 1720.19, 1602.03, 1451.33, 1315.13, 1273.67, 1178.58, 1108.97, 1093.98, 1059.31, 1026.80, 909.62. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (m, 4H, Ar-H), 7.54 – 7.36 (m, 4H, H^{Bz}), 7.35 – 7.24 (m, 7H, Ar-H), 5.79 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 8.0 Hz, 1H, H-2), 5.58 (ddt, J_{trans} = 16.2, J_{cis} =10.9, J_{CH2} =6.7 Hz, 1H, C*H*=CH_2), 5.47 (s, 1H, -$CH^{benzylidene}$), 5.29 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.6 Hz, 1H, H-3), 4.76 – 4.69 (m, 2H, -CH_2=$CH_{trans,}$ -CH_2=CH_{cis}), 4.66 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.51 (dd, $J_{3,4}$ = 3.6, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 4.32 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 1.6 Hz, 1H, H-6a), 4.06 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6b}$ = 1.8 Hz, 1H, H-6b), 3.89 (dt, J_{gem} = 9.6, $J_{CH2pent}$ =6.1 Hz, 1H, -$OCH_2^{pentenyl}$), 3.59 (m, 1H, H-5), 3.46 (ddd, J_{gem} = 9.6, $J_{CH2pent}$ =7.3, $J_{CH2pent}$ = 6.2 Hz, 1H, -$OCH_2^{pentenyl}$), 1.99 – 1.79 (m, 2H, -$CH_2^{pentenyl}$), 1.68 – 1.42 (m, 2H, -$CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz,

$CDCl_3$) δ 166.38, 165.35, 138.09, 137.64, 133.47, 133.15, 130.07 (2C), 129.88, 129.80 (2C), 129.29, 129.05, 128.52 (2C), 128.43 (2C), 128.22 (2C), 126.42 (2C), 114.82, 101.35, 101.01, 73.76, 72.95, 69.27, 69.12, 68.90, 66.63, 29.97, 28.67. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{32}O_8Na$: 567.1995; Found 567.1998.

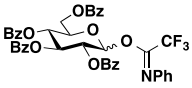
Pent-4-enyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranoside (155)



Trifluoroacetic acid (7.0 mL, 91.88 mmol) was added drop wise to a solution of **154** (10.0 g, 18.37 mmol) and triethylsilane (14.7 mL, 91.88 mmol) in CH_2Cl_2 (75 mL) at 0 °C. When the addition was complete (10 min), the reaction was heated to 22 °C and stirred for 5 h. The mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford **155**. R_f 0.38 (9:1 Tol/EtOAc). Yield: 7.1 (72%)

$[\alpha]_D^{20}$ = 37.9° (c 1.0, $CDCl_3$). IR(neat): 3483.76, 3066.25, 3032.49, 2937.28, 2874.13 ,1719.34, 1601.94, 1451.65, 1315.18, 1265.13, 1177.72, 1106.62, 1069.16, 1027.79, 709.34. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 4H, H^{Bz}), 7.47 – 7.38 (m, 2H, H^{SPh}), 7.33 – 7.19 (m, 9H, H^{SPh}, H^{Bz}), 5.75 – 5.65 (dd, $J_{1,2} = J_{2,3}$ = 9.5, H-2), 5.57 (ddt, J_{trans} = 15.7, J_{cis} = 11.2, J_{CH2} = 6.6 Hz, 1H, -C*H*=CH_2), 5.21 (dt, $J_{2,3}$ = 9.5, $J_{3,4}$ =1.6 Hz, 1H, H-3), 4.76-4.73 (m, 2H, C*H*$_2$=$CH_{trans,}$ C*H*$_2$=CH_{cis}), 4.60 (d, $J_{1,2}$ = 9.5, 1H, H-1), 4.52 (m, 2H, , CH_2^{Bn}), 4.31 – 4.28 (m, 1H, H-4), 3.85 (dt, J_{gem} = 9.7, $J_{CH2pent}$ = 6.2 Hz, 1H, -$OCH_2^{pentenyl}$), 3.80 – 3.69 (m, 3H, H-5, H-6a, H-6b), 3.51 – 3.39 (m, 1H, -$OCH_2^{pentenyl}$), 1.98 – 1.81 (m, 2H, -$CH_2^{pentenyl}$), 1.62 – 1.45 (m, 2H, -$CH_2^{pentenyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.95, 165.35, 137.90, 137.65, 137.64, 133.37, 133.06, 129.89 (2C), 129.69 (2C), 129.18, 128.51 (3C), 128.44 (2C), 128.32 (2C) , 127.89, 127.81 (2C), 114.78, 101.55, 74.45, 74.43, 73.80, 73.32, 69.75, 69.28, 69.17, 68.12, 29.84, 28.62. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{34}O_8Na$: 569.2151; Found 569.2150

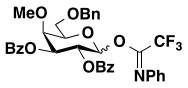
2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose *N*-phenyl trifluoroacetimidate (156)



To a solution of perbenzoylated glucopyranoside (2 g; 2.85 mmol) was dissolved in CH_2Cl_2 (10 mL) followed by addition of 30% HBr/AcOH (1.33 mL). The reaction mixture was stirred for 3 h and then poured into ice water (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Without further purification the off-white solid was dissolved in acetone (10 mL) and H_2O (0.5 mL). Ag_2CO_3 (0.4 g; 1.46 mmol) was added and the reaction mixture was stirred for 2 h at 22 °C. The solution dispension was filtered through a plug of celite and concentrated to give the product in quantitative yield. R_f 0.36 (2:1 heptane/EtOAc). The residue was dissolved in CH_2Cl_2 (20 mL). The solution was cooled to 0 °C followed by addition of PTFAICl (1.2 g; 5.70 mmol) and Cs_2CO_3 (1.9 g; 5.7 mmol). The reaction was stirred at 0 °C for 5 h. The reaction was filtered, concentrated and the crude was purified by flash chromatography (9:1 Tol/EtOAc) to give the product **156** as a white powder. Yield: 1.7 g (79% over two steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.3, 1.4 Hz, 2H, Ar-H^{Bz}), 7.93 – 7.88 (m, 2H, Ar-H^{Bz}), 7.83 (dd, J = 8.3, 1.4 Hz, 2H, Ar-H^{Bz}), 7.81 – 7.76 (m, 2H, Ar-H^{Bz}), 7.53 – 6.98 (m, 17H, Ar-H), 6.69 – 6.62 (m, 2H, Ar-H^{NPh}), 6.29 – 5.98 (m, 1H), 5.89 (t, J = 9.2 Hz, 1H), 5.79 – 5.61 (m, 2H), 4.57 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$= 2.9 Hz, 1H, H-6a), 4.43 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$= 5.5 Hz, 1H, H-6b). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.08, 165.67, 165.10, 164.82, 142.95, 133.60, 133.54, 133.43, 133.19, 129.88-119.23 (25C), 94.70, 73.30, 72.54, 70.80, 68.97, 62.79.

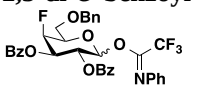
2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*O*-methyl-D-galactopyranose *N*-phenyl trifluoroacetimidate (157)



157 (1.6 g; 2.94 mmol) was dissolved in MeCN (20 mL) and water (1 mL). NBS (1.3 g; 5.89 mmol) was added and the reaction was stirred at 22 °C for 3 h. The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was filtered through a plug of silica (2:1 Tol/EtOAc) and the resulting yellow oil was used directly in the next step. The residue was dissolved in CH_2Cl_2 (30 mL). The solution was cooled to 0 °C followed by addition of PTFAICl (1.2 g; 5.89 mmol) and Cs_2CO_3 (1.9 g; 5.89 mmol). The reaction was stirred at 0 °C until TLC showed full conversion (6 h). The reaction was filtered, concentrated and the crude was purified by flash chromatography (9:1 Tol/EtOAc) to give the product **157** as an oil. Yield: 1.44 g (74% over two steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 2H), 7.91 – 7.86 (m, 2H), 7.61 – 6.89 (m, 14H), 6.63 (d, *J* = 7.7 Hz, 2H, Ar-H^{NPh}), 5.90 (d, *J* = 9.6 Hz, 1H), 5.41 – 5.23 (m, 1H), 4.62 – 4.37 (m, 2H), 3.91 (d, *J* = 2.8 Hz, 1H), 3.69 (m, 2H), 3.41 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.86, 164.97, 143.15, 137.65, 133.55, 133.31, 129.90, 129.75, 129.23, 128.90, 128.73, 128.58, 128.49, 128.43, 127.91, 127.90, 124.42, 119.26, 95.23, 75.95, 74.54, 74.28, 73.61, 69.25, 67.50, 61.55.

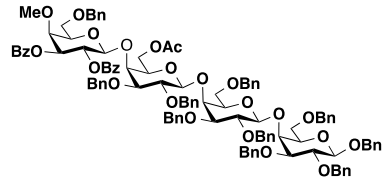
2,3-di-*O*-benzoyl-6-*O*-benzyl-4-deoxy-4-fluoro-D-galactopyranose *N*-phenyl trifluoroacetimidate (158)



149 (2.0 g; 3.64 mmol) was dissolved in MeCN (20 mL) and water (1 mL). NBS (1.6 g; 7.29 mmol) was added and the reaction was stirred at 22 °C for 6 h. The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was filtered through a plug of silica (3:1 Tol/EtOAc) and the resulting yellow oil was used directly in the next step. The residue was dissolved in CH_2Cl_2 (30 mL). The solution was cooled to 0 °C followed by addition of PTFAICl (1.5 g; 7.28 mmol) and Cs_2CO_3 (2.4 g; 7.28 mmol). The reaction was stirred at 5 °C for 12 h. The reaction was filtered, concentrated and the crude was purified by flash chromatography (6:1 Tol/EtOAc) to give the product **158** as a sticky oil. Yield: 1.40 g (59% over two steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.92 – 7.87 (m, 2H), 7.52 – 6.94 (m, 14H, Ar-H), 6.64 (d, *J* = 7.7 Hz, 2H, Ar-H^{NPh}), 5.95 – 5.82 (m, 1H), 5.37 (m, 1H), 5.18 – 4.96 (m, 1H), 4.52 (m, 2H, CH_2^{Bn}), 3.73 (m, 2H, H-6a, H-6b). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.73, 164.83, 142.96, 137.45, 133.67, 133.47, 130.01-119.22(20C), 94.92, 86.77, 84.91, 73.71, 73.49 (d, *J* = 18.1 Hz), 71.94 (d, *J* = 17.7 Hz), 68.56.

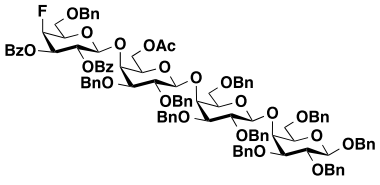
Benzyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*O*-methyl-β-D-galactopyranosyl-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)- 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (159)



To a 50 mL flame-dried flask was added **148** (1000 mg, 0.74 mmol) and **157** (978 mg, 1.47 mmol). The mixture was co-evaporated with toluene (2x20 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (20 mL) and cooled to -20 °C. TMSOTf (16 μL; 0.07 mmol) was added and the reaction mixture was stirred at 0 °C for 2.5h. Et_3N (1 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (12:1 Tol/EtOAc) to afford **159**. R_f 0.25 (9:1 Tol/EtOAc). Yield: 1046 mg (78%)

$[\alpha]_D^{20}$ = 15.0° (c 1.0, $CDCl_3$)**. IR**(neat, cm^{-1}): 3062.51, 3030.28, 2920.72, 2866.91, 1730.42, 1602.22, 1496.29, 1452.97, 1364.06, 1276.54, 1105.38, 1070.11, 737.05, 697.93 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.82 (m, 4H, H^{Bz}), 7.58 – 6.87 (m, 38H, H^{Bz}, H^{Bn}), 5.71 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 7.9 Hz, 1H, H-2^4), 5.25 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.1 Hz, 1H, H-3^4), 4.93 (d, *J* = 7.9 Hz, 1H, H-1^4), 4.90 (d, J_{CH2} = 4.6 Hz, 1H, -CH_2^{Bn}), 4.87 (d, J_{CH2} = 5.7 Hz, 1H, -CH_2^{Bn}), 4.84 (d, $J_{1,2}$ = 7.2 Hz, 1H, H-$1^{2/3}$), 4.78 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-$1^{2/3}$), 4.65 – 4.46 (m, 14H, 7xCH_2^{Bn}), 4.40 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1^1), 4.38 – 4.24 (m, 6H, H-$4^{1/2/3}$, H-$6a^3$, 2xCH_2^{Bn}), 4.12 (d, *J* = 2.8 Hz, 1H, H-$4^{1/2/3}$), 4.02 (dd, $J_{6a,6b}$ = 11.8, $J_{5,6b}$ = 6.8 Hz, 1H, H-$6b^3$), 3.88 (d, *J* = 3.1 Hz, 2H, H-$4^{2/3}$, H-4^4), 3.81 – 3.26 (m, 17H, H-2^1, H-$2^{2/3}$, H-3^1, H-$3^{2/3}$, H-5^1-H-5^4, H-6^1-H-6^3, -OCH_3), 3.25 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 2.7 Hz, 1H, H-$3^{2/3}$), 3.20 (dd, $J_{2,3}$ = 9.7, $J_{1,2}$ = 7.2 Hz, 1H, H-$2^{2/3}$), 1.86 (s, 3H, -CH_3^{Ac}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.63, 166.04, 165.12, 139.21, 138.81, 138.76, 138.72, 138.70, 138.59, 138.56, 138.55, 137.94, 137.83, 133.34, 132.74, 130.05-127.06 (60C), 103.22, 102.75, 101.83, 101.76, 82.04, 81.77, 80.83, 80.14, 80.04, 79.92, 77.25, 76.34, 75.26, 74.87, 74.65, 74.61, 74.25, 74.21, 73.87, 73.69, 73.59, 73.55, 73.47, 73.23, 72.73, 72.71, 71.95, 70.79, 70.65, 70.06, 69.77, 69.28, 68.15, 64.37, 61.40, 20.94.

Benzyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-4-deoxy-4-fluoro-β-D-galactopyranosyl-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)- 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (160)



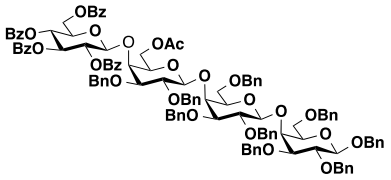
To a 25 mL flame-dried flask was added **148** (600 mg, 0.44 mmol) and **158** (575 mg, 0.88 mmol). The mixture was co-evaporated with toluene (2x10 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (10 mL) and cooled to -20 °C. TMSOTf (8 μL; 0.04 mmol) was added and the reaction mixture was stirred at 0 °C for 4h. Et_3N (0.5 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (12:1 Tol/EtOAc) to afford **160**. R_f 0.38 (9:1 Tol/EtOAc). Yield: 589 mg (74%)

$[\alpha]_D^{20}$ = 28.24° (c 1.0, $CDCl_3$) **IR**(neat, cm^{-1}): 3088.39, 3063.00, 2922.52, 1733.08, 1602.25, 1584.91, 1496.35, 1363.55, 1313.81, 1276.07, 1261.75, 1104.44, 1069.34, 1028.39.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 7.73 (m, 4H), 7.59 – 6.90 (m, 40H), 5.69 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 7.9 Hz, 1H, H-2^4), 5.27 (ddd, $J_{3,F}$ = 27.3, $J_{2,3}$ = 10.5, $J_{3,4}$ =2.7 Hz, 1H, H-3^3), 5.04 (dd, $J_{4,F}$ = 50.1, $J_{3,4}$ = 2.7 Hz, 1H, H-4^4), 5.01 (d, *J* = 7.9 Hz, 1H, H-1^4), 4.92 – 4.83 (m, 3H, H-$1^{2/3}$, -CH_2^{Bn}), 4.78 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-$1^{2/3}$), 4.66 – 4.47 (m, 14H, -7xCH_2^{Bn}), 4.40 (d, *J* = 7.6 Hz, 1H, H-1^1), 4.38 – 4.23 (m, 6H, H-$4^{2/3}$ H-$6a^3$, 2xCH_2^{Bn}), 4.12 (d, $J_{3,4}$ = 2.8 Hz, 1H, H-

$4^{2/3}$), 4.00 (dd, $J_{6a,6b}$ = 11.7, $J_{5,6b}$ = 6.8 Hz, 1H, H-6b^3), 3.90 (d, $J_{3,4}$ = 2.8 Hz, 1H, H-4^1), 3.78 – 3.31 (m, 16H, H-2^1, H-2$^{2/3}$, H-3^1, H-3$^{2/3}$ H-5^1-H-5^4, H-6^1-H-6^4), 3.27 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 2.8 Hz, 1H, H-3$^{2/3}$), 3.18 (dd, $J_{2,3}$ = 9.7, $J_{1,2}$ = 7.4 Hz, 1H, H-2$^{2/3}$), 1.87 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.57, 165.92, 164.94, 139.18, 138.80, 138.71 (2C), 138.64, 138.54 (2C), 138.51, 137.82, 137.70, 133.48, 132.95, 130.06-127.07 (60C), 103.27, 102.75, 101.74, 101.50, 82.04, 81.75, 80.77, 80.19, 80.04, 79.92, 77.24, 75.26, 74.87, 74.58, 74.26, 74.18, 73.86, 73.83, 73.73 (2C), 73.50, 73.45 (2C), 72.77, 72.73, 72.28, 72.06, 71.80, 70.80, 70.63, 69.69, 69.45, 69.30, 67.48, 64.16, 20.90.

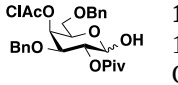
Benzyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (161)



To a 25 mL flame-dried flask was added **148** (620 mg, 0.46 mmol) and **156** (699 mg, 0.91 mmol). The mixture was co-evaporated with toluene (2x10 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (10 mL) and cooled to -20 °C. TMSOTf (8 µL; 0.04 mmol) was added and the reaction mixture was stirred at 0 °C for 4h. Et_3N (0.5 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (12:1 Tol/EtOAc) to afford **161**. R_f 0.32 (9:1 Tol/EtOAc). Yield: 627 mg (74%)

$[\alpha]_D^{20}$ = 13.8° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3088.42, 3062.89, 3030.58, 2918.98, 2868.34, 1733.36, 1601.76, 1584.39, 1496.02, 1452.52, 1364.00, 1314.43, 1262.07, 1091.21, 1067.85, 1027.25, 735.31, 709.52, 697.82. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.88 (m, 4H, H^{Bz}), 7.80 (m, 5H, H^{Bz}), 7.49 – 6.96 (m, 56H), 5.83 (t, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, 1H, H-3^4), 5.58 (t, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, 1H, H-4^4), 5.46 (dd, $J_{2,3}$ = 9.8, $J_{1,2}$ = 8.1 Hz, 1H, H-2^4), 5.17 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1^4), 4.93 – 4.81 (m, 3H, H-1$^{2/3}$, CH_2^{Bn}), 4.78 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1$^{2/3}$), 4.67 – 4.21 (m, 21H, H-1^1, H-4$^{2/3}$, H-6a^3, H-6a^4, H-6b^4, 8xCH_2^{Bn}), 4.16 – 4.11 (m, 1H, H-4^1), 4.07 (dd, $J_{6a,6b}$ = 11.6, $J_{5,6b}$ = 6.6 Hz, 1H, H-6b^3), 3.96 (dt, $J_{4,5}$ = 9.8, $J_{5,6}$ = 4.2 Hz, 1H, H-5^4), 3.93 – 3.89 (m, 1H, H-4$^{2/3}$), 3.83 – 3.10 (m, 13H, H-2^1-H-2^3, H-3^1-H-3^3, H-5^1-H-5^3, H-6^1, H-6^2), 1.87 (s, 3H, -CH_3^{Ac}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.52, 166.14, 165.81, 165.27, 164.90, 139.18, 138.82, 138.74, 138.69 (2C), 138.55, 138.53 (2C), 137.82, 133.44, 133.23, 133.17, 133.07, 130.10 - 127.10 (65C), 103.30, 102.78, 101.86, 101.49, 82.02, 81.78, 80.66, 80.24, 80.05, 79.93, 77.28, 75.28, 74.89, 74.69, 74.41, 74.21, 73.86, 73.78, 73.55, 73.47, 72.83, 72.77, 72.75, 72.10, 72.01 (2C), 71.71, 70.83, 70.65, 70.05, 69.79, 69.62, 63.88, 63.18, 20.86.

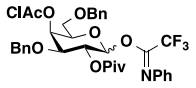
3,6-*O*-dibenzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranose (165a)



169 (29.5 g; 48.27 mmol) was dissolved in acetone (360 mL) and water (40 mL). NBS (34.4 g; 193.07 mmol) was added and the reaction was stirred at 22 °C for 3 h. The solution was diluted with CH_2Cl_2 (500 mL) and washed with sat. aq. NaS_2O_3 (250 mL) and sat. aq. $NaHCO_3$ (250 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product **165a** was purified by flash chromatography (12:1 Tol/EtOAc). R_f 0.23 (9:1 Tol/EtOAc). Yield: 21.8 g (88%)

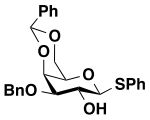
$[\alpha]_D^{20}$ = 45.0° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3447.69, 3064.18, 3031.62, 2971.66, 2932.75, 2909.68, 2872.70, 1763.56, 1730.54, 1496.83, 1479.89, 1454.78, 1398.86, 1366.02, 1283.02, 1156.41, 1095.43, 1064.77, 738.54, 698.63. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 10H, H^{Bn}), 5.61 (td, $J_{3,4}$ = 3.8, $J_{4,5}$ = 1.1 Hz, 1H, H-4a, H-4b), 5.39 (d, J = 3.7 Hz, 1H, H-1a), 4.89 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ =3.7 Hz, 1H, H-2a), 4.84 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 8.1 Hz, 1H, H-2b), 4.66 (d, J = 4.4 Hz, 1H, -CH_2^{Bn}), 4.63 (d, J = 4.2 Hz, 1H, -CH_2^{Bn}), 4.52 – 4.48 (m, 1H, -CH_2^{Bn}), 4.48 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1b), 4.42 – 4.34 (m, 2H, -CH_2^{Bn}), 4.32 – 4.26 (m, 1H, H-5a), 4.05 – 3.88 (m, 3H, H-3a, -CH_2^{AcCl}), 3.73 (ddd, $J_{5,6a}$ = 7.0, $J_{5,6b}$ = 5.6, $J_{4,5}$ = 1.2 Hz, 1H, H-5b), 3.59 (dd, J = 10.1, 3.3 Hz, 1H, H-3b), 3.53 (dd, $J_{6a,6b}$ = 9.3, $J_{5b,6a}$ = 5.6 Hz, 1H, H-6a^b), 3.49 – 3.36 (m, 3H, H-6b^b, H-6a^a, H-6b^a), 1.13 (s, 9H, 3xCH_3^{Piv}), 1.12 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.43, 177.99, 166.99, 166.85, 137.26, 137.24, 137.16, 136.85, 129.01, 128.56, 128.54, 128.52, 128.49, 128.44, 128.39, 128.36, 128.30, 128.27, 128.23, 128.20, 128.11, 128.08, 128.05, 128.01, 127.90, 96.32, 90.64, 77.24, 76.46, 73.76, 73.73, 72.98, 72.89, 72.12, 72.07, 71.97, 70.10, 69.87, 69.29, 68.22, 68.10, 68.02, 67.69, 67.31, 67.14, 40.82, 40.76, 38.95, 38.78, 27.10, 27.07, 27.04. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{33}ClO_8Na$: 543.1762; Found 543.1766.

4,6-O-benzylidene-3-O-chloroacetyl-2-O-pivaloyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (165)



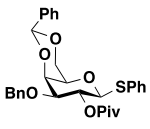
141a (21.3 g; 40.86 mmol) was dissolved in DCM (100 mL) and cooled to 0 °C. Cs_2CO_3 (26.6 g; 81.74 mmol) was added followed by *N*-phenyl trifluoroacetimidoyl chloride (17.0 g; 81.73 mmol). The ice bath was removed and the reaction mixture was stirred until TLC showed full conversion (6 h). It was then filtered, concentrated and purified by flash chromatography (20:1 Tol/EtOAc) to give a white crystalline product. Yield: 22.3 g (80%)

Phenyl 4,6-*O*-benzylidene-3-*O*-benzyl-1-thio-β-D-galactopyranoside (166)[364]



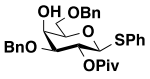
A mixture of **56** (10.0 g, 27.7 mmol), n-Bu_2SnO (7.6 g, 30.5 mmol), and 200 mL of dry benzene was stirred at reflux for 12 h. The reaction mixture was concentrated and the stannylidene derivative was redissolved in toluene (100 mL). Then n-Bu_4NBr (13.4 g, 41.6 mmol) and benzyl bromide (5.0 mL, 41.9 mmol) were added and the reaction mixture was stirred for 5 h at 60 °C. The reaction mixture was then concentrated and the product was purified by flash chromatography (9:1 Tol/EtOAc) to give **166** as an amorphous solid. R_f 0.19 (9:1 Tol/EtOAc). Yield: 10.5 g (84%)
$[\alpha]_D^{20}$= 6.4° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3454.08, 3061.88, 2971.92, 1583.10, 1496.37, 1453.87, 1363.13, 1339.19, 1286.57, 1212.72, 1167.31, 1078.73, 1042.32, 1026.56, 994.77. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 2H), 7.41 – 7.08 (m, 13H), 5.35 (s, 1H, $CH^{benzylidene}$), 4.66 (d, J_{CH2} = 12.3 Hz, 1H, CH_2^{Bn}), 4.62 (d, J_{CH2} = 12.3 Hz, 1H, CH_2^{Bn}), 4.44 (d, $J_{1,2}$ = 9.3 Hz, 1H, H-1), 4.27 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.6 Hz, 1H, H-6a), 4.06 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4), 3.89 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ = 1.7 Hz, 1H, H-6b), 3.87 (t, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, 1H, H-2), 3.43 (dd, $J_{2,3}$ = 9.3, $J_{3,4}$ = 3.3 Hz, 1H, H-3), 3.36 (m, 1H, H-5), 2.42 (m, 1H, -OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.97, 137.84, 133.76 (2C), 130.70, 129.06, 128.90 (2C), 128.49 (2C), 128.13 (2C), 128.10, 127.94, 127.92 (2C), 126.54 (2C), 101.14, 87.08, 80.28, 73.26, 71.65, 70.09, 69.41, 67.21. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{26}NaO_5S$ 473.1399; Found 473.1392.

Phenyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (167)[365]



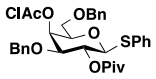
166 (40 g; 88.78 mmol) was dissolved in CH_2Cl_2 (500 mL). Et_3N (21.7 mL; 21.65 mmol), DMAP (5.4 g; 44.39 mmol) and pivaloyl chloride (16.4 mL; 133.17 mmol) was added to the solution and the reaction mixture was heated to 45 °C for 6 h. The reaction mixture was cooled to 0 °C, quenched with MeOH (10 mL), washed with water (2x150 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc) to afford **167** as a white crystalline powder. R_f 0.47 (9:1 Tol/EtOAc). Yield 43.7 g (92%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H, H^{SPh}), 7.41 – 7.06 (m, 13H, H^{SPh}, H^{Bn}, Ar-H), 5.36 (s, 1H, $-CH^{benzylidene}$), 5.27 (t, $J_{1,2}$ = $J_{2,3}$ = 9.7 Hz, 1H, H-2), 4.62 (d, $J_{1,2}$ = 9.7 Hz, 1H, H-1), 4.55 (d, J_{CH2} = 1.8 Hz, 2H, $-CH_2^{Bn}$), 4.27 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ =1.6 Hz, 1H, H-6a), 4.08 (dd, $J_{3,4}$ = 3.4, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.90 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6b}$ = 1.7 Hz, 1H), 3.61 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 3.35 (m, 1H, H-5), 1.17 (s, 9H, 3x-CH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.56, 138.05, 137.77, 133.39 (2C), 132.25, 129.09, 128.83 (2C), 128.44 (2C), 128.20 (2C), 127.95, 127.86, 127.66 (2C), 126.65 (2C), 101.22, 85.87, 78.85, 73.47, 71.42, 70.07, 69.43, 68.05, 38.88, 27.35, 27.33 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{34}NaO_6S$ 557.1974; Found 557.1975.

Phenyl 3,6-di-*O*-benzyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (168)



Trifluoroacetic acid (23.7 mL, 309.46 mmol) was added drop wise to a solution of **167** (32.97 g, 61.89 mmol) and triethylsilane (49.4 mL, 309.46 mmol) in CH_2Cl_2 (400 mL) at 0 °C. When the addition was complete (10 min), the reaction was warmed to 22 °C and stirred for 3 hr. The mixture was diluted with ethyl acetate and washed with sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (12:1 Tol/EtOAc) to afford **168**. R_f 0.31 (9:1 Tol/EtOAc). Yield: 26.8 g (81%).
$[\alpha]_D^{20}$= -54.3° (c 1.0, $CDCl_3$)**. IR**(neat, cm^{-1}): 3468.17, 3062.04, 2904.62, 1731.80, 1583.86, 1496.63, 1478.63, 1454.44, 1396.64, 1366.07, 1277.93, 1229.95, 1207.26, 1151.67, 1095.40, 1063.86. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 2H, H^{SPh}), 7.30 – 7.13 (m, 13H, , H^{Bn}, H^{SPh}),), 5.20 (dd, $J_{1,2}$ = 10.1, $J_{2,3}$ = 9.3 Hz, 1H, H-2), 4.60 – 4.54 (m, 2H, H-1, $-CH_2^{Bn}$), 4.54 – 4.48 (m, 3H, 3x-CH_2^{Bn}), 4.02 (dd, $J_{3,4}$ = 3.3, $J_{4,5}$ =1.1 Hz, 1H, H-4), 3.73 (dd, $J_{5,6a}$ = $J_{5,6b}$ = 5.9, $J_{6a,6b}$ = 1.5 Hz, 2H, H-6a, H-6b), 3.59 (td, $J_{5,6a}$ = $J_{5,6b}$ = 5.9, $J_{4,5}$ = 1.1 Hz, 1H, H-5), 3.51 (dd, $J_{2,3}$ =9.3, $J_{3,4}$ = 3.3 Hz, 1H, H-3), 1.17 (s, 9H, 3x-CH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.97, 138.12, 137.35, 133.91, 132.03 (2C), 128.96 (2C), 128.65 (2C), 128.54 (2C), 128.17, 127.89 (2C), 127.87, 127.76 (2C), 127.71, 87.14, 80.18, 77.53, 73.84, 71.97, 69.43, 68.74, 66.66, 38.91, 27.32. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{36}ClNaO_6S$: 559.2130; Found 559.2140.

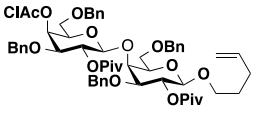
Phenyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (169)



168 (30 g; 56.11 mmol) was dissolved in CH_2Cl_2 (350 mL) and cooled to 0 °C. $(ClAc)_2O$ (16.3 g; 95.38 mmol), Et_3N (15.6 mL; 112.21 mmol) and DMAP (137 mg; 1.12 mmol) was added and the reaction was stirred at 0 °C for 3 h. The reaction mixture was concentrated and purified by flash chromatography (30:1 Tol/EtOAc) to afford **169** as a yellowish crystalline powder. R_f 0.59 (9:1 Tol/EtOAc). Yield 31.8 g (93%)
$[\alpha]_D^{20}$= 14.7° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3087.86, 3061.83, 3030.97, 2969.93, 2932.50, 2906.70, 2870.91, 1763.39, 1738.73, 1478.57, 1454.85, 1366.32, 1277.76, 1145.59, 1098.56, 1064.02, 743.79, 697.64. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 2H, H^{SPh}), 7.34 – 7.05 (m, 13H, H^{Bn}, H^{SPh}), 5.64 (dd, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 5.06 (t, $J_{1,2}$

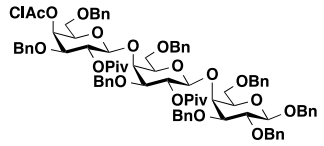
= $J_{2,3}$ =9.8 Hz, 1H, H-2), 4.64 (d, J_{CH2} =11.4 Hz, 1H, -CH_2^{Bn}), 4.61 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.49 (d, J_{CH2} =11.7 Hz, 1H, -CH_2^{Bn}), 4.37 (d, J_{CH2} =11.7 Hz, 1H, -CH_2^{Bn}), 4.33 (d, J_{CH2} = 11.4 Hz, 1H, -CH_2^{Bn}), 3.99 (d, J_{CH2} = 15.2 Hz, 1H, -CH_2^{AcCl}), 3.89 (d, J_{CH2} = 15.2 Hz, 1H, -CH_2^{AcCl}), 3.76 (ddd, $J_{5,6a}$ = 7.1, $J_{5,6b}$ = 5.9, $J_{4,5}$ =1.1 Hz, 1H, H-5), 3.57 (m, 2H, H-3, H-6b), 3.46 (dd, $J_{6a,6b}$ = 9.4, $J_{5,6a}$ = 7.1 Hz, 1H, H-6a), 1.14 (s, 9H, 3x-CH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.87, 167.01, 137.46, 137.04, 133.30, 132.39 (2C), 129.00 (2C), 128.64 (2C), 128.51 (2C), 128.30 (2C), 128.17 (2C), 128.15, 128.05, 128.02, 87.35, 78.20, 75.81, 73.86, 71.90, 68.50, 68.47, 67.61, 40.90, 38.87, 27.28 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{33}H_{37}ClNaO_7$: 635.1846; Found 635.1844.

Pent-4-enyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranoside (170)



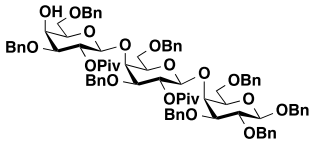
To a 500 mL flame-dried flask was added **142** (20 g, 39.01 mmol) and the **165** (35.1 g, 50.72 mmol). The mixture was co-evaporated with toluene (2x200 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (250 mL) and cooled to -40 °C. TMSOTf (0.7 mL; 3.9 mmol) was added and the reaction mixture was stirred at -40 °C for 2h. Et_3N (4 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (20:1 Tol/EtOAc) to give disaccharide **170**. R_f 0.49 (9:1 Tol/EtOAc). Yield: 32.8 g (83%) $[\alpha]_D^{20}$= 3.3° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3064.08, 2973.10, 2871.20, 1738.29, 1497.01, 1479.43, 1454.62, 1366.91, 1278.31, 1149.83, 1135.46, 1089.27, 1066.29, 912.64, 738.48, 698.59. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.00 (m, 20H, H^{Bn}), 5.70 (dddd, J_{trans} = 15.5, J_{cis} =10.1, J_{CH2} =7.3, J_{CH2} = 5.9 Hz, 1H), 5.50 (dd, $J_{3',4'}$ = 3.2, $J_{4',5'}$ = 1.3 Hz, 1H, H-4'), 5.07 (dd, $J_{2,3}$ = 9.9, $J_{1,2}$ = 7.7, 1H, H-2), 5.01 – 4.96 (m, 2H, H-1', H-2'), 4.91 (dd, J = 17.4, 1.7 Hz, 1H, CH_2=CH_{trans}), 4.84 (m, 1H, CH_2=CH_{cis}), 4.62 – 4.54 (m, 2H, -CH_2^{Bn}), 4.52 – 4.35 (m, 5H, 3x-CH_2^{Bn}), 4.35 – 4.21 (m, 3H, H-1, H-4, -CH_2^{Bn}), 3.92 (d, J = 15.1 Hz, 1H, -CH_2^{AcCl}), 3.77 (d, J = 15.1 Hz, 1H, -CH_2^{AcCl}), 3.73 – 3.56 (m, 3H, -OC$H_2^{pentenyl}$, H-6'), 3.56 – 3.49 (m, 1H, H-5), 3.45 (m, 3H, H-3, H-3', H-5'), 3.39 – 3.25 (m, 3H, H-6, -$OCH_2^{pentenyl}$), 2.08 – 1.87 (m, 2H, -$CH_2^{pentenyl}$), 1.62 – 1.44 (m, 2H, -$CH_2^{pentenyl}$), 1.16 (s, 9H, 3xCH_3^{Piv}), 1.10 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.37, 176.70, 166.84, 138.54, 138.24, 137.77, 137.38, 137.15, 129.04, 128.54 (2C), 128.39 (2C), 128.34 (2C), 128.31 (2C), 128.23, 128.06 (2C), 128.02, 127.96 (2C), 127.80, 127.70 (3C), 127.61, 127.01, 114.65, 101.43, 99.03, 80.65, 76.94, 73.80, 73.64, 73.55, 71.97, 71.91, 71.81, 70.75, 69.25, 68.54, 68.46, 67.83, 67.28, 40.76, 38.88, 38.76, 30.07, 28.91, 27.31 (3C), 27.21 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{57}H_{71}ClNaO_{14}$: 1037.4430; Found 1037.4437.

Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (171)



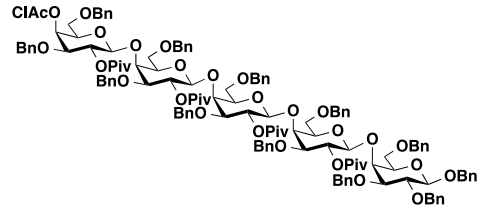
To a 100 mL flame-dried flask was added acceptor **113** (2.8 g, 5.17 mmol) and donor **170** (6.8 g, 6.73 mmol). The mixture was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (30 mL) and dry MeCN (30 mL), cooled to -40 °C, followed by addition of NIS (1.6 g; 6.99 mmol) and TESOTf (273 mg; 1.03 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc) to afford a white crystalline material. R_f 0.48 (9:1 Tol/EtOAc). Yield: 6.5 g (85%) $[\alpha]_D^{20}$= -1.4° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3088.25, 3063.40, 3030.60, 2970.63, 2929.85, 2869.72, 1737.84, 1603.01, 1585.50, 1496.62, 1479.30, 1453.95, 1364.45, 1277.23, 1134.25, 1098.69, 1064.19, 910.75. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 – 7.01 (m, 40H), 5.49 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4^3), 5.11 – 4.92 (m, 3H, H-2^2, H-2^3, H-$1^{2/3}$), 4.88 – 4.75 (m, 3H, H-$1^{2/3}$, -CH_2^{Bn}), 4.70 – 4.24 (m, 16H, H-1^1, H-4^1, 7x-CH_2^{Bn}), 4.05 (d, $J_{3,4}$ = 2.6 Hz, 1H, H-4^2), 3.87 (d, J_{CH2} = 15.0 Hz, 1H, -CH_2^{AcCl}), 3.73 (d, J_{CH2} = 15.0 Hz, 1H, -CH_2^{AcCl}), 3.70 – 3.55 (m, 13H, H-2^1, H-3^1 – H-3^3, H-5^1-H-5^3, H-6^1-H-6^3), 3.50 – 3.23 (m, 9H, 3xCH_3^{Piv}), 1.20 (s, 9H, 3xCH_3^{Piv}), 1.08 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.34, 176.68, 166.82, 138.80 (2C), 138.60, 138.50, 137.84, 137.81, 137.42, 137.08, 128.56-126.87 (40C), 102.62, 100.62, 99.16, 81.85, 81.24, 79.45, 75.08, 73.95, 73.68, 73.66, 73.53, 73.30, 72.91, 72.02, 71.99, 71.81, 71.06 (2C), 70.68, 70.52, 70.13, 68.94, 68.49, 67.31, 67.29, 40.74, 38.95, 38.77, 27.51(3C), 27.39(3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{86}H_{97}ClNaO_{19}$: 1491.6210; Found 1491.6223.

Benzyl 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (172)



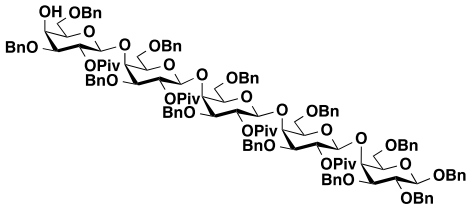
To a solution of **171** (4.35 g; 2.96 mmol) in THF (50 mL) at 0 °C was added a 0.02M $NaOCH_3$ solution in CH_3OH (100 mL). The reaction mixture was stirred at 0 °C for 1h, quenched with amberlite 120-H^+ resin, filtered and concentrated. The residue was purified by flash chromatography (9:1 Tol/EtOAc) to give **172** as a white crystalline material. R_f 0.19 (Tol/EtOAc). Yield: 3.7 g (91%)
$[\alpha]_D^{20}$ = -1.7° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3441.58, 3063.04, 3030.23, 2969.23, 2929.93, 2870.10, 1737.07, 1496.64, 1479.39, 1454.15, 1365.69, 1278.01, 1154.12, 1100.98, 1070.66, 737.48, 697.65. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.08 (m, 40H, H^{Bn}), 5.16 – 5.04 (m, 2H, H-$2^{2/3}$, H-$2^{2/3}$), 4.92 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-$1^{2/3}$), 4.84 (d, J_{CH2} = 12.1 Hz, 1H, 0.5xCH_2^{Bn}), 4.79 (d, J_{CH2} = 10.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.75 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-$1^{2/3}$), 4.65 – 4.43 (m, 12H, 5.5xCH_2^{Bn}), 4.43 – 4.26 (m, H-1^1, H-$4^{1/2/3}$, 1.5xCH_2^{Bn}), 4.10 – 4.03 (d, *J* = 3.1 Hz,1H, H-$4^{1/2/3}$), 3.85 (d, *J* = 3.3 Hz, 1H, H-$4^{1/2/3}$), 3.71 – 3.55 (m, 5H, H-2^1, H-$6^{1/2/3}$, H-$6^{1/2/3}$), 3.55 – 3.23 (m, 8H, H-3^1-H-3^3, H-5^1-H-5^3, H-$6^{1/2/3}$), 1.23 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.52, 176.77, 138.81, 138.80, 138.60, 138.52, 138.06, 137.87 (2C), 137.33, 129.78-127.00 (40C), 102.61, 100.60, 98.96, 81.83, 81.14, 79.44, 79.00, 77.27, 75.08, 74.03, 73.70, 73.65, 73.60, 73.52, 73.36, 72.83, 72.06, 71.63, 71.13, 71.04, 70.80, 70.52, 70.26, 69.47, 68.97, 67.12, 66.40, 38.99, 38.76, 27.54(3C), 27.40(3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{84}H_{96}NaO_{18}$: 1415.6494; Found 1415.6498.

Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (173)



To a 100 mL flame-dried flask was added acceptor **172** (4 g, 2.87 mmol) and donor **170** (3.8 g, 3.73 mmol). The mixture was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (30 mL) and dry MeCN (30 mL), cooled to -40 °C, followed by addition of NIS (870 mg; 3.87 mmol) and TESOTf (151 mg; 0.57 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (1h). The solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc) to afford compound **173** as white crystalline material. R_f 0.58 (2:1 Tol/EtOAc). Yield: 5.4 g (83%)
$[\alpha]_D^{20}$ = 4.3° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3088.59, 2930.71, 2870.06, 1738.23, 1496.61, 1479.31, 1454.21, 1365.07, 1277.37, 1150.19, 1132.87, 1098.81, 1059.86, 910.25, 734.25, 697.19. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 6.96 (m, 60H, H^{Bn}), 5.50 (d, $J_{3,4}$ = 3.8 Hz, 1H, H-4^5), 5.10 – 4.91 (m, 4H, H-2^2 – H-2^5), 4.89 – 4.67 (m, 7H, H-1^2 – H-1^5, CH_2^{Bn}), 4.66 – 4.22 (m, 24H, H-1^1, H-4^1, 11xCH_2^{Bn}), 4.20 – 4.00 (m, 4H, H-4^2-H-4^4), 3.86 (d, *J* = 14.9 Hz, 1H, CH_2^{AcCl}), 3.76 (d, *J* = 14.9 Hz, 1H, CH_2^{AcCl}), 3.72 – 3.10 (m, 21H, H-2^1, H-3^1 – H-3^5, H-5^1-H-5^5, H-6^1-H-6^5), 1.17 (s, 9H, 3xCH_3^{Piv}), 1.12 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.14, 176.73, 176.62, 176.57, 166.81, 138.93, 138.87, 138.83, 138.60, 138.55 (2C), 138.04, 137.95, 137.91, 137.90, 137.41, 137.04, 129.07-125.34 (60C), 102.55, 100.63, 99.96 (2C), 99.70, 81.75, 80.90, 80.62, 79.43, 77.28, 75.07, 74.33, 74.08, 73.89, 73.68, 73.64, 73.60, 73.55, 73.52, 73.50, 72.75, 72.65, 72.02, 71.99, 71.69, 71.64, 71.37, 71.20, 71.09, 71.05, 70.69, 70.48, 70.43, 70.13, 69.64, 69.40, 69.24, 68.37, 68.29, 67.85, 67.27, 40.78, 38.87, 38.83, 38.78, 38.74, 27.56(3C), 27.49(3C), 27.42(3C), 27.38(3C)

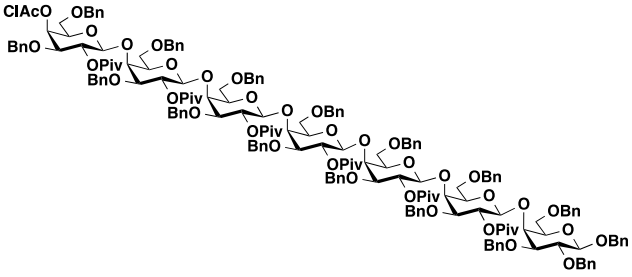
Benzyl 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (174)



To a solution of **173** (4.0 g; 1.76 mmol) in THF (25 mL) at 0 °C was added a 0.02M NaOMe solution in CH_3OH (75 mL). The reaction mixture was stirred at 0 °C for 1h, quenched with amberlite 120-H^+ resin, filtered and concentrated. The residue was purified by flash chromatography (9:1 Tol/EtOAc) to afford **174** as a white crystalline material. R_f 0.30 (9:1 Tol/EtOAc). Yield: 3.6 g (93%)
$[\alpha]_D^{20}$ = -2.14° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3088.36, 3063.23, 3030.39, 2969.66, 2930.24, 2869.29, 1737.79, 1496.65, 1479.28, 1454.16, 1365.24, 1277.26, 1152.03, 1099.26, 1069.52, 910.28, 735.06, 697.07. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44

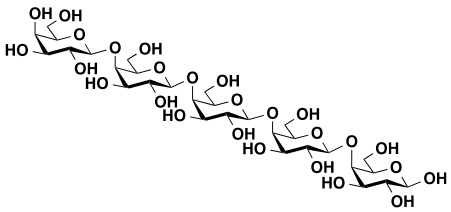
– 7.03 (m, 60H, H^{Bn}), 5.09 (dd, $J_{2,3}$ = 9.8, $J_{1,2}$ = 8.0 Hz, 1H, $H^{2/3/4/5}$), 5.02 (m, 3H, H-2^2-H-$2^{4/5}$), 4.86 – 4.69 (m, 6H, H-1^2-H-1^5, CH_2^{Bn}), 4.64 – 4.26 (m, 24H, H-1^1, H-$4^{1/2/3/4/5}$ 11xCH_2^{Bn}), 4.17 (dd, $J_{3,4}$ = 3.0, $J_{4,5}$ = 1.2 Hz, 1H, H-$4^{1/2/3/4/5}$), 4.15 (dd, $J_{3,4}$ = 3.0, $J_{4,5}$ = 1.0 Hz, 1H, H-$4^{1/2/3/4/5}$), 4.03 (dd, $J_{3,4}$ = 3.1, $J_{4,5}$ = 1.1 Hz, 1H, H-$4^{1/2/3/4/5}$), 3.86 (dd, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.1 Hz, 1H, H-$4^{1/2/3/4/5}$), 3.73 – 3.44 (m, 10H, H-2^1, H-6^1-H-$6a^5$), 3.43 – 3.20 (m, 11H, H-3^1-H-3^5, H-5^1-H-5^5, H-$6b^{1/2/3/4/5}$), 1.17 (s, 9H, 3xCH_3^{Piv}), 1.12 (s, 18H, 6xCH_3^{Piv}), 1.06 (s, 8H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.27, 176.70, 176.65, 176.56, 138.94, 138.88, 138.87, 138.85, 138.64, 138.60, 138.04 (2C), 137.97, 137.92, 137.91, 137.32, 128.53-127.16 (60C), 102.54, 100.61, 99.95, 99.71, 99.65, 81.75, 80.89, 80.54, 79.43, 79.17, 77.28, 75.07, 74.33, 74.12, 74.00, 73.93, 73.60, 73.53, 73.50, 73.22, 72.73, 72.27, 71.97, 71.94, 71.57, 71.35, 71.16, 71.07, 70.68, 70.60, 70.41, 70.20, 69.75, 69.05, 68.87, 68.33, 67.73, 66.23, 38.86, 38.82, 38.73, 27.57(3C), 27.50(3C), 27.42 (6C).

Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (175)



To a 100 mL flame-dried flask was added acceptor **174** (2.5 g, 1.11 mmol) and donor **170** (1.6 g, 1.55 mmol). The mixture was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (20 mL) and dry MeCN (20 mL), cooled to -40 °C, followed by addition of NIS (360 mg; 1.60 mmol) and TESOTf (59 mg; 0.22 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford **175** as a white crystalline material. R_f 0.48 (9:1 Tol/EtOAc). Yield: 2.8 g (80%)
$[\alpha]_D^{20}$ = 6.9° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3088.61, 3063.52, 3030.46, 2971.54, 2930.92, 2869.87, 1738.32, 1496.70, 1479.31, 1454.28, 1365.19, 1277.24, 1071.43, 910.17, 734.27, 697.12 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.01 (m, 80H), 5.50 (d, J = 3.3 Hz, 1H, H-4^7), 4.99 (m, 6H, H-2^2 – H-2^7), 4.89 – 4.75 (m, 6H, H-1^2 – H-1^7), 4.73–4.22 (m, 34H, H-1^1, H-4^1, 16xCH_2^{Bn}), 4.21 – 3.99 (m, 5H, H-4^2-H-4^6), 3.86 (d, J = 14.9 Hz, 1H, CH_2^{AcCl}), 3.76 (d, J = 14.8 Hz, 1H, CH_2^{AcCl}), 3.72 – 3.19 (m, 29H, H-2^1, H-3^1 – H-3^7, H-5^1-H-5^7, H-6^1-H-6^7), 1.17 (s, 9H, 3xCH_3^{Piv}), 1.11 (s, 9H, 3xCH_3^{Piv}), 1.10 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.05 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.12, 176.65 (2C), 176.60, 176.56, 176.54, 138.98, 138.92, 138.87 (2C), 138.85, 138.60, 138.52, 138.02, 137.96 (2C), 137.94, 137.92, 137.90, 137.40, 137.02, 129.07-127.15 (80C), 102.54, 100.59, 100.26, 100.10, 99.99, 99.88, 99.47, 81.75, 80.87, 80.68, 80.57, 80.46, 79.43, 77.40, 77.28, 77.08, 76.76, 75.06, 74.45, 74.31, 74.09, 73.76, 73.68, 73.57, 73.49, 73.40, 72.71, 72.64, 72.23, 72.05, 71.99, 71.92, 71.69, 71.30, 71.12, 70.93, 70.64, 70.47, 70.41, 70.19, 69.50, 69.44, 69.23, 68.81, 68.35, 68.05, 67.28, 40.77, 38.86, 38.84, 38.80 (2C), 38.76, 38.73, 27.58(3C), 27.48(3C), 27.47(3C), 27.44(3C), 27.41(3C), 27.38(3C).

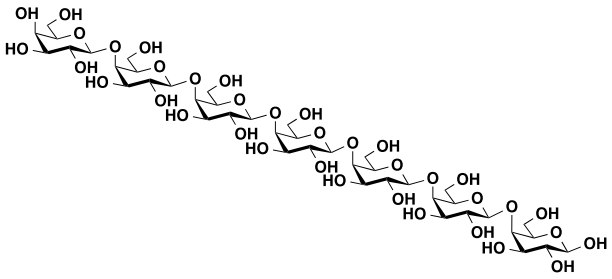
β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranoside (132)



173 (1.0 g; 0.43 mmol) was dissolved in THF (20 mL) and a 1M Et_4NOH in MeOH solution (10.8 mL; 10.8 mmol) was added. The reaction mixture was stirred stirred at 65 °C until TLC showed full conversion (24 hours). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (2:1 Tol/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (20 mL), THF (5 mL). 20% $Pd(OH)_2$/C (302 mg; 0.43 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **132** as a white solid. Yield: 278 mg (78% over two steps)
^{1}H NMR (400 MHz, D_2O) δ 5.18 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1α), 4.58 – 4.48 (m, 14H, H-1^1β-H-1^5β, H-1^2α-H-1^5α), 4.14 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 4.08 (m, 12H, 9xH-4), 4.04 (t, J = 6.5 Hz, 1H, H-5α), 3.90 – 3.43 (m, 49H). **^{13}C NMR** (101 MHz, D_2O) δ 104.34, 104.30, 104.24, 96.35, 92.27, 78.80, 77.82, 77.56, 77.53, 77.07, 75.12, 74.48,

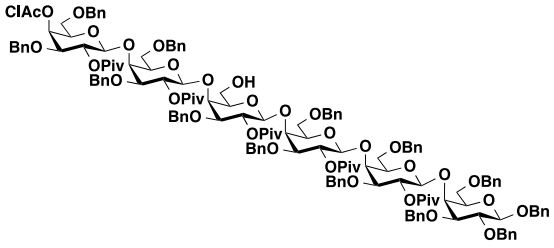
74.46, 74.41, 74.28, 73.27, 73.24, 73.19, 72.71, 72.19, 71.80, 71.75, 71.32, 69.82, 69.66, 68.78, 68.58, 60.95, 60.86, 60.67, 60.50.

β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranoside (176)



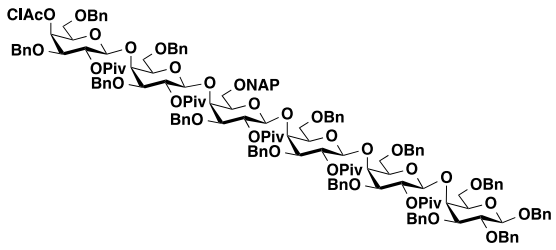
173 (890 mg; 0.28 mmol) was dissolved in THF (20 mL) and a 1M Et_4NOH in MeOH solution (9.8 mL; 9.81 mmol) was added. The reaction mixture was stirred at 65 °C until TLC showed full conversion (24 hours). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (1:1 Toluene/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (20 mL), THF (5 mL). 20% $Pd(OH)_2$/C (196 mg; 0.28 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **176** as a white solid. Yield: 242 mg (75% over two steps).
^{1}H NMR (400 MHz, D_2O) δ 5.18 (d, *J* = 3.7 Hz, 1H, H-1α), 4.60 – 4.48 (m, 13H, H-1^{1}β-H-1^{7}β, H-1^{2}α-H-1^{7}α), 4.14 (d, *J* = 3.0 Hz, 1H, H-4α), 4.08 (m, 19H, 13xH-4), 4.04 (t, *J* = 6.5 Hz, 1H), 3.86 (dd, *J* = 10.3, 3.0 Hz, 1H), 3.83 – 3.43 (m, 68H). **^{13}C NMR** (101 MHz, D2O) δ 104.33, 104.30, 104.25, 96.35, 92.27, 78.80, 77.82, 77.58, 77.56, 77.07, 75.12, 74.46, 74.41, 74.28, 73.25, 73.19, 72.71, 72.19, 71.80, 71.75, 71.32, 68.58, 60.95, 60.68, 60.50. Full characterization will be performed in collaboration with the Carlsberg Laboratories

Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (178)



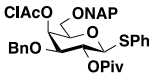
To a solution of **179** (3.75 g, 1.34 mmol) in CH_2Cl_2 (35 mL) and water (3.5 mL) was added DDQ (0.46 g, 2.01 mmol). The mixture was stirred for 90 min at 22 °C in the dark. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with an aqueous solution of ascorbic acid (0.7%), citric acid (1.5%) and NaOH (0.9%). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (9:1 Tol/EtOAc) afforded **178** as a white solid. R_f 0.21 (9:1 Tol/EtOAc).Yield: 2.63g (75%)
$[\alpha]_D^{20}$= -1.9° (c 1.0, $CDCl_3$)**. IR**(neat, cm^{-1}): 3517.23, 3063.61, 3030.38, 2970.41, 2930.60, 2869.68, 1739.44, 1496.83, 1479.49, 1454.46, 1365.36, 1277.43, 1134.73, 1100.35, 1071.60. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.10 (m, 65H), 5.45 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4^6), 5.11 – 4.89 (m, 5H, H-2^2-H-2^6), 4.86 (d, J_{CH2} = 12.8 Hz, 1H, 0.5xCH_2), 4.82 – 4.76 (m, 3H, H-1$^{2/3/4/5/6}$, H-1$^{2/3/4/5/6}$, 0.5xCH_2), 4.72 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1$^{2/3/4/5/6}$), 4.62 (d, *J* = 7.9 Hz, 1H, H-1$^{2/3/4/5/6}$), 4.60 – 4.20 (m, 27H, H-1^1, H-1$^{2/3/4/5/6}$, H-4^1, 12xCH_2^{Bn}), 4.10 – 4.06 (m, 1H, H-4$^{2/3/4/5/6}$), 4.06 – 4.02 (m, 2H, H-4$^{2/3/4/5/6}$, H-4$^{2/3/4/5/6}$), 3.98 (m, 1H, H-4$^{2/3/4/5/6}$), 3.96 (d, J_{CH2} = 15.0 Hz, 1H, 0.5xCH_2^{AcCl}), 3.86 (d, J_{CH2} = 15.0 Hz, 1H, 0.5xCH_2^{AcCl}), 3.78 – 3.52 (m, 8H, H-2^1, 3.5xH-6), 3.50 – 3.05 (m, 17H, H-3^1 – H-3^6, H-5^1-H-5^6, 2.5xH-6), 1.19 (s, 9H, 3xCH_3^{Piv}), 1.12 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.05 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.27, 176.73, 176.59 (2C), 176.25, 166.84, 138.95, 138.91, 138.86, 138.78, 138.60, 138.07, 137.99, 137.95, 137.91, 137.85, 137.63, 137.40, 137.05, 128.55-127.08 (65C), 102.54, 101.79, 100.65, 100.52, 99.44, 81.73, 80.95, 80.66, 80.30, 80.05, 79.43, 77.26, 76.97, 75.06, 74.28, 74.18, 74.03, 73.89, 73.63, 73.57, 73.53, 73.48, 73.04, 72.76, 72.59, 71.97, 71.79, 71.33, 71.23, 71.10, 70.57 (2C), 70.39, 70.28, 69.86, 69.80, 69.44, 69.39, 68.92, 68.41, 67.33, 67.06, 40.81, 38.86, 38.82, 38.77, 38.75, 38.71, 27.57 (3C), 27.46 (3C), 27.40 (3C), 27.25 (6C).

Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (179)



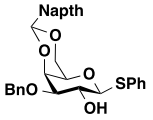
To a 100 mL flame-dried flask was added acceptor **185** (3.95 g, 2.11 mmol) and the donor **170** (3.00 g, 2.96 mmol). The mixture was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (30 mL) and dry MeCN (30 mL), cooled to -40 °C, followed by addition of NIS (683 mg; 3.04 mmol) and TESOTf (112 mg; 0.42 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford **179** as white crystalline material. R_f 0.48 (9:1 Tol/EtOAc). Yield: 4.9 g (84%)
$[\alpha]_D^{20}$= -2.1° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3088.09, 3063.03, 2970.86, 2930.82, 2869.91, 1738.33, 1496.77, 1454.35, 1365.07, 1277.30, 1151.02, 1099.14, 1072.34, 1060.16. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 2H, H^{NAP}), 7.71 (m, 2H, H^{NAP}), 7.44 (m, 1H, H^{NAP}), 7.39 – 6.95 (m, 80H), 5.52 (d, J = 3.4 Hz, 1H, H-4^6), 5.01 (ddt, J = 11.5, 8.1, 5.8 Hz, 5H, H-2$^{2\text{-}6}$), 4.86 – 4.75 (m, 4H, H-1$^{2/3/4/5/6}$, H-1$^{2/3/4/5/6}$, -CH_2^{Bn}), 4.73 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1$^{2/3/4/5/6}$), 4.71 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1$^{2/3/4/5/6}$), 4.65 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1$^{2/3/4/5/6}$), 4.62 – 4.26 (m, 26H, H-1^1, H-4^1, 12xCH_2^{Bn}), 4.19 – 4.15 (m, 1H, H-4$^{2/3/4/5}$), 4.11 (m, 2H, H-4$^{2/3/4/5}$, H-4$^{2/3/4/5}$), 4.09 (d, J_{CH2} = 12.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.04 – 4.02 (m, 1H, H-4$^{2/3/4/5}$), 3.98 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 3.74 (d, J = 15.0 Hz, 1H, 0.5xCH_2^{AcCl}), 3.69 – 3.47 (m, 8H, H-2^1, 4.5xH-6), 3.46 – 3.18 (m, 15H, H-3^1 – H-3^6, H-5^1-H-5^6, 1.5xH-6), 1.17 (s, 9H, 3xCH_3^{Piv}), 1.12 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 18H, 6xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.18, 176.62, 176.58, 176.57, 176.54, 166.87, 138.94 (2C), 138.88, 138.87, 138.60, 138.47, 138.03, 137.97, 137.95, 137.93, 137.89, 137.39, 137.00, 136.44, 133.38, 132.97, 129.07-125.69 (71C), 102.54, 100.58, 100.31, 100.17, 99.90, 99.50, 81.75, 80.91, 80.62, 80.58, 80.35, 79.43, 77.39, 77.27, 77.07, 76.75, 75.06, 74.37, 74.29, 74.11, 73.73, 73.67 (2C), 73.58, 73.56 (2C), 73.52, 73.41, 73.21, 72.71, 72.67, 72.23, 72.05, 71.99, 71.72, 71.37, 71.27, 71.23, 71.11, 70.92, 70.61, 70.43, 70.39, 70.24, 69.65, 69.40, 69.27, 69.17, 68.37, 68.13, 67.31, 67.15, 40.72, 38.87, 38.85, 38.79 (2C), 38.72, 27.58(3C), 27.47(3C), 27.45(3C), 27.42 (6C).

Phenyl 3-*O*-benzyl-4-*O*-chloroacetyl-6-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (180)



183 (8 g; 13.68 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. $(ClAc)_2O$ (3.98 g; 23.26 mmol), Et_3N (3.8 mL; 27.36 mmol) and DMAP (33 mg; 0.27 mmol) was added and the reaction was stirred at 0 °C for 3 h. The reaction mixture was concentrated and purified by flash chromatography (30:1 Tol/ EtOAc) to afford **180** as a yellowish crystalline powder. R_f 0.60 (19:1 Tol/EtOAc). Yield 8.6 g (95%)
$[\alpha]_D^{20}$= 6.0° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3058.81, 3031.83, 2970.28, 2932.03, 2907.12, 2870.85, 1762.73, 1738.25, 1478.31, 1366.63, 1277.06, 1145.62, 1097.91, 1063.23, 1026.74. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.71 (m, 3H, Ar-H), 7.67 (s, 1H, Ar-H), 7.50 – 7.09 (m, 13H, Ar-H), 5.65 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 5.06 (t, $J_{1,2}$ =$J_{2,3}$ = 9.8 Hz, 1H, H-2), 4.65 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.63 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.62 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.54 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.32 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 3.95 (d, J_{CH2} = 15.1 Hz, 1H, CH_2^{AcCl}), 3.84 (d, J_{CH2} = 15.1 Hz, 1H, CH_2^{AcCl}), 3.77 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.3 Hz, 1H, H-5), 3.63 – 3.54 (m, 2H, H-3, H-6a), 3.49 (dd, $J_{6a,6b}$ = 9.4, $J_{5,6b}$ = 6.3 Hz, 1H, H-6b), 1.13 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.86, 167.03, 137.04, 134.91, 133.29, 133.21, 132.38 (2C), 129.00 (2C), 128.51 (2C), 128.16 (2C), 128.05 (2C), 128.01, 127.85, 127.18, 126.37, 126.23, 126.07, 87.32, 78.20, 75.86, 73.98, 71.89, 68.52, 68.46, 67.67, 40.90, 38.87, 27.28 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{37}H_{39}ClNaO_7S$: 685.2003; Found 685.2007.

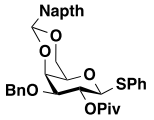
Phenyl 3-*O*-benzyl-4,6-*O*-(2-naphthyl)methylene-1-thio-β-D-galactopyranoside (181)



A mixture of **24** (10.0 g, 24.36 mmol) and *n*-Bu_2SnO (6.67 g, 26.80 mmol) in 250 mL of dry toluene was stirred at reflux for 12 h. Then *n*-Bu_4NBr (11.78 g, 36.54 mmol) and benzyl bromide (4.4 mL, 36.78 mmol) were added and the reaction mixture was stirred for 5 h at 60 °C. The reaction mixture was concentrated and the product **181** was purified by flash chromatography (9:1 Tol/EtOAc). Rf 0.19 (9:1 Tol/EtOAc). Yield: 10.0 g (82%, TBAB impurities have been accounted for based on NMR)

$[\alpha]_D^{20}$ = 34.4° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3455.75, 3059.89, 3029.46, 2955.09, 1690.50, 1626.83, 1581.91, 1477.54, 1454.00, 1440.08, 1404.30, 1363.52, , 1271.45, , 1170.33, 1118.18, 1099.63, 1078.25, 1045.28, 881.95. **^{1}H NMR** (400 MHz, CDCl3) δ 7.87 – 7.70 (m, 4H, H^{napth}), 7.69 – 7.55 (m, 2H, H^{SPh}), 7.50 – 7.36 (m, 3H, H^{napth},), 7.35 – 7.08 (m, 8H, H^{Bn}, H^{SPh}), 5.51 (s, 1H, CH^{napth}), 4.66 (d, *J* = 3.8 Hz, 2H, -CH_2^{Bn}), 4.46 (d, $J_{1,2}$ = 9.5 Hz, 1H, H-1), 4.32 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6a}$ = 1.6 Hz, 1H, H-6a), 4.13 (dd, $J_{3,4}$= 3.3, $J_{4,5}$ =1.0 Hz, 1H, H-4), 4.02 – 3.84 (m, 2H, H-2, H-6b), 3.46 (dd, $J_{2,3}$ = 9.3, $J_{3,4}$ =3.3 Hz, 1H, H-3), 3.40 (dd, $J_{5,6a}$ = $_{5,6b}$ = 1.6 Hz, 1H, H-5) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.06, 135.31, 133.86 (2C), 133.01, 130.81, 129.04 (2C), 128.60 (2C), 128.47, 128.24, 128.09, 128.04 (2C), 127.82, 126.42, 126.15, 125.93, 124.32, 101.37, 87.24, 80.40, 73.45, 71.76, 70.24, 69.63, 67.33. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{28}NaO_5S$: 523.1555; Found 523.1559.

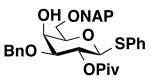
Phenyl 3-*O*-benzyl-4,6-*O*-(2-naphthyl)methylene-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (182)



181 (11 g; 21.93 mmol) was dissolved in CH_2Cl_2 (200 mL). Et_3N (5.4 mL; 38.45 mmol), DMAP (1.34 g; 10.99 mmol) and pivaloyl chloride (4.1 mL; 32.96 mmol) was added to the solution and the reaction mixture was heated to 45 °C for 8 h. The reaction mixture was cooled to 0 °C, quenched with MeOH (10 mL), washed with water (2x100 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc). R_f 0.47 (9:1 Tol/EtOAc). Yield 11.69 g (91%).

$[\alpha]_D^{20}$ = 11.3° (c 1.0, $CDCl_3$) **IR**(neat, cm^{-1}): 3477.69, 3060.53, 2903.49, 1731.71, 1691.98, 1627.05, 1478.12, 1455.97, 1365.18, 1275.90, 1152.13, 1098.34, 1042.34, 994.28. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.60 (m, 4H, H^{napth}), 7.56 – 7.48 (m, 2H, H^{napth}), 7.44 – 7.33 (m, 5H, H^{SPh}, H^{napth}), 7.28 (m, 3H, H^{SPh}, Ar-H), 7.22 – 7.10 (m, 3H, H^{SPh}, Ar-H), 5.50 (s, 1H, -$CH^{benzylidene}$), 5.29 (t, $J_{1,2}$ = $J_{2,3}$ = 9.8 Hz, 1H, H-2), 4.63 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.56 (s, 2H, CH_2^{Bn}), 4.30 (d, $J_{6a,6b}$ = 12.3, $J_{5,6a}$ = 1.2 Hz, 1H, H-6a), 4.12 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4), 3.95 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6a}$ = 1.4 Hz, 1H, H-6b), 3.63 (dd, $J_{2,3}$ = 9.8, J_{34} = 3.2 Hz, 1H, H-3), 3.36 (m, 1H, H-5), 1.19 (s, 9H, 3x-CH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.61, 138.05, 135.17, 133.85, 133.38 (2C), 132.99, 132.31, 128.85 (2C), 128.57, 128.46 (2C), 128.07, 127.98, 127.88, 127.80, 127.69 (2C), 126.35, 126.05, 125.91, 124.36, 101.41, 85.93, 78.83, 73.60, 71.43, 70.11, 69.54, 68.14, 38.88, 27.35. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{36}NaO_6S$: 607.2130; Found 607.2137.

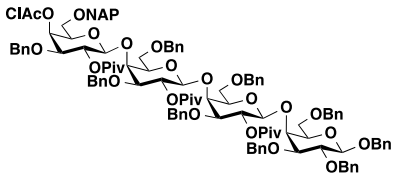
Phenyl 3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (183)



Trifluoroacetic acid (6.54 mL, 85.5 mmol) was added drop wise to a solution of **182** (10.0 g, 17.1 mmol) and triethylsilane (13.65 mL, 85.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C. When the addition was complete (10 min), the reaction was warmed to 22 °C and stirred for 3 hr. The mixture was diluted with ethyl acetate and washed with sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc) to afford **183**. R_f 0.27 (9:1 Tol/EtOAc). Yield: 7.8 g (78%).

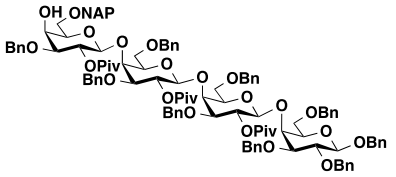
$[\alpha]_D^{20}$ = -6.2° (c 1.0, $CDCl_3$) **IR**(neat, cm^{-1}): 3493.70, 3058.30, 3030.44, 2970.76, 2930.47, 2904.90, 2871.41, 1732.46, 1583.84, 1497.18, 1366.80, 1277.92, 1153.31, 1097.56, 1064.57, 818.28, 742.73, 695.56 **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.79 – 7.65 (m, 4H, H^{NAP}), 7.47 – 7.31 (m, 5H, H^{NAP}, H^{SPh}), 7.29 – 7.07 (m, 8H, H^{Bn}, H^{SPh}), 5.21 (dd, $J_{1,2}$ = 10.1, $J_{2,3}$ =9.3 Hz, 1H, H-2), 4.65 (s, 2H, -CH_2^{bn}), 4.58 (d, $J_{1,2}$ = 10.1 Hz, 1H, H-1), 4.56 (d, J_{CH2} = 11.8 Hz, 1H, -CH_2^{NAP}), 4.49 (d, J_{CH2} = 11.8 Hz, 1H, -CH_2^{NAP}), 4.03 (dd, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.1 Hz, 1H, H-4), 3.82 – 3.73 (m, 2H, H-6a, H-6b), 3.61 (td, $J_{5,6a}$ = $J_{5,6b}$ = 5.9, $J_{4,5}$ = 1.1 Hz, 1H, H-5), 3.51 (dd, $J_{2,3}$ = 9.3, $J_{3,4}$ = 3.3 Hz, 1H, H-3), 1.16 (s, 9H, 3x-CH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 176.95, 137.34, 135.59, 133.92, 133.38, 133.14, 131.99 (2C), 128.97 (2C), 128.65 (2C), 128.32, 128.17, 128.03, 127.81, 127.76 (2C), 127.70, 126.68, 126.24, 126.04, 125.89, 87.13, 80.15, 77.58, 73.95, 71.97, 69.51, 68.73, 66.69, 38.90, 27.32. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{38}NaO_6S$: 609.2287; Found 607.2290.

Benzyl 3-*O*-benzyl-4-*O*-chloroacetyl-6-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (184)



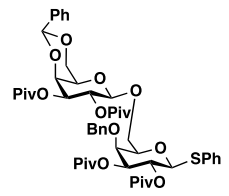
To a 100 mL flame-dried flask was added acceptor **172** (2.6 g, 1.87 mmol) and donor **180** (1.7 g, 2.61 mmol). The mixture was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (20 mL) and dry MeCN (20 mL), cooled to -40 °C, followed by addition of NIS (603 mg; 2.69 mmol) and TESOTf (98 mg; 0.37 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (20:1 Tol/EtOAc) to afford **184** as a white crystalline material. R_f 0.45 (9:1 Tol/EtOAc). Yield: 2.7 g (76%).
$[\alpha]_D^{20}$ = 1.1° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (m, 3H, H^{NAP}), 7.62 (s, 1H, H^{NAP}), 7.41 (m, 2H, H^{NAP}), 7.37 – 6.99 (m, 45H), 5.55 – 5.50 (m, 1H, H-4^4), 5.10 – 4.91 (m, 3H, H-2^2-H-2^4), 4.88 – 4.77 (m, 3H, H-$1^{2/3/4}$, -CH_2^{Bn}), 4.76 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-$1^{2/3/4}$), 4.72 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-$1^{2/3/4}$), 4.66 – 4.20 (m, 20H, H-1^1, H-4^1, 9xCH_2^{Bn}), 4.13 – 4.06 (m, 1H, H-$4^{2/3}$), 4.06 – 3.99 (m, 1H, H-$4^{2/3}$), 3.82 (dd, J_{CH2} = 14.8, 1.3 Hz, 1H, -CH_2^{AcCl}), 3.73 (dd, J_{CH2} = 14.8, 1.3 Hz, 1H), 3.69 – 3.16 (m, 17H, H-2^1, H-3^1 – H-3^4, H-5^1-H-5^4, H-6^1-H-6^4), 1.19 (s, 9H, 3xCH_3^{Piv}), 1.11 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.12, 176.64 (2C), 166.84, 138.90, 138.85, 138.81, 138.59, 138.49, 138.00, 137.92, 137.89, 137.02, 134.90, 133.21, 133.15, 128.47-125.84 (51C), 102.59, 100.79, 100.12, 99.43, 81.71, 81.12, 80.45, 79.46, 77.32, 77.28, 75.06, 74.20, 73.79, 73.73, 73.64, 73.55, 73.49 (2C), 72.86, 72.70, 71.99, 71.70, 71.48, 71.45, 71.23, 71.18, 70.45 (2C), 70.41, 69.79, 69.43, 69.32, 68.37, 67.27, 66.91, 40.80, 38.89, 38.85, 38.74, 27.57(3C), 27.41(3C), 27.39(3C).

Benzyl 3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (185)



To a solution of **184** (4.0 g; 1.76 mmol) in THF (25 mL) at 0 °C was added a 0.02M NaOMe solution in MeOH (75 mL). The reaction mixture was stirred at 0 °C for 1h, quenched with amberlite 120-H^+ resin, filtered and concentrated. The residue was purified by flash chromatography (9:1 Tol/EtOAc) to afford **185** as a white crystalline material. R_f 0.21 (9:1 Tol/EtOAc). Yield: 4.91 g (94%)
$[\alpha]_D^{20}$ = -3.0° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3088.25, 3062.66, 3030.44, 2970.17, 2930.30, 2869.44, 1738.21, 1496.78, 1479.22, 1454.24, 1364.74, 1277.39, 1150.54, 1133.50, 1061.69. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.68 (m, 3H, H^{NAP}), 7.64 (m, 1H, H^{NAP}), 7.42 – 7.04 (m, 49H), , 5.09 (dd, J = 9.8, 8.0 Hz, 1H, H-$2^{2/3/4}$), 5.03 (m, 2H, H-$2^{2/3/4}$), 4.83 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.81 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-$1^{2/3/4}$), 4.79 (d, J_{CH2} = 10.6 Hz, 1H, 0.5xCH_2^{Bn}), 4.73 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-$1^{2/3/4}$), 4.72 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-$1^{2/3/4}$), 4.65 – 4.23 (m, 20H, , H-1^1, H-4^1, 9xCH_2^{Bn}), 4.15 – 4.09 (m, 1H, H-$4^{2/3/4}$), 4.06 – 4.00 (m, 1H, H-$4^{2/3/4}$), 3.89 – 3.85 (m, 1H, H-$4^{2/3/4}$), 3.73 – 3.48 (m, 7H, H-2^1, 3.5xH-6), 3.46 – 3.20 (m, 9H, H-3^1 – H-3^4, H-5^1-H-5^4, 0.5xH-6), 1.18 (s, 9H), 1.14 (s, 9H), 1.06 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.28, 176.67, 176.64, 138.91, 138.86, 138.81, 138.63, 138.59, 138.02, 137.93, 137.90, 137.30, 135.52, 133.26, 133.03, 129.07-125.71 (51C), 102.58, 100.75, 99.87, 99.42, 81.73, 81.05, 80.36, 79.45, 79.20, 77.27, 75.06, 74.24, 74.00, 73.72, 73.68, 73.66, 73.51 (2C) , 73.24, 72.83, 72.33, 71.96, 71.39, 71.34, 71.21, 70.53, 70.51, 70.43, 69.85, 69.56, 69.46, 68.94, 66.88, 66.26, 38.88 (2C), 38.73, 27.58(3C), 27.44(3C), 27.41(3C).

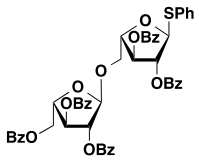
Phenyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-1-thio-β-D-galactopyranoside (186)



To a 250 mL flame-dried flask was added **353** (6.2 g, 11.68 mmol) and the **352** (8.52 g, 14.02 mmol). The mixture was co-evaporated with toluene (2x100 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (100 mL) and cooled to -40 °C. TMSOTf (0.26 mL; 1.17 mmol) was added and the reaction mixture was stirred at -40 °C for 1.5h. Et_3N (2 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (19:1 Tol/EtOAc) to afford **186**. R_f 0.52 (9:1 Tol/EtOAc). Yield: 10.1 g (91%)
$[\alpha]_D^{20}$ = 11.4° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 4H, H^{SPh}), 7.29 – 7.13 (m, 11H, H^{SPh}. Ar-*H*), 5.43 (s, 1H, -$CH^{benzylidene}$), 5.38 (t, $J_{1,2}$ = $J_{2,3}$ =9.8 Hz, 1H, H-2), 5.33 (dd, $J_{2,3}$ = 9.7, $J_{1,2}$ =8.0 Hz, 1H, H-2'),

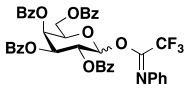
5.02 (dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 2.9 Hz, 1H, H-3), 4.79 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.7 Hz, 1H, H-3'), 4.68 (d, J_{CH2} = 11.2 Hz, 1H, -CH_2^{Bn}), 4.59 (d, J = 9.8 Hz, 1H, H-1), 4.55 (d, J_{CH2} = 11.2 Hz, 1H, -CH_2^{Bn}), 4.45 (d, J = 8.0 Hz, 1H, H-1'), 4.33 – 4.28 (m, 1H, H-4'), 4.22 – 4.15 (m, 1H, H-6a'), 3.95 (dd, J = 12.5, 1.9 Hz, 1H, H-6b'), 3.86 (m, 2H, H-4, H-6a), 3.75 – 3.63 (m, 2H, H-6b, H-5), 3.39 – 3.35 (m, 1H, H-5'), 1.13 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.13, 177.46, 176.53, 176.44, 138.12, 137.59, 132.82, 132.11 (2C), 128.91 (2C), 128.80, 128.24 (2C), 128.08 (2C), 127.77, 127.59 (2C), 127.48, 125.98 (2C), 100.73, 100.51, 86.43, 77.65, 74.93, 74.68, 74.56, 73.09, 71.86, 68.77, 68.14, 67.37, 66.95, 66.43, 38.92, 38.89, 38.74, 27.22, 27.21 (3C), 27.16 (3C), 27.12 (3C), 27.04 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{52}H_{58}NaO_{14}S$: 971.4228; Found 971.4229.

Phenyl 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl-(1→5)-2,3-di-*O*-benzoyl-1-thio-α-L-arabinofuranoside (187)



To a 100 mL flame-dried flask was added **192** (1.5 g, 3.33 mmol) and the **189** (3.0 g, 4.66 mmol). The mixture was co-evaporated with toluene (2x50 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (50 mL) and cooled to -40 °C. TMSOTf (60μL; 0.33 mmol) was added and the reaction mixture was stirred at -40 °C for 2h. Et_3N (1 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (20:1 Tol/EtOAc) to afford **187**. R_f 0.56 (9:1 Tol/EtOAc). Yield: 2.54 g (86%) $[\alpha]_D^{20}$= -38.0° (c 1.0, $CDCl_3$). **IR**(neat , cm^{-1}): 3062.91, 3034.46, 2946.99, 2884.40, 1718.36, 1601.47, 1584.22, 1491.44, 1451.53, 1315.29, 1261.51, 1177.39, 1096.15, 1069.01, 1026.22, 707.83. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.82 (m, 10H, H^{Bz}), 7.54 – 7.44 (m, 4H, H^{Bz}), 7.43 – 7.33 (m, 5H, H^{Bz}), 7.30 (m, 4H, H^{Bz}, H^{SPh}), 7.23 – 7.09 (m, 7H, , H^{Bz}, H^{SPh}), 5.73 (d, $J_{1,2}$ = 1.1 Hz, 1H, H-1'), 5.68 (dd, $J_{3,4}$ = 4.8, 1.5 Hz, 1H, H-3), 5.65 (s, 1H, H-2), 5.55 (d, $J_{1,2}$ = 1.1 Hz, 1H, H-2'), 5.50 (d, $J_{3,4}$ = 4.9 Hz, 1H, H-3'), 5.37 (s, 1H, H-1'), 4.74 (dd, $J_{5a,5b}$ = 11.8, $J_{4,5b}$ = 3.2 Hz, 1H, H-5a), 4.71 – 4.62 (m, 2H, H-4, H-4'), 4.57 (dd, $J_{5a,5b}$ = 11.8, $J_{4,5b}$ = 4.8 Hz, 1H, H-5b), 4.20 (dd, $J_{5a,5b}$ = 11.3, $J_{4,5a}$ =4.3 Hz, 1H, H-5a'), 3.93 (dd, $J_{5a,5b}$ = 11.3, $J_{4,5b}$ =3.1 Hz, 1H, H-5b'). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.21, 165.74, 165.52, 165.30, 165.25, 133.77, 133.60, 133.58, 133.49, 133.35, 133.03, 131.92 (2C), 130.00 (2C), 129.90 (2C), 129.83 (3C), 129.78 (2C), 129.72, 129.06 (2C), 128.92, 128.87, 128.56 (3C), 128.52 (2C), 128.36 (2C), 128.31 (2C), 127.64, 105.97, 91.29, 82.15, 82.09, 81.96, 81.28, 77.80 (2C), 65.98, 63.68. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{51}H_{42}NaO_{13}S$: 917.2244; Found 917.2252.

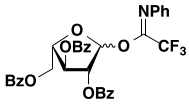
2,3,4,6-tetra-*O*-benzoyl-D-galactopyranosyl *N*-phenyl trifluoroacetimidate (188)



196 (0.50 g; 0.84 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Cs_2CO_3 (0.55 g; 1.68 mmol) was added followed by *N*-phenyl trifluoro-acetimidoyl chloride (0.24 mL; 1.68 mmol). The ice bath was removed and the reaction mixture was stirred for 12 h. It was then filtered, concentrated and purified by flash chromatography (9:1) to give a white crystalline product. R_f 0.37 (9:1 Tol/EtOAc) Yield: 522 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (m, 2H, Ar-H^{Bz}), 8.02 (m, 2H, Ar-H^{Bz}), 8.02 (m, 2H, Ar-H^{Bz}), 7.78 (m, 2H, Ar-H^{Bz}), 7.62–7.34 (m, 12H, Ar-H), 7.26 (m, 2H, Ar-H), 7.10 (m, 2H, Ar-H), 7.02 (m, 1H, Ar-H), 6.86 (m, 1H, bs), 6.43 (d, J = 6.6 Hz, 2H), 6.17 (d, J = 2.2 Hz, 1H), 6.04 (dd, J = 10.5, 3.0 Hz, 1H), 5.92(dd, J = 10.5, 3.3 Hz, 1H), 4.81 (m, 1H), 4.63 (dd, J = 11.2, 6.9 Hz, 1H), 4.40 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.9, 165.4, 165.5, 164.9, 142.94, 133.7, 133.5, 133.4, 133.2, 130.0-119.1(20C), 95.1, 72.6, 71.3, 68.7, 67.8, 62.1.

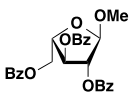
2,3,5-tri-*O*-benzoyl-L-arabinofuranosyl *N*-phenyl trifluoroacetimidate (189)



191 (5 g; 10.8 mmol) was dissolved in DCM (150 mL) and cooled to 0 °C. Cs_2CO_3 (7.1 g; 21.6 mmol) was added followed by *N*-phenyl trifluoroacet-imidoyl chloride (3.1 mL; 21.6 mmol). The ice bath was removed and the reaction mixture was stirred until TLC showed full conversion (8 h). the solution was filtered, concentrated and purified by flash chromatography to give a white crystalline product. Yield: 5.8 g (85%)

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 165.9, 165.6, 165.4, 165.3, 164.9, 143.2, 143.1, 133.7, 133.7, 133.6, 133.0, 129.8, 129.8, 129.7, 129.6, 129.4, 129.4, 129.1, 128.6, 128.5, 128.4, 128.4, 128.2, 124.4, 124.1, 120.4, 119.4, 119.1, 102.1, 96.7, 84.1, 80.6, 80.4, 76.9, 76.0, 75.4, 64.7, 63.4.

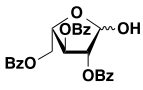
Methyl 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranoside (190)



To a suspension of L-arabinose (15 g, 100 mmol) in MeOH (150 ml) was added acetyl chloride (2.1 ml, 30.0 mmol) in a dropwise fashion and the mixture was stirred overnight at 22 °C. The mixture was neutralized with pyridine (50 ml) and concentrated under reduced pressure. The residue was coevaporated with pyridine (50 ml). Pyridine (110 ml) was added and the solution cooled to 0 °C. Benzoyl chloride (46 ml, 400 mmol) was added, the mixture was slowly allowed to warm to 22 °C and stirred for 4 hours. The reraction was quenched with water (4.5 ml) The mixture was taken up in DCM and washed with water, 1 M aq. HCl, sat. aq. $NaHCO_3$ and brine. The mixture was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was crystallized from ethanol yielding **190** as white crystals. R_f 0.54 (9:1 Tol/EtOAc). Yield: 23.0 g (47 %).

$[\alpha]_D^{20}$ = 22.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3063.81, 2996.07, 2938.30, 2836.07, 1718.38, 1601.65, 1451.40, 1263.34, 1106.44, 1068.93, 1026.56. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.88 (m, 6H, Ar-H), 7.58 – 7.16 (m, 9H, Ar-H), 5.51 (d, J = 4.9 Hz, 1H, H-3), 5.44 (s, 1H, H-2), 5.11 (s, 1H, H-1), 4.77 (dd, $J_{5a,5b}$ = 12.0, $J_{4,5a}$ = 3.4 Hz, 1H), 4.62 (dd, $J_{5a,5b}$ = 12.0, $J_{4,5b}$ =4.9 Hz, 1H), 4.50 (td, $J_{4,5b}$ = $J_{3,4}$ = 4.9, $J_{4,5a}$ = 3.6 Hz, 1H, H-4), 3.42 (s, 1H, CH_3^{OMe}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.25, 165.85, 165.51, 133.55, 133.53, 133.08, 129.99 (2C), 129.89 (2C), 129.78 (2C), 129.76, 129.12, 129.07, 128.53 (2C), 128.50 (2C), 128.34 (2C), 106.90, 82.23, 80.89, 77.96, 63.74, 55.03.

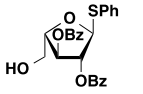
2,3,5-tri-*O*-benzoyl-L-arabinofuranose (191)



190 (5 g, 10.5 mmol) was dissolved in a mixture of acetone (2.5 mL) and 90% aq trifluoacetic acid (15 mL). The mixture was stirred at 50 °C for 6 h. The reaction mixture was directly concentrated to dryness *in vacuo* and then purified by flash chromatography (2:1 Heptane/EtOAc) to give **191** as a sticky oil. Yield: 3.7 (76%).

$[\alpha]_D^{20}$ = 24.7° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3485.15, 3087.54, 3062.46, 3029.88, 2918.20, 2866.56, 1496.41, 1453.53, 1362.30, 1096.57, 1058.07, 909.54. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.83 (m, 6H, Ar-H), 7.55 – 7.10 (m, 9H, Ar-H), 5.83 (dd, $J_{3,4}$ = 5.8, $J_{2,3}$ = 5.3 Hz, 1H, H-3α), 5.77 (d, J = 4.4 Hz, 1H, H-1β), 5.68 (s, 1H), 5.61 (s, 1H, H-1α), 5.50 (d, $J_{3,4}$ = 4.7 Hz, 1H, H-3α), 5.47 (s, 1H, H-2α), 5.45 (dd, $J_{1,2}$ = 4.4 $J_{2,3}$ = 5.3 Hz, 1H), 4.74 (dd, $J_{5a,5b}$ = 11.5, $J_{4,5a}$ = 3.4 Hz, 1H, H-5aα), 4.70 – 4.65 (m, 2H, H-4α, H-5β), 4.58 (dd, $J_{5a,5b}$ = 11.6, $J_{4,5b}$ = 5.1 Hz, 1H, H-5bα), 4.37 (dt, $J_{4,5a}$ = 6.9, $J_{3,4}$ = $J_{4,5b}$ = 4.5 Hz, 1H, H-4β). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.65, 166.43, 166.03, 165.97, 165.96, 165.71, 133.74, 133.71, 133.68 (2C), 133.25, 133.21, 130.09-128.43 (30C), 101.09, 95.61, 82.69, 81.49, 79.11, 78.05, 77.75, 76.67, 65.96, 64.03. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{22}NaO_8$: 485.1212; Found 485.1218.

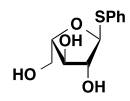
Phenyl 2,3-di-*O*-benzoyl-1-thio-α-L-arabinofuranoside (192)



To a solution of **194** (2 g, 2.90 mmol) in THF (40 mL) was added TBAF (11.61 mL, 1.0 M in THF) and AcOH (1.46 mL; 12.77 mmol) at 0 °C. The resulting mixture was warmed gradually to 22 °C and was stirred for 3 h. The reaction was diluted with CH_2Cl_2 (200 mL), washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography (9:1 Tol/EtOAc) to afford **192** as colorless syrup. R_f 0.24 (9:1 Tol/EtOAc). Yield: 1.15 g (88%)

$[\alpha]_D^{20}$ = -38.2° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3536.60, 3061.70, 2928.61, 1722.59, 1601.41, 1584.05, 1451.88, 1266.22, 1108.93, 1069.37, 1026.67. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 – 8.00 (m, 2H), 8.01 – 7.94 (m, 2H), 7.74 – 7.11 (m, 11H), 5.72 (s, 1H, H-1), 5.67 (t, $J_{2,3}$ = 1.8 Hz, 1H, H-2), 5.48 (dd, $J_{3,4}$ = 3.9, $J_{2,3}$ = 1.8 Hz, 1H, H-3), 4.52 (ddd, $J_{4,5a}$ = $J_{4,5b}$ = $J_{3,4}$ = 3.9 Hz, 1H, H-4), 3.96 (d, $J_{3,4}$ = 3.9 Hz, 2H, H-5a, H-5b). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.98, 165.24, 133.72, 133.69, 133.66, 132.22 (2C), 130.04 (2C), 129.89 (2C), 129.11 (2C), 128.98, 128.91, 128.60 (2C), 128.58 (2C), 127.84, 91.49, 83.73, 82.23, 77.83, 61.99. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{22}NaO_6$: 473.1035; Found 473.1039.

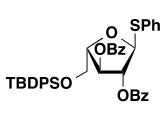
Phenyl 1-thio-α-L-arabinofuranoside (193)



To a solution of **190** (19.5 g, 41 mmol) in CH_2Cl_2 (28.5 mL) at 0 °C was added thiophenol (6 mL, 58 mmol). The reaction mixture was stirred at 0 °C for 15 min, then $BF_3{\cdot}Et_2O$ (34 mL, 268 mmol) was added and the resulting mixture was warmed gradually to 22 °C. The reaction was stirred for 8 h at the same temperature. The reaction was quenched with Et_3N and the mixture was concentrated. The resulting residue was purified by column chromatography (7:1, Heptane/EtOAc) to give a colorless syrup. The syrup was dissolved in MeOH and CH_2Cl_2 (7:1, 400 mL) followed by addition of NaOMe (320 mg) at 22 °C. The mixture was stirred at the same temperature for 2 h. The solution was concentrated to dryness, and the resulting residue was purified by column chromatography (15:1, CH_2Cl_2–MeOH) to afford **193** as a colorless syrup. Yield: 7.6 g, 64%)

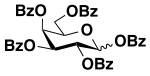
^{1}H NMR (400 MHz, CD_3OD): δ 7.52–7.49 (m, 2H, Ar-H),7.31–7.21(m, 3H, Ar-H), 5.26 (d, 1H, $J_{1,2}$ = 4.6 Hz, H-1), 3.98 (dd, 1H, $J_{2,3}$= 4.8 Hz, H-2), 3.97–3.93 (m, 1H, H-4), 3.91 (dd, 1H, $J_{3,4}$ = 7.2 Hz, H-3), 3.77 (dd, 1H, $J_{5a,5b}$= 12.1 Hz, $J_{4,5a}$ = 2.6 Hz, H-5a), 3.64 (dd, 1H, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5b}$ = 4.6 Hz, H-5b); **^{13}C NMR** (101 MHz, CD_3OD): δ 136.4, 132.6, 129.9, 128.2, 93.1, 84.3, 83.4, 77.6, 62.4.

Phenyl 2,3-di-*O*-benzoyl-5-*O*-(*tert*-butyldiphenylsilyl)-1-thio-α-L-arabinofuranoside (194)



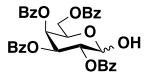
To a solution of **193** (3.7 g, 15.3 mmol) in dry DMF (40 mL) was added imidazole (3.5 g) followed by *t*-$BuPh_2SiCl$ (6 mL) at 0 °C and the resulting mixture was warmed gradually to 22 °C. The mixture was stirred overnight at the same temperature. The mixture was diluted with EtOAc (500 mL), and then the reaction mixture was washed with water and brine. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (3:1 Heptane/EtOAc) to afford C5-O-TBDPS analogue. This was used directly in the next step. The TBDPS-protected thioglycoside (3.4 g, 7.2 mmol) was dissolved in pyridine (70 mL) after which BzCl (6 mL) was slowly added at 0 °C. The resulting mixture was heated gradually to 22 °C. The reaction was stirred for 5 h at the same temperature. The reaction was quenched with methanol (1.5 mL), diluted with CH_2Cl_2 (300 mL), and then the mixture was washed with water and brine. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (20:1 Tol/EtOAc) to afford **194** (4.4 g, 77% over two steps) as a pale yellow syrup. R_f 0.72 (9:1 Tol/EtOAc).
$[\alpha]_D^{20}$ = -35.7° (c 1.0, $CDCl_3$)
IR (neat, cm^{-1}): 3070.50, 2957.78, 2931.11, 2857.66, 1724.55, 1601.78, 1451.68, 1427.88, 1258.52, 1106.43, 1068.24, 1025.07 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 - 7.13 (m, 25H, Ar-H), 5.69 (d, $J_{1,2}$ = 2.1 Hz, 1H, H-1), 5.67 – 5.61 (m, 1H, H-3), 5.59 (t, $J_{1,2}$ = 2.1 Hz, 1H, H-2), 4.55 (ddd, $J_{3,4}$ =$J_{4,5a}$ = $J_{4,5b}$ = 4.6 Hz, 1H, H-4), 3.97 (d, $J_{4,5}$ = 4.9 Hz, 2H, H-5), 0.97 (s, 9H, $3xCH_3^{TBDPS}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.60, 165.46, 135.82, 135.78, 134.09, 133.59, 133.32, 133.19, 132.22, 130.14, 130.08, 129.85, 129.83, 129.42, 129.16, 129.11, 128.62, 128.55, 127.84, 127.83, 127.73, 91.19, 83.40, 82.55, 77.69, 63.64, 26.91 (3C), 19.43.

1,2,3,4,6-Penta-O-benzoyl-α,β-D-galactopyranoside (195)



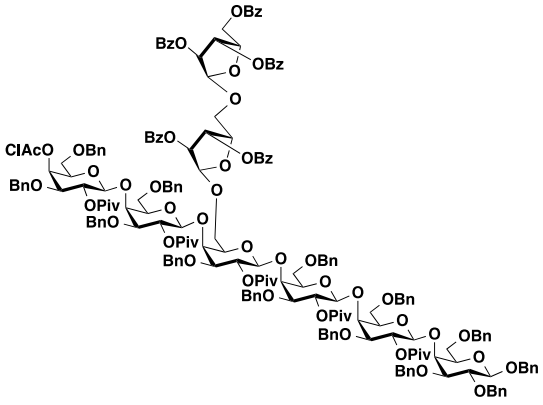
To a solution of D-galactose (10.03 g; 55 mmol) in pyridine (120 mL) was added benzoyl chloride (40 mL; 330 mmol). The solution was stirred in an oil bath 60-65 °C for 1 h. The resulting suspension was quenched with H_2O (5 mL) and stirred for 10 min after which H_2O (50 mL) was added. The mixture was poured into ice water (1 L) and stirred for 1 h. The white precipitate was filtered and recrystallized from MeOH/acetone to afford **195** as a white solid. R_f 0.56 (2:1 heptane/EtOAc). Yield: 18.5 g (48%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.10 (m, 25H, Ar-H), 6.86 (d, 1H, $J_{1,2}$ =4.8 Hz, H-1α), 6.31 (t, 1H, J = 7.2 Hz), 5.89-5.93 (m, 2H), 4.84-4.67 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.13, 165.64, 165.16, 133.85, 133.80, 133.66, 133.32, 133.29, 130.14-128.41(25C), 94.28, 79.71, 76.26, 73.95, 70.48, 63.25.

2,3,4,6-Penta-O-benzoyl-α,β-D-galactopyranose (196)



To a solution of **195** (10.04 g; 14.33 mmol) was dissolved in CH_2Cl_2 (25 mL) followed by addition of 30% HBr/AcOH (5 mL). The reaction mixture was stirred for one hour and then poured into ice water (200 mL). The aqueous phase was extracted with CH_2Cl_2 (2x50 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated. Without further purification the white solid was dissolved in acetone (45 mL) and H_2O (2 mL). Ag_2CO_3 (2.0 g; 7.29 mmol) was added and the reaction mixture was stirred for 1.5 h at 22 °C. The solution dispension was filtered through a plug of celite and concentrated to give the product in quantitative yield. R_f 0.3 (2:1 heptane/EtOAc)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-7.29 (m, 20H, Ar-H), 6.10-6.06 (m, 2H), 5.73-5.71 (m, 1H), 5.65 (d, 1H, J = 5.1 Hz), 4.88-4.85 (m, 1H), 4.77-4.68 (m, 2H).

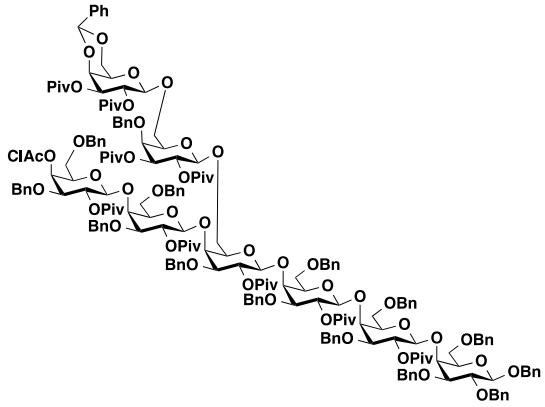
Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-[2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl-(1→5)-2,3-di-*O*-benzoyl-α-L-arabinofuranosyl-(1→6)]-3-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (197)



To a 25 mL flame-dried flask was added acceptor **178** (600 mg, 0.23 mmol) and the donor **187** (403 mg, 0.45 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -40 °C, followed by addition of NIS (106 mg; 0.47 mmol) and TESOTf (12 mg; 0.045 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (2.5h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford **197** as a white crystalline material. R_f 0.48 (9:1 Tol/EtOAc). Yield: 651 mg (83%)

$[\alpha]_D^{20}$ = 3.0° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.76 (m, 10H, Ar-H^{Bz}), 7.52 – 7.02 (m, 80H), 5.65 (dd, $J_{3,4}$ = 4.9, $J_{2,3}$ = 1.2 Hz, 1H, H-3^{ara}), 5.57 (d, $J_{2,3}$ = 1.1 Hz, 1H, H-2$^{ara'}$), 5.48 (d, $J_{3,4}$ =4.9 Hz, $J_{2,3}$ = 1.1 Hz, 1H, H-3$^{ara'}$), 5.46 (d, $J_{1,2}$ = 1.2 Hz, 1H, H-2^{ara}), 5.44 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4^6), 5.32 (s, 1H, H-1^{ara}), 5.23 (s, 1H, H-1^{ara}), 5.05 – 4.89 (m, 5H, 5xH-2), 4.88 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.82 (d, J_{CH2} = 12.1 Hz, 1H, 0.5xCH$_2^{Bn}$), 4.78 (d, J_{CH2} = 10.8 Hz, 1H, 0.5xCH$_2^{Bn}$), 4.77 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1), 4.73 (m, 2H, H-5$^{ara'}$, H-1), 4.69 (m, 2H, 2xH-1), 4.67 – 4.62 (m, 1H, H-4$^{ara'}$), 4.62 – 4.20 (m, 30H, H-1^1, H-4^{ara}, H-5^{ara}, 3xH-4, 12xCH$_2^{Bn}$), 4.15 (dd, $J_{6a,6b}$ = 11.1, $J_{5,6a}$ = 3.1 Hz, 1H, H-6^4), 4.05 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4), 4.02 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 3.85 (d, J_{CH2} = 15.0 Hz, 1H, 0.5xCH$_2^{AcCl}$), 3.82 – 3.73 (m, 2H, H-6b^4, H-6a), 3.71 (d, J_{CH2} = 15.0 Hz, 1H, 0.5xCH$_2^{AcCl}$), 3.68 – 3.12 (m, 22H, H-2^1, 6xH-3, 6xH-5, 4.5xH-6), 1.17 (s, 9H, 3xCH$_3^{Piv}$), 1.12 (s, 9H, 3xCH$_3^{Piv}$), 1.10 (s, 9H, 3xCH$_3^{Piv}$), 1.06 (s, 9H, 3xCH$_3^{Piv}$), 1.04 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.46, 176.89, 176.77, 176.63, 176.62, 166.88, 166.31, 165.81, 165.77, 165.46, 165.21, 139.06, 138.96, 138.95, 138.91, 138.66, 138.58, 138.49, 138.02, 137.96, 137.88, 137.88, 137.48, 137.17, 133.51(3C), 133.34, 133.07, 130.03-127.03(90C), 106.93, 105.96, 102.61, 100.61, 100.12, 99.97, 99.62, 99.21, 81.99, 81.93, 81.80, 81.34, 81.07, 80.85, 80.78, 80.47, 79.50, 78.03, 77.36, 76.90, 75.12, 74.41, 74.15, 74.10, 73.74, 73.73, 73.67, 73.60, 73.22, 72.77, 72.43, 72.20, 71.97, 71.92, 71.75, 71.51, 71.37, 71.27, 71.12, 70.76, 70.65, 70.45, 70.21, 70.03, 69.35, 69.30, 68.59, 68.32, 67.82, 67.44, 67.29, 65.72, 63.77, 40.83, 38.92, 38.91, 38.91, 38.84, 38.81, 27.62, 27.60, 27.53, 27.49, 27.44.

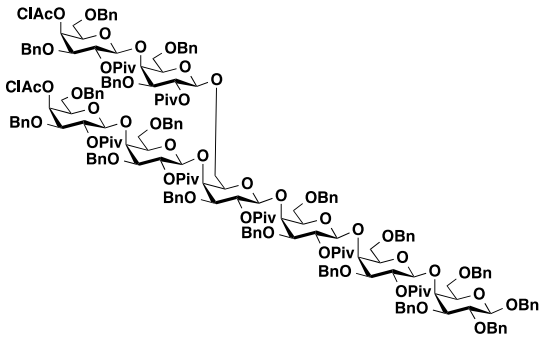
Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-[4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)]-3-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (198)



To a 25 mL flame-dried flask was added acceptor **178** (600 mg, 0.23 mmol) and the donor **186** (300 mg, 0.32 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -40 °C, followed by addition of NIS (73 mg; 0.32 mmol) and TESOTf (6 mg; 0.02 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (1h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc) to afford **198** as a white

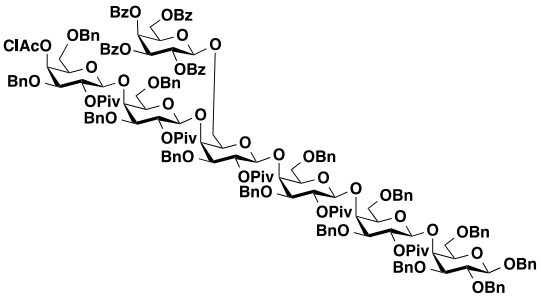
crystalline material. R_f 0.31 (9:1 Tol/EtOAc). Yield: 648 mg (82%)
$[\alpha]_D^{20}$ = 5.0° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}):3064.21, 3031.20, 2971.30, 2932.48, 2870.87, 1737.19, 1479.50, 1454.68, 1365.99, 1277.98, 1137.43, 1070.12. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 6.92 (m, 75H, Ar-H), 5.49 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4^6), 5.32 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 8.0 Hz, 1H, H-2^{digal}), 5.31 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.7 Hz, 1H, H-2^{digal}) 5.23 (s, 1H, $H^{benzylidene}$), 5.11 – 4.79 (m, 9H, 2xH-1, 5xH-2, H-3^{digal}, 0.5xCH_2^{Bn}), 4.79 – 4.75 (m, 2H, H-3^{digal}, 0.5xCH_2^{Bn}), 4.74 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 4.70 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.64 (d, $J_{1,2}$ = 8.6 Hz, 1H, H-1), 4.62 – 4.18 (m, 32H, H-1^1, 2xH-1^{digal}, 3xH-4, 13xCH_2^{Bn}), 4.13 – 4.01 (m, 3H, H-4, H-6), 3.99 (d, $J_{3,4}$ = 3.9 Hz, 1H, H-4), 3.92 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 3.87 (d, J_{CH2} = 15.1 Hz, 1H, CH_2^{AcCl}), 3.82 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 3.78 – 3.44 (m, 14H, 2xH-3, 6xH-6) 3.71 (d, J_{CH2} = 15.1 Hz, 1H, CH_2^{AcCl}), 3.45 – 3.01 (m, 14H, 4xH-3, 8xH-5, H-6), 1.17 (s, 9H, 3xCH_3^{Piv}), 1.16 (s, 9H, 3xCH_3^{Piv}), 1.09 (m, 27H, 9xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.05 (s, 9H, 3xCH_3^{Piv}), 1.02 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, CDCl3) δ 178.11, 177.47, 177.27, 176.89, 176.82, 176.82, 176.67, 176.66, 176.65, 167.01, 139.11, 139.03, 138.96, 138.96, 138.71, 138.58, 138.48, 138.20, 138.01, 137.99, 137.91, 137.89, 137.77, 137.45, 137.17, 128.82-126.12(75C), 102.63, 100.93, 100.78, 100.72, 100.46, 100.09, 99.94, 99.52, 99.23, 81.83, 81.20, 81.10, 80.97, 80.81, 79.52, 77.36, 77.32, 75.52, 75.16, 74.70, 74.40, 74.33, 74.21, 73.74, 73.66, 73.47, 73.10, 73.03, 72.79, 72.47, 72.39, 72.35, 72.18, 71.96, 71.90, 71.43, 71.30, 71.05, 70.82, 70.75, 70.49, 70.10, 69.75, 69.27, 68.82, 68.71, 68.44, 67.87, 67.47, 67.18, 66.37, 65.03, 40.81, 39.03, 38.98, 38.96, 38.95, 38.89, 38.89, 38.84, 38.82, 38.73, 27.63, 27.61, 27.56, 27.51, 27.49, 27.36, 27.35, 27.33, 27.18.

Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-[3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4) 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)]-3-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (199)



To a 25 mL flame-dried flask was added acceptor **178** (600 mg, 0.23 mmol) and donor **170** (321 mg, 0.32 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -40 °C, followed by addition of NIS (73 mg; 0.47 mmol) and TESOTf (12 mg; 0.045 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (12:1 Tol/EtOAc) to afford **199** as a white crystalline material. R_f 0.38 (9:1 Tol/EtOAc). Yield: 638 mg (79%)
$[\alpha]_D^{20}$ = 1.9° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 – 6.80 (m, 85H), 5.51 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4), 5.46 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4), 5.10 – 4.88 (m, 7H, 7xH-2), 4.86 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1), 4.85 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1), 4.82 (d, J_{CH2} = 12.1 Hz, 1H, 0.5xCH_2^{Bn}), 4.80 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1), 4.78 (d, J_{CH2} = 10.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.72 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.67 – 4.17 (m, 40H, 4xH-1, 4xH-4, 16xCH_2^{Bn}), 4.04 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 3.86 (d, $J_{3,4}$ = 2.9 Hz, 1H, H-4), 3.78 (d, J_{CH2} = 15.1 Hz, 1H, 0.5xCH_2^{AcCl}), 3.76 (d,J_{CH2} = 15.1 Hz, 1H, 0.5xCH_2^{AcCl}), 3.73 – 3.15 (m, 34H, CH_2^{AcCl}, H-2, 7xH-3, 8xH-5, 8xH-6), 3.06 (dd, $J_{2,3}$ = 10.1, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 1.15 (s, 9H, 3xCH_3^{Piv}), 1.12 (s, 18H, 6xCH_3^{Piv}), 1.05 (s, 18H, 6xCH_3^{Piv}), 1.02 (s, 9H, 3xCH_3^{Piv}), 1.01 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.29, 177.19, 176.78, 176.72, 176.71, 176.70, 176.35, 166.91, 166.90, 139.42, 139.05, 139.05, 138.97, 138.80, 138.71, 138.68, 138.51, 138.07, 138.05, 138.03, 137.97, 137.94, 137.48, 137.47, 137.17, 137.17, 128.67-127.08 (85C), 102.62, 101.96, 100.65, 100.24, 100.10, 100.03, 99.43, 99.35, 81.83, 80.99, 80.85, 80.68, 80.52, 79.52, 77.36, 77.24, 75.15, 75.00, 74.35, 74.31, 74.20, 73.73, 73.67, 73.63, 73.56, 73.47, 73.34, 73.18, 72.75, 72.61, 72.42, 72.09, 72.01, 71.83, 71.75, 71.56, 71.29, 71.22, 71.15, 70.93, 70.84, 70.74, 70.68, 70.66, 70.49, 70.45, 70.32, 69.71, 69.21, 69.11, 69.06, 68.48, 68.44, 67.93, 67.24, 67.19, 66.77, 40.77, 40.75, 38.96, 38.92, 38.89, 38.85, 38.84, 38.80, 38.71, 27.61(3C), 27.575(3C), 27.57(3C), 27.51(3C), 27.47(3C), 27.34(3C), 27.31(3C).

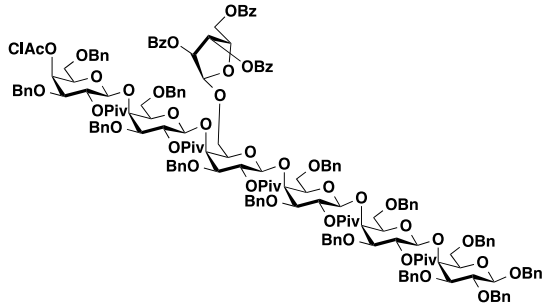
Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-[2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→6)]-3-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (200)



To a 25 mL flame-dried flask was added acceptor **178** (600 mg, 0.23 mmol) and the donor **188** (338 mg, 0.45 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (10 mL), cooled to -40 °C, followed by addition of TMSOTf (5 mg; 0.023 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (1h). The reaction mixture was quenched with Et_3N (0.5 mL) and concentrated. The product was purified by flash chroma-tography (14:1 Tol/EtOAc) to afford **200** as a white crystalline material. R_f 0.38 (9:1 Tol/EtOAc). Yield: 551 mg (75%)

$[\alpha]_D^{20}$ = 11.5° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3063.82, 3031.21, 2971.29, 2870.44, 1730.96, 1453.03, 1397.21, 1365.48, 1267.63, 1150.75, 1095.20, 1068.04, 1028.16. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 2H, Ar-H), 7.89 – 7.82 (m, 2H Ar-H), 7.75 (m, 2H, Ar-H), 7.68 – 7.61 (m, 2H, Ar-H), 7.40 – 6.99 (m, 77H, Ar-H), 5.97 (d, J = 2.9 Hz, 1H, H-4^{gal}), 5.73 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.9, 1H, H-2^{gal}), 5.51 (dt, $J_{2,3}$ = 10.3, $J_{3,4}$ = 2.9 Hz, 1H, H-3^{gal}), 5.45 (d, $J_{3,4}$ = 3.5 Hz, 1H, H-4^6), 5.07 – 4.73 (m, 9H, 2xH-1, 5xH-2, CH_2^{Bn}), 4.71 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.66 (m, $J_{6a,6b}$ = 6.7, $J_{5,6a}$ = 5.0, 1H, H-6a^{gal}), 4.63 – 4.11 (m, 32H, 4xH-1, 3xH-4, H-6b^{gal}, 12xCH_2^{Bn}), 4.02 (m, 2H, 2xH-4), 3.96 (m, 2H, H-6), 3.83 (d, J_{CH2} = 15.1 Hz, 1H, 0.5xCH_2^{AcCl}), 3.74 – 3.23 (m, 18H, 0.5xCH_2^{AcCl}, 6xH-3, H-5, 5xH-6), 3.21 (s, 1H, H-5), 3.18 (s, 1H, H-5), 3.11 (s, 1H, H-5), 3.09 (s, 1H, H-5), 2.99 (s, 1H, H-5), 2.97 (s, 1H, H-5), 1.17 (s, 9H, 3xCH_3^{Piv}), 1.16 (d, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.01 (s, 18H, 6xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.24, 176.75, 176.65, 176.64, 176.40, 167.09, 165.93, 165.59, 165.56, 165.11, 139.58, 139.04, 139.01, 138.95, 138.71(2C), 138.63, 138.34, 138.02, 138.00, 137.88, 137.52, 137.09, 133.67, 133.47, 133.28, 133.20, 130.01-126.62(85C), 102.64, 101.14, 100.73, 100.45, 99.63, 99.31, 99.22, 81.83, 81.55, 81.00, 80.74, 80.03, 79.54, 77.36, 75.15, 74.39, 74.38, 74.09, 73.76, 73.69, 73.66, 73.57, 73.43, 73.31, 72.86, 72.44, 72.05, 71.97, 71.53, 71.45, 71.38, 71.31, 71.17, 71.10, 70.99, 70.92, 70.90, 70.81, 70.70, 70.50, 70.18, 70.09, 69.28, 68.41, 68.20, 67.51, 67.16, 40.83, 39.06, 38.93, 38.84, 38.83, 38.80, 27.70, 27.61, 27.58, 27.46, 27.45.

Benzyl 3,6-di-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-[2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl-(1→6)]-3-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (201)

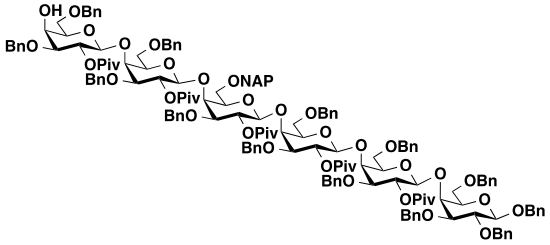


To a 25 mL flame-dried flask was added acceptor **178** (600 mg, 0.23 mmol) and the donor **189** (285 mg, 0.45 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (10 mL), cooled to -40 °C, followed by addition of TMSOTf (5 mg; 0.023 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (1h). The reaction mixture was quenched with Et_3N (0.5 mL) and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford **201** as a white crystalline material. R_f 0.42 (9:1 Tol/EtOAc). Yield: 567 mg (81%)

$[\alpha]_D^{20}$ = 5.3° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}):3063.86, 3030.69, 2971.83, 2930.37, 2870.36, 1737.69, 1453.53, 1365.70, 1274.60, 1152.50, 1102.57, 1070.27, 1028.90. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 7.77 (m, 6H, Ar-H^{Bz}), 7.60 – 6.78 (m, 74H, Ar-H), 5.49 (dd, J = 5.2, 1.4 Hz, 1H, H-3^{ara}), 5.45 (d, J = 3.4 Hz, 1H, H-4^6), 5.44 (d, J = 1.4 Hz, 1H, H-2^{ara}), 5.26 (s, 1H, H-1^{ara}), 5.06 – 4.89 (m, 5H, H-2^2-H-2^6), 4.87 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.82 (d, $J_{6a,6b}$ = 12.1 Hz, 1H, 0.5xCH_2^{Bn}), 4.78 (d, $J_{6a,6b}$ = 11.1 Hz, 1H, 0.5xCH_2^{Bn}) 4.76 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1), 4.74 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.70 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1), 4.68 (d, $J_{1,2}$ = 8.2 Hz, 1H), 4.65 – 4.60 (m, 2H, H-5^{ara}), 4.60 – 4.20

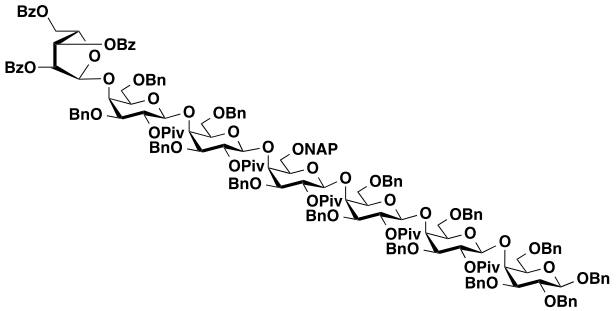
(m, 29H, H-1[1], H-4[ara], 3xH-4, 12xCH_2[Bn]), 4.05 (d, $J_{3,4}$ = 3.6 Hz, 1H, H-4), 4.02 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 3.86 (d, J = 15.0 Hz, 1H, CH_2[AcCl]), 3.83 – 3.43 (m, 11H, H-3, 5xH-6), 3.72 (d, J = 15.0 Hz, 1H, CH_2[AcCl]), 3.44 – 3.14 (m, 8H, H-2[1], 5xH-3, H-6), 1.15 (s, 9H, 3xCH_3[Piv]), 1.12 (s, 9H, 3xCH_3[Piv]), 1.11 (s, 9H, 3xCH_3[Piv]), 1.06 (s, 9H, 3xCH_3[Piv]), 1.05 (s, 9H, 3xCH_3[Piv]). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.44, 176.88, 176.76, 176.64, 176.62, 166.93, 166.26, 165.89, 165.53, 139.07, 138.97(3C), 138.96, 138.94, 138.68, 138.60, 138.40, 138.02, 138.01, 137.91, 137.50, 137.19, 133.66, 133.54, 133.06, 130.00-125.42 (80C), 107.01, 102.63, 100.63, 100.17, 100.05, 99.63, 99.37, 82.40, 81.81, 81.02, 80.83, 80.75, 80.69, 80.63, 79.52, 78.35, 77.36, 77.00, 75.15, 75.02, 74.42, 74.26, 74.12, 73.74, 73.72, 73.68, 73.63, 73.27, 72.79, 72.49, 72.26, 72.02, 71.92, 71.83, 71.51, 71.36, 71.15, 70.76, 70.73, 70.48, 70.23, 70.07, 69.50, 69.36, 68.58, 68.44, 68.07, 67.47, 67.32, 63.69, 40.85, 38.93, 38.93, 38.92, 38.87, 38.82, 27.61, 27.60, 27.53, 27.51, 27.43.

Benzyl 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (202)



To a solution of **179** (800 mg; 0.29 mmol) in THF (10 mL) at 0 °C was added a 0.02M NaOMe solution in MeOH (30 mL). The reaction mixture was stirred at 0 °C for 1h, quenched with amberlite 120-H^+ resin, filtered and concentrated. The residue was purified by flash chromatography (9:1 Tol/EtOAc) to afford **202** as a white crystalline material. R_f 0.4 (9:1 Tol/EtOAc). Yield: 720 mg (95%)

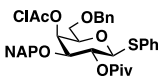
Benzyl 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (203)



To a 25 mL flame-dried flask was added acceptor **202** (600 mg, 0.23 mmol) and the donor **189** (279 mg, 0.45 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (10 mL), cooled to -40 °C, followed by addition of TMSOTf (5 mg; 0.023 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (1.5h). The reaction mixture was quenched with Et_3N (0.5 mL) and concentrated. The product was purified by flash chromatography (20:1 Tol/EtOAc) to afford **203** as a white solid. R_f 0.50 (9:1 Tol/EtOAc). Yield: 518 mg (74%).

$[\alpha]_D^{20}$ = 1.2° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3063.31, 3031.07, 2970.07, 2930.73, 2869.78, 1736.22, 1453.32, 1365.04, 1274.28, 1153.05, 1097.62, 1069.80, 1049.66, 909.24. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H, Ar-H), 7.85 (m, 2H, Ar-H), 7.81 – 7.64 (m, 5H), 7.51 – 6.93 (m, 78H), 5.71 (s, 1H, H-1[ara]), 5.58 (s, 1H, H-2[ara]), 5.39 (d, $J_{3,4}$ = 4.5 Hz, 1H, H-3[ara]), 5.33 (dd, $J_{2,3}$ = 10.0, $J_{1,2}$ = 8.1 Hz, 1H, H-2), 5.03 (m, 4H, 4xH-2), 4.84 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.82 (d, J_{CH2} = 12.1 Hz, 1H, 0.5xCH_2[Bn]), 4.78 (d, J_{CH2} = 11.0 Hz, 1H, 0.5xCH_2[Bn]), 4.78 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.72 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.69 (d, $J_{1,2}$ = 7.4 Hz, 1H, H-1), 4.67 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.65 (d, J_{CH2} = 12.4 Hz, 1H, 0.5xCH_2[Bn]), 4.61 – 3.90 (m, 34H, 12.5xCH_2[Bn], H-4[ara], H-5[ara], H-1[1], 5xH-4,), 3.73 – 3.48 (m, 11H, H-2[1], 5xH-6), 3.45 – 3.16 (m, 13H, 6xH-3, 6xH-5, H-6), 1.17 (s, 9H, 3xCH_3[Piv]), 1.15 (s, 9H, 3xCH_3[Piv]), 1.10 (s, 9H, 3xCH_3[Piv]), 1.09 (s, 9H, 3xCH_3[Piv]), 1.05 (s, 9H, 3xCH_3[Piv]). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.19, 176.74, 176.71, 176.69, 176.68, 166.28, 165.98, 165.25, 139.05, 139.04, 138.98, 138.97, 138.70, 138.56, 138.12, 138.07, 138.06, 138.02, 137.99, 137.66, 137.51, 136.44, 133.54, 133.47, 133.35, 133.02, 130.20-125.76 (85C), 106.41, 102.63, 100.68, 100.30, 100.25, 100.20, 99.59, 82.70, 82.28, 81.84, 80.98, 80.81, 80.66, 80.42, 80.25, 79.52, 78.29, 77.36, 75.15, 74.52, 74.39, 74.19, 74.07, 73.66, 73.56, 73.48, 73.41, 73.11, 72.80, 72.64, 72.44, 72.19, 72.18, 71.43, 71.38, 71.28, 71.20, 71.16, 71.09, 70.72, 70.48, 70.32, 70.01, 69.73, 69.52, 69.14, 68.89, 68.87, 68.38, 67.39, 63.79, 38.98, 38.94, 38.88 (2C), 38.81, 27.66 (3C), 27.60 (3C), 27.56 (3C), 27.54 (3C), 27.50 (3C).

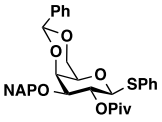
Phenyl 6-O-benzyl-4-O-chloroacetyl-3-O-(2-naphthyl)methyl-2-O-pivaloyl-1-thio-β-D-galactopyranoside (204)



206 (4 g; 6.84 mmol) was dissolved in CH_2Cl_2 (68 mL) and cooled to 0 °C. $(ClAc)_2O$ (1.99 g; 11.62 mmol), Et_3N (1.91 mL; 13.68 mmol) and DMAP (17 mg; 0.14 mmol) was added and the reaction was stirred at 0 °C for 4 h. The reaction mixture was concentrated and purified by flash chromatography (19:1 Tol/EtOAc) to afford **204** as a yellowish crystalline powder. R_f 0.57 (9:1 Tol/EtOAc). Yield 4.24 g (94%)

$[\alpha]_D^{20}$= 22.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3059.56, 3029.48, 2970.67, 2931.40, 2906.53, 2870.20, 1763.22, 1738.34, 1478.56, 1367.36, 1277.26, 1145.22, 1098.10, 1064.55. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.58 (m, 4H, Ar-H), 7.45 – 7.13 (m, 13H, Ar-H), 5.68 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 5.10 (t, $J_{1,2}$ = $J_{2,3}$ = 9.8 Hz, 1H, H-2), 4.79 (d, J_{CH2} = 11.6 Hz, 1H, 0.5xCH_2^{Bn}), 4.60 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.49 (m, 2H, CH_2^{Bn}), 4.37 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.01 (d, J_{CH2} = 15.1 Hz, 1H, CH_2^{AcCl}), 3.90 (d, J_{CH2} = 15.1 Hz, 1H, CH_2^{AcCl}), 3.75 (dd, $J_{5,6b}$ =7.3, $J_{5,6a}$ = 5.8 Hz, 1H, H-5), 3.62 (dd, $J_{2,3}$ = 9.8, $J_{2,3}$ = 3.0 Hz, 1H, H-3), 3.56 (dd, $J_{6a,6b}$ = 9.4, $J_{5,6a}$ = 5.8 Hz, 1H, H-6a), 3.46 (dd, $J_{6a,6b}$ = 9.4, $J_{5,6b}$ = 7.3 Hz, 1H, H-6b), 1.14 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.81, 166.97, 137.38, 134.41, 133.22, 133.19, 133.10, 132.28 (2C), 129.07, 128.91 (2C), 128.56 (2C), 128.25, 128.21 (2C), 128.06, 127.95, 127.93, 127.69, 126.97, 126.17, 126.05, 125.94, 87.29, 78.06, 75.72, 73.76, 71.90, 68.45, 68.40, 67.51, 40.83, 38.78, 27.20 (3C).

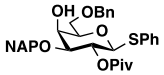
Phenyl 4,6-*O*-benzylidene-3-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (205)



56 (14 g; 27.97 mmol) was dissolved in CH_2Cl_2 (200 mL). Et_3N (6.8 mL; 48.94 mmol), DMAP (1.71 g; 13.98 mmol) and pivaloyl chloride (5.2 mL; 41.95 mmol) was added to the solution and the reaction mixture was heated to 45 °C for 4 h. The reaction mixture was cooled to 0 °C, quenched with MeOH (10 mL), washed with water (2x100 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to give compound **205**. R_f 0.5 (9:1 Tol/EtOAc). Yield 15.3 g (93%)

$[\alpha]_D^{20}$= 9.1° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.60 (m, 4H, H^{napth}), 7.56 – 7.48 (m, 2H, H^{napth}), 7.44 – 7.33 (m, 5H, H^{SPh}, H^{napth}), 7.28 (dt, *J* = 5.0, 1.6 Hz, 3H, H^{SPh}, Ar-H), 7.22 – 7.10 (m, 3H, H^{SPh}, Ar-H), 5.34 (s, 1H, -$CH^{benzylidene}$), 5.31 (t, $J_{1,2}$ = $J_{2,3}$ = 9.8 Hz, 1H, H-2), 4.74 (d, J_{CH2} = 12.7 Hz, 1H, -CH_2^{NAP}), 4.68 (d, J_{CH2} = 12.7 Hz, 1H, -CH_2^{NAP}), 4.62 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.25 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 1.6 Hz, 1H, H-6a), 4.08 (dd, $J_{3,4}$ = 3.4, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.87 (dd, $J_{6a,6b}$ =12.4, $J_{5,6b}$ 1.7 Hz, 1H, H-6b), 3.66 (dd, $J_{2,3}$ = 9.8, J_{34} = 3.4 Hz, 1H, H-3), 3.33 (m, 1H, H-5), 1.19 (s, 9H, 3x-CH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.49, 137.65, 135.50, 133.30 (2C), 133.14, 133.00, 132.13, 129.02, 128.73 (2C), 128.13 (2C), 128.12, 127.85, 127.84, 127.71 (2C), 126.57 (2C), 126.19, 125.98, 125.55, 101.15, 85.77, 78.82, 73.44, 71.54, 69.95, 69.29, 67.96, 38.80, 27.28 (3C). **HRMS** (ESI-TOF) m/z: [M + NH_4]+ Calcd for $C_{35}H_{40}NO_6S$ 602.2576 Found 602.2574.

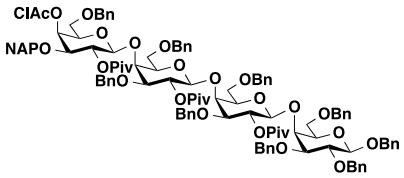
Phenyl 6-*O*-benzyl-3-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (206)



Trifluoroacetic acid (3.5 mL, 45.32 mmol) was added drop wise to a solution of **205** (5.3 g, 9.06 mmol) and triethylsilane (7.2 mL, 45.32 mmol) in CH_2Cl_2 (100 mL) at 0 °C. When the addition was complete (10 min), the reaction was heated to 22 °C and stirred for 2h. The mixture was diluted with ethyl acetate and washed with sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc) to afford **206**. R_f 0.31 (9:1 Tol/EtOAc). Yield: 4.22 g (79%)

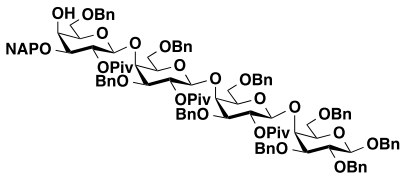
$[\alpha]_D^{20}$= 3.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3478.37, 3059.04, 2930.64, 1732.14, 1583.69, 1509.48, 1496.37 ,1478.63, 1455.17, 1367.17, 1277.64, 1152.50, 1123.46, 1098.39, 1065.56. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 3H, Ar-H), 7.76 (s, 1H, Ar-H), 7.59 – 7.48 (m, 4H, Ar-H), 7.47 – 7.23 (m, 9H, Ar-H), 5.37 5.37 (t, $J_{1,2}$ = $J_{2,3}$ = 9.8 Hz, 1H, H-2), 4.85 (d, *J* = 12.0 Hz, 1H, CH_2^{Bn}), 4.78 (d, *J* = 12.0 Hz, 1H, CH_2^{Bn}), 4.69 (d, *J* = 9.8 Hz, 1H), 4.60 (s, 2H, CH_2^{NAP}), 4.22 – 4.14 (m, 1H, H-4), 3.89 – 3.81 (m, 2H, H-6a, H-6b), 3.69 (m, 2H, H-3, H-5), 2.71 – 2.50 (m, 1H, -OH), 1.29 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.89, 138.02, 134.71, 133.81, 133.18, 133.09, 131.93 (2C), 128.87 (2C), 128.44 (2C), 127.90, 127.78 (2C), 127.75, 127.61, 126.48, 126.33, 126.16, 125.46, 87.05, 80.08, 77.44, 73.73, 71.97, 69.37, 68.67, 66.66, 38.82, 27.25 (3C). **HRMS** (ESI-TOF) m/z: [M + $Na]^+$ Calcd for $C_{35}H_{38}NaO_6S$: 609.2287; Found 609.2282.

Benzyl 6-*O*-benzyl-4-*O*-chloroacetyl-3-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (207)



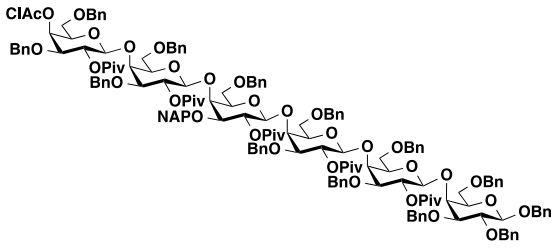
To a 50 mL flame-dried flask was added acceptor **172** (2.6 g, 1.87 mmol) and the donor **204** (1.7 g, 2.61 mmol). The mixture was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (12.5 mL) and dry MeCN (12.5 mL), cooled to -40 °C, followed by addition of NIS (603 mg; 2.69 mmol) and TESOTf (98 mg; 0.37 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (2.5h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (15:1 Tol/EtOAc) to afford **207** as a white crystalline material. R_f 0.49 (9:1 Tol/EtOAc). Yield: 2.91 g (79%).
$[\alpha]_D^{20}$ = 4.6° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3088.43, 3062.42, 3030.60, 2969.24, 2929.46, 2869.91, 1738.42, 1496.71, 1479.37, 1454.23, 1365.97, 1277.68, 1154.68, 1100.72, 1072.51. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.65 (m, 3H, Ar-H^{NAP}), 7.60 (s, 1H, Ar-H^{NAP}), 7.44 – 7.04 (m, 48H, Ar-H), 5.54 (s, 1H, H-4^4), 5.12 – 4.94 (m, 3H, H-2^2-H-2^4), 4.90 – 4.68 (m, 7H, H-1^2-H-1^4, 2xCH$_2^{Bn}$), 4.66 – 4.22 (m, 22H, H-1^1, H-4^1, 8xCH$_2^{Bn}$), 4.08 (s, 1H, H-4$^{3/4}$), 4.03 (s, 1H, H-4$^{3/4}$), 3.89 (d, J_{CH2} = 14.8 Hz, 1H, 0.5xCH$_2^{AcCl}$), 3.80 (d, J_{CH2} = 14.8 Hz, 1H, 0.5xCH$_2^{AcCl}$), 3.73 – 3.47 (m, 6H, H-2^1, 2.5xH-6), 3.46 – 3.19 (m, 11H, 1.5xH-6, H-5^1-H-5^4, H-3^1-H-3^4), 1.19 (s, 9H), 1.12 (s, 9H), 1.06 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.16, 176.65, 176.62, 166.86, 138.91, 138.86, 138.84, 138.60, 138.55, 137.98, 137.93, 137.90, 137.44, 134.49, 133.20, 133.09, 129.07, 128.58-127.00 (44C), 126.09, 126.04, 125.98, 102.60, 100.79, 100.16, 99.42, 81.72, 81.13, 80.43, 79.47, 77.26, 77.22, 75.06, 74.21, 73.74, 73.68, 73.56, 73.48, 72.86, 72.72, 72.06, 71.67, 71.47, 71.43, 71.27, 71.18, 70.44, 69.89, 69.45, 69.37, 68.40, 67.31, 66.87, 40.82, 38.88 (2C), 38.73, 27.56 (3C), 27.41 (3C), 27.40 (3C).

Benzyl 6-*O*-benzyl-3-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)- 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (208)



To a solution of **207** (4.33 g; 2.22 mmol) in THF (25 mL) at 0 °C was added a 0.02M NaOMe solution in MeOH (75 mL). The reaction mixture was stirred at 0 °C for 2h, quenched with amberlite 120-H^+ resin, filtered and concentrated. The residue was purified by flash chroma-tography (9:1 Tol/EtOAc) to afford **208** as a white crystalline material. R_f 0.22 (9:1 Tol/EtOAc) Yield: 4.00 g (96%)
$[\alpha]_D^{20}$ = -1.9° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3062.57, 3030.57, 2970.81, 2929.84, 2869.47, 1739.33, 1454.25, 1365.88, 1277.69, 1152.09, 1134.64, 1099.41, 1073.10. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.55 (m, 4H, Ar-H), 7.55 – 6.99 (m, 48H, Ar-H), 5.13 (dd, $J_{2,3}$ = 9.8, 8.0 Hz, 1H, H-2$^{2/3/4}$), 5.04 (m, 2H, H-2$^{2/3/4}$, H-2$^{2/3/4}$), 4.90 – 4.22 (m, 25H, H-1^1-H-1^4, H-4$^{1/2/3/4}$,10xCH$_2^{Bn}$), 4.15 – 4.09 (m, 1H, H-4$^{1/2/3/4}$), 4.08 – 4.00 (m, 1H, H-4$^{1/2/3/4}$), 3.90 (dd, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.7 Hz, 1H, H-4$^{1/2/3/4}$), 3.75 – 3.19 (m, 17H, H-2^1, H-3^1-H-3^4, H-5^1-H-5^4, H-6^1-H-6^4), 1.19 (s, 9H, 3xCH$_3^{Piv}$), 1.16 (s, 9H, 3xCH$_3^{Piv}$), 1.06 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.42, 176.77, 176.75, 139.02, 138.96, 138.93, 138.74, 138.70, 138.13, 138.11, 138.03, 138.01, 134.84, 133.29, 133.21, 128.55-125.66(52C), 102.69, 100.86, 99.99, 99.51, 81.83, 81.16, 80.48, 79.56, 79.22, 77.36, 75.17, 74.35, 74.11, 73.79 (2C), 73.70 (2C), 73.62 (3C), 73.30, 72.94, 72.48, 72.15, 71.50, 71.43, 71.35, 71.30, 70.66, 70.61, 70.54, 69.96, 69.69, 69.60, 68.99, 66.98, 66.41, 39.01, 38.98, 38.84, 27.68(3C), 27.58(3C), 27.51(3C).

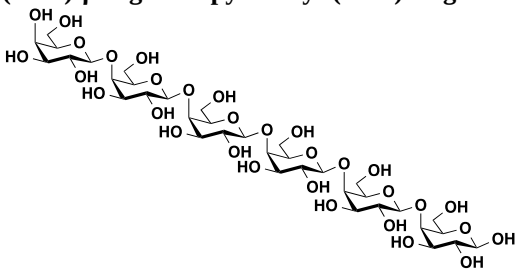
Benzyl 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-(2-naphthyl)methyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (209)



To a 100 mL flame-dried flask was added acceptor **208** (3.5 g, 1.87 mmol) and the donor **170** (2.7 g, 2.62 mmol). The mixture was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (20 mL) and dry MeCN (20 mL), cooled to -40 °C, followed by addition of NIS (606 mg; 2.69 mmol) and TESOTf (99 mg; 0.37 mmol). The reaction mixture was stirred at -40 °C until TLC revealed full conversion of the

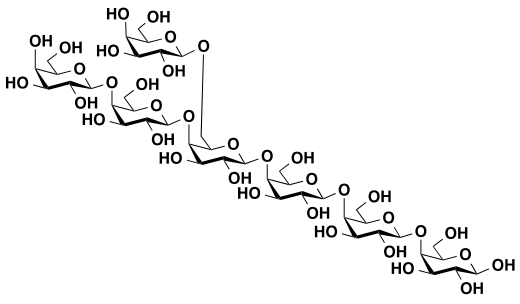
donor (2h). The solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (12:1 Tol/EtOAc) to afford **209** as a white crystalline material. R_f 0.44 (9:1 Tol/EtOAc). Yield: 4.34 g (83%).
$[\alpha]_D^{20}$ = -4.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3088.32, 3063.11, 3030.60, 2970.62, 2930.57, 2870.02, 1739.54, 1496.77, 1479.43, 1397.40, 1366.02, 1277.67, 1152.19, 1101.13, 1074.37. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.56 (m, 4H, Ar-H), 7.42 – 7.01 (m, 68H, Ar-H), 5.49 (d, J = 3.3 Hz, 1H, H-4^6), 5.09 – 4.89 (m, 5H, H-2^2-H-2^6), 4.89 – 4.65 (m, 6H, H-1^2-H-1^6, CH_2^{Bn}), 4.64 – 4.21 (m, 29H, H-1^1, H-$4^{1/2/3/4/5}$, H-$4^{1/2/3/4/5}$,13xCH_2^{Bn}), 4.17 – 4.09 (m, 1H, H-$4^{1/2/3/4/5}$), 4.08 – 4.04 (m, 1H, H-$4^{1/2/3/4/5}$), 4.03 (m, 1H, H-$4^{1/2/3/4/5}$), 3.87 (d, J_{CH2} = 14.9 Hz, 1H, 0.5xCH_2^{AcCl}), 3.77 (d, J = 14.8 Hz, 1H, 0.5xCH_2^{AcCl}), 3.70 – 3.15 (m, 25H, H-2^1, H-3^1-H-3^6, H-5^1-H-5^6, H-6^1-H-6^6), 1.17 (s, 9H, 3xCH_3^{Piv}), 1.11 (s, 9H, 3xCH_3^{Piv}), 1.11 (s, 9H, 3xCH_3^{Piv}), 1.10 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.20, 176.78, 176.70, 176.68, 176.65, 166.90, 139.04 (2C), 138.98, 138.97 (2C), 138.70, 138.67, 138.10, 138.05, 138.02, 137.99, 137.50, 137.12, 135.56, 133.30, 132.99, 129.16-125.43 (72C), 102.64, 100.68, 100.36, 100.07 (2C), 99.60, 81.85, 81.00, 80.76, 80.48, 79.53, 77.37, 75.16, 74.46, 74.39, 74.22, 73.90, 73.75, 73.71, 73.69, 73.66, 73.53, 73.51, 72.81, 72.78, 72.32, 72.12, 72.07, 71.75, 71.48, 71.38, 71.33, 71.21, 71.04, 70.72, 70.54, 70.50, 70.37, 70.33, 69.61, 69.41, 69.27, 68.43, 68.24, 67.44, 67.35, 40.88, 38.96, 38.93 (2C), 38.90, 38.82, 27.67 (3C), 27.60 (3C), 27.58 (3C), 27.51 (3C), 27.48 (3C).

β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4) -D-galactopyranose (210)



179 (800 mg; 0.29 mmol) was dissolved in THF (20 mL) and a 1M Et_4NOH in MeOH solution (8.6 mL; 8.6 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h and then poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (2:1 Tol/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (20 mL), THF (5 mL). 20% $Pd(OH)_2$/C (200 mg; 0.28 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **210** as a white solid. Yield: 203 mg (72% over two steps)
^{1}H NMR (400 MHz, D_2O) δ 5.18 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1α), 4.59 – 4.48 (m, 11H, H-1^2α-H-1^6α, H-1^1β- H-1^7β), 4.14 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 4.08 (m, 10H, 10xH-4), 4.04 (t, J = 6.5 Hz, 1H), 3.86 (dd, J = 10.3, 3.0 Hz, 1H), 3.81 (d, $J_{3,4}$ = 3.4 Hz, 1H), 3.79 – 3.45 (m, 58H). **^{13}C NMR** (101 MHz, D2O) δ 104.30, 104.25, 96.35, 92.27, 77.82, 77.58, 77.55, 77.53, 77.07, 75.11, 74.46, 74.41, 74.28, 73.26, 73.19, 72.71, 72.19, 71.75, 71.32, 69.81, 69.66, 68.77, 68.58, 60.95, 60.67, 60.50. Full characterization is currently being done in collaboration with the Carlsberg Laboratories.

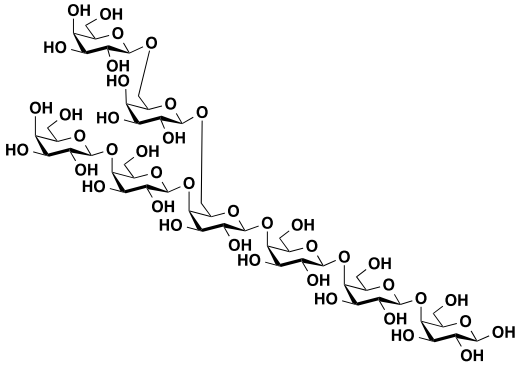
β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-[β-D-galactopyranosyl-(1→6)]-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4) -D-galactopyranose (211)



200 (500 mg; 0.15 mmol) was dissolved in THF (20 mL) and a 1M Et_4NOH in MeOH solution (5.4 mL; 5.40 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h and then poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (1:1 Tol/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (16 mL), THF (4 mL). 20% $Pd(OH)_2$/C (108 mg; 0.15 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **211** as a white solid. Yield: 133 mg (75% over two steps)
^{1}H NMR (400 MHz, D_2O) δ 5.18 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1α), 4.61 – 4.46 (m, 11H, H-1^1β-H-1^6β, H-1^2α-H-1^6α), 4.35 (d, $J_{1,2}$ = 7.9 Hz, 2H, H-1^{gal}α, H-1^{gal}β), 4.14 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 4.11 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4), 4.10 – 3.98 (m, 12H, 12xH-4), 3.94 – 3.37 (m, 70H). **^{13}C NMR** (101 MHz, D_2O) δ 104.34, 104.25, 104.18, 103.56, 96.36,

92.27, 81.68, 78.79, 77.82, 77.54, 77.02, 75.10, 75.07, 74.46, 74.33, 74.28, 73.70, 73.23, 73.20, 72.70, 72.66, 72.19, 71.77, 71.61, 71.31, 70.69, 68.56, 60.96, 60.87, 60.67, 60.62, 60.40.

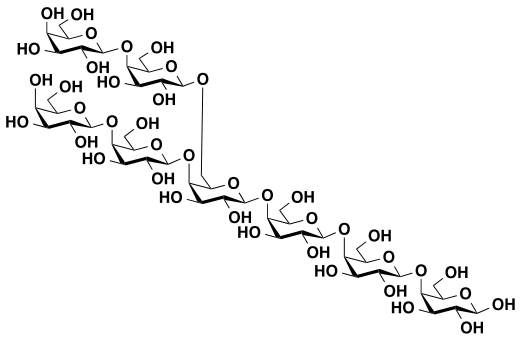
β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-[β-D-galactopyranosyl-(1→6)-β-D-galactopyranosyl-(1→6)]-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4) -D-galactopyranose (212)



198 (600 mg; 0.17 mmol) was dissolved in THF (20 mL) and a 1M Et_4NOH in MeOH solution (10.3 mL; 10.29 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h and then poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (1:2 Toluene/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (20 mL), THF (5 mL). 20% $Pd(OH)_2/C$ (120 mg; 0.17 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **212** as a white solid. Yield: 157 mg (70% over two steps)

^{1}H NMR (400 MHz, D_2O) δ 5.18 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1), 4.62 – 4.48 (m, 11H, H-1^{1}β-H-1^{6}β, H-1^{2}α-H-1^{6}α), 4.37 (d, $J_{1,2}$ = 7.9 Hz, 2H, H-1$^{6\text{-branch}}$α, H-1$^{6\text{-branch}}$β), 4.35 (d, $J_{1,2}$ = 7.9 Hz, 2H, H-1'$^{6\text{-branch}}$α, H-1'$^{6\text{-branch}}$β), 4.14 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4α), 4.13 – 4.06 (m, 11H, 1xH-4), 4.04 (t, J = 6.5 Hz, 1H), 4.01 – 3.38 (m, 84H). **^{13}C NMR** (101 MHz, D_2O) δ 104.34, 104.25, 103.67, 103.44, 96.36, 92.27, 81.68, 78.79, 77.88, 77.81, 77.62, 77.56, 77.03, 75.11, 74.48, 74.40, 74.28, 74.26, 73.56, 73.48, 73.21, 72.72, 72.69, 72.51, 72.19, 71.80, 71.64, 71.31, 70.69, 70.64, 70.41, 68.97, 68.60, 68.54, 68.49, 60.97, 60.73, 60.67, 60.48, 60.46.

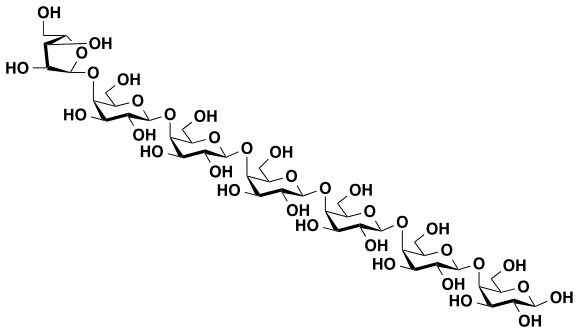
β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-[β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→6)]-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-D-galactopyranose (213)



199 (595 mg; 0.17 mmol) was dissolved in THF (20 mL) and a 1M Et_4NOH in MeOH solution (9.9 mL; 9.95 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (2:1 Tol/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (20 mL), THF (5 mL). 20% $Pd(OH)_2/C$ (116 mg; 0.17 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **213** as a white solid. Yield: 159 mg (73% over two steps).

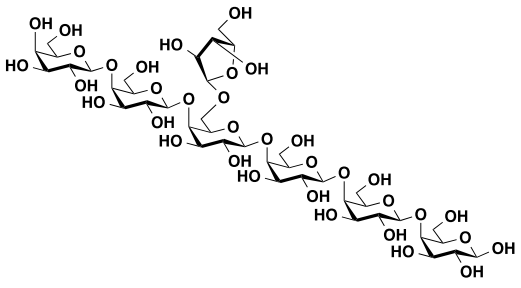
^{1}H NMR (400 MHz, D_2O) δ 5.18 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1α), 4.61 – 4.46 (m, 13H, 13xH-1), 4.38 (d, J = 7.9 Hz, 1H, 2xH-1), 4.20 – 3.94 (m, 24H, 16xH-4), 3.94 – 3.43 (m, 96H, 80H). **^{13}C NMR** (101 MHz, D_2O) δ 104.34, 104.26, 104.19, 103.47, 96.35, 92.27, 81.68, 77.87, 77.81, 77.62, 77.54, 77.06, 76.96, 75.10, 75.04, 74.46, 74.35, 74.31, 74.30, 74.28, 74.14, 73.72, 73.22, 73.19, 73.08, 72.70, 72.68, 72.18, 71.80, 71.77, 71.62, 71.36, 71.31, 71.19, 70.21, 68.56, 60.96, 60.67, 60.37.

L-arabinofuranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4) -D-galactopyranose (214)



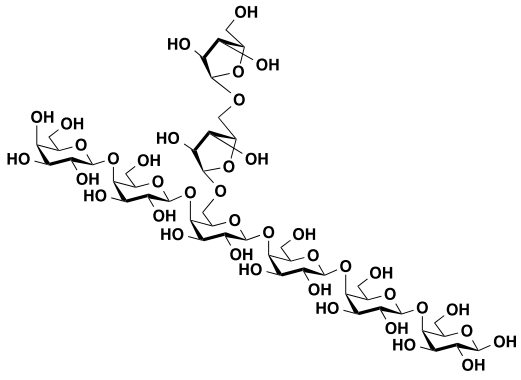
203 (489 mg; 0.15 mmol) was dissolved in THF (20 mL) and a 1M Et_4NOH in MeOH solution (5.4 mL; 5.40 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h and then poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (1:1 Tol/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (20 mL), THF (5 mL). 20% $Pd(OH)_2/C$ (108 mg; 0.15 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **214** as a white solid. Yield: 111 mg (65% over two steps)
^{1}H NMR (400 MHz, D_2O) δ 5.19 – 5.15 (m, 1H, H-1α, H-1^{ara}α, H-1^{ara}β), 4.61 – 4.48 (m, 11H, H-1^{1}β-H-1^{6}β, H-1^{2}α-H-1^{6}α), 4.17 – 4.12 (m, 2H), 4.11 – 4.06 (m, 11H, 11xH-4), 4.06 – 3.96 (m, 4H), 3.92 (d, $J_{3,4}$ = 3.3 Hz, 1H), 3.87 – 3.53 (m, 65H), 3.47 (dd, *J* = 10.0, 7.9 Hz, 1H). **^{13}C NMR** (101 MHz, D_2O) δ 109.15, 104.34, 104.29, 96.35, 92.27, 84.17, 81.68, 81.03, 78.80, 77.82, 77.57, 77.45, 76.42, 75.03, 74.97, 74.46, 74.28, 73.29, 73.24, 73.07, 72.19, 71.80, 71.76, 71.72, 71.33, 61.25, 61.21, 60.67.

β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-[α-L-arabinofuranosyl-(1→6)]- β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-D-galactopyranosyl-(1→4) -D-galactopyranose (215)



201 (485 g; 0.16 mmol) was dissolved in THF (20 mL) and a 1M Et_4NOH in MeOH solution (5.5 mL; 5.47 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h and then poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (1:1 Tol/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (20 mL), THF (5 mL). 20% $Pd(OH)_2/C$ (109 mg; 0.16 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **215** as a white solid. Yield: 120 mg (68% over two steps).
^{1}H NMR (400 MHz, D_2O) δ 5.18 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1α), 4.99 – 4.97 (m, 2H, H-1^{ara}α, H-1^{ara}β), 4.59 – 4.46 (m, 11H, H-1^{1}β-H-1^{6}β, H-1^{2}α-H-1^{6}α), 4.14 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 4.10 – 4.06 (m, 11H, 11xH-4), 4.05 – 4.01 (m, 1H), 3.99 (dd, *J* = 3.6, 1.8 Hz, 2H), 3.97 – 3.92 (m, 2H), 3.90 – 3.44 (m, 66H). **^{13}C NMR** (101 MHz, D_2O) δ 107.96, 104.36, 104.34, 104.24, 104.19, 96.35, 92.27, 83.71, 81.68, 80.97, 78.79, 77.82, 77.54, 77.02, 76.30, 75.11, 74.46, 74.36, 74.28, 73.58, 73.24, 73.19, 72.70, 72.19, 71.80, 71.60, 71.31, 69.81, 69.66, 68.77, 68.59, 68.13, 61.10, 60.96, 60.85, 60.67, 60.40.

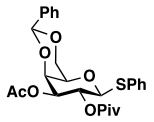
β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-[α-L-arabinofuranosyl-(1→5)-α-L-arabinofuranosyl-(1→6)]-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranose (216)



197 (600 mg; 0.17 mmol) was dissolved in THF (20 mL) and a 1M Et_4NOH in MeOH solution (8.7 mL; 8.71 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (1:2 Toluene/EtOAc) to yield colorless crystals. The product was dissolved in MeOH (20 mL), THF (5 mL). 20% $Pd(OH)_2/C$ (122 mg; 0.17 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid.

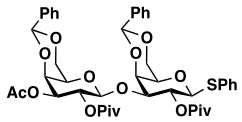
Purified by reverse phase chromatography to afford **216** as a white solid. Yield: 147 mg (67% over two steps) **^{1}H NMR** (400 MHz, D_2O) δ 5.18 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1a), 5.02 – 4.96 (m, 4H, H-1^{ara}α, H-1^{ara}β, H-1'^{ara}α, H-1'^{ara}β), 4.59 – 4.49 (m, 11H, H-1^{1}β-H-1^{6}β, H-1^{2}α-H-1^{6}α), 4.14 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4^{1}α), 4.13 – 3.96 (m, 11H, 11xH-4), 3.92 (dd, *J* = 6.1, 3.5 Hz, 2H), 3.89 – 3.44 (m, 79H). **^{13}C NMR** (101 MHz, D_2O) δ 108.11, 107.39, 104.36, 104.24, 96.35, 92.27, 83.91, 82.11, 81.68, 80.87, 78.79, 77.83, 77.54, 76.96, 76.54, 76.47, 75.11, 74.46, 74.36, 74.28, 74.28, 73.55, 73.20, 72.70, 72.19, 72.19, 71.80, 71.61, 71.31, 69.66, 68.78, 68.59, 68.23, 66.66, 61.13, 60.96, 60.67, 60.36.

Phenyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (251)



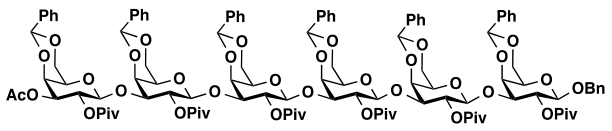
254 (30 g; 74.54 mmol) was dissolved in CH_2Cl_2 (500 mL). Et_3N (20.9 mL; 149.1 mmol), DMAP (4.55 g; 37.3 mmol) and pivaloyl chloride (9.5 mL; 111.8 mmol) was added to the solution and the reaction mixture was heated to 45 °C for 4 h. The reaction mixture was cooled to 0 °C, quenched with MeOH (10 mL), washed with water (2x500 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (Tol/EtOAc 15:1) to afford **251** as a white crystalline powder. R_f 0.44 (9:1 Tol/EtOAc). Yield 32.0 g (88%)
$[\alpha]_D^{20}$ = 3.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3061.41, 2975.48, 2872.21, 1746.23, 1479.26, 1458.20, 1440.23, 1369.52, 1276.88, 1232.47, 1171.24, 1144.91, 1093.84, 1048.73, 1025.24. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.43 (m, 2H, H^{SPh}), 7.38 – 7.26 (m, 5H, H^{SPh}, Ar-H), 7.25 – 7.14 (m, 3H, Ar-H), 5.40 (s, 1H, CH^{benzylidene}), 5.29 (t, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, 1H, H-2), 5.01 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 4.67 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.30 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$=1.6 Hz, 1H, H-6a), 4.27 (dd, $J_{3,4}$ = 3.4, $J_{4,5}$ = 0.9 Hz, 1H, H-4), 3.96 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6b}$ = 1.7 Hz, 1H, H-6b), 3.52 (m, 1H, H-5), 1.93 (s, 3H, -CH$_3^{Ac}$), 1.14 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.29, 170.55, 137.48, 133.58 (2C), 131.56, 129.13, 128.77 (2C), 128.14 (2C), 128.09, 126.50 (2C), 101.02, 85.53, 73.70, 72.97, 69.73, 69.13, 66.18, 38.74, 27.05, 20.80 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{30}NaO_7S$ 509.1610; Found 509.1595.

Phenyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)- 4,6-*O*-benzylidene-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (252)



To a 500 mL flame-dried flask was added **257** (7.0 g, 15.7 mmol) and the **256** (11.4 g, 20.5 mmol). The mixture was co-evaporated with toluene (2x200 mL) and subjected to vacuum overnight. The mixture dissolved in DCM (200 mL) and cooled to -40 °C. TMSOTf (0.24 mL; 1.6 mmol) was added and the reaction mixture was stirred at -40 °C (1h). Et_3N (1 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (9:1 Tol/EtOAc) affording **252**. R_f 0.23 (9:1 Tol/EtOAc). Yield: 11.9 g (92%).
$[\alpha]_D^{20}$ = 10.0° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 6H, Ar-H, H^{SPh}), 7.27 (m, 6H, , Ar-H, H^{SPh}), 7.20 – 7.06 (m, 3H, Ar-H, H^{SPh}), 5.48 (s, 1H, -CH^{benzylidene}), 5.43 (s, 1H, -CH^{benzylidene}), 5.33 (dd, $J_{2,3}$ = 10.6, $J_{1,2}$ = 8.0 Hz, 1H, H-1^2), 5.30 (t, $J_{1,2}$ =$J_{2,3}$ = 9.8 Hz, 1H, H-2^1), 4.85 (d, *J* = 8.0 Hz, 1H, H-1^2), 4.82 (dd, $J_{2,3}$ = 10.6, $J_{2,3}$ = 3.6 Hz, 1H, H-3^2), 4.59 (d, *J* = 9.8 Hz, 1H, H-1^1), 4.33 – 4.14 (m, 5H, H-3^1, H-4$^{1/2}$, H-4$^{1/2}$, H-6a^1, H-6a^2), 3.98 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ =1.8 Hz, 1H, H-6b^1), 3.92 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ =1.7 Hz, 1H, H-6b^2), 3.40 – 3.36 (m, 1H, H-5$^{1/2}$), 3.36 (s, 1H, H-5$^{1/2}$), 1.95 (s, 3H, CH$_3^{Ac}$), 1.22 (s, 9H, 3xCH$_3^{Piv}$), 1.00 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.84, 176.14, 170.65, 137.88, 137.47, 133.46, 132.29 (2C), 129.11, 128.73 (2C), 128.59 (2C), 128.24 (2C), 127.92 (2C), 127.56, 126.24 (2C), 126.21, 100.81, 100.14, 99.40, 86.83, 75.90, 73.58, 73.56, 71.82, 70.23, 69.40, 68.93, 68.78, 68.18, 66.75, 38.78, 38.72, 27.36 (3C), 26.96 (3C), 20.80. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{44}H_{52}NaO_{13}S$: 843.3026; Found 843.3014.

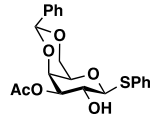
Benzyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (253)



To a 25 mL flame-dried flask was added **263** (1000 mg, 0.7 mmol) and **252** (740 mg, 0.9 mmol). The mixture was dried azeotropically with toluene (2x6 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (3 mL) and dry MeCN (3 mL), cooled to -30 °C, followed by addition of NIS (206 mg; 0.9 mmol) and TESOTf (18 mg; 0.07 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over

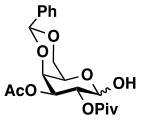
$MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (6:1 Tol/EtOAc) to afford a white crystalline material. R_f 0.20 (6:1 Tol/EtOAc). Yield: 1.2 g (79%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 12H, Ar-H), 7.33 – 7.14 (m, 23H, Ar-H), 5.52 – 5.22 (m, 12H, 6xCH^{benzylidene}, H-2^1-H-2^6), 4.86 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^1), 4.82 (d, J = 11.7 Hz, 1H, 0.5xCH$_2^{Bn}$), 4.80 (dd, $J_{2,3}$ = 10.7, $J_{3,4}$ = 3.3 Hz, 1H, H-3^6), 4.71 – 4.60 (m, 4H, H-1^2-H-1^5), 4.44 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH$_2^{Bn}$), 4.36 (d, J = 7.8 Hz, 1H, H-1^6), 4.30 – 3.91 (m, 23H, H-3^1-H-3^5, H-4^1-H-4^6, H-6^1-H-6^6), 3.36 – 3.32 (m, 1H, H-5$^{1/2/3/4/5/6}$), 3.30 (m, 1H, H-5$^{1/2/3/4/5/6}$), 3.25 (m, 1H, , H-5$^{1/2/3/4/5/6}$), 3.24 – 3.19 (m, 1H, H-5$^{1/2/3/4/5/6}$), 1.95 (m, 2H, H-5$^{1/2/3/4/5/6}$, H-5$^{1/2/3/4/5/6}$), 1.07 (s, 9H, 3xCH$_3^{Piv}$), 1.04 (s, 9H, 3xCH$_3^{Piv}$), 1.02 (s, 9H, 3xCH$_3^{Piv}$), 1.01 – 1.00 (m, 18H, 3xCH$_3^{Piv}$), 1.00 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.95, 176.23, 176.11 (2C), 176.06, 176.03, 170.72, 137.97, 137.87, 137.86, 137.84, 137.80, 137.55, 137.26, 129.19-125.40 (35C), 100.92, 100.45 (2C), 100.40, 100.35, 100.22, 100.17, 100.05, 99.83, 99.78 (2C), 99.31, 77.36, 75.99, 75.89, 75.73, 73.59, 72.10, 72.02, 71.93 (2C), 71.61, 71.57, 71.33, 71.25, 70.85, 70.06, 68.86, 68.76, 68.61, 68.34, 67.57, 67.50, 67.46, 67.02, 66.83, 38.81, 38.77, 38.73, 38.70 (2C), 38.68, 27.31 (3C), 27.28 (3C), 27.26 (9C), 27.09 (3C), 20.88.

Phenyl 3-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (254)



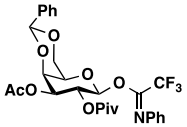
Di-*n*-butyl tin oxide (36.3 g; 145.7 mmol) was added to a solution of compound **56** (50.0 g, 138.7 mmol) in dry toluene (1000 mL) and stirred under refluxing temperature for 12 h. The reaction mixture was cooled to 0 °C, and freshly activated 4Å MS (50g) were added. After 30 min acetyl chloride (10.2 mL, 142.89 mmol) were added drop wise and stirring was maintained at this temperature for 1h. The reaction was quenched by addition of MeOH, filtered through a pad of celite and concentrated. The crude product was purified by flash chromatography (4:1 toluene/EtOAc) to give **254** as white crystals. R_f 0.12 (9:1 Tol/EtOAc). Yield: 49.72 g (91%)
$[\alpha]_D^{20}$ = 27.2° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 – 7.58 (m, 2H, H^{SPh}), 7.37 – 7.15 (m, 8H, H^{SPh}, H^{Bn}), 5.39 (s, 1H, -CH^{benzylidene}), 4.83 (dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 4.51 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.31 (m, 1H, H-4), 4.29 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.3 Hz, 1H, H-6a), 3.93 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ = 1.7 Hz, 1H, H-6b), 3.89 (td, $J_{1,2}$ = $J_{2,3}$ =9.8, $J_{2,OH}$ =1.9 Hz, 1H, H-2), 3.52 (m, 1H, H-5), 2.01 (s, 3H, -CH$_3^{Ac}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.07, 137.81, 133.80 (2C), 130.40, 129.24, 129.13 (2C), 128.40, 128.26 (2C), 126.53 (2C), 101.07, 87.61, 74.98, 73.71, 69.96, 69.27, 65.69, 21.20. **HRMS** (ESI-TOF) m/z: [M + NH_4]+ Calcd for $C_{21}H_{26}NO_6S$ 420.1481 Found 420.1478

3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-pivaloyl-D-galactopyranose (255)



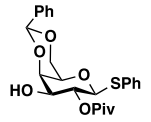
251 (20.0 g; 41.1 mmol) was dissolved in MeCN (270 mL) and water (30 mL). NBS (29.3 g; 164.4 mmol) and 2,6-lutidine (23.8 mL; 205.5 mmol) were added and the reaction was stirred at 50 °C until TLC showed full conversion (2h). The solution was diluted with CH_2Cl_2 (500 mL) and washed with sat. aq. NaS_2O_3 (200 mL) and sat. aq. $NaHCO_3$ (200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (6:1 Tol/EtOAc) to afford **255** as α/β mixture. R_f 0.12 (9:1 Tol/EtOAc). Yield: 17.2 g (84%)
$[\alpha]_D^{20}$ = 95.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3468.40, 2974.49, 2934.27, 2909.50, 2873.74, 1737.61, 1479.91, 1457.72, 1369.67, 1240.78, 1115.19, 1093.82, 1025.30, 977.04. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (m, 2H, Ar-H), 7.30 (m, 3H, Ar-H), 6.31 (d, $J_{1,2}$ = 3.6 Hz, 1H, H-1), 5.45 (s, 1H, H^{benzylidene}), 5.08 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 4.42 (dd, $J_{3,4}$ = 3.4, $J_{4,5}$ = 1.2 Hz, 1H, H-4), 4.35 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 3.6 Hz, 1H, H-2), 4.22 (dd, $J_{6a,6b}$ = 12.6, $J_{5,6a}$ = 1.6 Hz, 1H, H-6a), 3.97 (dd, $J_{6a,6b}$ = 12.6, $J_{5,6b}$ = 1.8 Hz, 1H, H-6b), 3.75 (m, 1H, H-5), 2.09 (s, 3H, CH$_3^{Ac}$), 1.20 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.00, 171.69, 137.54, 129.24, 128.35, 126.27, 100.92, 92.75, 73.80, 71.67, 69.10, 66.04, 64.66, 39.47, 27.25, 21.24. **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{26}NaO_8$: 417.1525; Found 417.1529.

3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (256)



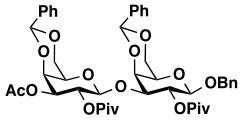
255 (13 g; 33.0 mmol) was dissolved in CH_2Cl_2 (300 mL) and cooled to 0 °C. Cs_2CO_3 (21.5 g; 65.9 mmol) was added followed by *N*-phenyl trifluoroacetimidoyl chloride (13.7 g; 65.9 mmol). The ice bath was removed and the reaction mixture was stirred until TLC showed full conversion (5 h). It was then filtered, concentrated and purified by flash chromatography (20:1 Tol/EtOAc) to give a white crystalline product. R_f 0.66 (9:1 Tol/EtOAc) Yield: 14.7 g (79%)

Phenyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (257)



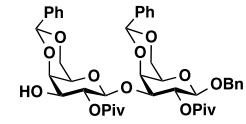
251 (10 g; 20.6 mmol) was dissolved in dry DCM (200 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (61.6 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (4h). The reaction mixture was poured into sat. aq. NH_4Cl (400 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography (9:1 Tol/EtOAc) to give a white crystalline product. Rf 0.23 (9:1 Tol/EtOAc) Yield: 8.6 g (94%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H, Ar-H), 7.38 – 7.10 (m, 10H, Ar-H), 5.45 (s, 1H, $CH^{benzylidene}$), 4.98 (t, $J_{1,2} = J_{2,3} = 9.7$ Hz, 1H, H-2), 4.60 (d, $J_{1,2} = 9.7$ Hz, 1H, H-1), 4.31 (dd, $J_{6a,6b} = 12.5$, $J_{5,6a} = 1.5$ Hz, 1H, H-6a), 4.14 (dd, $J_{3,4} = 3.6$, $J_{4,5} = 1.1$ Hz, 1H, H-4), 3.96 (dd, $J_{6a,6b} = 12.5$, $J_{5,6b} = 1.7$ Hz, 1H, H-6b), 3.67 (dd, $J_{2,3} = 9.7$, $J_{3,4} = 3.6$ Hz, 1H, H-3), 3.51 – 3.43 (m, 1H, H-5), 1.19 (s, 9H, $3xCH_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.61, 137.39, 133.58 (2C), 131.59, 129.35, 128.78 (2C), 128.24 (2C), 128.08, 126.52 (2C), 101.41, 85.06, 75.66, 72.92, 69.90, 69.52, 69.17, 38.83, 27.16 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{28}NaO_6S$: 467.1504; Found 467.1511.

Benzyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (260)



252 (2.0 g; 2.4 mmol) was dried azeotropically with toluene (2x20 mL) and subjected to vacuum overnight. Benzyl alcohol (0.8 g; 7.3 mmol) was added. The mixture was dissolved in dry CH_2Cl_2 (50 mL) and cooled to -40 °C. NIS (602 mg; 2.7 mmol) and TESOTf (64 mg; 0.24 mmol) was added and the reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 toluene/EtOAc) to afford **260** as a white crystalline material. R_f 0.10 (9:1 Tol/EtOAc)
Yield: 1.5 g (75%)
$[\alpha]_D^{20}$ = -0.8° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3524.57, 3065.71, 2973.85, 1733.56, 1497.34, 1479.42, 1454.83, 1398.37, 1278.46, 1249.26, 1167.19, 1139.04, 1087.54, 1060.73. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.38 (m, 4H, H^{SPh}), 7.35 – 7.13 (m, 11H, H^{SPh}, Ar-H), 5.51 (s, 1H, -$CH^{benzylidene}$), 5.43 (s, 1H, -$CH^{benzylidene}$), 5.42 (dd, $J_{2,3} = 10.4$, $J_{1,2} = 7.9$ Hz, 1H, H-2), 5.35 (dd, $J_{2,3} = 10.6$, $J_{1,2} = 8.1$ Hz, 1H, H-2'), 4.93 (d, $J_{1,2} = 8.1$ Hz, 1H, H-1'), 4.87 – 4.79 (m, 2H, H-3', -CH_2^{Bn}), 4.47 (d, $J = 11.9$ Hz, 1H, -CH_2^{Bn}), 4.37 (d, $J = 7.9$ Hz, 1H, H-1), 4.34 – 4.23 (m, 4H, H-4', H-4, H-6a', H-6b'), 4.13 (dd, $J_{2,3} = 10.4$, $J_{3,4} = 3.4$ Hz, 1H, H-3), 3.99 (m, 2H, H-6a, H-6b), 3.42 – 3.26 (m, 2H, H-5, H-5'), 1.96 (s, 3H, -CH_3^{Ac}), 1.10 (s, 9H, $3xCH_3^{Piv}$), 1.05 (s, 9H, $3xCH_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.84, 176.12, 170.68, 137.80, 137.50, 137.20, 129.08, 129.05, 128.59, 128.24, 128.22, 128.20, 127.96 (2C), 127.79 (2C), 127.52, 126.27 (2C), 126.10 (2C), 100.84, 100.33, 100.21, 99.50, 75.94, 73.63, 72.76, 71.86, 70.81, 69.90, 68.83, 68.77, 68.22, 66.90, 66.72, 38.76, 38.71, 27.22, 27.19, 27.19, 27.08 (3C), 27.02 (3C), 20.81. **HRMS** (ESI-TOF) m/z: $[M + NH_4]+$ Calcd for $C_{45}H_{58}NO_{14}$ 836.3857 Found 836.3843

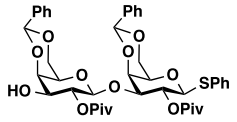
Benzyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (261)



260 (1.5 g; 1.8 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (5.5 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (5h). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography (6:1 Tol/EtOAc) yielding **261** as a white crystalline product. R_f 0.46 (2:1 Tol/EtOAc). Yield: 1.28 g (90%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.13 (m, 15H, Ar-H), 5.49 (s, 1H, $CH^{benzylidene}$), 5.47 (s, 1H, $CH^{benzylidene}$), 5.45 (dd, $J_{2,3} = 10.1$, $J_{1,2} = 7.9$ Hz, 1H, H-2^1), 5.00 (dd, $J_{2,3} = 10.1$, $J_{1,2} = 8.0$ Hz, 1H, H-2^2), 4.84 (d, $J_{CH2} = 11.8$ Hz, 1H, CH_2^{Bn}), 4.84 (d, $J_{1,2} = 8.0$ Hz, 1H, H-1^2), 4.48 (d, $J_{CH2} = 11.9$ Hz, 1H, CH_2^{Bn}), 4.39 (d, $J_{1,2} = 7.9$ Hz, 1H, H-1^1), 4.31 – 4.23 (m, 3H, H-4^1, H-$6a^2$, H-$6b^2$), 4.10 (d, $J_{3,4} = 3.7$ Hz, 1H, H-4^2), 4.08 (dd, $J_{2,3} = 10.1$, $J_{3,4} = 3.2$ Hz, 1H, H-3^1), 4.02 – 3.95 (m, 2H, H-$6a^1$, H-$6b^1$), 3.52 (dd, $J_{2,3} = 10.1$, $J_{3,4} = 3.7$ Hz, 1H, H-3^2), 3.34 (s, 1H, H-5^1), 3.33 (s, 1H, H-5^2), 1.10 (s, 9H, $3xCH_3^{Piv}$), 1.10 (s, 9H, $3xCH_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.95, 176.15, 137.90, 137.48, 137.30, 129.34, 129.14, 128.76, 128.38, 128.34, 128.30 (2C), 128.04, 127.91 (2C), 127.63 (2C), 126.38 (2C), 126.29, 101.34, 100.47, 100.39, 99.49, 76.11, 75.83, 73.18, 72.26, 72.16, 71.00, 69.99, 68.92, 66.97, 66.92, 38.99, 38.78,

27.31 (3C), 27.12 (3C). **HRMS** (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{43}H_{56}NO_{13}$ 794.3752 Found 794.3756.

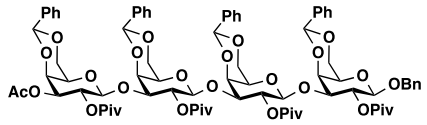
Benzyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (261_2)



285 (3.2 g; 3.8 mmol) was dissolved in dry CH_2Cl_2 (75 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (11.2 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (30 min). The reaction mixture was quenched with sat. aq. NH_4Cl (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography (4:1 Tol/EtOAc) to give a white crystalline material. R_f 0.48 (2:1 Tol/EtOAc) Yield: 2.7 g (92%)

$[\alpha]_D^{20}$ = -78.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3509.54, 3065.12, 3034.81, 2974.26, 2932.39, 2906.51, 2872.12, 1735.20, 1701.55, 1497.61, 1479.71, 1455.24, 1398.18, 1366.58, 1278.90, 1167.38, 1139.48, 1085.25, 1061.57, 1044.79. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.13 (m, 15H, Ar-H), 5.49 (s, 1H, $CH^{benzylidene}$), 5.47 (s, 1H, $CH^{benzylidene}$), 5.45 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 7.9 Hz, 1H, H-2^1), 5.00 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 8.0 Hz, 1H, H-2^2), 4.84 (d, J_{CH2} = 11.8 Hz, 1H, CH_2^{Bn}), 4.84 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^2), 4.48 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 4.39 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^1), 4.31 – 4.23 (m, 3H, H-4^1, H-6a^2, H-6b^2), 4.10 (d, $J_{3,4}$ = 3.7 Hz, 1H, H-4^2), 4.08 (dd, $J_{2,3}$ = 10.1, $J_{3,4}$ = 3.2 Hz, 1H, H-3^1), 4.02 – 3.95 (m, 2H, H-6a^1, H-6b^1), 3.52 (dd, $J_{2,3}$ = 10.1, $J_{3,4}$ = 3.7 Hz, 1H, H-3^2), 3.34 (s, 1H, H-5^1), 3.33 (s, 1H, H-5^2), 1.10 (s, 9H, 3xCH_3^{Piv}), 1.10 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.95, 176.15, 137.90, 137.48, 137.30, 129.34, 129.14, 128.76, 128.38, 128.34, 128.30 (2C), 128.04, 127.91 (2C), 127.63 (2C), 126.38 (2C), 126.29, 101.34, 100.47, 100.39, 99.49, 76.11, 75.83, 73.18, 72.26, 72.16, 71.00, 69.99, 68.92, 66.97, 66.92, 38.99, 38.78, 27.31 (3C), 27.12 (3C). **IR** (neat, cm^{-1}): 3065.11, 3034.05, 2973.45, 2933.97, 2906.79, 2872.38, 1741.81, 1479.57, 1455.08, 1397.80, 1366.82, 1311.84, 1277.42, 1232.57, 1173.76, 1132.82, 1087.46, 1047.65, 1026.57, 1001.49. **HRMS** (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{42}H_{54}NO_{12}S$ 796.3367 Found 796.3364

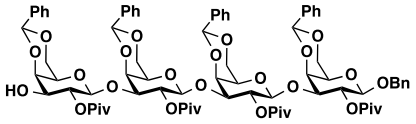
Benzyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (262)



To a 25 mL flame-dried flask was added **261** (1.1 g, 1.4 mmol) and the **252** (1.5 g, 1.8 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -30 °C, followed by addition of NIS (420 mg; 1.9 mmol) and TESOTf (56 mg; 0.2 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (6:1 toluene/EtOAc) to afford a white crystalline material. R_f 0.58 (2:1 Tol/EtOAc). Yield: 1.9 g (88%)

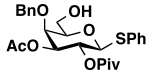
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.34 (m, 8H, Ar-H), 7.34 – 7.14 (m, 17H, Ar-H), 5.50 (s, 1H, $CH^{benzylidene}$), 5.49 (s, 1H, $CH^{benzylidene}$), 5.46 (s, 1H, $CH^{benzylidene}$), 5.43 (s, 1H, $CH^{benzylidene}$), 5.42 – 5.26 (m, 4H, H-2^1-H-2^4), 4.86 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1^1), 4.84 – 4.77 (m, 2H, H-3^4, 0.5xCH_2^{Bn}), 4.68 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1$^{2/3}$), 4.67 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1$^{2/3}$), 4.45 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^4), 4.31 – 4.17 (m, 8H, H-4^1-H-4^4, 2xH-6), 4.17 – 4.09 (m, 2H, H-3$^{1/2/3}$, H-3$^{1/2/3}$), 4.06 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.4 Hz, 1H, H-3$^{1/2/3}$), 4.03 – 3.92 (m, 4H, 2xH-6), 3.37 – 3.34 (m, 1H, H-5$^{1/2/3/4}$), 3.33 – 3.30 (m, 1H, H-5$^{1/2/3/4}$), 3.27 – 3.24 (m, 1H, H-5$^{1/2/3/4}$), 3.24 – 3.23 (m, 1H, H-5$^{1/2/3/4}$), 1.95 (s, 3H, -CH_3^{Ac}), 1.08 (s, 9H, -CH_3^{Piv}), 1.04 (s, 9H, -CH_3^{Piv}), 1.03 (s, 9H, -CH_3^{Piv}), 1.01 (s, 9H, -CH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.97, 176.28, 176.08 (2C), 170.73, 137.98, 137.85, 137.81, 137.56, 137.29, 129.19-126.11 (25C), 100.93, 100.44, 100.42, 100.25, 100.21, 100.10, 99.75, 99.35, 77.36, 76.01 (2C), 75.74, 73.60, 72.09, 71.98, 71.94 (2C), 71.55, 71.20, 70.86, 70.08, 68.87, 68.80, 68.75, 68.65, 68.36, 67.51, 67.48, 67.04, 66.85, 38.83, 38.78, 38.73 (2C), 27.32, 27.29, 27.27, 27.10, 20.89.

Benzyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (263)



262 (1.5 g; 1.8 mmol) was dissolved in dry DCM (30 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (5.5 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (5h). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concent-rating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography (4:1 Tol/EtOAc) to give a white crystalline product. R_f 0.46 (2:1 Tol/EtOAc). Yield: 1.28 g (90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.34 (m, 8H), 7.34 – 7.11 (m, 17H), 5.53 – 5.44 (m, 4H, 4xCH^{benzylidene}), 5.39 (dd, $J_{2,3}$ = 9.8, $J_{1,2}$ = 7.4 Hz, 1H, H-2$^{1/2/3/4}$), 5.34 (m, 2H, H-2$^{1/2/3/4}$, H-2$^{1/2/3/4}$), 4.97 (dd, $J_{2,3}$ = 10.0, $J_{1,2}$ = 8.0 Hz, 1H, H-2^4), 4.82 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH$_2^{Bn}$), 4.77 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^4), 4.69 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1$^{1/2/3/4}$), 4.68 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1$^{1/2/3/4}$), 4.44 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH$_2^{Bn}$), 4.36 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1$^{1/2/3/4}$), 4.31 – 3.90 (m, 15H, H-3^1-H-3^3, H-4^1-H-4^4, H-6^1-H-6^4), 3.51 (td, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.6 Hz, 1H, H-3^4), 3.37 – 3.21 (m, 4H, H-5^1-H-5^4), 1.07 (s, 9H, 3xCH$_3^{Piv}$), 1.06 (s, 9H, 3xCH$_3^{Piv}$), 1.05 (s, 9H, 3xCH$_3^{Piv}$), 1.03 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.81, 176.09, 175.99, 175.97, 137.90, 137.76, 137.66, 137.34, 137.17, 129.28-126.09 (25C), 101.25, 100.34 (2C), 100.30, 100.15, 99.99, 99.64, 99.20, 77.27, 76.00, 75.92, 75.64 (2C), 72.37, 72.14, 71.98, 71.88, 71.49, 71.11, 70.87, 70.00, 68.76, 68.65, 68.55, 67.41, 67.37, 66.93, 66.89, 38.87, 38.68, 38.64, 38.61, 27.23, 27.20, 27.16, 27.03 **HRMS** (ESI-TOF) m/z: [M + NH_4]+ Calcd for $C_{79}H_{100}NO_{25}$ 1462.6584 Found 1462.6579.

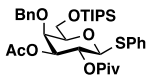
Phenyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (266)



A 1 M solution of BH_3·THF complex in THF (61.6 mL) was added to a solution of **251** (6 g; 12.33 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred for 10 min, and freshly dried $Cu(OTf)_2$ (669 mg, 1.85 mmol) was added to the solution. After stirring for a 5 h, the mixture was cooled to 0 °C, and the reaction was quenched by addition of Et_3N (1.7 mL, 12.33 mmol) and methanol (30 mL, caution: hydrogen gas was evolved). The resultant mixture was concentrated at reduced pressure followed by coevaporation with methanol. The residue was purified by flash chromatography (9:1 Tol/EtOAc). R_f 0.15 (9:1 Tol/EtOAc). Yield: 4.79 g (80%)

$[\alpha]_D^{20}$ = -5.5° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H, H^{SPh}), 7.32 – 7.14 (m, 8H, H^{SPh}, H^{Bn}), 5.36 (dd, $J_{1,2}$ = $J_{2,3}$ =10.0 Hz, 1H, H-2), 5.00 (dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.68 (d, J_{CH2}= 11.7 Hz, 1H, -CH$_2^{Bn}$), 4.65 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 4.44 (d, J_{CH2} = 11.7 Hz, 1H, -CH$_2^{Bn}$), 3.86 (dd, $J_{3,4}$ = 3.0, $J_{4,5}$ =1.0 Hz, 1H), 3.77 (ddd, $J_{6a,6b}$ = 11.0, $J_{5,6a}$ = 6.7, $J_{6a,OH}$ =3.9 Hz, 1H, H-6a), 3.59 – 3.50 (m, 1H, H-5), 3.48 (ddd, $J_{6a,6b}$ = 11.1, $J_{5,6b}$ = 8.6, $J_{6b,OH}$ =5.2 Hz, 1H, H-6b), 1.92 (s, 3H, -CH$_3^{Ac}$), 1.14 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.73, 170.17, 137.48, 133.18, 132.01 (2C), 128.93 (2C), 128.53 (2C), 128.29 (2C), 128.10, 127.81, 86.91, 78.88, 74.96, 74.72, 73.76, 67.49, 61.79, 38.78, 27.03 (3C), 20.77. **HRMS** (ESI-TOF) m/z: [M+NH_4]$^+$ Calcd for $C_{26}H_{36}NO_7S$ 506.2213 Found 506.2228

Phenyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-6-*O*-triisopropylsilyl-1-thio-β-D-galactopyranoside (267)

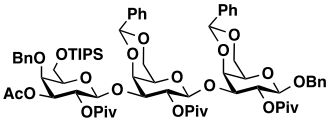


266 (1.3 g; 2.66 mmol) was dissolved in DMF (25 mL) and cooled to 0 °C. To the solution were added triisopropylsilyl chloride (0.85 mL; 3.99 mmol) and imidazole (0.36 g; 5.32 mmol). The reaction mixture was stirred at 0 °C for 1h and then at 22 °C for 18h. The mixture was diluted with Et_2O (200 mL) and washed with water (3 x 200 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (20:1 Tol/EtOAc) to give **267** as a white solid. R_f 0.63 (9:1 Tol/EtOAc).

Yield: 1.58 g (93%)

$[\alpha]_D^{20}$ = -14.4° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3061.27, 3032.58, 2865.93, 1745.83, 1584.53, 1496.52, 1479.01, 1461.73, 1366.26, 1276.30, 1231.32, 1147.24, 1113.13, 1077.71, 1047.98. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 2H, Ar-H), 7.35 – 7.07 (m, 8H, Ar-H), 5.34 (t, $J_{1,2}$ = $J_{2,3}$ = 10.0 Hz, 1H, H-2), 5.04 (dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.67 (d, J_{CH2} = 11.6 Hz, 1H, 0.5xCH$_2^{Bn}$), 4.56 (d, J = 11.6 Hz, 1H, 0.5xCH$_2^{Bn}$), 3.97 (dd, $J_{3,4}$ = 3.1, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.87 – 3.66 (m, 2H, H-6a, H-6b), 3.57 (ddd, $J_{5,6a}$ = 7.2, $J_{5,6b}$ =5.9, $J_{4,5}$ =1.0 Hz, 1H, H-5), 1.85 (s, 3H, CH$_3^{Ac}$), 1.12 (s, 9H, 3xCH$_3^{Piv}$), 0.98 (s, 6H, CH$_3^{TIPS}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.78, 170.38, 138.29, 133.63, 131.96 (2C), 128.90 (2C), 128.40 (2C), 128.02 (2C), 127.73, 127.67, 86.93, 79.26, 75.01, 74.20, 67.78, 61.66, 38.87, 27.16 (3C), 20.87, 18.14 (2C), 18.12 (2C), 17.84, 12.42, 11.98 (2C). **HRMS** (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{35}H_{52}NaO_7SSi$ 667.3101Found 667.3098.

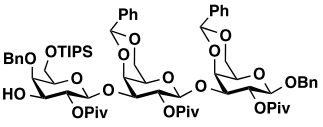
Benzyl 3-*O*-acetyl-4-*O*-benzyl-6-*O*-triisopropylsilyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (268)



To a 50 mL flame-dried flask was added **261** (0.92 g, 1.18 mmol) and **267** (1.14 g, 1.78 mmol). The mixture was dried azeotropically with toluene (2x20 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (10 mL) and dry MeCN (10 mL), cooled to -30 °C, followed by addition of NIS (413 mg; 1.84 mmol) and TESOTf (63 mg; 0.24 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1 h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (12:1 toluene/EtOAc) to afford a white crystalline material. Yield: 590 mg (38%). R_f 0.46 (9:1 Tol/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.01 (m, 20H, Ar-H), 5.48 (s, 1H, $CH^{benzylidene}$), 5.46 (s, 1H, $CH^{benzylidene}$), 5.39 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.8 Hz, 1H, H-2), 5.31 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 8.1 Hz, 1H, H-2), 5.27 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 8.0 Hz, 2H), 4.84 (dd, $J_{2,3}$ = 10.6, $J_{3,4}$ = 3.1 Hz, 1H, H-3^3), 4.82 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 4.71 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1), 4.70 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.70 (d, J_{CH2} = 12.2 Hz, 1H, 0.5xCH_2^{Bn}), 4.65 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.55 (d, J_{CH2} = 11.3 Hz, 1H, 0.5xCH_2^{Bn}), 4.45 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.37 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.31 – 4.21 (m, 2H, H-6), 4.20 (d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 4.15 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4), 4.12 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4), 4.06 – 3.91 (m, 5H, 3xH-3, H-6), 3.81 (m, 1H, H-6a^3), 3.71 (m, 1H, H-6b^3), 3.47 (dd, $J_{5,6a}$ = 8.7, $J_{5,6b}$ = 5.5 Hz, 1H, H-5^3), 3.31 (s, 1H, H-5), 3.27 (s, 1H, H-5), 1.83 (s, 3H, CH_3^{Ac}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.03 – 0.96 (m, 27H, 3xCH_3^{Piv}, 6xCH_3^{TIPS}), 0.99 (m, 3H, 3xCH^{TIPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.16, 176.07, 175.88, 170.27, 138.19, 137.85, 137.70, 137.27, 128.56-126.04 (20C), 100.21, 100.18, 100.12, 99.95, 99.40, 78.86, 77.65, 77.25, 75.69, 75.61, 75.27, 75.25, 74.77, 74.11, 74.01, 73.74, 73.51, 71.74, 71.42, 69.87, 69.31, 68.75, 68.72, 67.31, 66.98, 66.67, 60.93, 60.75, 38.71, 38.64, 38.58, 27.20(3C), 27.18(3C), 27.00(3C), 20.69, 18.06(3C), 18.06(3C), 18.03(3C), 18.02(3C), 18.00(3C), 17.96(3C), 11.85, 11.85, 11.83.

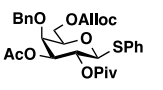
Benzyl 4-*O*-benzyl-6-*O*-triisopropylsilyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (269)



268 (350 mg; 0.27 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (1.1 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material was observed by TLC (3 h). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (2x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography (9:1 Tol/EtOAc) to give a white crystalline product. Yield: 0.31 g (92%). R_f 0.40 (9:1 Tol/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.31 (m, 4H, Ar-H), 7.35 – 7.05 (m, 16H, Ar-H), 5.49 (s, 1H, $CH^{benzylidene}$), 5.43 (s, 1H, $CH^{benzylidene}$), 5.40 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 7.7 Hz, 1H, H-2), 5.35 (dd, $J_{2,3}$ = 10.0, $J_{1,2}$ = 7.8 Hz, 1H, H-2), 4.84 (dd, $J_{2,3}$ = 9.6, $J_{1,2}$ = 7.4 Hz, 1H, H-2), 4.83 (d, J_{CH2} = 12.1 Hz, 1H, 0.5xCH_2^{Bn}), 4.73 – 4.71 (m, 2H, CH_2^{Bn}), 4.69 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.64 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.45 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.37 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.31 – 4.20 (m, 3H, H-4, H-6), 4.18 – 4.12 (m, 2H, H-3, H-4), 4.02 – 3.93 (m, 3H, H-3, H-6), 3.88 (dd, $J_{3,4}$ = 3.5, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.82 (dd, $J_{6a,6b}$ = 9.7, $J_{5,6a}$ = 8.6 Hz, 1H, H-6a), 3.75 (dd, $J_{6a,6b}$ = 9.7, $J_{5,6b}$ = 5.5 Hz, 1H, H-6b), 3.46 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.5 Hz, 1H, H-3), 3.37 (ddd, $J_{5,6a}$ = 8.6, $J_{5,6b}$ = 5.5, $J_{4,5}$ =1.1 Hz, 1H, H-5), 3.32 (d, J = 1.3 Hz, 1H, H-5), 3.29 (d, J = 1.4 Hz, 1H, H-5), 1.08 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 18H, 6xCH_3^{TIPS}), 0.99 (m, 3H, 3xCH^{TIPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.56, 176.10, 176.06, 137.91, 137.83, 137.32, 137.34, 127.63-125.05(20C), 99.28, 99.21, 99.14, 98.89, 98.32, 75.20, 74.81, 74.66, 74.60, 74.30, 72.55, 72.46, 70.84, 70.74, 70.71, 69.98, 68.85, 67.72, 67.69, 66.25, 65.94, 26.18(3C), 26.12(3C), 25.93(3C), 17.05(2C), 17.02(2C), 16.99(2C), 10.84(3C).

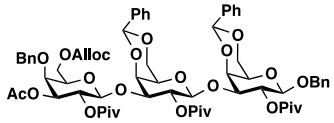
Phenyl 3-*O*-acetyl-6-*O*-allyloxycarbonyl-4-*O*-benzyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (270)



TMEDA (0.18 mL; 1.22 mmol) and allyl chloroformate (0.24 mL; 2.25 mmol) were added to a solution of **266** (1.0 g; 2.05 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0 °C. After 1h the mixture was diluted with CH_2Cl_2 (75 mL), washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (15:1 Tol/EtOAc) to give compound **270**. R_f 0.51 (9:1 Tol/EtOAc). Yield: 8.3 g (91%).

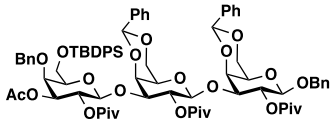
$[\alpha]_D^{20}$= -6.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3062.34, 2972.29, 2936.14, 2905.97, 1743.53, 1584.14, 1496.611455.38, 1440.49, 1366.40, 1256.83, 1230.13, 1143.53, 1084.39. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 2H, Ar-H), 7.34 – 7.09 (m, 8H, Ar-H), 5.85 (ddt, J_{trans} = 17.2, J_{cis} = 10.4, J_{CH2} = 5.8 Hz, 1H, -C*H*=CH_2), 5.34 (t, $J_{1,2}$ = $J_{2,3}$ = 10.1 Hz, 1H, H-2), 5.29 (dq, J_{trans} = 17.2, J_{CH2} = 1.4 Hz, 1H, CH_2=CH^{trans}), 5.21 (dd, J_{cis} = 10.4, J_{CH2} = 1.3 Hz, 1H, CH_2=CH^{trans}), 5.00 (dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 2.9 Hz, 1H, H-3), 4.68 (d, J_{CH2} = 11.6 Hz, 1H, CH_2^{Bn}), 4.62 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 4.54 (dt, $J_{CH=CH2}$ = 5.8, $J_{CH2=CH}$ = 1.4 Hz, 2H, CH_2^{allyl}), 4.47 (d, J_{CH2} = 11.6 Hz, 1H, CH_2^{Bn}), 4.31 (dd, $J_{6a,6b}$ = 11.0, $J_{5,6a}$ = 6.4 Hz, 1H, H-6a), 4.05 (dd, $J_{6a,6b}$ = 11.0, $J_{5,6b}$ = 6.4 Hz, 1H, H-6b), 3.88 (dd, $J_{3,4}$ = 3.0, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.74 (td, $J_{5,6b}$ = $J_{5,6a}$ = 6.4, $J_{4,5}$ =1.1 Hz, 1H, H-5), 1.91 (s, 3H, CH_3^{Ac}), 1.14 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.77, 170.20, 154.63, 137.51, 133.11, 132.52 (2C), 131.42, 128.97 (2C), 128.55 (2C), 128.24 (2C), 128.06, 128.02, 119.30, 87.07, 75.85, 75.02, 74.78, 73.88, 68.85, 67.39, 65.75, 38.88, 27.13 (3C), 20.83. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{36}NaO_9S$ 595.1978Found 595.1978.

Benzyl 3-*O*-acetyl-4-*O*-benzyl-6-*O*-allyloxocarbonyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (271)



To a 25 mL flame-dried flask was added **261** (1.0 g, 1.29 mmol) and the **270** (0.96 mg, 1.67 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -30 °C, followed by addition of NIS (385 mg; 1.71 mmol) and TESOTf (34 mg; 0.13 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2 h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 toluene/EtOAc) to afford **271** as a white crystalline material. Yield: 1.14 g (74%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 4H, Ar-H), 7.39 – 7.05 (m, 16H, Ar-H), 5.86 (ddt, J_{trans} = 17.2, J_{cis} = 10.3, J_{CH2} = 5.9 Hz, 1H, -*CH*=CH_2), 5.48 (s, 2H, 2x$CH^{benzylidene}$), 5.38 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 7.7 Hz, 1H, H-2), 5.33 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 7.8 Hz, 1H, H-2), 5.30 (dd, J_{trans} = 17.2, J_{CH2} = 1.5 Hz, 1H, *CH_2*=CH-), 5.28 (dd, $J_{2,3}$ = 10.9, $J_{1,2}$ = 7.0 Hz, 1H, H-2), 5.23 (dq, J_{cis} = 10.4, J_{CH2} = 1.2 Hz, 1H, *CH_2*=CH-), 4.83 (dd, $J_{2,3}$ = 10.9, $J_{3,4}$ = 3.6 Hz, 1H, H-3), 4.82 (d, J_{CH2} = 11.7 Hz, 1H), 4.72 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.70 (d, $J_{1,2}$ = 7.0 Hz, 1H, H-1), 4.67 (d, J_{CH2} = 11.5 Hz, 1H, CH_2^{Bn}), 4.55 (m, 2H, CH_2^{Alloc}), 4.45 (d, J_{CH2} = 12.0 Hz, 1H, CH_2^{Bn}), 4.44 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.37 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.31 – 4.19 (m, 3H, 1.5xH-6), 4.24 (d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 4.21 (dd, $J_{3,4}$ = 3.8, $J_{4,5}$ = 1.2 Hz, 1H, H-4), 4.14 (dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.10 (dd, $J_{6a,6b}$ = 11.1, $J_{5,6a}$ = 5.9 Hz, 1H, H-6a), 4.00 (m, 2H, H-6), 3.95 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 3.86 (dd, $J_{3,4}$ = 3.1, $J_{4,5}$ = 1.5 Hz, 1H, H-4), 3.67 (td, $J_{5,6a}$ = 5.9, $J_{5,6a}$ = 1.5 Hz, 1H, H-5), 3.34 – 3.27 (m, 2H, 2xH-5), 1.89 (s, 3H, CH_3^{Ac}), 1.09 (s, 8H, 3xCH_3^{Piv}), 1.05 (s, 9H, 3xCH_3^{Piv}), 1.01 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.06, 176.15, 176.13, 170.26, 154.67, 137.96, 137.83, 137.38, 137.37, 131.41-126.13(20C), 119.52, 100.36, 100.28, 100.24, 100.02, 99.94, 75.81, 75.76, 75.09, 73.82, 73.16, 72.81, 72.73, 71.92, 71.79, 70.85, 69.98, 68.88, 68.79, 67.39, 67.07, 65.96, 38.85, 38.77, 38.73, 27.29(6C), 27.13(3C), 20.78. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{67}H_{82}NaO_{22}$: 1261.5195; Found 1261.5197.

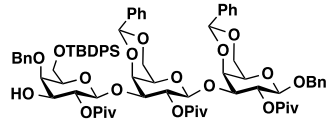
Benzyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (273)



To a 25 mL flame-dried flask was added **261** (800 mg, 1.03 mmol) and the **272** (1050 mg, 1.45 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -30 °C, followed by addition of NIS (333 mg; 1.48 mmol) and TESOTf (54 mg; 0.21 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 toluene/EtOAc) to afford a white crystalline material. Yield: 1020 mg (71%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 4H, Ar-H), 7.51 – 7.04 (m, 32H, Ar-H), 5.47 (s, 1H, $H^{benzylidene}$), 5.42 (s, 1H, $H^{benzylidene}$), 5.34 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.9 Hz, 1H), 5.26 (dd, $J_{2,3}$ = 10.7, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 5.25 (dd, $J_{2,3}$ = 10.6, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.85 (dd, $J_{2,3}$ = 10.6, $J_{3,4}$ = 3.1 Hz, 1H, H-3), 4.81 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.68 (d, J_{CH2} = 11.3 Hz, 1H, 0.5xCH_2^{Bn}), 4.64 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.59 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.54 (d, J_{CH2} = 11.3 Hz, 1H, 0.5xCH_2^{Bn}), 4.44 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.35 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.28 – 4.18 (m, 3H, H-4, H-6), 4.13 (d, $J_{3,4}$ = 3.6 Hz, 1H, H-4), 4.10 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 4.05 (d, $J_{3,4}$ = 3.7 Hz,

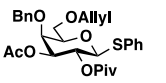
1H, H-4), 3.95 (m, 1H, H-6), 3.90 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 3.83 (t, $J_{6a,6b}$ = $J_{5,6a}$ = 9.8 Hz, 1H, H-6a), 3.66 (dd, $J_{6a,6b}$ = 9.8, $J_{5,6b}$ = 5.4 Hz, 1H, H-6b), 3.53 – 3.44 (m, 1H, H-5), 3.29 (m, 1H, H-5), 3.19 (m, 1H, H-5), 1.86 (s, 3H, CH_3^{Ac}), 1.00 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 12H, 3xCH_3^{Piv}), 0.98 (s, 9H, 3xCH_3^{Piv}), 0.91 (s, 9H, 3xCH_3^{TBDPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.26, 176.19, 176.06, 170.41, 138.28, 137.97, 137.83, 137.42, 135.62, 135.55, 132.99-126.17(30C), 100.36, 100.24, 100.20, 100.01, 99.53, 77.36, 75.75, 75.72, 75.41, 74.84, 74.37, 73.87, 71.80, 71.77, 71.65, 70.77, 69.95, 69.41, 68.88, 68.79, 67.37, 67.09, 61.39, 38.84, 38.70, 38.62, 27.28(3C), 27.21(3C), 27.13(3C), 27.05(3C), 20.85, 19.33. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{79}H_{96}NaO_{20}Si$: 1415.6162; Found 1415.6163.

Benzyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (274)



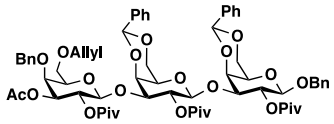
273 (1.0 g; 0.72 mmol) was dissolved in dry DCM (25 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (1.5 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (4h). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography to give a white crystalline product. Yield: 0.84 g (88%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 4H, Ar-H), 7.49 – 7.07 (m, 32H, Ar-H), 5.48 (s, 1H, $H^{benzylidene}$), 5.43 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.6 Hz, 1H) 5.40 (s, 1H, $H^{benzylidene}$), 5.26 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.83 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.80 – 4.72 (m, 1H, H-2), 4.75 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1), 4.67 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.47 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.38 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.36 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.25 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4), 4.21 (d, $J_{6a,6b}$ = 11.5 Hz, 1H, H-6a), 4.31 – 4.10 (m, 4H, H-1[1], 2xH-4, H-6b), 3.98 (d, $J_{6a,6b}$ = 12.4 Hz, 1H, H-6a), 3.89 – 3.78 (m, 4H, H-3, H-5, H-6b), 3.72 (m, 1H, H-6a), 3.66 – 3.59 (m, 1H, H-6b), 3.56 – 3.43 (m, 2H, 2xH-3), 3.30 (s, 1H, H-5), 3.18 (s, 1H, H-5), 1.15 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 0.97 (s, 9H, 3xCH_3^{TBDPS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.39, 178.26, 176.15, 138.07, 137.91, 137.79, 137.37, 135.68(2C), 135.60(2C), 133.35, 133.14, 130.02-126.36(26C), 105.71, 100.91, 100.49, 100.32, 99.58, 78.43, 76.17, 75.90, 75.38, 75.15(2C), 74.52, 72.33, 71.26, 70.54, 69.94, 69.38, 68.92, 68.76, 67.02(2C), 62.53, 39.18, 39.12, 38.80, 27.37(3C), 27.30(3C), 27.08(3C), 26.97(3C), 19.33. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{77}H_{94}NaO_{19}Si$: 1373.6056; Found 1373.6061.

Phenyl 3-*O*-acetyl-6-*O*-allyl-4-*O*-benzyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (275)



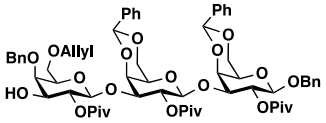
To a solution of $Pd_2(dba)_3$ (328 mg; 0.36 mmol) and 1,4-Bis(diphenyl-phosphino)butane (611 mg; 1.43 mmol) in dry THF (20 mL) was added the alcohol **266** (1.75 g; 3.6 mmol) and allyl ethyl carbonate (1.86 g; 14.32 mmol) in dry THF (20 mL). The solution was stirred at 65 °C for 4 h, the solvent was evaporated and the crude product was purified by flash chromatographed (30:1 Tol/EtOAc) to give the pure *O*-allylated compound **275**. R_f 0.60 (9:1 Tol/EtOAc). Yield: 1.56 g (83%)
$[\alpha]_D^{20}$ = 3.8° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3061.43, 3031.49, 2973.33, 2933.85, 2907.2, 2871.32, 1744.39, 1496.49, 1479.33, 1456.24, 1397.69, 1366.21, 1276.47, 1232.00, 1145.02, 1078.08 ,1047.78, 918.76 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.35 (m, 2H, Ar-H), 7.35 – 7.13 (m, 8H, Ar-H), 5.78 (ddt, J_{trans} = 17.2, J_{cis} = 10.8, J_{CH2} = 5.6 Hz, 1H, -C*H*=CH_2), 5.34 (t, $J_{1,2}$ = $J_{2,3}$ =10.0 Hz, 1H, H-2), 5.17 (dd, J_{trans} = 17.2, J_{CH2} = 1.7 Hz, 1H, CH_2=CH_{trans}), 5.10 (dt, J_{cis} = 10.4, J_{CH2} = 1.7 Hz, 1H, CH_2=CH_{cis}), 5.00 (dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.65 (d, J = 11.6 Hz, 1H, 0.5xCH_2^{Bn}), 4.63 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 4.50 (d, J_{CH2} = 11.6 Hz, 1H, 0.5xCH_2^{Bn}), 3.93 (dd, $J_{3,4}$ = 3.1, $J_{4,5}$ = 0.9 Hz, 1H, H-4), 3.89 (ddt, $J_{CH2a,CH2b}$= 12.8, $J_{CH=CH2,\ CH2}$= 5.6, $J_{CH2=CH,\ CH2}$ = 1.7 Hz, 0H), 3.82 (ddt, $J_{CH2a,CH2b}$ = 12.7, $J_{CH=CH2,\ CH2}$=5.6, $J_{CH2=CH,\ CH2}$=1.7 Hz, 1H), 3.68 (ddd, $J_{5,6a}$ = 6.9, $J_{5,6b}$ = 5.8, $J_{4,5}$ =1.0 Hz, 1H, H-5), 3.60 – 3.46 (m, 1H, H-6a, H-6b), 1.87 (s, 3H, CH_3^{Ac}), 1.13 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.84, 170.28, 138.09, 134.42, 133.56, 132.20 (2C), 128.96 (2C), 128.45 (2C), 128.16 (2C), 127.86, 127.81, 117.39, 87.11, 77.40, 74.99, 74.88, 74.35, 72.45, 68.23, 67.66, 38.88, 27.15 (3C), 20.85. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{36}NaO_7S$: 551.2079; Found 551.2082.

Benzyl 3-*O*-acetyl-6-*O*-allyl-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (276)



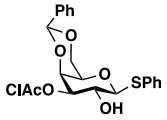
To a 25 mL flame-dried flask was added **261** (900 mg, 1.16 mmol) and **276** (918 mg, 1.74 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -30 °C, followed by addition of NIS (442 mg; 1.97 mmol) and TESOTf (61 mg; 0.23 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography to afford as a slightly yellow solid. Yield: 707 mg (51%). Several impurities made it impossible to assign the spectrum

Benzyl 6-*O*-allyl-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (277)



276 (200 mg; 0.17 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (0.7 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (3 h). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography to give a foamy white product. Yield: 191 mg (92%). Several impurities made it impossible to assign the spectrum

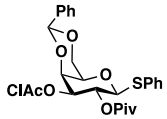
Phenyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-1-thio-β-D-galactopyranoside (278)[366]



Di-*n*-butyl tin oxide (21.8 g; 87.4 mmol) was added to a solution of compound **56** (30.0 g, 83.2 mmol) in dry toluene (600 mL) and stirred under refluxing temperature for 12 h. The reaction mixture was cooled to 0 °C, and freshly activated 4Å MS (30 g) were added. After 30 min chloroacetyl chloride (6.7 mL, 85.7 mmol) were added drop wise and stirring was maintained for 1 h at 0 °C. The reaction was quenched by addition of MeOH, filtered through a pad of celite and concentrated. The crude product was purified by flash chromatography (9:1 Tol/EtOAc) to give **278** as white crystals. R_f 0.16 (9:1 Tol/EtOAc). Yield: 33.1 g (91%)

$[\alpha]_D^{20}$ = 44.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3481.62, 3090.41, 2951.69, 2870.27, 1756.92, 1479.38, 1406.63, 1365.59, 1313.58, 1288.85, 1166.86, 1044.29, 1025.82. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 2H, Ar-H), 7.34 – 7.26 (m, 8H, Ar-H), 5.40 (s, 1H, -$CH^{benzylidene}$), 4.90 (dd, $J_{2,3}$ = 9.6, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 4.51 (d, $J_{1,2}$ = 9.6 Hz, 1H, H-1), 4.35 (dd, $J_{3,4}$ = 3.4, $J_{4,5}$ = 1.1 Hz, 1H, H-4), 4.32 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.6 Hz, 1H, H-6a), 4.05 (d, J_{CH2} = 15.3 Hz, 1H, 0.5xCH_2^{AcCl}), 4.00 (d, J = 15.3 Hz, 1H, 0.5xCH_2^{AcCl}), 3.96 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ = 1.7 Hz, 1H, H-6b), 3.90 (td, $J_{1,2}$ = $J_{2,3}$ = 9.6, $J_{2,OH}$ = 2.5 Hz, 1H, H-2), 3.55 (m, 1H, H-5), 2.34 (d, $J_{2,OH}$ = 2.5 Hz, 1H, OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.23, 137.53, 133.72 (2C), 130.06, 129.21, 129.09 (2C), 128.43, 128.19 (2C), 126.38 (2C), 100.98, 87.46, 76.45, 73.34, 69.78, 69.12, 65.50, 40.89. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{21}ClNaO_6S$ 459.0645; Found 459.0639.

Phenyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (279)

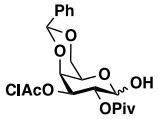


278 (25 g; 57.2 mmol) was dissolved in CH_2Cl_2 (400 mL). Et_3N (16.0 mL; 114.4 mmol), DMAP (3.5 g; 28.6 mmol) and pivaloyl chloride (7.3 mL; 85.8 mmol) was added to the solution and the reaction mixture was heated to 45 °C for 4 h. The reaction mixture was cooled to 0 °C, quenched with MeOH (10 mL), washed with water (2x400 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (15:1 Tol/EtOAc) to afford **279** as a white crystalline powder. R_f 0.44 (9:1 Tol/EtOAc). Yield 26.2 g (88%).

$[\alpha]_D^{20}$ = 16.5° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3061.25, 3036.54, 2974.08, 2935.25, 2905.99, 2871.97, 1764.64, 1733.56, 1479.53, 1457.77, 1402.52, 1366.86, 1312.92, 1281.38, 1249.15, 1147.33, 1092.80, 1048.41, 1025.97, 997.24. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.47 (m, 2H, Ar-H), 7.35 – 7.25 (m, 8H, Ar-H), 5.40 (s, 1H, $CH^{benzylidene}$), 5.28 (t, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, 1H, H-2), 5.07 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 3.5 Hz, 1H, H-3), 4.67 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.31 (dd, $J_{6a,6b}$ = 11.5, $J_{5,6a}$ = 0.9 Hz, 1H, H-6a), 4.30 (d, J = 3.5 Hz, 1H, H-4), 3.96 (dd, $J_{6a,6b}$ = 11.5, $J_{5,6b}$ = 1.8 Hz, 1H, H-6b), 3.95 (d, J_{CH2} = 15.2 Hz, 1H, CH_2^{AcCl}), 3.87 (d, J_{CH2} = 15.2 Hz, 1H, CH_2^{AcCl}), 3.53 (s, 1H, H-5), 1.14 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.47, 167.13, 137.42, 133.80 (2C), 131.35, 129.35, 128.93 (2C), 128.35, 128.30 (2C), 126.60 (2C), 101.18, 85.40,

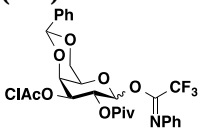
74.77, 73.52, 69.70, 69.17, 66.21, 40.70, 38.90, 27.19 (3C). **HRMS** (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{26}H_{33}ClNO_7S$ 538.1666 Found 538.1671.

4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-*O*-pivaloyl-D-galactopyranose (280a)



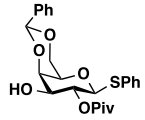
279 (20.0 g; 38.4 mmol) was dissolved in acetone (180 mL) and water (20 mL). NBS (27.3 g; 153.5 mmol) and 2,4-lutidine (22.2 mL; 107.2 mmol) were added and the reaction was stirred at 50 °C until TLC showed full conversion (3h). The solution was diluted with CH_2Cl_2 (500 mL) and washed with sat. aq. NaS_2O_3 (200 mL) and sat. aq. $NaHCO_3$ (200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (6:1 toluene/EtOAc) to afford **280a** as an α/β mixture. R_f 0.13 (9:1 toluene/EtOAc). Yield: 12.5 g (76%)
$[\alpha]_D^{20}$= 84.4° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}):3063.99, 3030.86, 2972.24, 2931.14, 2870.06, 1738.21, 1479.47, 1454.40, 1365.98, 1277.87, 1150.65, 1134.03, 1101.35, 1064.79. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.03 (m, 10H, Ar-H), 5.51 (d, $J_{1,2}$ = 3.5 Hz, 1H, H-1α), 5.45 (dd, $J_{2,3}$ = 10.1, $J_{3,4}$ = 2.9 Hz, 1H, H-3α), 5.43 (s, 1H, $H^{benzylidene}$β), 5.41 (s, 1H, $H^{benzylidene}$α), 5.18 (dd, $J_{2,3}$ =10.1, $J_{1,2}$ = 3.5 Hz, 1H, H-2α), 5.13 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2β), 5.02 (dd, $J_{2,3}$ =10.4, $J_{3,4}$ = 3.6 Hz, 1H, H-3β), 4.60 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1β), 4.32 (dd, $J_{3,4}$ = 2.9, $J_{4,5}$ = 1.1 Hz, 1H, H-4α), 4.29 – 4.22 (m, 1H, H-4b, H-6a,β) 4.16 (dd, $J_{6a,6b}$ = 12.6, $J_{5,6a}$ = 1.5 Hz, 1H, H-6a,α), 4.01 (d, J_{CH2} = 15.0 Hz, 1H, 0.5xCH_2^{AcCl}), 3.94 (m, 3H, H-6b,α; H-6b,β; 0.5xCH_2^{AcCl}), 3.91 (m, 2H, H-5α, H-5β), 1.11 (m, 18H, 6xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.66, 176.89, 165.94, 136.83, 136.36, 136.18, 128.21, 128.11, 128.00, 127.26, 127.22, 127.19, 125.15, 125.07, 124.27, 99.70, 99.60, 94.77, 89.79, 72.85, 72.19, 71.90, 69.46, 69.02, 68.14, 67.89, 67.19, 65.37, 60.89, 39.66, 39.51, 37.94, 37.79, 25.93. **HRMS** (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{20}H_{30}ClNO_8$ 447.1660 Found 447.1671

4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (280)



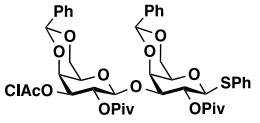
280a (10 g; 23.3 mmol) was dissolved in DCM (230 mL) and cooled to 0 °C. Cs_2CO_3 (15.2 g; 46.6 mmol) was added followed by *N*-phenyl trifluoroacetimidoyl chloride (9.7 g; 46.6 mmol). The ice bath was removed and the reaction mixture was stirred until TLC showed full conversion (5 h). It was then filtered, concentrated and purified by flash chromatography to give a white crystalline product. Yield: 11.2 g (80%)

Phenyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (281)



279 (10 g; 19.2 mmol) was dissolved in dry CH_2Cl_2 (190 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (57.6 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (1h). The reaction mixture was poured into sat. aq. NH_4Cl (400 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography to give **281** a white crystalline product. Yield: 8.2 g (96%)
$[\alpha]_D^{20}$= -20.0° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (m, 2H, Ar-H), 7.38 – 7.10 (m, 10H, Ar-H), 5.45 (s, 1H, $CH^{benzylidene}$), 4.98 (t, $J_{1,2}$ = $J_{2,3}$ = 9.7 Hz, 1H, H-2), 4.60 (d, $J_{1,2}$ = 9.7 Hz, 1H, H-1), 4.31 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ =1.5 Hz, 1H, H-6a), 4.14 (dd, $J_{3,4}$ = 3.6, $J_{4,5}$ =1.1 Hz, 1H, H-4), 3.96 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ = 1.7 Hz, 1H, H-6b), 3.67 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.6 Hz, 1H, H-3), 3.51 – 3.43 (m, 1H, H-5), 1.19 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.61, 137.39, 133.58 (2C), 131.59, 129.35, 128.78 (2C), 128.24 (2C), 128.08, 126.52 (2C), 101.41, 85.06, 75.66, 72.92, 69.90, 69.52, 69.17, 38.83, 27.16 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{28}NaO_6S$: 467.1504; Found 467.1511.

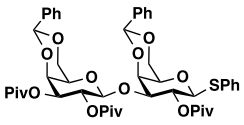
Phenyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (283)



To a 250 mL flame-dried flask was added **281** (6.5 g, 14.6 mmol) and the **280** (11.4 g, 19.0 mmol). The mixture was co-evaporated with toluene (2x150 mL) and subjected to vacuum overnight. The mixture dissolved in CH_2Cl_2 (150 mL) and cooled to -40 °C. TMSOTf (0.22 mL; 1.5 mmol) was added and the reaction mixture was stirred at -40 °C for 2h. Et_3N (1 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (9:1 Tol/EtOAc) affording **283**. R_f 0.26 (9:1 Tol/EtOAc). Yield: 10.5 g (84%).
$[\alpha]_D^{20}$= 12.4° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.36 (m, 5H), 7.35 – 7.22 (m, 6H), 7.17 – 7.04 (m, 3H), 5.49 (s, 1H, -$CH^{benzylidene}$), 5.43 (s, 1H, -$CH^{benzylidene}$), 5.33 (dd, $J_{2,3}$ = 9.7 $J_{1,2}$ = 8.1 Hz, 1H, H-2'), 5.30 (t,

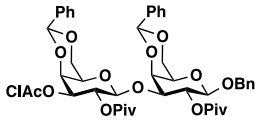
$J_{1,2}$ = $J_{2,3}$ = 9.7 Hz, 1H, H-2), 4.87 (d, *J* = 8.1 Hz, 1H, H-1'), 4.86 (d, *J* = 3.8 Hz, 1H), 4.60 (d, $J_{1,2}$ = 9.7 Hz, 1H, H-1), 4.34 – 4.17 (m, 4H, H-3, H-4, H-4', H-6a'), 4.00 (dd, *J* = 12.5, 1.5 Hz, 1H, H-6a), 3.99 (d, J_{CH2} = 15.3 Hz, 1H, CH_2^{AcCl}), 3.98 – 3.89 (dd, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6b}$ =1.5, 1H, H-6b), 3.93 (dd, $J_{6a,6b}$ = 12.3 Hz, $J_{5,6b}$ =1.1, 1H, H-6b'), 3.91 (d, J_{CH2} = 15.2 Hz, 1H, CH_2^{AcCl}), 3.38 (m, 2H, H-5, H-5'), 1.22 (s, 9H, -CH_3^{Piv}), 1.00 (s, 9H-CH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.90, 176.12, 167.12, 137.82, 137.25, 133.37, 132.34 (2C), 129.21, 128.73 (2C), 128.63, 128.27 (2C), 127.93 (2C), 127.58, 126.22 (2C), 126.19 (2C), 100.89, 100.18, 99.27, 86.79, 75.91, 73.65, 73.48, 73.33, 70.21, 69.49, 68.93, 68.70, 68.18, 66.60, 40.60, 38.79, 38.76, 27.35 (3C), 26.95 (3C). **HRMS** (ESI-TOF) m/z: [M + NH_4]+ Calcd for $C_{44}H_{55}ClNO_{13}S$ 872.3083 Found 872.3092

Phenyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (284)



283 (1.8 g; 2.1 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (5.3 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material was observed (30 min). The reaction mixture was quenched with sat. aq. NH_4Cl (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The residue was filtered through a plug of silica (9:1 Tol/EtOAc). The semi-crude alcohol (1.4 g; 1.8 mmol) was dissolved in CH_2Cl_2 (20 mL). Et_3N (0.5 mL; 3.6 mmol), DMAP (0.1 g; 0.9 mmol) and pivaloyl chloride (0.4 mL; 3.6 mmol) was added to the solution and the reaction mixture was heated to 45 °C for 4 h. The reaction mixture was cooled to 0 °C, quenched with MeOH (0.5 mL), washed with water (2x50 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (Tol/EtOAc 9:1) to afford **284** as a white crystalline powder. R_f 0.26 (9:1 Tol/EtOAc) Yield 1.3 g (80% over two steps)
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$= 10.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3065.46, 2933.04, 1734.90, 1479.30, 1455.98, 1397.64, 1366.82, 1279.26, 1173.33, 1140.59, 1091.22, 1048.23, 1026.27. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.34 (m, 6H, Ar-H), 7.26 (m, 9H, Ar-H), 5.47 (s, 1H, -$CH^{benzylidene}$), 5.45 (s, 1H, -$CH^{benzylidene}$), 5.37 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 8.0 Hz, 1H, H-2'), 5.29 (t, $J_{1,2}$ = $J_{2,3}$ = 9.8 Hz, 1H, H-2), 4.81 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1'), 4.69 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.7 Hz, 1H, H-3'), 4.60 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.38 – 4.17 (m, 5H, H-3, H-4, H-4', H-6a, H-6a'), 4.01 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ =1.8 Hz, 1H, H-6b'), 3.93 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6b}$ =1.6 Hz, 1H, H-6b), 3.42 – 3.34 (m, 2H, H-5, H-5'), 1.22 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}), 0.98 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.20, 176.81, 176.10, 137.89, 137.47, 133.41, 132.27 (2C), 128.90, 128.70 (2C), 128.52, 128.18 (2C), 127.86 (2C), 127.52, 126.19 (2C), 125.90 (2C), 100.43, 100.13, 99.34, 86.66, 75.75, 73.13 (2C), 71.88, 70.24, 69.74, 68.90, 68.82, 68.18, 66.76, 38.92, 38.78, 38.68, 27.39, 27.00, 26.98. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{47}H_{58}NaO_{13}S$ 885.3496; Found 885.3499.

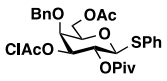
Benzyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (285)



283 (4.0 g; 4.7 mmol) was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. Benzyl alcohol (0.56 g; 5.17 mmol) was added. The mixture was dissolved in dry CH_2Cl_2 (50 mL) and cooled to -40 °C. NIS (1.2 g; 5.1 mmol) and TESOTf (124 mg; 0.47 mmol) was added and the reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (3h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 toluene/EtOAc) to afford a white crystalline material. R_f 0.15 (9:1 Tol/EtOAc). Yield: 3.3 g (83%)
IR (neat, cm^{-1}): 3522.75, 3034.88, 2907.39, 1738.58, 1700.58, 1479.70, 1455.33, 1398.71, 1366.79, 1310.93, 1277.82, 1173.90, 1135.07, 1087.56, 1047.93, 1026.20. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.14 (m, 15H), 5.50 (s, 1H, $CH^{benzylidene}$), 5.43 (s, 1H, $CH^{benzylidene}$), 5.42 (dd, $J_{2,3}$ = 10.6, $J_{1,2}$ = 7.9 Hz, 1H, H-2^1), 5.34 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 8.0 Hz, 1H, H-2^2), 4.94 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^2), 4.89 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.6 Hz, 1H, H-3^2), 4.83 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.47 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.37 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^1), 4.34 – 4.23 (m, 4H, H-4^1, H-4^2, H-$6a^2$, H-$6b^2$), 4.12 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.4 Hz, 1H, H-3^1), 4.04 – 3.96 (m, 2H, H-$6a^1$, H-$6b^1$), 3.98 (d, J_{CH2} = 15.2 Hz, 1H, CH_2^{AcCl}), 3.91 (d, J_{CH2} = 15.2 Hz, 1H, CH_2^{AcCl}), 3.38 (s, 1H, H-5^2), 3.33 (s, 1H, H-5^1), 1.10 (s, 9H, 3xCH_3^{Piv}), 1.05 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.02, 176.18, 167.22, 137.88, 137.42, 137.26, 129.28, 129.15, 128.72, 128.35 (2C), 128.34, 128.31 (2C), 128.07 (2C), 127.89 (2C), 127.64, 126.36 (2C), 126.19 (2C), 100.99, 100.41, 100.32, 99.48, 76.04, 73.60, 73.47, 72.96, 70.96, 70.03, 68.92, 68.78,

68.34, 66.98, 66.67, 40.71, 38.90, 38.80, 27.31 (3C), 27.12 (3C). HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{45}H_{57}ClNO_{14}$ 870.3468 Found 870.3467

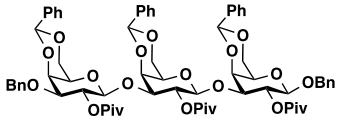
Phenyl 6-*O*-acetyl-4-*O*-benzyl-3-*O*-chloroacetyl-2-*O*-pivaloyl-1-thio-β-D-galactopyranoside (286)



A solution of 1M BH_3 in THF (76.7 mL) was added to a 250 ml dry flask containing **279** (4.0 g; 7.7 mmol) at 0 °C and the solution was stirred for 5 minutes. A solution of 1M $Cu(OTf)_2$ in CH_2CI_2 (8.1 mL) was then added to the clear solution slowly. After 1.5 hours at 0 °C, TLC showed full consumption of starting material. Triethylamine (2 mL) was added followed by careful addition of methanol until the evolution of H_2 had ceased. The reaction mixture was co-distilled with methanol three times and the crude was used in the next step. The crude material was dissolved in CH_2Cl_2 (50 mL). Et_3N (1.1 mL; 7.7 mmol), DMAP (0.01 g; 0.1 mmol) and acetic anhydride (0.61 mL; 6.5 mmol) was added to the solution and the reaction mixture was stirred until TLC revealed full conversion (1 h). The reaction was quenched with MeOH (1 mL), diluted with DCM (50 mL), washed with water (2x100 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (Tol/EtOAc 15:1) to afford **286** as a white crystalline powder R_f 0.42 (9:1 Tol/EtOAc). Yield: 2.8 g (68%) over two steps

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -5.2° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3061.37, 3031.47, 2972.29, 2906.59, 2872.68, 1739.50, 1584.17, 1496.32, 1479.63, 1455.92, 1440.05, 1398.67, 1369.01, 1277.91, 1232.53, 1172.17, 1139.11, 1088.80, 1043.02. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 2H), 7.33 – 7.15 (m, 8H), 5.34 (t, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, 1H, H-2), 5.06 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.62 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.63 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 4.53 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 4.26 (dd, $J_{6a,6b}$ = 11.2, $J_{5,6a}$ = 6.7 Hz, 1H, H-6a), 4.04 (dd, $J_{6a,6b}$ = 11.2, $J_{5,6b}$ = 6.2 Hz, 1H, H-6b), 3.88 (dd, $J_{3,4}$ = 3.0, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.80 (d, J = 14.9 Hz, 1H, 0.5xCH_2^{AcCl}), 3.74 (d, J = 15.0 Hz, 1H, 0.5xCH_2^{AcCl}), 3.72 – 3.67 (m, 1H, H-5), 1.95 (s, 3H, -CH_3^{Ac}), 1.13 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.80, 170.49, 166.80, 137.41, 132.95, 132.61 (2C), 128.97 (2C), 128.62 (2C), 128.37 (2C), 128.20, 128.14, 86.90, 76.54, 76.00, 75.13, 73.87, 67.41, 62.50, 40.42, 38.92, 27.16 (3C), 20.89. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{33}ClNaO_8S$ 587.1482; Found 587.1481.

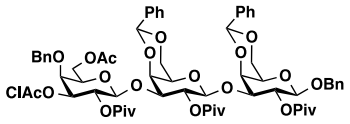
Benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside



To a 10 mL flame-dried flask was added **261** (500 mg, 0.64 mmol) and **167** (447 mg, 0.84 mmol). The mixture was dried azeotropically with toluene (2x5 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (2.5 mL) and dry MeCN (2.5 mL), cooled to -30 °C, followed by addition of NIS (192 mg; 0.86 mmol) and TESOTf (17 mg; 0.06 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. NaS_2O_3 (25 mL) and sat. aq. $NaHCO_3$ (25 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 toluene/EtOAc) to afford a white crystalline material. Yield: 1.1 g (86%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= 5.3° (c 1.0, $CDCl_3$). IR(neat): 3514.99, 3064.69, 3035.30, 2872.12, 1739.17, 1699.76, 1497.26, 1455.35, 1398.13, 1366.64, 1277.12, 1171.88, 1132.96, 1086.65, 1048.06, 1027.13. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (m, 6H, Ar-H), 7.35 – 7.11 (m, 19H), 5.48 (s, 2H, 2x$CH^{benzylidene}$), 5.40 (s, 1H, $CH^{benzylidene}$), 5.38 (dd, $J_{2,3}$ = 9.8, $J_{1,2}$ = 7.9 Hz, 1H, H-2^1), 5.36 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 8.0 Hz, 1H, H-2^2), 5.29 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 8.1 Hz, 1H, H-2^3), 4.82 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.75 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1^3), 4.69 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^2), 4.55 (s, 2H, CH_2^{Bn}), 4.45 (d, J_{CH2} = 11.9 Hz, 1H, CH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^1), 4.30 – 3.92 (m, 11H, H-3^1, H-3^2, H-4^1-H-4^3, H-6^1-H-6^3), 3.40 (dd, $J_{2,3}$ = 10.1, $J_{3,4}$ = 3.5 Hz, 1H, H-3^3), 3.30 (s, 1H, H-$5^{1/2/3}$), 3.26 (s, 1H, H-$5^{1/2/3}$), 3.19 (s, 1H, H-$5^{1/2/3}$), 1.05 (s, 9H, 3xCH_3^{Piv}), 1.03 (s, 9H, 3xCH_3^{Piv}), 1.02 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.18, 176.18, 176.13, 138.00, 137.93, 137.88, 137.72, 137.34, 129.16, 129.07, 128.69, 128.58, 128.45, 128.35, 128.30, 128.26, 128.04, 127.96, 127.92, 127.88, 127.69, 127.62, 126.40, 126.26, 101.03, 100.42, 100.29, 100.07, 99.41, 76.00, 75.76, 73.48, 71.92, 71.88, 71.47, 71.37, 70.96, 70.05, 69.85, 69.00, 68.88, 68.80, 67.48, 67.15, 67.06, 38.83, 38.75, 38.71, 27.31, 27.28, 27.22.

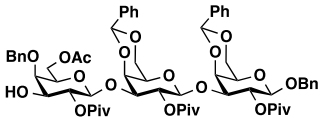
Benzyl 6-*O*-acetyl-4-*O*-benzyl-3-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (287)



To a 25 mL flame-dried flask was added **261** (3.0 g, 3.9 mmol) and the **286** (1.5 g, 1.8 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -30 °C, followed by addition of NIS (420 mg; 1.9 mmol) and TESOTf (56 mg; 0.2 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (6:1 Tol/EtOAc) to afford a white crystalline material. R_f 0.60 (2:1 Tol/EtOAc). Yield: 3.6 g (75%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.15 (m, 20H, Ar-H), 5.48 (s, 1H, $CH^{benzylidene}$), 5.47 (s, 1H, $CH^{benzylidene}$), 5.37 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 7.9 Hz, 1H, H-2^1), 5.31 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 8.0 Hz, 1H, H-2^3), 5.27 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 7.7 Hz, 1H, H-2^2), 4.88 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.0 Hz, 1H, H-3^3), 4.82 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.73 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1^2), 4.70 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^3), 4.63 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.51 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.45 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^1), 4.32 – 3.94 (m, 12H, H-3^1, H-3^2, H-4^1, H-4^2, 3xH-6), 3.86 (d, J = 3.0 Hz, 1H, H-4^3), 3.79 (d, J_{CH2} = 15.0 Hz, 1H, CH_2^{AcCl}), 3.72 (d, J_{CH2} = 15.0 Hz, 1H, CH_2^{AcCl}), 3.60 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, 1H, H-5^3), 3.31 (s, 1H, H-5$^{1/2}$), 3.29 (s, 1H, H-5$^{1/2}$), 1.95 (s, 3H, CH_3^{Ac}), 1.09 (s, 9H, CH_3^{Piv}), 1.05 (s, 9H, CH_3^{Piv}), 1.00 (s, 9H, CH_3^{Piv}).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.15, 176.11, 176.10, 170.27, 166.84, 137.95, 137.77, 137.32, 137.30, 128.76-126.12 (20C), 100.40, 100.27 (2C), 99.89, 99.71, 75.83, 75.77, 75.21, 75.01, 73.59, 72.59 (2C), 71.89, 71.81, 71.06, 70.01, 69.01, 68.85, 68.77, 67.36, 67.04, 62.01, 40.39, 38.87, 38.76, 38.72, 27.31 (3C), 27.25 (3C), 27.10 (3C), 20.92. **HRMS** (ESI-TOF) m/z: [M + NH_4]+ Calcd for $C_{64}H_{81}ClNO_{20}S$ 1250.4761 Found 1250.4763

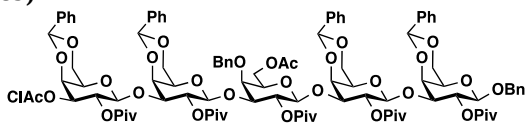
Benzyl 6-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (288)



287 (1.6 g; 1.3 mmol) was dissolved in 25 mL dry THF. Thiourea (382 mg; 5.0 mmol), Bu_4NI (93 mg; 0.25 mmol) and $NaHCO_3$ (464 mg; 5.5 mmol) was added and the reaction mixture was heated to 55 °C for 12 h. The mixture was filtered, concentrated and purified by flash chromatography (4:1 Tol/EtOAc) to give **288** as a yellowish amorphous material. R_f 0.49 (2:1 Tol/EtOAc). Yield: 1.2 g (82%).

$[\alpha]_D^{20}$ = -20.7° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}):3521.34, 2973.04, 2932.85, 2907.14, 2872.47, 1737.38, 1479.63, 1454.83, 1397.45, 1366.55, 1277.19, 1231.25, 1133.51, 1078.77, 1061.55, 1044.64. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.14 (m, 20H), 5.49 (s, 1H, $CH^{benzylidene}$), 5.45 (s, 1H, $CH^{benzylidene}$), 5.39 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 7.9 Hz, 1H, H-2^1), 5.36 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 8.0 Hz, 1H, H-2^2), 4.85 (dd, $J_{2,3}$ = 10.0, $J_{1,2}$ = 7.7 Hz, 1H, H-2^3), 4.83 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.76 (d, J_{CH2} = 11.5 Hz, 1H, 0.5xCH_2^{Bn}), 4.70 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^2), 4.65 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1^3), 4.61 (d, J_{CH2} = 11.5 Hz, 1H, 0.5xCH_2^{Bn}), 4.45 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.37 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^1), 4.33 – 4.13 (m, 6H, H-3^1, 2xH-4, 1.5xH-6), 4.01 (m, 3H, 1.5xH-6), 3.93 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.4 Hz, 1H, H-3^2), 3.71 (d, $J_{3,4}$ = 2.5 Hz, 1H, H-4^3), 3.55 – 3.46 (m, 2H, H-3^3, H-5^3), 3.32 (s, 1H, H-5), 3.30 (s, 1H, H-5), 1.94 (s, 3H, CH_3^{Ac}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.05 (s, 9H, 3xCH_3^{Piv}).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.36, 176.11, 176.05, 170.37, 137.99, 137.77, 137.74, 137.32, 129.87-126.13 (20C), 100.43 (2C), 100.29, 99.91, 99.67, 76.15, 75.97, 75.86, 75.83, 75.79, 73.98, 73.66, 72.70, 72.60, 71.88, 71.84, 71.13, 70.03, 68.87, 68.78, 67.38, 67.06, 62.54, 39.07, 38.78, 38.70, 27.32 (3C), 27.25 (3C), 27.05 (3C) 20.94. **HRMS** (ESI-TOF) m/z: [M + NH_4]+ Calcd for $C_{63}H_{82}NO_{20}$ 1172.5430 Found 1172.5440.

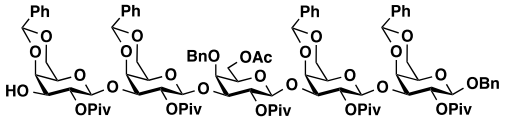
Benzyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-6-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (289)



To a 25 mL flame-dried flask was added **289** (1.2 g, 1.0 mmol) and the **283** (1.2 g, 1.4 mmol). The mixture was dried azeotropi-cally with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -30 °C, followed by addition of NIS (336 mg; 1.5 mmol) and TESOTf (27 mg; 0.1 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (6:1 Tol/EtOAc) to afford **289** as a white crystalline material. R_f 0.62 (2:1 Tol/EtOAc). Yield: 1.6 g (80%)

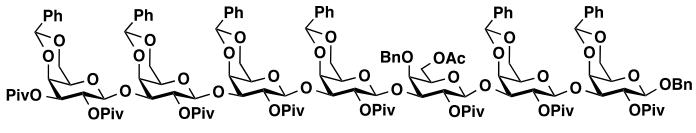
$[\alpha]_D^{20}$ = 4.7° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.36 (m, 8H), 7.34 – 7.07 (m, 22H), 5.53 (s, 1H, $CH^{benzylidene}$), 5.48 (s, 1H, $CH^{benzylidene}$), 5.46 (s, 1H, $CH^{benzylidene}$), 5.44 (s, 1H, $CH^{benzylidene}$), 5.45 – 5.23 (m, 1H, H-2^1-H-2^5), 4.93 – 4.86 (m, 2H, H-$1^{1/2/3/4/5}$, H-3^5), 4.83 (m, 2H, CH_2^{Bn}), 4.66 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-$1^{1/2/3/4/5}$), 4.63 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-$1^{1/2/3/4/5}$), 4.54 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-$1^{1/2/3/4/5}$), 4.49 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.44 (d, J_{CH2} = 12.3 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-$1^{1/2/3/4/5}$), 4.33 – 3.87 (m, 20H, H-3^1-H-3^4, H-$4^{1/2/4/5}$, H-$4^{1/2/4/5}$, H-$4^{1/2/4/5}$, H-$4^{1/2/4/5}$, H-6^1-H-6^5, CH_2^{AcCl}), 3.83 – 3.77 (m, 1H, H-4^3), 3.43 – 3.38 (m, 2H, H-5^3, H-$5^{1/2/4/5}$), 3.34 – 3.24 (m, 3H, H-$5^{1/2/4/5}$, H-$5^{1/2/4/5}$, H-$5^{1/2/4/5}$), 1.84 (s, 3H, CH_3^{Ac}), 1.10 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}), 1.02 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.94, 176.24, 176.03, 175.87, 175.83, 170.29, 167.08, 138.33, 137.92, 137.77, 137.71, 137.24, 137.15, 129.22-125.96 (30C), 100.88, 100.26 (2C), 100.16, 100.13, 100.09, 100.03, 99.89, 99.07, 77.26, 75.79, 75.63, 74.72, 74.44, 74.29, 73.46, 73.21, 72.99, 72.16, 71.81, 71.79, 71.76, 71.62, 71.44, 70.86, 69.95, 68.76, 68.65, 68.57, 68.21, 67.38, 66.94, 66.67, 62.02, 40.57, 38.76, 38.73, 38.66, 38.61, 38.57, 27.30 (3C), 27.23 (3C), 27.19 (3C), 27.14 (3C), 26.97 (3C), 20.80.

Benzyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-6-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (290)



289 (3.0 g; 1.6 mmol) was dissolved in 30 mL dry THF. Thiourea (481 mg; 6.3 mmol), Bu_4NI (116 mg; 0.3 mmol) and $NaHCO_3$ (584 mg; 6.9 mmol) was added and the reaction mixture was heated to 55 °C for 12 h. The mixture was filtered, concentrated and purified by flash chromatography (4:1 Tol/EtOAc) to give **290** as a colorless syrup. R_f 0.49 (2:1 Tol/EtOAc). Yield: 2.4 g (84%)
$[\alpha]_D^{20}$ = -19.5° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3064.90, 2906.56, 2871.51, 1740.83, 1479.69, 1454.99, 1397.85, 1366.58, 1276.77, 1229.22, 1172.47, 1134.96, 1087.71, 1047.90, 1027.22. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.36 (m, 8H, Ar-H), 7.33 – 7.02 (m, 22H, Ar-H), 5.52 (s, 1H, $CH^{benzylidene}$), 5.49 (s, 1H, $CH^{benzylidene}$), 5.48 (s, 1H, $CH^{benzylidene}$), 5.46 (s, 1H, $CH^{benzylidene}$), 5.43 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.9 Hz, 1H, H-$2^{1/2/4/5}$), 5.37 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 7.9 Hz, 1H, , H-$2^{1/2/4/5}$), 5.28 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 2H, H-$2^{1/2/4/5}$, H-$2^{1/2/4/5}$), 4.99 (dd, J = 10.1, 8.0 Hz, 1H, H-2^3), 4.85 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.81 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.80 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^3), 4.66 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-$2^{1/2/4/5}$), 4.65 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-$2^{1/2/4/5}$), 4.54 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-$2^{1/2/4/5}$), 4.51 (d, J = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.44 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-$2^{1/2/4/5}$), 4.31 – 3.88 (m, 18H, H-$3^{1/2/4/5}$, H-$3^{1/2/4/5}$, H-$3^{1/2/4/5}$, H-$3^{1/2/4/5}$, 4xH-4, H-6^1-H-6^5), 3.81 (dd, $J_{3,4}$ = 2.9, $J_{4,5}$ = 1.2 Hz, 1H, H-4), 3.54 (dd, $J_{2,3}$ = 10.1, $J_{3,4}$ = 3.7 Hz, 1H, H-3^3), 3.41 (dd, $J_{5,6a}$ = 7.4, $J_{5,6b}$ = 5.9 Hz, 1H, H-5^3), 3.36 – 3.32 (m, 1H, H-$5^{1/2/4/5}$), 3.32 – 3.29 (m, 1H, H-$5^{1/2/4/5}$), 3.28 (m, 2H, H-$5^{1/2/4/5}$), 1.84 (s, 3H, CH_3^{Ac}), 1.10 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}), 1.03 (s, 89H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.88, 176.29, 176.13, 175.99, 175.94, 170.39, 138.41, 138.01, 137.88, 137.79, 137.41, 137.25, 129.41-126.16 (30C), 101.35, 100.38, 100.36 (2C), 100.22 (2C), 100.13, 99.99, 99.26, 77.36, 75.99, 75.90, 75.73 (2C), 74.79, 74.55, 74.42, 73.10, 72.29, 72.20 (2C), 72.03, 71.92, 71.86, 71.73, 71.54, 71.04, 70.05, 68.86, 68.75, 68.67, 68.08, 67.48 (2C), 67.06, 67.03, 62.13, 38.96, 38.82, 38.76, 38.71, 38.69, 27.40 (3C), 27.34 (3C), 27.29 (3C), 27.24 (3C), 27.10 (3C), 20.91.

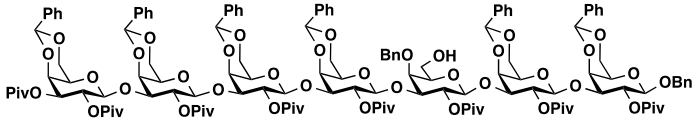
Benzyl 4,6-*O*-benzylidene-2,3-*O*-dipivaloyl-β-D-galactopyranosyl--(1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-6-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (291)



To a 25 mL flame-dried flask was added **290** (2.0 g, 1.1 mmol) and the **284** (1.2 g, 1.4 mmol). The mixture was dried azeotropically with toluene (2x15 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (7.5 mL) and dry MeCN (7.5 mL), cooled to -30 °C, followed by addition of NIS (329 mg; 1.5 mmol) and TESOTf (29 mg; 0.1 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (150 mL) and washed with sat. aq. NaS_2O_3 (150 mL) and sat. aq. $NaHCO_3$ (150 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc) to afford a white crystalline material. R_f 0.66 (2:1 Tol/EtOAc). Yield: 2.2 g (78%)

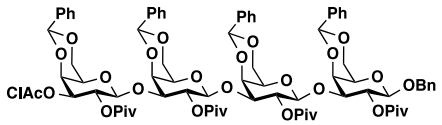
$[\alpha]_D^{20}$= -2.3° (c 1.0, $CDCl_3$), **IR** (neat, cm^{-1}): 3539.46, 3064.70, 2972.47, 2932.93, 2906.87, 2872.21, 1739.43, 1700.74, 1479.84, 1455.43, 1397.77, 1367.06, 1276.81, 1172.99, 1086.91, 1048.10, 1000.89. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.44 (m, 12H, Ar-H), 7.44 – 7.13 (m, 28H, Ar-H), 5.61 (s, 1H, $CH^{benzylidene}$), 5.59 (s, 1H, $CH^{benzylidene}$), 5.57 (s, 2H, $2xCH^{benzylidene}$), 5.56 (s, 1H, $CH^{benzylidene}$), 5.54 (s, 1H, $CH^{benzylidene}$), 5.52 – 5.34 (m, 7H, H-2^1-H-2^7), 4.96 – 4.87 (m, 3H, CH_2^{Bn}, H-1), 4.80 – 4.72 (m, 4H, 3xH-1, H-3^7), 4.70 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.64 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.62 (d, J_{CH2} = 12.1 Hz, 1H, $0.5xCH_2^{Bn}$), 4.55 (d, J_{CH2} = 11.9 Hz, 1H, $0.5xCH_2^{Bn}$), 4.46 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.40 – 4.01 (m, 25H, H-3^1-H-3^6, H-4^1, H-4^2, H-4^4, H-4^5, H-4^6, H-4^7, H-6^1, H-6^2, H-6a^3, H-6^4, H-6^5, H-6^6, H-6^7), 4.00 (dd, $J_{6a,6b}$ = 10.8, $J_{5,6b}$ = 6,6 Hz, 1H, H-6b^3), 3.89 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4^3), 3.50 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, 1H, H-5^3), 3.45 (s, 1H, H-$5^{1/2/4/5/6/7}$), 3.41 (s, 1H, H-$5^{1/2/4/5/6/7}$), 3.38 (s, 1H, H-$5^{1/2/4/5/6/7}$), 3.34 (s, 2H, H-$5^{1/2/4/5/6/7}$, H-$5^{1/2/4/5/6/7}$), 3.31 (s, 1H, H-$5^{1/2/4/5/6/7}$), 1.93 (s, 3H, CH_3^{Ac}), 1.19 (s, 9H, $3xCH_3^{Piv}$), 1.17 (s, 18H, $3xCH_3^{Piv}$), 1.13 (s, 9H, $3xCH_3^{Piv}$), 1.13 (s, 9H, $3xCH_3^{Piv}$), 1.13 (s, 9H, $3xCH_3^{Piv}$), 1.11 (s, 9H, $3xCH_3^{Piv}$), 1.10 (s, 9H, $3xCH_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.14, 176.80, 176.17, 176.06, 175.99, 175.95, 175.93, 175.83, 170.23, 137.92, 137.88, 137.86, 137.78, 137.74, 137.49, 137.19, 136.43, 129.74-125.30(40C), 100.44-99.19(13C), 75.80-62.07(35C), 38.93, 38.90, 38.72, 38.68, 38.65, 38.61, 38.60, 38.58, 27.29(3C), 27.22(3C), 27.19(3C), 27.19(3C), 27.16(3C), 27.14(3C), 27.05(3C), 26.99(3C), 20.77.

Benzyl 4,6-*O*-benzylidene-2,3-*O*-dipivaloyl-β-D-galactopyranosyl--(1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3) 4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (292)



291(2 g; 0.8 mmol) was dissolved in dry DCM (20 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (3.1 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (1h). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL). The aqueous phase was extract with DCM (100 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography to give a white crystalline product.
Yield: 1.6 g (79%)
$[\alpha]_D^{20}$= -3.9° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3511.92, 2972.77, 2933.51, 2907.86, 2873.19, 1736.95, 1700.87, 1479.95, 1397.88, 1366.87, 1276.67, 1168.85, 1135.17, 1080.83, 1046.25. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.07 (m, 40H, Ar-H), 5.50 (s, 1H, $CH^{benzylidene}$), 5.48 (s, 1H, $CH^{benzylidene}$), 5.47 (s, 2H, $2xCH^{benzylidene}$), 5.45 (s, 1H, $CH^{benzylidene}$), 5.43 (s, 1H, $CH^{benzylidene}$), 5.42 – 5.04 (m, 7H, 7xH-2), 4.88 – 4.74 (m, 3H, H-1, CH_2^{Bn}), 4.73 – 4.53 (m, 4H, 4xH-1, H-3^7), 4.48 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.44 (d, J_{CH2} = 12.0 Hz, 1H, $0.5xCH_2$Bn), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.31 (d, $J_{3,4}$ = 4.0 Hz, 1H, H-4), 4.29 – 3.80 (m, 23H, 6xH-3, 5xH-4, 6xH-6), 3.75 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4), 3.52 (dd, $J_{6a,6b}$ = 11.3, $J_{5,6a}$ = 5.8 Hz, 1H, H-6a), 3.41 – 3.35 (m, 1H, H-6b), 3.35 (s, 2H, 2xH-5), 3.31 (s, 1H, H-5), 3.27 (s, 1H, H-5), 3.26 – 3.24 (m, 2H, 2xH-5), 3.22 (s, 1H, H-5), 1.97 (s, 1H, -OH), 1.11 (s, 9H, $3xCH_3^{Piv}$), 1.06 (s, 9H, $3xCH_3^{Piv}$), 1.05 (s, 9H, $3xCH_3^{Piv}$), 1.04 (s, 9H, $3xCH_3^{Piv}$), 1.03 (s, 9H, $3xCH_3^{Piv}$), 1.03 (s, 9H, $3xCH_3^{Piv}$), 1.00 (s, 9H, $3xCH_3^{Piv}$), 0.98 (s, 9H, $3xCH_3^{Piv}$).**^{13}C NMR** (101 MHz, CDCl3) δ 178.28, 176.93, 176.31, 176.23, 176.20, 176.08, 176.06, 176.04, 138.08, 138.00, 137.90, 137.87, 137.86, 137.61, 137.33, 136.57, 129.87-125.43(40C), 100.58-99.31(13C), 75.94-66.90(35C), 39.04, 39.03, 38.87, 38.81, 38.79, 38.74, 38.73, 38.69, 27.46(3C), 27.36(3C), 27.33(3C), 27.32(3C), 27.28(3C), 27.24(3C), 27.18(3C), 27.12(3C).

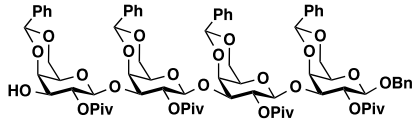
Benzyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)- 3-*O*-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (293)



To a 50 mL flame-dried flask was added **261** (2.0 g, 2.57 mmol) and the **283** (2.6 g, 3.09 mmol). The mixture was dried azeotropically with toluene (2x30 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (15 mL) and dry MeCN (15 mL), cooled to -30 °C, followed by addition of NIS (723 mg; 3.21 mmol) and TESOTf (68 mg; 0.26 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1½h). The solution was diluted with CH_2Cl_2 (150 mL) and washed with sat. aq. NaS_2O_3 (150 mL) and sat. aq. $NaHCO_3$ (150 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 toluene/EtOAc) to afford a white crystalline material. R_f 0.13 (9:1 Tol/EtOAc). Yield: 3.1 g (88%).

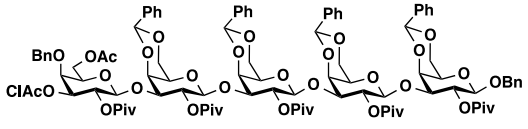
$[\alpha]_D^{20}$ = 21.6° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.36 (m, 8H), 7.33 – 7.14 (m, 17H), 5.49 (s, 1H, $CH^{benzylidene}$), 5.48 (s, 1H, $CH^{benzylidene}$), 5.46 (s, 1H, $CH^{benzylidene}$), 5.42 (s, 1H, $CH^{benzylidene}$), 5.39 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 7.9 Hz, 1H, H-$2^{1/2/3/4}$), 5.36 – 5.27 (m, 3H, H-$2^{1/2/3/4}$, H-$2^{1/2/3/4}$, H-$2^{1/2/3/4}$), 4.88 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-$1^{1/2/3/4}$), 4.86 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.6 Hz, 1H, H-3^4), 4.82 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.68 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-$1^{1/2/3/4}$), 4.67 (d, J = 7.9 Hz, 1H, H-$1^{1/2/3/4}$), 4.44 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.35 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-$1^{1/2/3/4}$), 4.30 – 3.84 (m, 17H, H-3^1-H-3^3, H-4^1-H-4^4, H-6^1-H-6^4, CH_2^{AcCl}), 3.35 (m, 1H, H-$5^{1/2/3/4}$), 3.30 (m, 1H, H-$5^{1/2/3/4}$), 3.25 (m, 1H, H-$5^{1/2/3/4}$), 3.24 (m, 1H, H-$5^{1/2/3/4}$), 1.08 (s, 9H, 3xCH_3^{Piv}), 1.05 (s, 9H, 3xCH_3^{Piv}), 1.03 (s, 9H, 3xCH_3^{Piv}), 1.01 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.93, 176.13, 175.98, 175.96, 167.08, 137.90, 137.75, 137.67, 137.28, 137.18, 129.20-125.31 (25C), 100.89, 100.33 (2C), 100.14 (2C), 99.99, 99.65, 99.14, 75.92 (2C), 75.63, 73.48, 73.25, 72.12, 71.87, 71.48, 71.13, 70.80, 69.99, 68.77, 68.63, 68.53, 68.27, 67.41, 67.36, 66.94, 66.60, 40.59, 38.77, 38.68, 38.63 (2C), 27.29-21.48 (12C).

Benzyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (294)



293 (2.5 g; 1.6 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (4.9 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (0.5 h). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL). The aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography (4:1 Tol/EtOAc) to give a white crystalline product. R_f 0.46 (2:1 Tol/EtOAc). Yield: 2.2 g (94%)
$[\alpha]_D^{20}$ = 4.7° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.34 (m, 8H), 7.34 – 7.11 (m, 17H), 5.53 – 5.44 (m, 4H, 4x$CH^{benzylidene}$), 5.39 (dd, $J_{2,3}$ = 9.8, $J_{1,2}$ = 7.4 Hz, 1H, H-$2^{1/2/3/4}$), 5.34 (m, 2H, H-$2^{1/2/3/4}$, H-$2^{1/2/3/4}$), 4.97 (dd, $J_{2,3}$ = 10.0, $J_{1,2}$ = 8.0 Hz, 1H, H-2^4), 4.82 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.77 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^4), 4.69 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-$1^{1/2/3/4}$), 4.68 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-$1^{1/2/3/4}$), 4.44 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-$1^{1/2/3/4}$), 4.31 – 3.90 (m, 15H, H-3^1-H-3^3, H-4^1-H-4^4, H-6^1-H-6^4), 3.51 (td, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.6 Hz, 1H, H-3^4), 3.37 – 3.21 (m, 4H, H-5^1-H-5^4), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.05 (s, 9H, 3xCH_3^{Piv}), 1.03 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.81, 176.09, 175.99, 175.97, 137.90, 137.76, 137.66, 137.34, 137.17, 129.28-126.09 (25C), 101.25, 100.34 (2C), 100.30, 100.15, 99.99, 99.64, 99.20, 77.27, 76.00, 75.92, 75.64 (2C), 72.37, 72.14, 71.98, 71.88, 71.49, 71.11, 70.87, 70.00, 68.76, 68.65, 68.55, 67.41, 67.37, 66.93, 66.89, 38.87, 38.68, 38.64, 38.61, 27.23, 27.20, 27.16, 27.03.

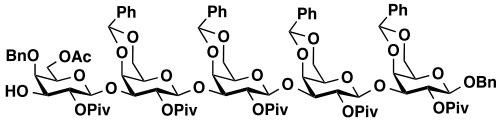
Benzyl 6-*O*-acetyl-4-*O*-benzyl-3-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (295)



To a 25 mL flame-dried flask was added **294** (2.8 g, 1.93 mmol) and the **286** (1.5 g, 2.7 mmol). The mixture was dried azeotropically with toluene (2x25 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (12.5 mL) and dry MeCN (12.5 mL), cooled to -30 °C, followed by addition of NIS (651 mg; 2.90 mmol) and TESOTf (51 mg; 0.19 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (3h). The solution was diluted with CH_2Cl_2 (150 mL) and washed with sat. aq. NaS_2O_3 (150 mL) and sat. aq. $NaHCO_3$ (150 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chroma-tography (4:1 Tol/EtOAc) to afford **295** as a white crystalline material. R_f 0.64 (2:1 Tol/ EtOAc). Yield: 2.5 g (69%)
$[\alpha]_D^{20}$ = 5.9° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.37 (m, 8H), 7.32 – 7.14 (m, 17H), 5.48 (s, 1H, $CH^{benzylidene}$), 5.47 (s, 1H, $CH^{benzylidene}$), 5.46 (s, 2H, 2x$CH^{benzylidene}$), 5.39 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 7.9 Hz, 1H, H-$2^{1/2/3/4/5}$), 5.33 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 8.0 Hz, 1H, H-$2^{1/2/3/4/5}$), 5.30 – 5.23 (m, 3H, H-$2^{1/2/3/4/5}$, H-$2^{1/2/3/4/5}$, H-$2^{1/2/3/4/5}$), 4.87 (dd, $J_{2,3}$ = 10.2, $J_{2,3}$ = 3.1 Hz, 1H, H-3^5), 4.82 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.71 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-$1^{1/2/3/4/5}$), 4.66 (m, 3H, H-$1^{1/2/3/4/5}$, H-$1^{1/2/3/4/5}$, H-$1^{1/2/3/4/5}$), 4.62 (d, J_{CH2} = 12.5 Hz, 1H, 0.5xCH_2^{Bn}), 4.50 (d, J_{CH2} = 11.6 Hz, 1H, 0.5xCH_2^{Bn}), 4.44 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, J = 7.9 Hz, 1H, H-$1^{1/2/3/4/5}$), 4.30 – 3.90 (m, 18H, H-3^1-H-3^4, H-4^1-H-4^4, H-6^1-H-6^5), 3.84 (d, $J_{3,4}$ = 2.8 Hz, 1H, H-4^5), 3.79 (d, J_{CH2} = 15.0 Hz, 1H, 0.5xCH_2^{AcCl}), 3.72 (d, J_{CH2} = 15.0 Hz, 1H, 0.5xCH_2^{AcCl}), 3.60 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, 1H, H-5^5), 3.31 (s, 1H, H-$5^{1/2/3/4}$), 3.27 – 3.23 (m, 2H, H-$5^{1/2/3/4}$), 3.21 (s, 1H, H-$5^{1/2/3/4}$), 1.94 (s, 3H, CH_3^{Ac}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}), 1.01 (s, 9H, 3xCH_3^{Piv}), 1.01 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$)

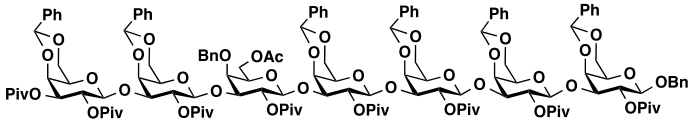
δ 177.01, 176.04, 176.01, 175.97, 175.93, 170.18, 166.74, 137.89, 137.76, 137.73, 137.65, 137.19, 137.17, 129.04-126.00 (30C), 100.36, 100.34, 100.26, 100.17, 100.13, 99.98, 99.69, 99.64, 99.54, 77.27, 75.89, 75.79, 75.63, 75.12, 74.91, 73.55, 72.55, 71.93, 71.84, 71.54, 71.44, 71.16, 71.08, 71.00, 69.98, 68.92, 68.76, 68.65, 68.49, 67.49, 67.41, 67.32, 66.93, 62.05, 40.30, 38.77, 38.67, 38.63, 38.59 (2C), 27.21 (3C), 27.19 (6C), 27.12 (3C), 27.01 (3C), 20.83.

Benzyl 6-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (296)



295 (2.0 g; 1.05 mmol) was dissolved in 30 mL dry THF. Thiourea (481 mg; 6.3 mmol), Bu_4NI (389 mg; 1.05 mmol) and $NaHCO_3$ (265 mg; 3.15 mmol) was added and the reaction mixture was heated to 55 °C for 12 h. The mixture was filtered, concentrated and purified by flash chromatography (19:1 Tol/EtOAc) to give **296** as colorless syrup. R_f 0.48 (9:1 Tol/EtOAc). Yield: 1.6 g (83%)
$[\alpha]_D^{20}$= 0.0° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3524.49, 3089.87, 2972.59, 2931.86, 2906.24, 2871.90, 1741.17, 1497.18, 1479.57, 1397.64, 1366.55, 1277.25, 1232.63, 1173.45, 1088.19, 1048.36, 1027.67. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.35 (m, 12H), 7.32 – 7.13 (m, 18H), 5.48 (s, 1H, $CH^{benzylidene}$), 5.47 (s, 1H, $CH^{benzylidene}$), 5.46 (s, 1H, $CH^{benzylidene}$), 5.45 (s, 1H, $CH^{benzylidene}$), 5.39 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 8.1 Hz, 1H, H-2), 5.36 – 5.26 (m, 4H, 4xH-2), 4.85 (d, J_{CH2} = 12.2 Hz, 1H, 0.5xCH_2^{Bn}), 4.83 (d, $J_{2,3}$ = 10.1, $J_{3,4}$ = 3.2 Hz, 1H, H-2^1), 4.75 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.69 – 4.59 (m, 4H, H-1^2-H-1^5), 4.61 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.45 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^1), 4.29 – 3.93 (m, 18H, 4xH-3, H-4^1-H-4^4, 5xH-6), 3.89 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.2 Hz, 1H, H-3), 3.69 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-4^5), 3.49 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.8 Hz, 1H, H-5^5), 3.31 (s, 1H, H-$5^{1/2/3/4}$), 3.26 (s, 2H, H-$5^{1/2/3/4}$, H-$5^{1/2/3/4}$), 3.22 (s, 1H, H-$5^{1/2/3/4}$), 1.94 (s, 3H, CH_3^{Ac}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}), 1.02 (s, 9H, 3xCH_3^{Piv}), 1.01 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.28, 176.14, 176.08 (2C), 176.04, 170.39, 137.99, 137.87, 137.85, 137.73, 137.69, 137.26, 128.69-126.17 (30C), 100.46, 100.44 (2C), 100.41, 100.39, 100.23, 100.07, 99.79, 99.72, 99.63, 77.36, 76.23, 75.99, 75.91, 75.82, 75.73, 73.94, 73.61, 72.80, 72.68, 72.03, 71.94, 71.59, 71.27, 71.18, 71.12, 70.08, 68.86, 68.74, 68.63, 67.58, 67.51, 67.43, 67.02, 62.71, 39.05, 38.76, 38.73, 38.69, 38.66, 27.31 (3C), 27.28 (6C), 27.21 (3C), 27.04 (3C), 20.94 (3C).

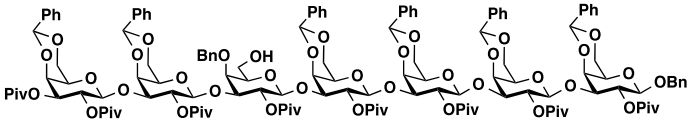
Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-6-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (297)



To a 25 mL flame-dried flask was added **296** (1.8 g, 0.99 mmol) and **284** (1.1 g, 1.3 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -30 °C, followed by addition of NIS (294 mg; 1.31 mmol) and TESOTf (26 mg; 0.1 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (3h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford a white crystalline material. R_f 0.58 (9:1 Tol/EtOAc). Yield: 1.95 g (77%)
$[\alpha]_D^{20}$= 7.1° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3065.85, 3035.79, 2972.47, 2871.63, 1738.98, 1479.57, 1454.98, 1397.69, 1366.40, 1276.70, 1172.84, 1132.25, 1087.66, 1047.67, 1027.15. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 6.91 (m, 40H, Ar-H), 5.51 (s, 1H, $CH^{benzylidene}$), 5.48 (s, 1H, $CH^{benzylidene}$), 5.46 (s, 2H, 2x$CH^{benzylidene}$), 5.45 (s, 2H, 2x$CH^{benzylidene}$), 5.44 – 5.18 (m, 7H, 7xH-2), 4.83 (d, J = 8.1 Hz, 1H, H-1), 4.83 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.82 (d, J_{CH2} =11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.70 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.7 Hz, 1H, H-3^7), 4.68 – 4.57 (m, 4H, 4xH-1), 4.52 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.49 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.44 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.35 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.33 (d, $J_{3,4}$ = 3.8 Hz, 1H, H-4), 4.27 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4), 4.26 – 3.93 (m, 24H, 6xH-3, 5xH-4, 6.5xH-6), 3.90 (dd, $J_{6a,6b}$ = 11.0, $J_{5,6b}$ = 7.1 Hz, 1H, H-6b^5), 3.78 (s, 1H, H-5), 3.41 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, 1H, H-5^5), 3.38 (s, 1H, H-5), 3.29 (s, 1H, H-5), 3.23 (m, 2H, 2xH-5), 3.21 (s, 1H, H-5), 1.83 (s, 3H, CH_3^{Ac}), 1.10 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 18H, 6xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}), 1.02 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 18H, 6xCH_3^{Piv}), 0.99 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.24, 176.98, 176.35, 176.15, 176.06, 176.02, 176.00, 175.90, 170.39, 138.38, 137.96, 137.89, 137.86 (2C), 137.84, 137.56, 137.26, 129.13-125.97 (40C), 100.50, 100.44 (2C), 100.33, 100.30, 100.21 (2C), 100.13, 100.09, 100.04, 99.71, 99.20, 77.36, 75.96, 75.87, 75.75, 75.72, 75.71, 74.79, 74.49, 74.38, 73.11 (2C), 72.28, 71.99, 71.96, 71.93, 71.73, 71.62, 71.55, 71.52, 71.35, 71.27, 71.24,

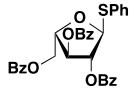
71.14, 70.06, 68.84 (2C), 68.73, 68.60 (2C), 68.32, 67.56, 67.49 (2C), 67.01, 66.91, 62.29, 38.99, 38.81, 38.76 (2C), 38.71, 38.66, 38.65 (2C), 27.40 (3C), 27.29 (6C), 27.26 (3C), 27.24 (3C), 27.19 (3C), 27.08 (6C), 20.89.

Benzyl 4,6-*O*-benzylidene-2,3-*O*-dipivaloyl-β-D-galactopyranosyl--(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-6-*O*-acetyl-4-*O*-benzyl-3-*O*-chloroacetyl-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (298)



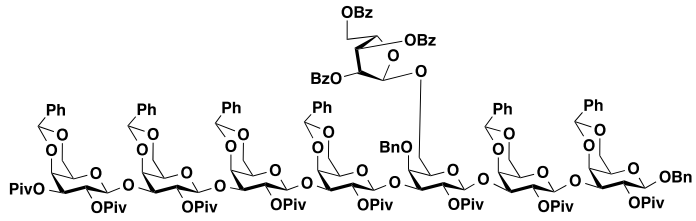
297(2 g; 0.8 mmol) was dissolved in dry DCM (20 mL) and cooled to 0 °C. A 1M L-selectride solution in THF (3.1 mL) was added and the reaction was stirred at 0 °C until complete consumption of the starting material (1h). The reaction mixture was poured into sat. aq. NH_4Cl (100 mL). The aqueous phase was extract with DCM (100 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated (avoid concentrating to dryness since the borane salts can be explosive). The crude product was purified by flash chromatography (9:1 Tol/EtOAc) to give **298** as a colorless crystalline material. Yield: 1.6 g (79%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.02 (m, 40H), 5.50 (s, 1H, $CH^{benzylidene}$), 5.47 (s, 1H, $CH^{benzylidene}$), 5.45 (m, 4H, 4x$CH^{benzylidene}$), 5.43 – 5.16 (m, 7H, 7xH-2), 4.84 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.82 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.79 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.70 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.7 Hz, 1H, H-3[7]), 4.67 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.64 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 4.62 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 4.61 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.57 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.56 (d, J_{CH2} = 12.1 Hz, 1H, 0.5xCH_2^{Bn}), 4.45 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.33 (d, $J_{3,4}$ = 3.8 Hz, 1H, H-4), 4.29 – 3.88 (m, 23H, 6xH-3, 5xH-4, 6xH-6), 3.74 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4), 3.52 (dd, $J_{6a,6b}$ = 11.6, $J_{5,6a}$ = 5.9 Hz, 1H, H-6a[5]), 3.39 (s, 1H, H-5), 3.40 – 3.31 (m, 1H, H-6b[5]), 3.30 (s, 1H, H-5), 3.24 (s, 2H, 2xH-5), 3.23 (s, 1H, H-5), 3.21 – 3.19 (m, 2H, 2xH-5), 2.08 (s, 1H, -OH), 1.12 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 18H,6xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}), 1.03 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 9H, 3xCH_3^{Piv}), 0.98 (s, 9H, 3xCH_3^{Piv}), 0.97 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.24, 176.96, 176.40, 176.30, 176.09, 176.07, 175.97, 175.97, 138.26, 138.01, 137.99, 137.98, 137.91, 137.87, 137.61, 137.32, 129.85-125.42(40C), 100.55-99.21(13C), 77.48, 76.17, 76.02, 75.94, 75.80, 75.78, 75.66, 74.96, 74.67, 74.20, 73.17, 72.47, 72.01, 71.94, 71.66, 71.60, 71.50, 71.41, 71.33, 71.21, 70.06, 70.03, 68.88, 68.77, 68.66, 68.62, 68.35, 67.60, 67.53, 67.52, 67.49, 67.07, 66.94, 39.02, 38.86, 38.79, 38.78, 38.77, 38.74, 38.73, 38.69, 27.48(3C), 27.36(3C), 27.32(3C), 27.29(3C), 27.27(3C), 27.25(3C), 27.11(3C), 27.10(3C).

Phenyl 2,3,5-tri-*O*-benzoyl-1-thio-α-L-arabinofuranoside (299)



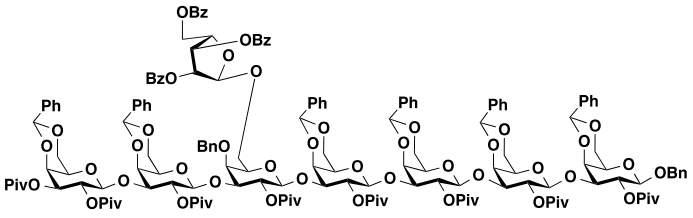
To a solution of **190** (7.8 g, 16.4 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added thiophenol (2.4 mL, 22.4 mmol) dropwise. The reaction mixture was stirred at 0 °C for 15 min, then $BF_3{\cdot}Et_2O$ (13.6 mL, 107.2 mmol) was added and the resulting mixture was warmed gradually to 22 °C. The reaction was stirred for 8 h at 22 °C. The reaction mixture was poured into sat. aq. $NaHCO_3$ (100 mL). The water phase was extracted with CH_2Cl_2 (50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by column chromatography (20:1 Tol/EtOAc) to afford **299** as an amorphous solid. R_f 0.65 (9:1 Tol/EtOAc). Yield: 7.4 g (81%)
$[\alpha]_D^{20}$ = 48.5° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3061.69, 1721.80, 1601.55, 1584.07, 1480.24, 1451.45, 1440.37, 1315.28, 1266.25, 1177.61, 1107.62, 1095.64, 1069.33, 1026.52 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (m, 2H, Ar-H), 8.03 – 7.91 (m, 4H, Ar-H), 7.62 – 7.14 (m, 14H, Ar-H), 5.77 (d, *J* = 3.7 Hz, 1H, H-1), 5.70 – 5.63 (m, 1H, H-2), 5.60 (s, 1H, H-3), 4.91 – 4.60 (m, 2H, H-4, H-5a, H-5b). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.18, 165.60, 165.37, 133.70-127.87 (24C), 91.45, 82.57, 81.17, 78.05, 63.52 **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{26}NaO_7S$ 577.1297; Found 577.1299.

Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-[2,3,5-tri-*O*-benzoyl-α-L-arabinosyl-(1→6)]-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (300)



To a 25 mL flame-dried flask was added **292** (600 mg, 0.24 mmol) and the **193** (197 mg, 0.36 mmol). The mixture was dried azeotropically with tol-uene (2x5 mL) and subject-ted to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (2 mL) and dry MeCN (2 mL), cooled to -30 °C, followed by addition of NIS (82 mg; 0.37 mmol) and TESOTf (13 mg; 0.05 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1h). The solution was diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford a white crystalline material. Yield: 486 mg (69%)
$[\alpha]_D^{20}$= 2.4° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3090.00, 3065.36, 2972.21, 2933.47, 2907.23, 2872.02, 1722.44, 1452.75, 1366.69, 1269.93, 1174.22, 1130.12, 1088.96, 1048.87, 1026.90
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.0, 1.0 Hz, 2H, Ar-H^{Bz}), 8.00 (dd, *J* = 8.2, 1.3 Hz, 1H, Ar-H^{Bz}), 7.96 (dd, *J* = 8.1, 1.2 Hz, 2H, Ar-H^{Bz}), 7.60 – 7.46 (m, 12H, Ar-H), 7.46 – 7.24 (m, 31H, Ar-H), 7.24 – 7.14 (m, 6H, Ar-H), 5.65 (s, 1H, $CH^{benzylidene}$), 5.59 – 5.56 (m, 4H, 4x$CH^{benzylidene}$), 5.55 (s, 1H, $CH^{benzylidene}$), 5.54 – 5.33 (m, 9H, H-2^1-H-2^7, H-2', H-3'), 5.25 (s, 1H, H-1'), 4.94 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.92 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.81 (dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 3.1 Hz, 1H, H-3^7), 4.79 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.78 – 4.72 (m, 4H, 4xH-1), 4.69 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.64 (dd, $J_{5a,5b}$ = 12.1, $J_{4,5a}$ = 3.4 Hz, 1H, H-5a'), 4.55 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.48 (dd $J_{5a,5b}$ = 12.1, $J_{4,5a}$ = 4.7 Hz, 1H, H-5b'), 4.45 – 4.02 (m, 27H, H-1, H-3^1-H-3^6, 6xH-$4^{1/2/4/5/6/7}$, 6xH-$6^{1/2/4/5/6/7}$, H-4', 0.5xCH_2^{Bn}), 3.94 (d, $J_{3,4}$ = 3.7 Hz, 1H, H-4^3), 3.92 (dd, $J_{6a,6b}$ = 9.6, $J_{5,6a}$ = 6.6 Hz, 1H, H-$6a^3$), 3.66 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, 1H, H-5^3), 3.56 (dd, $J_{6a,6b}$ = 9.6, $J_{5,6b}$ = 6.6 Hz, 1H, H-$6b^3$), 3.50 (s, 1H, H-$4^{1/2/4/5/6/7}$), 3.48 (s, 1H, H-$4^{1/2/4/5/6/7}$), 3.41 (s, 1H, H-$4^{1/2/4/5/6/7}$), 3.37 (s, 1H, H-$4^{1/2/4/5/6/7}$), 3.35 (s, 1H, H-$4^{1/2/4/5/6/7}$), 3.31 (s, 1H, H-$4^{1/2/4/5/6/7}$), 1.19 (s, 9H, 3xCH_3^{Piv}), 1.17 (s, 9H, 3xCH_3^{Piv}), 1.15 (s, 9H, 3xCH_3^{Piv}), 1.15 (s, 18H, 6xCH_3^{Piv}), 1.10 (s, 18H, 6xCH_3^{Piv}), 1.05 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.26, 176.96, 176.21, 176.06 (2C), 175.94, 175.92, 175.90, 166.26, 165.80, 165.54, 138.76, 137.98, 137.95 (2C), 137.89, 137.84, 137.56, 137.29, 134.05, 133.72, 133.15, 130.16-125.42 (55C), 106.43, 100.56, 100.45 (2C), 100.38, 100.28, 100.24 (2C), 100.21 (2C), 100.08, 99.84, 99.80, 99.42, 82.14, 81.50, 77.58, 77.36, 76.91, 76.12, 76.03, 75.99, 75.91, 75.86, 75.73, 74.48, 74.42, 74.19, 73.14, 72.43, 72.01, 71.96, 71.89, 71.56, 71.46, 71.29, 71.03, 70.06, 68.86, 68.75, 68.63, 68.44, 67.75, 67.59, 67.52, 67.41, 67.05, 66.95, 66.07, 63.57, 39.03, 38.83, 38.77, 38.73, 38.70 (2C), 38.68, 38.65, 27.41 (3C), 27.35 (3C), 27.32 (6C), 27.26 (3C), 27.20 (6C), 27.12 (3C).

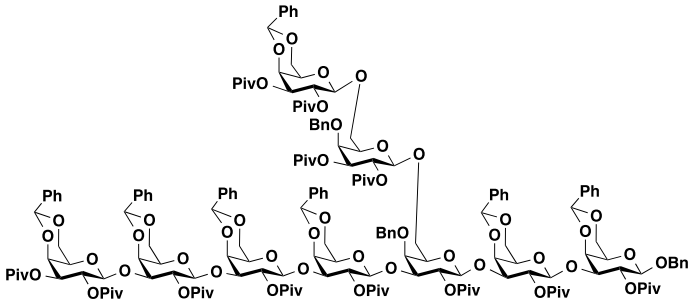
Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-[2,3,5-tri-*O*-benzoyl-α-L-arabinosyl-(1→6)]-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (301)



To a 25 mL flame-dried flask was added **298** (400 mg, 0.13 mmol) and the **193** (111 mg, 0.20 mmol). The mixture was dried azeotropically with toluene (2x5 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (2 mL) and dry MeCN (2 mL), cooled to -30 °C, followed by addition of NIS (51 mg; 0.31 mmol) and TESOTf (9 mg; 0.04 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1h). The solution was diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford a white crystalline material**.** Yield: 245 mg (72%)
$[\alpha]_D^{20}$= -4.7° (c 1.0, $CDCl_3$). **IR** (neat,cm^{-1}):3524.96, 2972.52, 2933.68, 2906.86, 2872.57, 1734.93, 1496.69, 1456.03, 1397.62, 1366.61, 1277.07, 1170.07, 1082.44, 1046.46, 1001.32. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 – 7.81 (m, 6H, Ar-H^{Bz}), 7.58 – 6.99 (m, 49H, Ar-H), 5.53 (s, 1H, $CH^{benzylidene}$), 5.49 (s, 1H, $CH^{benzylidene}$), 5.47 (s, 1H,

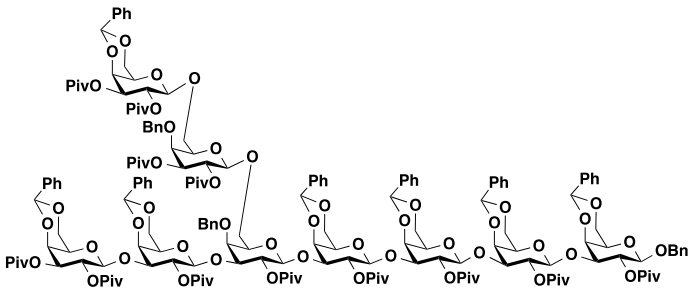
$CH^{benzylidene}$), 5.47 (s, 1H, $CH^{benzylidene}$), 5.45 (s, 1H, $CH^{benzylidene}$), 5.44 (s, 1H, $CH^{benzylidene}$), 5.43 – 5.42 (m, 1H, H-2'/H-3',), 5.40 – 5.25 (m, 8H, H-2'/H-3', H-2^1-H-2^7), 5.14 (s, 1H, H-1'), 4.83 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1), 4.79 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.75 – 4.59 (m, 8H, 5xH-1, H-3^7, H-5a', 0.5xCH_2^{Bn}), 4.50 (dd, $J_{5a,5b}$ = 12.3, $J_{4,5b}$ = 4.6 Hz, 1H, H-5b'), 4.43 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.34 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.33 – 3.90 (m, 26H, H-3^1-H-3^6, 6xH-$4^{1/2/3/4/6/7}$, 6xH-$6^{1/2/3/4/6/7}$, H-4', 0.5xCH_2^{Bn}), 3.84 (d, $J_{3,4}$ = 2.9 Hz, 1H, H-4^5), 3.76 (dd, $J_{6a,6b}$ = 9.5, $J_{5,6a}$ = 6.0 Hz, 1H, H-6a^5), 3.55 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.0 Hz, 1H, H-5^5), 3.48 (dd, $J_{6a,6b}$ = 9.5, $J_{5,6b}$ = 6.0 Hz, 1H, H-6b^5), 3.43 (s, 1H, H-$5^{1/2/3/4/6/7}$), 3.37 (s, 1H, H-$5^{1/2/3/4/6/7}$), 3.30 (s, 1H, H-$5^{1/2/3/4/6/7}$), 3.26 (s, 1H, H-$5^{1/2/3/4/6/7}$), 3.23 (s, 1H, H-$5^{1/2/3/4/6/7}$), 3.22 (s, 1H, H-$5^{1/2/3/4/6/7}$), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.05 (s, 18H, 6xCH_3^{Piv}), 1.00 (s, 9H, 3xCH_3^{Piv}), 0.99 (s, 9H, 3xCH_3^{Piv}), 0.99 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.27, 176.94, 176.20, 176.18, 176.02, 175.98, 175.97, 175.84, 166.26, 166.24, 166.22, 138.73, 138.03, 137.96, 137.92, 137.86, 137.83, 137.58, 137.31, 133.84, 133.72, 133.27, 130.15-125.41 (55C), 106.45, 101.11, 100.56, 100.46, 100.39, 100.34, 100.29 (2C), 100.21 (2C), 100.06, 99.98, 99.75, 99.30, 82.64, 82.09, 81.52, 81.35, 78.09, 77.62, 77.36, 76.91, 76.03, 75.95, 75.91, 75.74, 74.54, 74.46, 74.22, 73.15, 72.31, 72.03, 71.92, 71.74, 71.69, 71.64, 71.52, 71.39, 71.25, 71.14, 69.96, 68.85, 68.62, 68.39, 67.77, 67.65, 67.53, 67.33, 67.06, 66.87, 64.02, 63.83, 63.55, 39.01, 38.80, 38.73 (5C), 38.68, 27.39 (3C), 27.34 (6C), 27.32 (6C), 27.20 (3C), 27.16 (3C), 27.10 (3C).

Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-[4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)]-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (302)



To a 25 mL flame-dried flask was added **292** (600 mg, 0.24 mmol) and the **186** (337 mg, 0.36 mmol). The mixture was dried azeotropically with tol-uene (2x5 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (2 mL) and dry MeCN (2 mL), cooled to -30 °C, followed by addition of NIS (82 mg; 0.37 mmol) and TESOTf (13 mg; 0.05 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford a white crystalline material. Yield: 583 mg (73%)

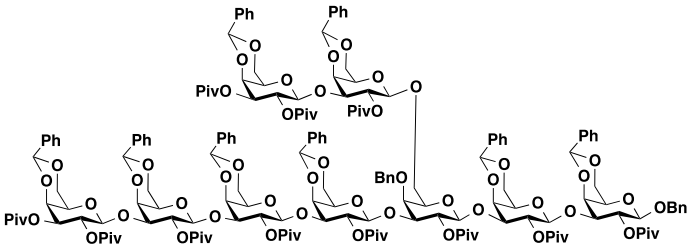
Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-[4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)]-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (303)



To a 25 mL flame-dried flask was added **298** (500 mg, 0.20 mmol) and the **186** (281 mg, 0.30 mmol). The mixture was dried azeotropically with tol-uene (2x5 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (2 mL) and dry MeCN (2 mL), cooled to -30 °C, followed by addition of NIS (69 mg; 0.31 mmol) and TESOTf (10 mg; 0.04 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1h). The solution was diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford a white crystalline material. Yield: 505 mg (76%)

$[\alpha]_D^{20}$ = 4.2° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3524.96, 2972.52, 2933.68, 2906.86, 2872.57, 1734.93, 1496.69, 1456.03, 1397.62, 1366.61 1277.07, 1170.07, 1082.44, 1046.46, 1001.32. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (m, 14H, Ar-H), 7.33 – 7.03 (m, 38H, Ar-H), 5.53 – 5.11 (m, 16H, 7xCH^{benzylidene}, H-2^1-H-2^7, H-2$^{1'}$, H-2$^{2'}$), 4.94 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.1 Hz, 1H, H-3$^{7/1'/2'}$), 4.84 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.89 – 4.74 (m, 3H, , H-3$^{7/1'/2'}$, CH_2^{Bn}), 4.73 – 4.60 (m, 5H, 3xH-1, H-3$^{7/1'/2'}$, 0.5xCH_2^{Bn}), 4.59 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1), 4.55 (d, J_{CH2} = 11.2 Hz, 1H, 0.5xCH_2^{Bn}), 4.47 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.45 (d, J_{CH2} = 11.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.41 (d, J_{CH2} = 12.2 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.32 (d, J = 3.8 Hz, 1H, H-4$^{1/2/3/4/6/7/2'}$), 4.28 (d, J = 4.0 Hz, 1H, H-4$^{1/2/3/4/6/7/2'}$), 4.25 – 3.87 (m, 30H, H-3^1-H-3^6, H-4$^{1/2/3/4/6/7/2'}$, H-4$^{1/2/3/4/6/7/2'}$, H-4$^{1/2/3/4/6/7/2'}$, H-4$^{1/2/3/4/6/7/2'}$, H-4$^{1/2/3/4/6/7/2'}$, H-6^1-H-6^7, H-6$^{1'}$, H-6$^{2'}$), 3.79 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4$^{5/1'}$), 3.74 (d, $J_{3,4}$ = 3.8 Hz, 1H, H-4$^{5/1'}$), 3.52 (dd, $J_{5,6a}$ = 9.6, $J_{5,6b}$ = 6.4 Hz, 1H, H-5$^{5/1'}$), 3.48 (dd, $J_{5,6a}$ = 7.9, $J_{5,6b}$ = 5.6 Hz, 1H, H-5$^{5/1'}$), 3.39 (s, 1H, H-5$^{1/2/3/4/6/7/2'}$), 3.35 (s, 1H, H-5$^{1/2/3/4/6/7/2'}$), 3.33 (s, 1H, H-5$^{1/2/3/4/6/7/2'}$), 3.31 (s, 1H, H-5$^{1/2/3/4/6/7/2'}$), 3.29 (s, 1H, H-5$^{1/2/3/4/6/7/2'}$), 3.26 (s, 1H, H-5$^{1/2/3/4/6/7/2'}$), 3.20 (s, 1H, H-5$^{1/2/3/4/6/7/2'}$), 1.08 (s, 9H, 3xCH_3^{Piv}), 1.08 (s, 9H, 3xCH_3^{Piv}), 1.075 (s, 18H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.04 (s, 18H, 3xCH_3^{Piv}), 1.02 (s, 9H, 3xCH_3^{Piv}), 1.02 (s, 9H, 3xCH_3^{Piv}), 0.99 (s, 9H, 3xCH_3^{Piv}), 0.98 (s, 9H, 3xCH_3^{Piv}), 0.98 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.15, 178.10, 177.51, 176.84, 176.44, 176.28, 176.20, 176.10, 175.97, 175.89, 175.87, 175.80, 139.11, 138.11, 137.88, 137.87, 137.85, 137.82, 137.77, 137.63, 137.48, 137.18, 129.37-125.90 (38C), 101.66, 100.80, 100.53 (2C), 100.44, 100.34, 100.28, 100.19, 100.16 (2C), 100.13, 100.07, 99.99, 99.71, 99.55, 99.10, 77.26, 75.93, 75.87, 75.78, 75.70, 75.66, 75.28, 74.46, 74.31, 74.25, 73.22, 73.06, 72.29, 71.89, 71.83, 71.68, 71.50, 71.27, 71.19, 71.06, 70.88, 69.96, 69.76, 68.75, 68.69, 68.57, 68.52, 68.28, 68.21, 67.44, 67.27, 66.94, 66.79, 66.44, 66.34, 38.91, 38.91, 38.87, 38.74, 38.71, 38.67 (2C), 38.63, 38.61, 38.59, 38.58, 38.53, 27.29 (6C), 27.25 (3C), 27.23 (3C), 27.21 (3C), 27.19 (3C), 27.16 (3C), 27.14 (3C), 27.11 (3C), 27.03 (6C), 26.99 (3C).

Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-[4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)]-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (304)

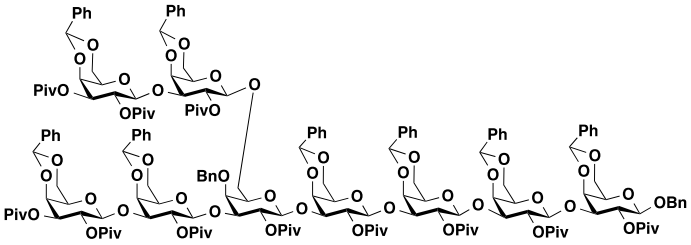


To a 25 mL flame-dried flask was added **292** (600 mg, 0.24 mmol) and the **284** (306 mg, 0.36 mmol). The mixture was dried azeotropically with toluene (2x5 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (2 mL) and dry MeCN (2 mL), cooled to -30 °C, followed by addition of NIS (82 mg; 0.37 mmol) and TESOTf (13 mg; 0.05 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (2h). The solution was diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford a white crystalline material. Yield: 575 mg (74%)

$[\alpha]_D^{20}$ = 9.5° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3535.58, 2972.41, 2872.16, 1736.19, 1700.99, 1479.69, 1455.60, 1397.63, 1366.51, 1276.86, 1171.43, 1132.66, 1084.76, 1046.59, 999.84. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (m, 16H, Ar-H), 7.34 – 7.14 (m, 34H, Ar-H), 5.49 (s, 1H, CH^{benzylidene}), 5.48 – 5.46 (m, 2H, 2xCH^{benzylidene}), 5.45 (s, 2H, 2xCH^{benzylidene}), 5.44 (s, 2H, 2xCH^{benzylidene}), 5.42 (s, 1H, CH^{benzylidene}), 5.40 – 5.25 (m, 7H, 7xH-2), 5.21 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.9 Hz, 1H, H-2), 5.13 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 8.0 Hz, 1H, H-2), 4.85 – 4.76 (m, 4H, 2xH-1, CH_2^{Bn}), 4.74 – 4.62 (m, 5H, 3xH-1, H-3^7, H-3$^{2'}$), 4.55 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.50 (d, J_{CH2} = 12.5 Hz, 1H, 0.5xCH_2^{Bn}), 4.49 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1), 4.44 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.34 (d, J = 8.0 Hz, 1H, H-1), 4.33 – 3.91 (m, 29H, H-3^1-H-3^6, H-3$^{1'}$, 8xH-4$^{1/2/4/5/6/7/1'/2'}$, 7.5xH-6$^{1/2/4/5/6/7/1'/2'}$), 3.89 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1$^{1'}$), 3.84 (d, $J_{6a,6b}$ = 11.9 Hz, 1H, H-6$^{1/2/4/5/6/7/1'/2'}$), 3.74 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4^3), 3.64 – 3.52 (m, 1H, H-6^3), 3.47 (t, $J_{5,6a}$ = $J_{5,6b}$ = 5.6 Hz, 1H, H-5^3), 3.38 (s, 1H, H-5$^{1/2/4/5/6/7/1'/2'}$), 3.35 (s, 1H, H-5$^{1/2/4/5/6/7/1'/2'}$), 3.30 (s, 1H, H-5$^{1/2/4/5/6/7/1'/2'}$), 3.27 (s, 1H, H-5$^{1/2/4/5/6/7/1'/2'}$), 3.22 (s, 1H, H-5$^{1/2/4/5/6/7/1'/2'}$), 3.20 (s, 2H, 2xH-5$^{1/2/4/5/6/7/1'/2'}$), 3.04 (s, 1H, H-5$^{1/2/4/5/6/7/1'/2'}$), 1.13 (s, 9H, 3xCH_3^{Piv}), 1.08 (s, 9H, 3xCH_3^{Piv}), 1.06 (s, 9H, 3xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}), 1.03 (s, 18H, 6xCH_3^{Piv}), 1.01 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 9H, 3xCH_3^{Piv}), 0.99 (s, 9H, 3xCH_3^{Piv}), 0.97 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.32, 178.26, 176.94, 176.82, 176.47, 176.19, 176.18, 176.13, 176.04 (2C), 175.65, 138.91, 138.17, 138.03, 138.00, 137.98, 137.86, 137.82, 137.57 (2C), 137.37, 129.15-125.41 (50C), 102.58, 100.70, 100.57, 100.54, 100.39, 100.29 (4C), 100.20 (3C), 100.04, 99.85, 99.73, 99.60, 99.29, 77.36, 76.03, 75.89, 75.81, 75.72, 75.53, 75.18, 74.81, 74.40, 74.17, 73.23, 73.15, 73.03, 72.58, 72.34, 72.10, 72.00, 71.89, 71.68, 71.58, 71.53,

71.37, 71.25, 71.11, 69.89, 69.20, 68.96, 68.93, 68.88, 68.83, 68.60, 68.38, 68.03, 67.62, 67.51, 67.30, 67.04, 66.94, 66.86, 66.83, 66.70, 65.19, 39.05, 39.03, 39.01, 38.83, 38.80, 38.79, 38.77, 38.71 (3C), 38.68, 38.67, 27.50 (3C), 27.37 (6C), 27.29 (3C), 27.27 (3C), 27.25 (3C), 27.20 (3C), 27.15 (6C), 27.12 (3C), 27.10 (3C).

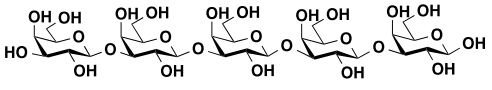
Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene -2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-[4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)]-4-*O*-benzyl-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl- (1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-pivaloyl-β-D-galactopyranoside (305)



To a 25 mL flame-dried flask was added **298** (500 mg, 0.20 mmol) and the **284** (255 mg, 0.30 mmol). The mixture was dried azeotropically with tol-uene (2x5 mL) and subject-ted to vacuum over night. It was then dissolved in dry CH_2Cl_2 (2 mL) and dry MeCN (2 mL), cooled to -30 °C, followed by addition of NIS (69 mg; 0.31 mmol) and TESOTf (10 mg; 0.04 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1h). The solution was diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to afford a white crystalline material. Yield: 460 mg (71%)

$[\alpha]_D^{20}$ = 8.9° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 2973.10, 2933.38, 2906.81, 2872.23, 1736.16, 1701.44, 1479.68, 1455.34, 1397.62, 1366.36, 1276.86, 1171.55, 1132.07, 1085.98, 1046.35, 1026.49, 999.26. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (m, 16H, Ar-H), 7.23 (m, 34H, Ar-H), 5.57 – 5.07 (m, 17H, H-2^1-H-2^7, H-$2^{1'}$, H-$2^{2'}$, 8x$CH^{benzylidene}$), 4.88 – 4.81 (m, 3H, 2xH-1, 0.5xCH_2^{Bn}), 4.79 (d, J_{CH2} = 11.5 Hz, 1H, 0.5xCH_2^{Bn}), 4.74 – 4.66 (m, 3H, H-$3^{7/2'}$, H-$3^{7/2'}$, H-1), 4.65 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.61 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.55 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.53 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.47 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.45 (d, J_{CH2} = 11.6 Hz, 1H, CH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.33 – 3.84 (m, 31H, H-3^1-H-3^6, H-$3^{1'}$, 8xH-$4^{1/2/3/4/6/7/1'/2'}$, 8xH-$6^{1/2/3/4/6/7/1'/2'}$), 3.89 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-$1^{1'}$), 3.82 (m, 1H, H-6a^5), 3.78 (t, $J_{3,4}$ = 3.4 Hz, 1H, H-4^5), 3.69 – 3.53 (m, 1H, H-6b^5), 3.47 (d, $J_{5,6a}$ = $J_{5,6b}$ = 5.3 Hz, 1H, H-5^5), 3.38 – 3.35 (m, 2H, 2xH-$5^{1/2/3/4/6/7/1'/2'}$), 3.30 (s, 1H, H-$5^{1/2/3/4/6/7/1'/2'}$), 3.24 (s, 1H, H-$5^{1/2/3/4/6/7/1'/2'}$), 3.23 (s, 1H, H-$5^{1/2/3/4/6/7/1'/2'}$), 3.21 (s, 1H, H-$5^{1/2/3/4/6/7/1'/2'}$), 3.17 (s, 1H, H-$5^{1/2/3/4/6/7/1'/2'}$), 3.00 (s, 1H, H-$5^{1/2/3/4/6/7/1'/2'}$), 1.11 (s, 9H, 3xCH_3^{Piv}), 1.08 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 27H, 9xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}), 1.02 (s, 9H, 3xCH_3^{Piv}), 1.00 (s, 9H, 3xCH_3^{Piv}), 0.98 (s, 9H, 3xCH_3^{Piv}), 0.98 (s, 9H, 3xCH_3^{Piv}), 0.95 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.30, 178.24, 176.96, 176.88, 176.34, 176.31, 176.10, 176.07, 176.01, 175.97, 175.69, 138.93, 138.13, 138.03, 137.98 (2C), 137.89, 137.65, 137.59 (2C), 137.29, 129.14-125.40 (34C), 102.44, 100.69, 100.54 (2C), 100.42, 100.32, 100.25 (3C), 100.16, 100.11 (2C), 99.80, 99.72, 99.59, 99.54, 99.21, 77.36, 76.02, 75.91, 75.85, 75.71, 75.26, 75.21, 74.70, 74.39, 74.16, 73.23, 73.15, 73.02, 72.51, 72.41, 72.03, 71.99, 71.93, 71.50, 71.23, 71.09, 70.97, 70.05, 69.18, 68.94, 68.81, 68.61, 68.37, 68.32, 68.03, 67.57, 67.53, 67.36, 67.04, 66.91, 66.87, 66.82, 66.69, 39.02, 39.00, 38.79 (2C), 38.77 (3C), 38.71, 38.69, 38.66, 38.61, 27.40 (6C), 27.36 (3C), 27.30 (3C), 27.29 (3C), 27.215 (3C), 27.21 (3C), 27.15 (3C), 27.12 (6C), 27.09 (3C).

β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-D-galactopyranose (306)

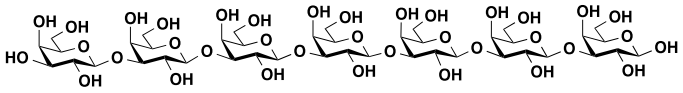


289 (350 mg; 0.18 mmol) was dissolved in THF (40 mL) and a 1M Et_4NOH in MeOH solution (7.4 mL; 7.4 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield colorless crystals. The product was dissolved in MeOH (40 mL), THF (10 mL). 20% $Pd(OH)_2$/C (129 mg; 0.18 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **306** as a white solid. Yield: 119 mg (78% over two steps).

^{1}H NMR (400 MHz, D_2O) δ 5.19 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-1α), 4.62 – 4.49 (m, 9H, H-1^1β-H-1^5β, H-1^2α-H-1^5α), 4.17 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-4), 4.11 (m, 9H, 9xH-4), 4.03 (t, J = 6.3 Hz, 1H), 3.90 (t, J = 3.0 Hz, 1H), 3.83 (d, J = 3.3 Hz, 3H), 3.80 – 3.47 (m, 45H). **^{13}C NMR** (101 MHz, D_2O) δ 104.24, 103.98, 103.92, 96.11, 92.11, 82.38, 81.98,

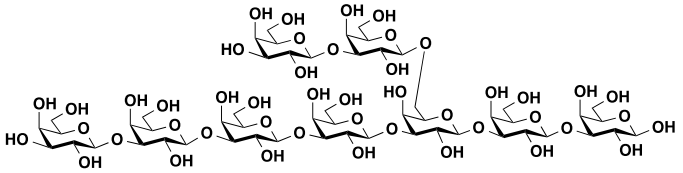
81.91, 81.68, 79.33, 75.02, 74.72, 74.64, 74.59, 72.46, 70.98, 70.89, 70.17, 70.06, 69.09, 68.51, 68.34, 68.28, 67.34, 60.91, 60.88, 60.84, 58.55.

β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-D-galactopyranose (307)



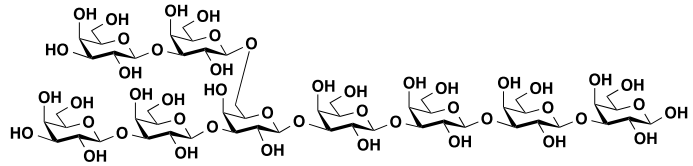
291 (325 mg; 0.13 mmol) was dissolved in THF (40 mL) and a 1M Et_4NOH in MeOH solution (7.6 mL; 7.6 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield colorless crystals. The product was dissolved in MeOH (40 mL), THF (10 mL). 20% $Pd(OH)_2$/C (88 mg; 0.13 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **307** as a white solid. Yield: 107 mg (74% over two steps).
^{1}H NMR (400 MHz, D_2O) δ 5.19 (d, $J_{1,2}$ = 3.0 Hz, 1H, H-1α), 4.63 – 4.48 (m, 13H, H-1^{1}β-H-1^{7}β, H-1^{2}α-H-1^{7}α), 4.16 (d, $J_{3,4}$ = 3.2 Hz, 1H), 4.11 (m, 13H), 4.03 (t, J = 6.3 Hz, 1H), 3.90 (t, J = 3.0 Hz, 2H), 3.83 (d, J = 3.2 Hz, 2H), 3.80 – 3.47 (m, 65H). **^{13}C NMR** (101 MHz, D_2O) δ 104.24, 103.92, 96.11, 92.11, 82.38, 81.97, 81.91, 81.68, 75.02, 74.64, 72.46, 70.98, 70.89, 70.17, 70.06, 69.09, 68.51, 68.34, 68.28, 67.34.

β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-[β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→6)]-β-D-galactopyranosyl- (1→3)-β-D-galactopyranosyl-(1→3)-D-galactopyranose (308)



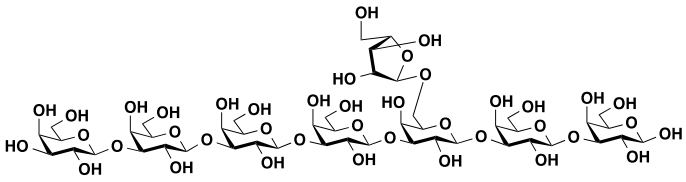
304 (380 mg; 0.12 mmol) was dissolved in THF (30 mL) and a 1M Et_4NOH in MeOH solution (9.24 mL; 9.24 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield colorless crystals. The product was dissolved in MeOH (40 mL), THF (10 mL). 20% $Pd(OH)_2$/C (84 mg; 0.12 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **308** as a white solid. Yield: 112 mg (66% over two steps).
^{1}H NMR (400 MHz, D_2O) δ 5.29 (d, $J_{1,2}$ = 3.1 Hz, 1H, H-1α), 4.73 – 4.58 (m, 15H, H-1^{1}β-H-1^{7}β, H-1^{2}α-H-1^{7}α, H-1'^{6branch}α, H-1'^{6branch}β), 4.49 (d, $J_{1,2}$ = 7.8 Hz, 2H, H-1^{6branch}α, H-1^{6branch}β), 4.26 (d, $J_{3,4}$ = 3.3 Hz, 1H, H-4^{1}a), 4.22 (m, 17H, 17xH-4), 4.12 (t, J = 6.3 Hz, 1H), 4.08 – 3.55 (m, 89H). **^{13}C NMR** (101 MHz, D_2O) δ 104.37, 104.25, 103.98, 103.92, 103.78, 103.12, 96.11, 92.12, 82.47, 82.39, 81.97, 81.91, 81.86, 81.68, 79.35, 75.02, 74.70, 74.64, 73.33, 72.46, 71.00, 70.98, 70.89, 70.17, 70.17, 70.11, 69.82, 68.51, 68.39, 68.34, 68.30, 68.28, 60.90, 60.85.

β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-[β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→6)]-β-D-galactopyranosyl- (1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-D-galactopyranose (309)



305 (318 mg; 0.097 mmol) was dissolved in THF (30 mL) and a 1M Et_4NOH in MeOH solution (7.7 mL; 7.7 mmol) was added. The reac-tion mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield colorless crystals. The product was dissolved in MeOH (40 mL), THF (10 mL). 20% $Pd(OH)_2$/C (68 mg; 0.097 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **309** as a white solid. Yield: 102 mg (72% over two steps).
^{1}H NMR (400 MHz, D_2O) δ 5.28 (d, $J_{1,2}$ = 3.0 Hz, 1H, H-1α), 4.73 – 4.58 (m, 15H, H-1^{1}b-H-1^{7}b, H-1^{2}a-H-1^{7}a, H-1'^{branch}α, H-1'^{branch}β), 4.49 (d, $J_{1,2}$ = 7.9 Hz, 3H, H-1^{branch}α, H-1^{branch}β), 4.26 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4α), 4.22 (m, 17H, 17xH-4), 4.12 (t, J = 6.2 Hz, 1H), 4.09 – 3.56 (m, 89H).

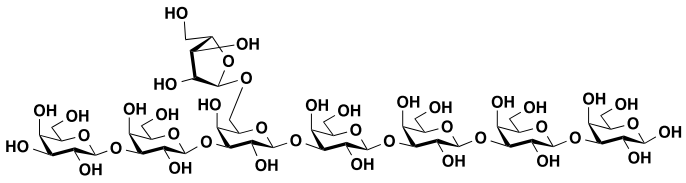
β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-[α-L-arabinosyl-(1→6)]-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-D-galactopyranose (310)



300 (320 mg; 0.11 mmol) was dissolved in THF (30 mL) and a 1M Et_4NOH in MeOH solution (9.24 mL; 9.24 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield a colorless foam. The product was dissolved in MeOH (30 mL), THF (7.5 mL). 20% $Pd(OH)_2$/C (75 mg; 0.11 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **310** as a white solid. Yield: 82 mg (60% over two steps).

^{1}H NMR (400 MHz, D_2O) δ 5.19 (d, $J_{1,2}$ = 3.1 Hz, 1H, H-1α), 4.97 (m, 2H, H-1^{ara}α, H-1^{ara}β), 4.63 – 4.51 (m, 11H, H-1^{1}β-H-1^{7}β, H-1^{2}α-H-1^{7}α), 4.16 (d, $J_{3,4}$ = 3.5 Hz, 1H, H-4α),4.13 – 4.08 (m, 13H, 13xH-4), 4.03 (t, J = 6.2 Hz, 1H), 4.00 – 3.92 (m, 4H), 3.90 (t, J = 2.9 Hz, 2H), 3.88 – 3.46 (m, 69H). **^{13}C NMR** (101 MHz, D_2O) δ 107.84, 104.24, 103.93, 103.74, 96.11, 83.87, 82.38, 82.38, 81.97, 81.91, 81.81, 81.00, 76.39, 75.02, 74.72, 74.63, 73.28, 72.46, 70.98, 70.89, 70.16, 70.13, 70.07, 68.51, 68.48, 68.39, 68.38, 68.34, 68.27, 68.27, 67.29, 61.14, 60.94, 60.91, 60.87, 60.84.

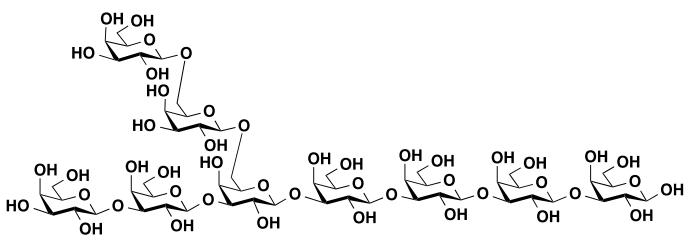
β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-[α-L-arabinosyl-(1→6)]-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-D-galactopyranose (311)



301 (300 mg; 0.10 mmol) was dissolved in THF (30 mL) and a 1M Et_4NOH in MeOH solution (8.1 mL; 8.1 mmol) was added. The reac-tion mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield colorless crystals. The product was dissolved in MeOH (40 mL), THF (10 mL). 20% $Pd(OH)_2$/C (70 mg; 0.097 mmol) was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **311** as a white solid. Yield: 84 mg (65% over two steps).

^{1}H NMR (400 MHz, D_2O) δ 5.29 (d, $J_{1,2}$ = 3.0 Hz, 1H, H-1α), 5.08 – 5.04 (m, 2H, H-1^{ara}α, H-1^{ara}β), 4.74 – 4.57 (m, 13H, H-1^{1}β-H-1^{7}β, H-1^{2}α-H-1^{7}α), 4.26 (d, $J_{3,4}$ = 3.1 Hz, 1H, H-4α), 4.21 (m, 13H, 13xH-4), 4.12 (t, J = 6.2 Hz, 1H), 4.10 – 3.36 (m, 79H). **^{13}C NMR** (101 MHz, D_2O) δ 107.86, 104.25, 103.95, 96.12, 92.12, 83.88, 82.38, 82.04, 81.98, 81.91, 81.81, 81.01, 76.40, 75.02, 74.73, 74.65, 73.30, 72.47, 70.98, 70.90, 70.18, 70.07, 68.52, 68.49, 68.40, 68.34, 68.28, 67.29, 61.15, 60.91, 60.85.

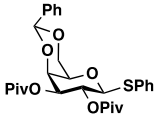
β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-[β-D-galactopyranosyl-(1→6)-β-D-galactopyranosyl-(1→6)]-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl- (1→3)-β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-D-galactopyranose (312)



303 (328 mg; 0.097 mmol) was dissolved in THF (30 mL) and a 1M Et_4NOH in MeOH solution (7.78 mL; 7.78 mmol) was added. The reaction mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield a colorless foam. The product was dissolved in MeOH (30 mL), THF (7.5 mL). 20% $Pd(OH)_2$/C (68 mg; 0.097 mmol)

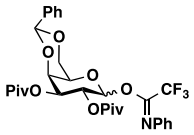
was added and an atmosphere of H_2 (1 atm.) was installed. The reaction was stirred at 22 °C for 48h, filtered through celite, and concentrated to give a grey solid. Purified by reverse phase chromatography to afford **312** as a white solid. Yield: 99 mg (69% over two steps).
^{1}H NMR (400 MHz, D_2O) δ 5.19 (d, $J_{1,2}$ = 3.1 Hz, 1H, H-1α), 4.64 – 4.48 (m, 13H, H-1^{1}β-H-1^{7}β, H-1^{2}α-H-1^{7}α), 4.36 (d, $J_{1,2}$ = 7.8 Hz, 2H, H-1^{6branch}α, H-1^{6branch}β), 4.35 (d, $J_{1,2}$ = 7.8 Hz, 2H, H-1'^{6branch}α, H-1'^{6branch}β), 4.19 – 4.08 (m, 18H, 18xH-4), 4.03 (t, *J* = 6.3 Hz, 1H), 3.98 – 3.38 (m, 89H).

Phenyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-1-thio-β-D-galactopyranoside (351)



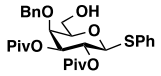
56 (10 g; 27.74 mmol) was dissolved in CH_2Cl_2 (250 mL). Et_3N (15.5 mL; 110.98 mmol), DMAP (1.70 g; 13.87 mmol) and pivaloyl chloride (9.4 mL; 110.98 mmol) was added to the solution and the reaction mixture was heated to 45 °C for 4 h. The reaction mixture was cooled to 0 °C, quenched with MeOH (20 mL), washed with water (2x200 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (Tol/EtOAc 19:1) to afford **351** as a white crystalline powder. R_f 0.58 (9:1 Tol/EtOAc). Yield 13.79 g (94%)
$[\alpha]_D^{20}$= 18.6° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3062.19, 2972.17, 2933.64, 2906.05, 2872.25, 1732.66, 1584.21, 1479.49, 1457.92, 1397.86, 1367.04, 1281.29, 1157.55, 1139.36, 1092.48, 1045.78, 1026.31. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H, Ar-H), 7.31 (m, 8H, Ar-H), 5.42 (s, 1H, -CH^{benzylidene}), 5.36 (t, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, 1H, H-2), 4.88 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 3.5 Hz, 1H, H-3), 4.66 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.33 (d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 4.31 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6z}$ = 1.1 Hz, 1H, H-6a), 3.95 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6b}$ = 1.7 Hz, 1H, H-6b), 3.52 (m, 1H, H-5), 1.14 (s, 9H, 3xCH$_3^{Piv}$), 1.04 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.22, 176.20, 137.72, 133.15 (2C), 131.98, 129.00, 128.85 (2C), 128.18 (2C), 128.08, 126.23 (2C), 100.66, 85.77, 73.31, 73.16, 69.77, 69.21, 65.98, 39.00, 38.80, 27.26 (3C), 27.09 (3C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{36}NaO_7S$ 551.2079; Found 551.2071.

4-*O*-benzyl-6-*O*-chloroacetyl-2,3-*O*-dipivaloyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (352)



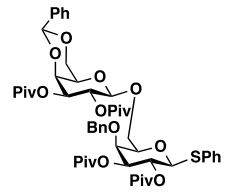
351 (10.0 g; 18.91 mmol) was dissolved in MeCN (250 mL) and water (25 mL). NBS (13.5 g; 75.66 mmol) was added and the reaction was stirred at 50 °C for 4 h. The solution was diluted with EtOAc (500 mL) and washed with sat. aq. NaS_2O_3 (200 mL) and sat. aq. $NaHCO_3$ (200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (4:1 Tol/EtOAc) to afford the hemiacetal **352a**. R_f 0.17 (4:1 Tol/EtOAc). Hemiacetal **352a** was dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. Cs_2CO_3 (11.9 g; 36.65 mmol) was added followed by *N*-phenyl trifluoroacetimidoyl chloride (7.6 g; 36.65 mmol). The ice bath was removed and the reaction mixture was stirred for 12 h. It was then filtered, through a plug of celite, concentrated and purified by flash chromatography (9:1 Tol/EtOAc) to give **352** as white crystalline product. Yield: 6.9 g (62% over two steps)

Phenyl 4-*O*-benzyl-2,3-di-*O*-pivaloyl-1-thio-β-D-galactopyranoside (353)



A 1 M solution of BH_3·THF complex in THF (189.2 mL) was added to a solution of **351** (20 g; 37.8 mmol) in DCM (100 mL) at 0 °C. The mixture was stirred for 10 min, and freshly dried $Cu(OTf)_2$ (2.1 g, 5.67 mmol) was added to the solution. After stirring for a 5 h, the mixture was cooled to 0 °C, and the reaction was quenched by addition of triethylamine (5.3 mL, 37.8 mmol) and methanol (69 mL, caution: hydrogen gas was evolved). The resultant mixture was concentrated at reduced pressure followed by coevaporation with methanol. The residue was purified by flash column chroma-tography (9:1 Tol/EtOAc) to afford **353** as a slightly yellow crystalline material. R_f 0.21 (9:1 Tol/EtOAc). Yield: 18.1 g (90%)
$[\alpha]_D^{20}$= 2.2° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3522.91, 3062.40, 3032.17, 2970.89, 2934.65, 2906.13, 2872.39, 1733.22, 1479.27, 1457.71, 1397.86, 1365.42, 1279.86, 1162.53, 1138.14, 1082.72, 1041.90
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H, Ar-H), 7.32 – 7.14 (m, 8H, Ar-H), 5.42 (t, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, 1H, H-2), 5.01 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 2.9 Hz, 1H, H-3), 4.74 (d, J_{CH2} = 11.3 Hz, 1H, 0.5xCH$_2^{Bn}$), 4.64 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.39 (d, J_{CH2} = 11.3 Hz, 1H, 0.5xCH$_2^{Bn}$), 3.89 (d, $J_{3,4}$ = 2.9 Hz, 1H, H-4), 3.76 (dd, $J_{6a,6b}$ = 11.2, $J_{5,6a}$ =6.9 Hz, 1H, H-6a), 3.61 – 3.53 (dd, $J_{5,6a}$ =6.9, $J_{5,6b}$ =5.2 Hz, 1H), 3.47 (dd, $J_{6a,6b}$ =11.2, $J_{5,6b}$ =5.2 Hz, 1H, H-6b), 1.14 (s, 9H, 3xCH$_3^{Piv}$), 1.11 (s, 9H, 3xCH$_3^{Piv}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.74, 176.52, 137.57, 132.98, 131.96 (2C), 128.90 (2C), 128.51 (2C), 128.00, 127.86 (2C), 127.77, 86.72, 78.84, 75.11, 74.83, 74.25, 67.42, 61.83, 38.96, 38.77, 27.25 (3C), 27.21 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{38}NaO_7S$ 553.2236; Found 553.2231.

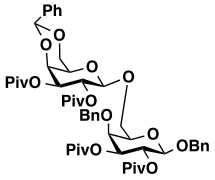
Phenyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-1-thio.galactopyranoside (354)



To a 250 mL flame-dried flask was added **353** (4.7 g, 8.76 mmol) and the **352** (6.4 g, 10.50 mmol). The mixture was co-evaporated with toluene (2x100 mL) and subjected to vacuum overnight. The mixture dissolved in CH_2Cl_2 (100 mL) and cooled to -40 °C. TMSOTf (0.20 mL; 0.88 mmol) was added and the reaction mixture was stirred at -40 °C for 1.5h. Et_3N (1 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (19:1 Tol/EtOAc) to afford **354**. R_f 0.52 (9:1 Tol/EtOAc). Yield: 7.6 g (91%)

$[\alpha]_D^{20}$ = 11.4° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 4H, H^{SPh}), 7.29 – 7.13 (m, 11H, H^{SPh}. Ar-*H*), 5.43 (s, 1H, -$CH^{benzylidene}$), 5.38 (t, $J_{1,2}$ = $J_{2,3}$ =9.8 Hz, 1H, H-2), 5.33 (dd, $J_{2,3}$ = 9.7, $J_{1,2}$ =8.0 Hz, 1H, H-2'), 5.02 (dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 2.9 Hz, 1H, H-3), 4.79 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.7 Hz, 1H, H-3'), 4.68 (d, J_{CH2} = 11.2 Hz, 1H, -CH_2^{Bn}), 4.59 (d, J = 9.8 Hz, 1H, H-1), 4.55 (d, J_{CH2} = 11.2 Hz, 1H, -CH_2^{Bn}), 4.45 (d, J = 8.0 Hz, 1H, H-1'), 4.33 – 4.28 (m, 1H, H-4'), 4.22 – 4.15 (m, 1H, H-6a'), 3.95 (dd, J = 12.5, 1.9 Hz, 1H, H-6b'), 3.86 (m, 2H, H-4, H-6a), 3.75 – 3.63 (m, 2H, H-6b, H-5), 3.39 – 3.35 (m, 1H, H-5'), 1.13 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}), 1.07 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.13, 177.46, 176.53, 176.44, 138.12, 137.59, 132.82, 132.11 (2C), 128.91 (2C), 128.80, 128.24 (2C), 128.08 (2C), 127.77, 127.59 (2C), 127.48, 125.98 (2C), 100.73, 100.51, 86.43, 77.65, 74.93, 74.68, 74.56, 73.09, 71.86, 68.77, 68.14, 67.37, 66.95, 66.43, 38.92, 38.89, 38.74, 27.22, 27.21 (3C), 27.16 (3C), 27.12 (3C), 27.04 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{52}H_{58}NaO_{14}S$: 971.4228; Found 971.4229.

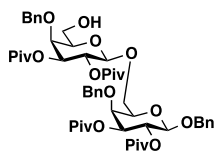
Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranoside (355)



354 (2.0 g; 2.11 mmol) was dried azeotropically with toluene (2x30 mL) and left under vacuum over night. Freshly distilled benzyl alcohol (0.26 mL; 2.52 mmol) was added and the mixture was dissolved in dry CH_2Cl_2 (30 mL) and cooled to -40 °C. Then NIS (497 mg; 2.21 mmol) and TESOTf (45 µL; 0.21 mmol) were added and the reaction mixture was stirred at -40 °C until TLC revealed full conversion of the donor (4h min). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. Na_2SO_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (4:1 Heptan/EtOAc) to yield a white crystalline solid. R_f 0.35 (9:1 Tol/EtOAc). Yield: 1.7 g (86 %)

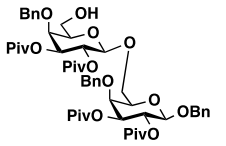
$[\alpha]_D^{20}$ = 24.6° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (m, 2H, H^{Bn}), 7.35 – 7.13 (m, 13H, H^{Bn}, Ar-H), 5.45 (s, 1H, -$CH^{benzylidene}$), 5.42 (dd, $J_{2,3}$ = 10.6, $J_{1,2}$ = 8.1 Hz, 1H, H-2), 5.37 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2'), 4.96 (dd, $J_{2,3}$ = 10.6, $J_{3,4}$ = 3.1 Hz, 1H, H-3), 4.82 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.8 Hz, 1H, H-3'), 4.77 (d, J_{CH2} = 12.0 Hz, 1H, CH_2^a), 4.70 (d, J_{CH2} = 11.2 Hz, 1H, CH_2^b), 4.55 (d, J_{CH2} = 11.2 Hz, 1H, CH_2^a), 4.49 (d, J_{CH2} = 12.0 Hz, 1H, CH-$_2^a$), 4.48 (d, J = 7.9 Hz, 1H, H-1'), 4.42 (d, J = 7.9 Hz, 1H, H-1), 4.32 (dd, $J_{3,4}$ = 3.8, $J_{4,5}$ = 1.0 Hz, 1H, H-4'), 4.20 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.6 Hz, 1H, H-6a'), 3.97 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ 1.8 Hz, 1H, H-6b'), 3.89 (dd, J = 9.8, 5.9 Hz, 1H, H-6a), 3.85 (d, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 3.73 – 3.62 (m, 1H, H-5, H-6b), 3.41 – 3.37 (m, 1H, H-5'), 1.11 (s, 9H, 3x-CH_3^{Piv}), 1.09 (s, 18H, 6x-CH_3^{Piv}), 1.04 (s, 9H, 3x-CH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.15, 177.60, 176.76, 176.51, 138.03, 137.58, 137.01, 128.81, 128.26 (4C), 128.08 (2C), 127.88 (2C), 127.73 (2C), 127.65, 127.57, 125.98 (2C), 100.84, 100.53, 100.18, 77.22, 75.14, 74.71, 73.85, 73.51, 73.09, 71.90, 70.31, 69.34, 68.78, 68.17, 66.99, 66.42, 38.92, 38.91, 38.77, 38.74, 27.24 (3C), 27.17 (3C), 27.14 (3C), 27.03 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{53}H_{70}NaO_{15}$ 969.4612; Found 969.4614.

Benzyl 4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranoside (356)



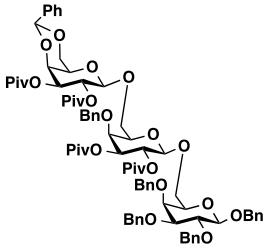
A solution of 1M BH_3 in THF (10 mL) was added to a 50 ml dry flask containing l mmol of compound **355** at 0 °C and the solution was stirred for 5 minutes. A solution of of 1M Bu_2BOTf in CH_2Cl_2 (1 mL) was then added to the clear solution slowly. After 1 hour at 0 °C, TLC showed that the starting material had disappeared. Triethylamine (0.5 mL) was added followed by careful addition of methanol until the evolution of H_2 had ceased. The reaction mixture was co-distilled with methanol three times after which the product was purified by flash chromatography (9:1 Tol/EtOAc) to afford **356** as a colorless crystalline material. Yield: 749 mg (79%)

Benzyl 4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dipivaloyl-β-D-galactopyranoside (356_2)



362 (2.9 g; 2.83 mmol) was dissolved in dry THF (50 mL). Thiourea (645 mg; 8.48 mmol), Bu_4NI (209 mg; 0.57 mmol) and $NaHCO_3$ (784 mg; 9.33 mmol) were added and the reaction mixture was heated to 55 °C for 6h. The mixture was filtered, concentrated and purified by flash chromatography (9:1 Tol/EtOAc). R_f 0.22 (9:1 Tol/EtOAc). Yield: 2.39 g (89%) $[\alpha]_D^{20}$= -8.0° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.00 (m, 15H, Ar-H), 5.40 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2), 5.34 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.8 Hz, 1H, H-2'), 4.93 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 2.8 Hz, 1H, H-3), 4.93 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 2.8 Hz, 1H, H-3'), 4.80 – 4.74 (m, 2H, CH_2^{Bn}), 4.72 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.50 (d, J = 11.3 Hz, 1H, 0.5xCH_2^{Bn}), 4.49 (d, J_{CH2}= 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.41 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.37 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.33 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1'), 3.87 (d, $J_{3,4}$ = 2.8 Hz, 1H, H-4'), 3.85 (d, $J_{3,4}$ = 2.8 Hz, 1H, H-4), 3.83 – 3.77 (m, 1H, H-6a), 3.67 – 3.56 (m, 3H, H-6b, H-6a', H-5), 3.50 – 3.43 (m, 1H, H-5'), 3.43 – 3.34 (m, 1H, H-6b'), 1.14 (s, 9H, 3xCH_3^{Piv}), 1.11 (s, 9H, 3xCH_3^{Piv}), 1.10 (s, 9H, 3xCH_3^{Piv}), 1.03 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.76, 176.73, 175.70, 175.68, 137.00, 136.50, 135.88, 127.53 (2C), 127.27 (2C), 127.23 (2C), 127.10 (2C), 126.80 (2C), 126.69 (2C), 126.65 (2C), 100.38, 98.97, 73.94, 73.92, 73.43, 73.03, 72.82, 72.63, 72.58, 69.21, 68.39, 68.25, 66.46, 60.61, 37.94, 37.90, 37.78, 37.70, 26.23 (3C), 26.21 (3C), 26.16 (3C), 26.11 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{53}H_{72}NaO_{15}$ 971.4769; Found 971.4774.

Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-galactopyranoside

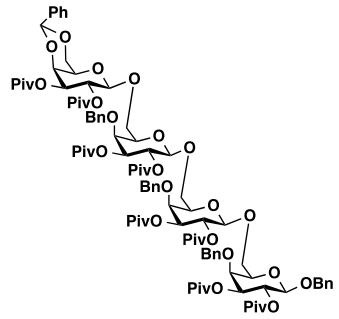


To a 10 mL flame-dried flask was added **113** (300 mg, 0.55 mmol) and **186** (632 mg, 0.67 mmol). The mixture was dried azeotropically with toluene (2x5 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (2.5 mL) and dry MeCN (2.5 mL), cooled to -30 °C, followed by addition of NIS (152 mg; 0.68 mmol) and TESOTf (15 mg; 0.06 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography to afford a white crystalline material. Yield: 918 mg (85%).

$[\alpha]_D^{20}$= -4.4° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3501.69, 3033.79, 2905.82, 1736.89, 1700.15, 1497.26, 1479.42, 1454.79, 1397.64, 1366.09, 1277.36, 1170.93, 1082.97, 1046.55, 1000.25.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.01 (m, 30H, Ar-H), 5.43 (s, 1H, $CH^{benzylidene}$), 5.34 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 8.0 Hz, 1H, H-2^3), 5.31 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2^2), 4.99 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.0 Hz, 1H, H-3^2), 4.86 (d, J_{CH2} = 11.7 Hz, 1H, CH_2^{Bn}), 4.84 – 4.79 (m, 3H, H-3^3, CH_2^{Bn}), 4.72 – 4.59 (m, 6H, 3xCH_2^{Bn}), 4.55 (d, J = 12.1 Hz, 1H, 0.5xCH_2^{Bn}), 4.42 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1^2), 4.40 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^3), 4.36 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1^1), 4.31 (d, $J_{3,4}$ = 3.8 Hz, 1H, H-4^3), 4.15 (dd, $J_{6a,6b}$ = 12.6, $J_{5,6a}$ = 1.0 Hz, 1H, H-6a), 3.99 – 3.94 (m, 1H, H-6a), 3.94 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$ = 1.4 Hz, 1H, H-6b), 3.86 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-4), 3.82 – 3.75 (m, 4H, 2xH-4, H-2^1, H-6b), 3.63 (dd, $J_{6a,6b}$ = 10.2, $J_{5,6a}$ = 6.1 Hz, 1H, H-6b), 3.58 (dd, $J_{5,6a}$ = 8.0, $J_{5,6b}$ = 5.5 Hz, 1H, H-5^2), 3.47 (dd, $J_{6a,6b}$ = 9.5, $J_{5,6b}$ = 5.2 Hz, 1H, H-6b), 3.42 – 3.33 (m, 2H, H-3^1, H-5^1, H-5^3), 1.11 (s, 8H), 1.09 (s, 17H), 1.07 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.21, 177.58, 176.82, 176.64, 138.76, 138.76, 138.53, 138.44, 137.74, 137.71, 128.91-126.11 (24C), 102.94, 101.32, 100.92, 100.66, 82.16, 79.49, 75.42, 75.38, 74.59, 74.47, 73.99, 73.36, 73.27, 73.18, 73.13, 73.00, 71.99, 71.03, 69.91, 68.82, 68.33, 67.78, 66.54, 66.10, 39.03, 39.01, 38.89, 38.88, 27.35, 27.33, 27.29, 27.23, 27.14.

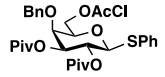
Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl- β-D-galactopyranosyl- (1→6)-2,3,4-tri-*O*-benzyl-β-D-galactopyranoside (357)



To a 25 mL flame-dried flask was added **356** (500 mg, 0.53 mmol) and **354** (658 mg, 2.05 mmol). The mixture was dried azeotropically with toluene (2x10 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (5 mL) and dry MeCN (5 mL), cooled to -30 °C, followed by addition of NIS (157 mg; 0.70 mmol) and TESOTf (14 mg; 0.05 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1.5h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc)

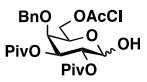
to afford **357** as a white crystalline material. R_f 0.45 (9:1 Tol/EtOAc).Yield: 792 mg (81%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.01 (m, 35H), 5.44 (s, 1H, $CH^{benzylidene}$), 5.42 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 8.7 Hz, 1H, H-2), 5.37 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 8.0 Hz, 1H, H-2), 5.30 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2), 5.29 (dd, $J_{2,3}$ = 10.7, $J_{1,2}$ = 8.0 Hz, 1H, H-2), 4.99 (dd, $J_{2,3}$ = 10.6, $J_{3,4}$ = 2.8 Hz, 1H, H-3), 4.96 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 2.7 Hz, 1H, H-3), 4.94 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 2.9 Hz, 1H, H-3), 4.82 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.7 Hz, 1H, H-3), 4.76 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.70 – 4.45 (m, 7H, 3.5xCH_2^{Bn}), 4.41 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.36 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.36 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.32 (d, $J_{3,4}$ = 3.1 Hz, 1H), 4.29 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.14 (d, J = 11.8 Hz, 1H, 0.5xH-6), 4.01 – 3.77 (m, 8H, 3xH-4, 2.5xH-6), 3.72 – 3.32 (m, 5H, 4xH-5, H-6), 1.11 – 1.02 (m, 72H, 24xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.22, 177.64, 177.56, 177.53, 176.88 (2C), 176.84, 176.64, 138.50, 138.46, 138.22, 137.72, 137.03, 128.92-126.09 (35C), 101.20, 101.16, 100.96, 100.68, 100.09, 75.43, 75.26, 75.16, 74.79, 74.52, 74.49, 73.95, 73.70, 73.62, 73.51, 73.15, 73.09, 72.00, 71.93, 70.42, 70.31, 69.77, 69.46, 68.88, 68.79, 68.28, 67.08, 67.04, 66.57, 66.52, 66.11, 66.02, 39.02 (2C), 38.99 (2C), 38.88 (2C), 38.84 (2C), 27.34 (3C), 27.33 (6C), 27.30 (3C), 27.28 (3C), 27.25 (6C), 27.13 (3C).

Phenyl 4-*O*-benzyl-6-*O*-chloroacetyl-2,3-di-*O*-pivaloyl-1-thio-β-D-galactopyranoside (358)



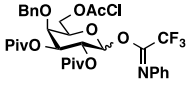
353 (30.0 g; 56.53 mmol) was dissolved in CH_2Cl_2 (560 mL) and cooled to 0 °C. $(ClAc)_2O$ (15.0 g; 87.62 mmol), Et_3N (12.7 mL; 90.45 mmol) and DMAP (138 mg; 1.13 mmol) was added and the reaction was stirred at 0 °C for 1 h. The reaction mixture was concentrated and purified by flash chromatography (20:1 Tol/EtOAc) to afford **358** as a yellowish crystalline powder. R_f 0.57 (9:1 Toluene/EtOAc). Yield 30.2 g (88%)
$[\alpha]_D^{20}$ = -6.7° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.33 (m, 2H, H^{SPh}), 7.31 – 7.11 (m, 8H, H^{SPh}, H^{Bn}), 5.41 (t, $J_{1,2}$ = $J_{2,3}$ =9.9 Hz, 1H, H-2), 5.02 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 2.9 Hz, 1H, H-3), 4.78 (d, J_{CH2} = 11.4 Hz, 1H, -CH_2^{Bn}), 4.62 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.38 (d, J_{CH2} = 11.4 Hz, 1H, -CH_2^{Bn}), 4.29 (dd, $J_{6a,6b}$ = 11.2, $J_{5,6a}$ = 6.9 Hz, 1H, H-6a), 4.04 (dd, $J_{6a,6b}$ = 11.2, $J_{5,6b}$ = 5.8 Hz, 1H, H-6b), 3.98 – 3.80 (m, 3H, -CH_2^{AcCl}, H-4), 3.73 (ddd, $J_{5,6a}$ = 6.9, $J_{5,6b}$ = 5.8, $J_{4,5}$ = 1.2 Hz, 1H, H-5), 1.15 (s, 9H, 3xCH_3^{Piv}), 1.13 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.84, 176.60, 166.87, 137.40, 133.00, 132.45 (2C), 128.97 (2C), 128.63 (2C), 128.15, 128.08 (2C), 128.07, 87.04, 75.68, 74.99, 74.97, 73.96, 67.35, 64.32, 40.65, 39.10, 38.90, 27.38 (3C), 27.33 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{40}ClNaO_8S$ 630.2030; Found 630.2030.

4-*O*-benzyl-6-*O*-chloroacetyl-2,3-di-*O*-pivaloyl-β-D-galactopyranose (359)



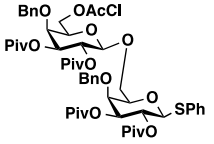
358 (20.0 g; 32.94 mmol) was dissolved in acetone (330 mL) and water (30 mL). NBS (14.8 g; 65.88 mmol) was added and the reaction was stirred at 22 °C for 3 h. The solution was diluted with EtOAc (500 mL) and washed with sat. aq. NaS_2O_3 (200 mL) and sat. aq. $NaHCO_3$ (200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (4:1 Tol/EtOAc) to afford **359**. R_f 0.19 (4:1 Tol/EtOAc) Yield: 14.9 g (88%)

4-*O*-benzyl-6-*O*-chloroacetyl-2,3-*O*-dipivaloyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (360)



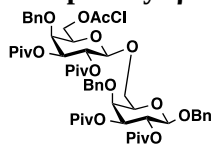
Hemiacetal **359** (14.9 g; 28.88 mmol) was dissolved in CH_2Cl_2 (300 mL) and cooled to 0 °C. Cs_2CO_3 (18.8 g; 57.75 mmol) was added followed by *N*-phenyl trifluoroacetimidoyl chloride (12.0 g; 57.75 mmol). The ice bath was removed and the reaction mixture was stirred for 12 h. It was then filtered, through a plug of celite, concentrated and purified by flash chromatography (15:1 Tol/EtOAc) to give **360** as white crystalline product. Yield: 15.5 g (78%)

Phenyl 4-*O*-benzyl-6-*O*-chloroacetyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-1-thio-β-D-galactopyranoside (361)



To a 500 mL flame-dried flask was added **353** (7.2 g, 13.56 mmol) and **360** (11.2 g, 16.28 mmol). The mixture was co-evaporated with toluene (2x200 mL) and subjected to vacuum overnight. The mixture dissolved in CH_2Cl_2 (200 mL) and cooled to -40 °C. TMSOTf (0.23 mL; 1.35 mmol) was added and the reaction mixture was stirred at -40 °C for 2h. Et_3N (1 mL) was added and the reaction mixture was concentrated. The crude compound was purified by flash chromatography (9:1 Tol/EtOAc) affording **361**. R_f 0.5 (4:1 Tol/EtOAc). Yield: 12.5 g (90%).

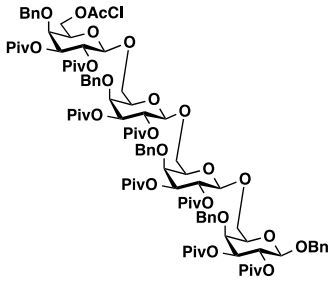
Benzyl 4-*O*-benzyl-6-*O*-chloroacetyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranoside (362)



361 (3.0 g; 2.92 mmol) was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. Benzyl alcohol (378 mg; 3.50 mmol) was added. The mixture was dissolved in dry CH_2Cl_2 (50 mL) and cooled to -40 °C. NIS (689 mg; 3.06 mmol) and TESOTf (77 mg; 0.29 mmol) was added and the reaction mixture was stirred at -40 °C until

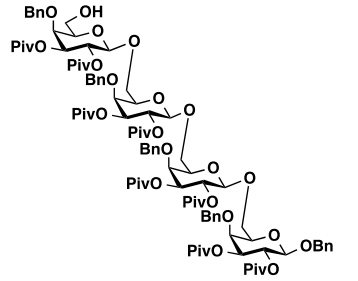
TLC revealed full conversion of the donor (4h). The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (19:1 toluene/EtOAc) to afford **362** as a white crystalline material. R_f 0.49 (9:1 Tol/EtOAc). Yield: 2.60 g (87%)
$[\alpha]_D^{20}$ = -14.3° (c 1.0, $CDCl_3$). **IR** (neat, cm^{-1}): 3064.94, 3031.76, 2971.70, 2935.70, 2906.97, 2872.91, 1734.87, 1496.96, 1479.65, 1456.10, 1397.62, 1366.40, 1278.65, 1141.72, 1073.10, 1041.77, 910.10. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 6.88 (m, 15H, Ar-H), 5.40 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ =7.9 Hz, 1H, H-2), 5.35 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.8 Hz, 1H, H-2'), 4.95 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.0 Hz, 1H, H-3'), 4.94 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.1 Hz, 1H, H-3), 4.80 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.77 (d, J_{CH2} = 11.6 Hz, 1H, 0.5xCH_2^{Bn}), 4.70 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.48 (d, J_{CH2} = 11.6 Hz, 1H, 0.5xCH_2^{Bn}), 4.42 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.38 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.39 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1'), 4.15 (dd, $J_{6a,6b}$ = 11.1, $J_{5,6a}$ = 6.4 Hz, 1H, H-6a'), 4.02 (dd, $J_{6a,6b}$ = 11.1, $J_{5,6b}$ = 6.5 Hz, 1H, H-6b'), 3.88 – 3.78 (m, 5H, H-4, H-4', H-6a, CH_2^{AcCl}), 3.68 – 3.54 (m, 3H, H-5, H-5', H-6b), 1.15 (s, 9H, 3xCH_3^{Piv}), 1.11 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.04 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.90, 177.72, 176.84, 176.74, 166.83, 138.01, 137.38, 137.03, 128.66 (2C), 128.41 (2C), 128.37 (2C), 128.29 (2C), 128.24, 127.91 (2C), 127.83 (2C), 127.80 (2C), 101.34, 100.14, 75.20, 75.10, 74.75, 73.81, 73.72 (2C), 73.59, 71.94, 70.37, 69.39, 69.33, 67.58, 63.83, 40.61, 39.10, 39.02, 38.93, 38.84, 27.38 (3C), 27.35 (3C), 27.30 (3C), 27.25 (3C). **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{55}H_{73}ClNaO_{16}$ 1047.4485; Found 1047.4484.

Benzyl 4-*O*-benzyl-6-*O*-chloroacetyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranoside (363)



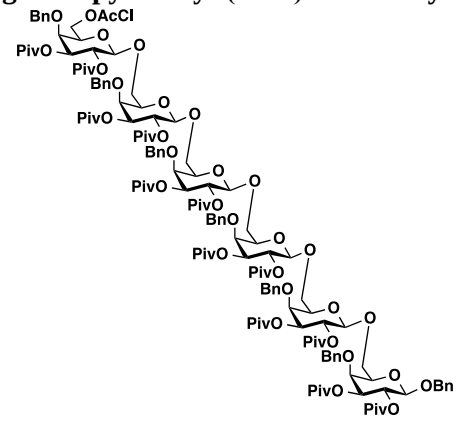
To a 100 mL flame-dried flask was added **356** (1.5 g, 1.58 mmol) and the **361** (2.11 g, 2.05 mmol). The mixture was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (25 mL) and dry MeCN (25 mL), cooled to -30 °C, followed by addition of NIS (472 mg; 2.10 mmol) and TESOTf (42 mg; 0.16 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1.5h). The solution was diluted with CH_2Cl_2 (150 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (20:1 Tol/EtOAc) to afford a white crystalline material. R_f 0.43 (9:1 Tol/EtOAc). Yield: 2.6 g (88%)
$[\alpha]_D^{20}$ = -18.8° (c 1.0, $CDCl_3$) **IR** (neat, cm^{-1}):2971.30, 2935.59, 2907.15, 2872.55, 1733.73, 1479.62, 1456.66, 1397.50, 1365.79, 1278.22, 1132.71, 1070.76, 1042.84 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 6.98 (m, 25H, Ar-H), 5.39 (dd, $J_{2,3}$= 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2), 5.33 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 7.7 Hz, 1H, H-2), 5.29 (dd, $J_{2,3}$= 10.3, $J_{1,2}$ = 7.7 Hz, 1H, H-2), 5.28 (dd, $J_{2,3}$= 10.4, $J_{1,2}$ = 7.8 Hz, 1H, H-2), 5.01 – 4.90 (m, 4H, H-3^1-H-3^4), 4.79 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.76 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.65 (m, 3H, 1.5xCH_2^{Bn}), 4.54 (d, J_{CH2} = 11.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.53 (d, J_{CH2} = 11.1 Hz, 1H, 0.5xCH_2^{Bn}), 4.49 (d, J_{CH2} = 11.3 Hz, 1H, 0.5xCH_2^{Bn}), 4.48 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.40 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.37 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.36 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.29 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.29 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.09 (dd, $J_{6a,6b}$ = 11.0, $J_{5,6a}$ = 6.2 Hz, 1H, H-6a^4), 4.00 (dd, $J_{6a,6b}$ = 11.0, $J_{5,6b}$ = 6.6 Hz, 1H, H-6b^4), 3.95 – 3.76 (m, 7H, H-4^1-H-4^4, 1.5xH-6), 3.73 (d, J = 1.5 Hz, 1H, H-5^4), 3.67 – 3.48 (m, 4H, H-5^1-H-5^3, 0.5xH-6), 3.42 – 3.31 (m, 2H, H-6), 1.15 (s, 9H, 3xCH_3^{Piv}), 1.10 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.09 (s, 9H, 3xCH_3^{Piv}), 1.08 (s, 9H, 3xCH_3^{Piv}), 1.08 (s, 18H, 6xCH_3^{Piv}), 1.03 (s, 9H, 3xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.90, 177.65, 177.58, 177.55, 176.87, 176.85, 176.83, 176.81, 166.82, 138.48, 138.33, 138.25, 137.41, 137.04, 128.67, 128.37, 128.35, 128.31, 128.25, 127.93, 127.83, 127.79, 127.66, 127.62, 127.57, 127.47, 101.32, 101.20, 101.18, 100.09, 77.36, 75.35, 75.27, 75.17, 75.14, 74.81, 74.55, 74.42, 73.76, 73.68, 73.51, 73.13, 73.08, 73.04, 71.99, 70.30, 69.76, 69.72, 69.46, 69.30, 67.02, 66.41, 66.24, 63.80, 40.57, 39.11, 39.01, 38.99, 38.99, 38.92, 38.89, 38.88, 38.84, 27.37, 27.35, 27.33, 27.33, 27.30, 27.29, 27.28, 27.26.

Benzyl 4-*O*-benzyl-2,3-*O*-dipivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dipivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dipivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dipivaloyl-β-D-galactopyranoside (364)



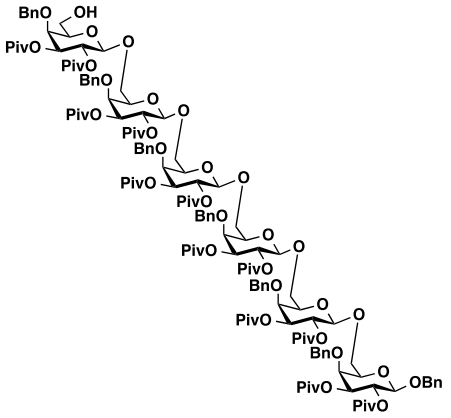
363 (3.1 g; 1.66 mmol) was dissolved in dry THF (50 mL). Thiourea (380 mg; 4.98 mmol), Bu_4NI (123 mg; 0.33 mmol) and $NaHCO_3$ (460 mg; 5.48 mmol) was added and the reaction mixture was heated to 55 °C for 8h. The mixture was filtered, concentrated and purified by flash chromatography (9:1 Tol/EtOAc) to give **364**. R_f 0.17 (9:1 Tol/EtOAc). Yield: 2.59 g (87%)
$[\alpha]_D^{20}$= -14.8° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.00 (m, 25H), 5.47 – 5.20 (m, 4H, H-2^1-H-2^4), 5.03 – 4.86 (m, 4H, H-3^1-H-3^4), 4.81 – 4.44 (m, 9H, 4.5xCH_2^{Bn}), 4.40 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1$^{1/2/3/4}$), 4.35 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1$^{1/2/3/4}$), 4.28 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1$^{1/2/3/4}$), 4.24 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1$^{1/2/3/4}$), 3.94 – 3.74 (m, 8H, H-4^1-H-4^4, 2xH-6), 3.64 – 3.25 (m, 8H, H-5^1-H-5^4, 2xH-6), 1.13 (s, 9H, 3xCH_3^{Piv}), 1.12 – 1.06 (m, 54H, 18xCH_3^{Piv}), 1.03 (s, 9H, 3xCH_3^{Piv}).
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.78, 177.62, 177.53, 177.45, 176.77, 176.73 (2C), 176.70, 138.37, 138.30, 138.11, 137.58, 136.92, 128.56, 128.25, 128.19, 128.15, 128.12, 128.07, 127.82, 127.72, 127.66, 127.57, 127.54, 127.51, 127.47, 127.41, 101.40, 101.09, 101.06, 99.96, 77.24, 75.14, 75.07, 75.06, 75.04, 74.97, 74.66, 74.14, 73.81, 73.58, 73.40, 73.17, 73.08, 73.05, 73.00, 70.18, 69.64, 69.55, 69.41, 69.36, 66.95, 66.46, 66.20, 61.66, 38.97, 38.92, 38.88 (2C), 38.80, 38.77 (2C), 38.73, 27.25-27.15 (24C).

Benzyl 4-*O*-benzyl-6-*O*-chloroacetyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dipivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dipivaloyl-β-D-galactopyranoside (365)



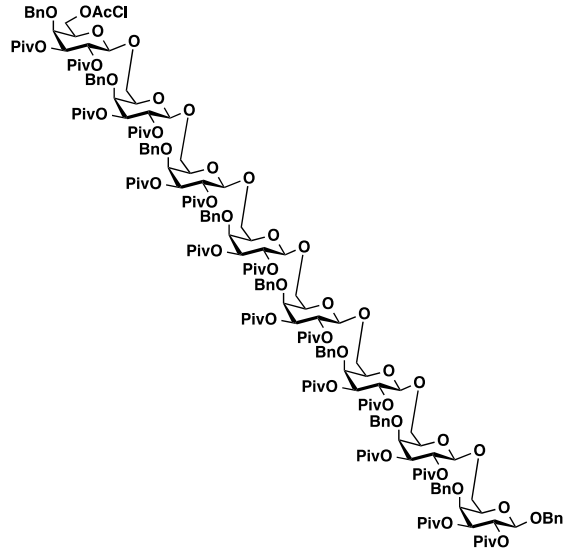
To a 100 mL flame-dried flask was added **364** (2.15 g, 1.20 mmol) and the **361** (1.60 g, 1.56 mmol). The mixture was dried azeotropically with toluene (2x50 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (20 mL) and dry MeCN (20 mL), cooled to -30 °C, followed by addition of NIS (359 mg; 1.60 mmol) and TESOTf (32 mg; 0.12 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1h). The solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (20:1 Tol/EtOAc) to afford **365** as a white crystalline material. R_f 0.45 (9:1 Tol/EtOAc). Yield: 2.95 g (91%)
$[\alpha]_D^{20}$ = -11.6° (c 1.0, $CDCl_3$). **IR**(neat, cm^{-1}): 3065.46, 3031.60, 2971.56, 2935.77, 2906.25, 2872.58, 1733.63, 1479.50, 1457.02, 1397.49, 1365.53, 1278.11, 1132.52, 1070.03, 910.36. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.00 (m, 35H), 5.48 – 5.14 (m, 6H, H-2^1-H-2^6), 5.05 – 4.88 (m, 6H, H-3^1-H-3^6), 4.79 (d, J_{CH2} = 11.3 Hz, 1H, 0.5xCH_2^{Bn}), 4.76 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.69 – 4.44 (m, 11H, 5.5xCH_2^{Bn}), 4.40 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1$^{1/2/3/4/5/6}$), 4.375 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1$^{1/2/3/4/5/6}$), 4.37 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.35 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1$^{1/2/3/4/5/6}$), 4.30 – 4.21 (m, 3H, H-1$^{1/2/3/4/5/6}$, H-1$^{1/2/3/4/5/6}$, H-1$^{1/2/3/4/5/6}$), 4.07 (dd, $J_{6a,6b}$ = 11.1, $J_{5,6a}$ = 6.2 Hz, 1H, H-6a^6), 3.99 (dd, $J_{6a,6b}$ = 11.1, $J_{5,6b}$ = 6.6 Hz, 1H, H-6b^6), 3.94 – 3.75 (m, 11H, H-4^1-H-4^6, 2.5xH-6), 3.71 (d, J_{CH2} = 2.1 Hz, 2H, -CH_2^{AcCl}), 3.68 – 3.44 (m, 8H, H-5^1-H-5^6, H-6), 3.36 (dd, $J_{6a,6b}$ = 9.3, $J_{5,6a}$ = 5.3 Hz, 1H, 0.5xH-6), 3.27 (m, 2H, H-6), 1.15 (s, 9H, 3xCH_3^{Piv}), 1.11 – 1.05 (m, 90H, 30xCH_3^{Piv}), 1.03 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.78, 177.53, 177.46, 177.39 (2C), 177.35, 176.75 (2C), 176.71 (2C), 176.67, 166.69, 138.50 (2C), 138.38, 138.28, 138.12, 137.29, 136.91, 128.55-127.19 (35C), 101.21, 101.10 (2C), 99.98, 77.24, 75.24, 75.13, 75.04, 74.69, 74.44, 74.22, 73.67, 73.57, 73.40, 73.04, 72.93, 72.81, 71.89, 70.19, 69.69, 69.64, 69.34, 69.17, 66.96, 65.83, 63.69, 40.44-38.73 (12C), 27.26-27.15 (36C).

Benzyl 4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)- 4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranoside (366)



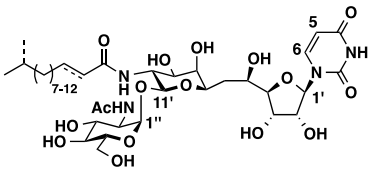
365 (2.15 g; 0.79 mmol) was dissolved in dry THF (50 mL). Thiourea (241 mg; 3.18 mmol), Bu_4NI (59 mg; 0.16 mmol) and $NaHCO_3$ (293 mg; 3.49 mmol) was added and the reaction mixture was heated to 55 °C for 8h. The mixture was filtered, concentrated and purified by flash chromatography (9:1 Tol/EtOAc) to afford **366** as a slightly yellow crystalline material. R_f 0.22 (9:1 Tol/EtOAc). Yield: 1.75 g (84%) $[\alpha]_D^{20}$= -22.5° (c 1.0, $CDCl_3$) **IR** (neat, cm^{-1}):2971.76, 2935.69, 2872.84, 1734.05, 1496.96, 1479.64, 1278.40, 1133.95, 1070.54, 1045.28. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.08 (m, 35H), 5.39 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 7.9 Hz, 1H, H-2), 5.29 (m, 5H, 5xH-2), 5.04 – 4.89 (m, 6H, 6xH-3), 4.76 (d, J_{CH2} = 11.8 Hz, 1H, 0.5xCH_2^{Bn}), 4.72 – 4.45 (m, 12H, 6xCH_2^{Bn}), 4.43 – 4.19 (m, 7H, 0.5xCH_2^{Bn}, 6xH-1), 3.96 – 3.77 (m, 11H, 6xH-4, 2.5xH-6), 3.64 – 3.18 (m, 13H, 6xH-5, 3.5xH-6), 1.15 – 1.02 (m, 108H, 36xCH_3^{Piv}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.91-176.84 (12C), 138.60-137.04 (7C), 128.68-127.41 (35C), 101.51-100.10 (6C), 75.25, 75.17, 75.09, 74.81, 74.56, 74.43, 74.27, 73.91, 73.70, 73.52, 73.15, 73.05, 70.31, 69.78, 69.53, 69.46, 67.22, 67.07, 66.33, 61.75, 39.08-38.85 (12C), 27.33-27.26 (36C).

Benzyl 4-*O*-benzyl-6-*O*-chloroacetyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)- 4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-pivaloyl-β-D-galactopyranoside (367)



To a 50 mL flame-dried flask was added **366** (1.2 g, 0.46 mmol) and the **361** (609 mg, 0.59 mmol). The mixture was dried azeotropically with toluene (2x25 mL) and subjected to vacuum overnight. It was then dissolved in dry CH_2Cl_2 (20 mL) and dry MeCN (20 mL), cooled to -30 °C, followed by addition of NIS (136 mg; 0.61 mmol) and TESOTf (12 mg; 0.05 mmol). The reaction mixture was stirred at -30 °C until TLC revealed full conversion of the donor (1h). The solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. NaS_2O_3 (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (15:1 Tol/EtOAc) to afford **367** as a white crystalline material. R_f 0.37 (9:1 Tol/EtOAc). Yield: 1.4 g (87%) $[\alpha]_D^{20}$= -15.7° (c 1.0, $CDCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 6.97 (m, 45H), 5.42 – 5.20 (m, 8H, H-2^1-H-2^8), 5.02 – 4.90 (m, 8H, H-3^1-H-3^8), 4.79 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.76 (d, J_{CH2} = 12.1 Hz, 1H, 0.5xCH_2^{Bn}), 4.72 – 4.44 (m, 15H, 7.5xCH_2^{Bn}), 4.40 (d, J = 7.9 Hz, 1H, H-$1^{1/2/3/4/5/6}$), 4.37 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.35 (d, J = 7.8 Hz, 1H, H-$1^{1/2/3/4/5/6}$), 4.30 – 4.19 (m, 6H, 6xH-1), 4.06 (dd, $J_{6a,6b}$ = 11.1, $J_{5,6a}$ = 6.2 Hz, 1H, H-6a^8), 3.99 (dd, $J_{6a,6b}$ = 11.0, $J_{5,6a}$ = 6.6 Hz, 1H, H-6b^8), 3.95 – 3.73 (m, 17H, H-4^1-H-4^8, 4.5xH-6), 3.70 (d, J_{CH2} = 2.3 Hz, 2H, CH_2^{AcCl}), 3.67 – 3.44 (m, 10H, H-5^1-H-5^8, H-6), 3.36 (dd, J = 9.3, 5.2 Hz, 1H, 0.5xH-6), 3.32 – 3.14 (m, 4H, 2xH-6), 1.15 (s, 9H, 3xCH_3^{Bn}), 1.08 (dd, 126H, 42xCH_3), 1.03 (s, 9H, 3xCH_3^{Bn}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.78-176.66 (16C), 166.69, 138.59, 138.56, 138.53, 138.50, 138.38, 138.29, 138.12, 137.29, 136.92, 128.55-127.13 (45C), 101.21-101.10 (7C), 99.98, 77.25, 75.24, 75.11, 75.04, 74.69, 74.31, 74.21, 73.67, 73.58, 73.55, 73.40, 73.03, 72.93, 72.84, 72.82, 72.76, 72.72, 71.89, 70.19, 69.70, 69.64, 69.33, 69.17, 40.43, 39.00-38.73 (16C), 27.26-27.06 (48C).

Preparative scale isolation of tunicamycins (368)



50 mL of TYD media (Trypton (2 g/L), Yeast extract (2 g/L), $MgCl_2.6H_2O$ (0.3 g/L) and glucose (6 g/L)) in a 250 mL spring coiled flask was inoculated with dense S. chartreusis spore suspension (10 μL) and incubated at 28 °C and 200 rpm. After 24 h, aliquots of this culture (12 × 1 mL) were used to inoculate 12 × 1 L of TYD media in unbaffled 2 L conical flasks, which were subsequently incubated at 28 °C and 200 rpm for 6-8 days. After this time the cultures adopted a characteristic red color which was used as a qualitative indicator of tunicamycin production. Most of the supernatant was decanted off and the cells were collected by centrifugation (8000 × g, 10 min).

Extraction from cell culture supernatant:

Amberlite XAD-16 was preconditioned by washing with MeOH (× 3), then distilled water (× 2). This preconditioned resin (15 g/L) was added to the cell culture supernatant and stirred for 2 h. The magnetic stirrer was then turned off and the XAD-16 resin allowed to settle to the bottom of the flask, after which the majority of the supernatant was decanted along with any remaining cell debris. The remaining supernatant was removed by filtration through cotton wool. The combined resin was next stirred in water (300 mL, 10 min) and the water was decanted off. This process was repeated with water (2 × 300 mL), MeOH (2 × 300 mL) and ^{i}PrOH (2 × 300 mL) with a final wash in MeOH (200 mL, 60 min). TLC analysis (H_2O/^{i}PrOH/EtOAc 1:2:4) identified tunicamycin containing fractions (R_f = 0.4), which were combined and concentrated. The residue was washed with 1 M aq. HCl (2 × 50 mL) and the collected by centrifugation (3500 × g, 5 min).

Extraction from cell pellet

The cell pellet was stirred in 1M aq. HCl (800 mL, 20 min) and the cells collected by centrifugation (8000 × *g*, 10 min). This process was repeated, after which the cell pellet was stirred in MeOH (800 mL, 2 h). The cells were collected by centrifugation (3500 × *g*, 5 min) and the supernatant decanted. The cells were then re-suspended in MeOH (800 mL) and vortexed for 5 min, prior to centrifugation (3500 × *g*, 5 min) and collection of the supernatant. The resulting MeOH fractions were combined and concentrated.

The combined tunicamycin extracts were precipitated from acetone (400 mL) at 0 °C over 24 h. R_f = 0.3 (water/isopropanol/ethyl acetate (W.IP.E) 1:3:6)

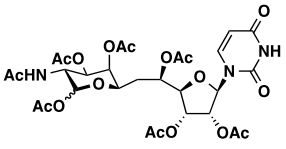
^{1}H NMR (500 MHz, MeOD) 7.93 (d, $J_{6,5}$ = 8.2 Hz, 1H, H-6^{uracil}), 6.84 (dt, $J_{HC=CH\ trans}$ = 15.4 Hz, *J* = 6.9 Hz, 1H, -CH_2*H*C=), 5.96 (d, 3$J_{HC=CH\ trans}$ = 15.4 Hz, 1H, =C*H*C(O)-), 5.95 (d, $J_{1',2'}$ = 5.7 Hz, 1 H, H-1´), 5.77 (d, $J_{5,6}$ = 8.2 Hz, 1H, H-5^{uracil}), 4.95 (d, *J* = 3.2 Hz, 1H, H-1´´), 4.59 - 4.63 (m, H-11´), 4.21 (t, $J_{2',1'}$ = 5.7 Hz, *J* = 5.7 Hz, 1H, H-2´), 4.10 (t, *J* = 9.3 Hz, 1H, H-10´), 3.35 -4.05 (m, -CH_2^{sugar}, -CH^{sugar}), 1.95 (s, 3H, -CH_3 ^{NHAc}),1.16 - 1.61 (m, n × CH2 $^{fatty\ acid}$), 0.89, 0.90 (2 × s, 2 × 3H, -CH(C*H*$_3$)$_2$)

The presence of at least 9 homologues prevented full assignment, resulting in broad multiplets in the □3 - 4 (sugar C-H) and □1.1 - 1.6 (fatty acid CH_2) regions.

Analytical Scale Analysis of Purity
HPLC Column: Waters Symmetry C18 3.5μM 4.6x150mm
Flow rate: 1 mL/min.
Solvent: 50% Acetonitrile with 0.1% formic acid in H_2O, degassed.
UV: 260 nm
Sample injection volume: 20μL
Run time: 15 minutes

Solvent:	A. 5% Acetonitrile with 0.1% formic acid in H_2O,
	B. 99.9% Acetonitrile with 0.1% formic acid
Gradient	
100%A	from 0-1min.
0%A-100%B	from 1-28 min.
100%B	from 28-32 min.
100%A	from 32-35min.

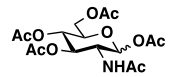
Heptaacetyl-tunicaminyl-uracil (371)



Tunicamycin (1.5 g (40% purity), 1.22 mmol) was suspended in 3M aq. HCl (30 mL) and refluxed. After 3 h the reaction mixture was concentrated, and the residue dissolved in dry pyridine (15 mL) and acetic anhydride (15 mL). After 24 h at 22 °C, TLC (MeOH/EtOAc 1:19) showed three products at R_f 0.3 (product), R_f 0.50 (pentaacetyl-**D**-glucosamine) and R_f 0.7 (non-degraded acetylated tunicamycin). After

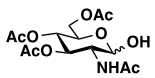
removal of solvent *in vacuo*, flash chromatography (MeOH/EtOAc 1:19), afforded heptaacetyltunicaminyl-uracil **371** as a white foam. Yield: 311 mg (36%) α/β□ratio 56:44.
IR (neat, cm^{-1}): 3500-3700, 1747, 1717, 1698, 1684, 1653, 1636, 1558, 1540, 1521, 1374, 1224. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.82 (d, *J* = 1.9 Hz, 1H, N-H$^{uracil,\ \beta}$), 8.70 (d, *J* = 2.0 Hz, 1H, N-H$^{uracil,\ \alpha}$), 7.22 (d, $J_{6,5}$ = 8.2 Hz, 1H, H-6$^{uracil,\ \alpha}$),7.19 (d, $J_{6,5}$ = 8.2 Hz, 1H, H-6$^{uracil,\ \beta}$), 6.14 (d, $J_{11',10'}$ = 3.8 Hz, 1H, H-11´$^{\alpha}$), 5.91 (d, $J_{1',2'}$= 5.7 Hz, 1H, H-1´$^{\alpha}$), 5.82 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H-1´$^{\beta}$), 5.81 (m, *J* = 2.0 Hz, $J_{5,6}$ = 8.2 Hz, 1H, H-5$^{uracil,\ \alpha}$), 5.78 (dd, *J* = 1.9 Hz, $J_{5,6}$ = 8.2 Hz, 1H, H-5$^{uracil,\ \beta}$), 5.71 (d, $J_{N\text{-}H,10'}$ = 9.8 Hz, 1H, N-H$^{Ac,\ \beta}$), 5.64 (d, $J_{11',10'}$ = 8.8 Hz, 1H, H-11´$^{\beta}$), 5.50 (d, $J_{N\text{-}H,10'}$ = 9.5 Hz, 1H, NH$^{Ac,\ \alpha}$), 5.43 (dd, $J_{3',4'}$ = 4.9 Hz, $J_{3',2'}$ = 6.1 Hz, 1H, H-3´$^{\beta}$), 5.37 (dd, $J_{3',4'}$ = 4.7 Hz, $J_{3',2'}$ = 5.8 Hz, 1H, H-3´$^{\alpha}$), 5.34 (app t, $J_{2',1'}$ = 5.7 Hz, $J_{2',3'}$ = 5.8 Hz, 1H, H-2´$^{\alpha}$), 5.30 (app t, $J_{2',1'}$ = 5.0, $J_{2',3'}$ = 6.1 Hz, 1H, H-2´$^{\beta}$), 5.24 (dd, $J_{9',8'}$ = 2.8 Hz, $J_{9',10'}$ = 11.5 Hz, 1H, H-9´$^{\alpha}$), 5.22 (dd, $J_{8',7'}$ = 1.0 Hz, $J_{8',9'}$ = 3.2 Hz, 1H, H-8´$^{\beta}$), 5.20 (m, 1H, H-5´$^{\beta}$), 5.19 (dd, $J_{8',7'}$ = 1.0 Hz, $J_{8',9'}$ = 2.8 Hz, 1H, H-8´$^{\alpha}$), 5.11 (ddd, *J* = 2.8 Hz, $J_{5',4'}$ = 4.7 Hz, $J_{5',6b'}$ = 8.3 Hz, 1H, H-5´$^{\alpha}$), 5.08 (dd, $J_{9',8'}$ = 3.2 Hz, $J_{9',10'}$ = 11.0 Hz, 1H, H-9´$^{\beta}$), 4.71 (ddd, $J_{10',11'}$ = 3.8 Hz, $J_{10',N\text{-}H}$ = 9.5 Hz, $J_{10',9'}$ = 11.5 Hz, 1H, H-10´$^{\alpha}$), 4.42 (ddd, $J_{10',9'}$ = 8.8 Hz, $J_{10',N\text{-}H'}$ = 9.8 Hz, $J_{10',9'}$ = 11.0 Hz, 1H, H-10´$^{\beta}$), 4.13 (app t, $J_{4',5'}$ = $J_{4',3'}$ = 4.9 Hz, 1H, H-4´$^{\beta}$), 4.08 (app t, $J_{4',5'}$ = $J_{4',3'}$ = 4.7 Hz, 1H, H-4´$^{\alpha}$), 4.07 (m, 1H, H-7´$^{\alpha}$), 3.92 (ddd, $J_{7',8'}$ = 1.0 Hz, $J_{7',6b'}$ = 3.2 Hz, *J* = 9.6 Hz, 1H, H-7´$^{\beta}$), 2.20 (s, 3 H, -$CH_3^{Ac,\ \alpha}$), 2.20 (s, 3 H, -$CH_3^{Ac,\ \beta}$), 2.18, 2.13 (2 × s, 2 × 3 H, 2 × -$CH_3^{Ac,\ \alpha}$), 2.12, 2.12 (2 × s, 2 × 3 H, 2 × -$CH_3^{Ac,\ \beta}$), 2.11 (s, 6H, 2 × - $CH_3^{Ac,\ \beta}$), 2.09 (s, 6H, 2 × -$CH_3^{Ac,\ \alpha}$), 2.03 (s, 3H, -$CH_3^{Ac,\ \alpha}$), 2.01 (s, 3H, -$CH_3^{Ac,\ \beta}$), 2.00 - 2.02 (m, 1H, H-6a´$^{\beta}$), 1.97 - 1.99 (m, 1H, H-6a´$^{\alpha}$), 1.96 (s, 3H, -$CH_3^{NHAc,\ \alpha}$), 1.94 (s, 3H, -$CH_3^{NHAc,\ \beta}$), 1.75 (ddd, $J_{6b',7'}$ = 3.2 Hz, *J* = 8.2 Hz, $^2J_{6b',6a'}$ = 14.8 Hz, 1H, H-6b´$^{\beta}$), 1.57 (ddd, *J* = 1.7 Hz, $J_{6b',5'}$ = 8.3 Hz, $^2J_{6b',6a'}$ = 14.9 Hz, 1H, H-6b´$^{\alpha}$); **^{13}C NMR** (126 MHz, MeOD-d_4) δ ppm 171.2, 170.7, 170.6, 170.6, 170.4, 170.2, 170.1, 170.0, 169.7, 169.6, 169.5, 169.3, 169.3, 169.1 (14 × s, 14 × C, C=O$^{NHAc,\ \alpha}$, C=O$^{NHAc,\ \beta}$, 6 × C=O$^{Ac,\ \alpha}$, 6 × C=O$^{Ac,\ \beta}$), 162.5 (C-4 C=O$^{\beta}$), 162.5 (C-4 C=O$^{\alpha}$), 149.9 (C-2 C=O$^{\alpha}$), 149.9 (C-2 C=O$^{\beta}$),140.2 (C-6$^{uracil,\ \beta}$), 139.8 (C-6$^{uracil,\ \alpha}$), 103.4 (C-5$^{uracil,\ \alpha}$), 103.3 (C-5$^{uracil,\ \beta}$), 93.0 (C-11´$^{\beta}$), 91.1 (C-11´$^{\alpha}$), 88.7 (C-1´$^{\beta}$), 88.1 (C-1´$^{\alpha}$), 82.5 (C-4´$^{\beta}$), 82.4 (C-4´$^{\alpha}$), 72.4 (C-2´$^{\alpha}$), 72.4 (C- 2´$^{\beta}$), 70.9 (C-7´$^{\beta}$), 70.5 (C-9´$^{\beta}$), 69.6, 69.6, 69.3, 68.7, 68.1 (5 × s, 7 × C, C-3´$^{\alpha}$, C-3´$^{\beta}$, C- 5´$^{\alpha}$, C-5´$^{\beta}$, C-8´$^{\alpha}$, C-8´$^{\beta}$, C-9´$^{\alpha}$)67.6 (C-7´$^{\alpha}$), 49.5 (C-10´$^{\beta}$), 46.7 (C-10´$^{\alpha}$), 32.5 (C-6´$^{\alpha}$), 31.6 (C-6´$^{\beta}$), 23.3 (-$CH_3^{NHAc,\ \beta}$), 23.2 (-$CH_3^{NHAc,\ \alpha}$), 20.4 – 21.0 (12 × C, 6 × -$CH_3^{Ac,\ \alpha}$, 6 × - $CH_3^{Ac,\ \beta}$); **HRMS** m/z (ESI^+) : calc. for $C_{29}H_{37}N_3NaO_{17}$ $(M + Na)^+$ 722.2015. Found 722.2019.

2-acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-D-glucopyranoside (372)



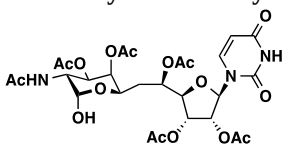
To a solution of *N*-acetyl glucosamine (12.1 g; 54.6 mmol) in anhydrous CH_2Cl_2 (50 mL) was added pyridine (22 mL), DMAP (0.33 g; 2.7 mmol) and Ac_2O (26 mL; 273 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then 12 h at 22 °C. The reaction was cooled to 0 °C, poured into H_2O (200 mL) and the aqueous layer was extracted with EtOAc (3x100 mL). The combined organic phase was washed with sat. aq. NaCl (200 mL), dried and concentrated in vacuo. Recrystallization from EtOAc/hexane resulted in **372** as a white crystalline material. Yield: 19.3 g (91%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (d, *J* = 3.6 Hz, 1H), 5.62 (d, $J_{1,2}$ = 9.0 Hz, 1H, H-1), 5.29 – 5.17 (m, 2H, H-3, H-5), 4.58 – 4.43 (m, 1H, H-2), 4.24 (dd, *J* = 12.5, 4.0 Hz, 1H, H-6a), 4.06 (dd, *J* = 12.5, 2.3 Hz, 1H, H-6b), 4.02 – 3.96 (m, 1H, H-4), 2.19 (s, 3H, -CH_3), 2.08 (s, 3H, -CH_3), 2.05 (s, 3H, -CH_3), 2.04 (s, 3H, -CH_3), 1.93 (s, 3H, -CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.72, 170.70, 169.96, 169.09, 168.64, 90.66, 70.64, 69.68, 67.42, 61.49, 51.02, 23.04, 20.94, 20.72, 20.69, 20.56. **MS** m/z (ESI^+): 412.3 [$(M+ Na)^+$]

2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-D-glucopyranose (373)



A mixture of **372** (5g; 12.8 mmol) and freshly activated, powdered 4Å MS (5 g) in dry MeOH (100 mL) was stirred at 22 °C for 2 h. The mixture was filtered through a celite plug, concentrated and purified by flash chromatography (MeOH:CH_2Cl_2 1:19) to give **373** as white crystals. R_f 0.3 (1:19 MeOH:CH_2Cl_2).Yield 3.65 g (82%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.02 (d, $J_{NHAc,2}$ = 9.3 Hz, 1 H, NHAc), 5.30 *(t,* $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 9.6 Hz, 1 H, H-3), 5.25 (d, $J_{1,2}$ = 3.3 Hz, 1 H, H-1), 5.13 (t, $J_{4,5}$ = $J_{3,4}$ = 9.6 Hz, 1 H, H-4), 4.29 (dt, $J_{2,3}$ = $J_{NHAc,2}$ = 10.6 Hz, $J_{1.2}$ = 3.5 Hz), 4.21 (m, 2 H, H-5, H-6a), 4.13 (m, 1 H, H-6b), 2.09, 2.03, 2.02, 1.97 (4 x s, 4 x 3 H, 4 x Ac_{Me}).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.46, 171.07, 170.79, 169.52, 91.42, 70.97, 68.28, 67.36, 62.12, 52.32, 23.06, 20.77, 20.74, 20.63. **MS** m/z (ESI^+): 554.3 [$(M+ Na)^+$]

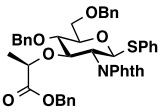
Hexaacetyl-tunicaminyl-uracil (374)



Glacial acetic acid in dry THF (36.1 mg; 0.60 mmol) was added to a solution of ethylenediamine (30.9 mg; 0.51) in THF (20 mL). After 10 min heptaacetyl tunicaminyl uridine **371** (300 mg; 0.43 mmol) was added and the mixture was stirred at 22 °C for 24h. At this point the reaction showed app. 50% conversion. The reaction mixture was poured into sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude was purified by

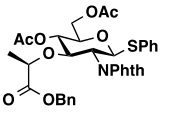
flash chromatography (40:1 EtOAc/MeOH) to give starting material **371** and product **374**. R_f 0.15 (19:1 EtOAc/MeOH). Yield: 110 mg (39%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H, N-H^{uracil}), 7.21 (d, $J_{5,6}$ = 8.1 Hz, 1H, H-6^{uracil}), 5.83 (d, $J_{1,2}$ = 5.4 Hz, 1H, H-1'), 5.79 (d, $J_{5,6}$ = 8.1 Hz, 1H, H-6^{uracil}), 5.43 (dd, $J_{2,3}$ = 5.4, $J_{3,4}$ = 4.9 Hz, 1H, H-3'), 5.37 (t, $J_{1,2}$ = $J_{2,3}$ = 5.4 Hz, 1H, H-2'), 5.32 (ddd, $J_{5,6b}$ = 9.5, $J_{4,5}$ = 4.9, $J_{5,6a}$ = 3.0 Hz, 1H, H-5'), 5.28 (t, $J_{10,11}$ = 3.0 Hz, 1H, H-11'), 5.24 – 5.18 (m, 2H, H-8', H-9'), 4.58 – 4.50 (m, 1H, H-10'), 4.30 – 4.24 (m, 1H, C-11'-O*H*), 4.16 (dd, $J_{6a,7}$ = 9.2, $J_{6b,7}$ = 2.2 Hz, 1H, H-7'), 4.11 (t, $J_{3,4}$ = $J_{4,5}$ = 4.9 Hz, 1H, H-4'), 2.19 (s, 3H, CH_3^{Ac}), 2.14 (s, 3H, CH_3^{Ac}), 2.13 (s, 3H, CH_3^{Ac}), 2.10 (s, 3H, CH_3^{Ac}), 2.01 (s, 3H, CH_3^{Ac}), 1.98 (s, 3H, CH_3^{Ac}), 1.97 – 1.90 (m, 1H, H-6a'), 1.60 (ddd, $J_{6a,6b}$ = 14.7, $J_{5,6b}$ = 9.5, $J_{6b,7}$ = 2.2 Hz, 1H, H-6b'). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.02, 171.00, 170.73, 170.30, 169.73, 169.34, 162.52, 149.89, 140.19, 103.39, 91.93, 88.62, 82.56, 77.19, 72.33, 70.12, 69.57, 68.48, 64.55, 47.86, 32.19, 29.68, 23.32, 21.05, 20.80, 20.79, 20.47, 20.41. **HRMS**: calc. $[M+Na]^+$: 680.19150 found $[M+Na]^+$: 680.1951

Phenyl 4,6-*O*-dibenzyl-3-*O*-(benzyl (S)-lactate)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (375)



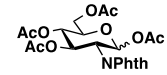
A solution of **384** (600 mg; 1.06 mmol) and KI (530 mg; 3.19 mmol) in DMF (12 mL) was cooled to 0 °C. BnBr (1.01 mL; 8.51 mmol) and Ag_2O (2.0 g; 8.62 mmol) was added and the reaction was stirred at 3 °C for 12h. The reaction mixture was filtered through a celite plug, diluted with CH_2Cl_2 (150 mL) and washed with sat. aq. $Na_2S_2O_3$ (3x50 mL) and H_2O (2x50 mL). The organic phase was dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (9:1 Tol/EtOAc). R_f 0.58 (5:1 Tol/EtOAc)Yield: 510 mg (41%).
MS m/z (ESI^+): 767 $[(M+ Na)^+]$

Phenyl 4,6-*O*-diacetyl-3-*O*-(benzyl (S)-lactate)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (376)



To a solution of **384** (3 g; 5.32 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Et_3N (2.23 mL; 15.97 mmol), Ac_2O (1.26 mL; 13.31 mmol) and DMAP (13 mg; 0.11 mmol). The reaction mixture was stirred at 0 °C until TLC showed full conversion (2h). The solution was diluted with DCM (100 mL) and washed with H_2O (100 mL). The organic phase was dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (8:1 Tol/EtOAc) to give **376** as a white crystalline material. R_f 0.4 (5:1 Tol/EtOAc). Yield: 3.2 g (96%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.79 (m, 2H), 7.74 (dd, *J* = 5.5, 2.7 Hz, 2H), 7.42 (dd, *J* = 6.3, 2.8 Hz, 2H), 7.35 – 7.23 (m, 6H), 7.11 (dd, *J* = 6.4, 2.9 Hz, 2H), 5.58 (d, $J_{1,2}$ = 10.1 Hz, 1H, H-1), 5.15 (dd, $J_{4,5}$ = 9.8, $J_{3,4}$=8.8 Hz, 1H, H-4), 4.68 (dd, *J* = 31.0, 12.2 Hz, 2H, *CH*$_2$-Ph), 4.43 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$=8.8 Hz, 1H, H-3), 4.37 (t, $J_{1,2}$=$J_{2,3}$ = 10.2 Hz, 1H, H-2), 4.23 (dd, *J* = 12.2, 5.4 Hz, 1H, H-6a), 4.16 (dd, *J* = 12.2, 2.3 Hz, 1H, H-6b), 4.09 (q, *J* = 6.8 Hz, 1H, *CH*-CH_3), 3.77 (ddd, $J_{6a,6b}$ = 9.9, $J_{5,6a}$=5.3, $J_{5,6b}$=2.4 Hz, 1H, H-5), 2.10 (s, 3H), 2.09 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 3H, *CH*$_3$-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.98, 170.75, 168.71(1C), 167.67, 169.28, 135.25, 133.91, 132.82 (2C), 131.71, 128.83 (2C), 128.50 (2C), 128.33, 128.11 (2C), 123.70, 122.92, 83.59, 78.01, 75.98, 75.91, 71.94, 66.34, 62.41, 54.21, 20.89, 20.81, 18.92. **HRMS**: calc. $[M+H]^+$: 502.1661 found $[M+ H]^+$: 502.1667

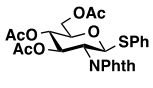
1,3,4,6-Tetra-*O*-acetyl-2-phthalimido-2-deoxy-β-D-glucopyranoside (380)



A 1 M NaOMe solution was prepared by adding Na metal (5.33 g, 0.232 mol) in small pieces to MeOH (232 mL) at –5 °C in a 500 mL round-bottomed flask equipped with a reflux condenser, which was swirled until the metal had been completely consumed. This was slowly added at 0 °C to a 1 L round-bottomed flask containing glucosamine hydrochloride (50 g, 0.232 mol). The reactionmixture was mechanically agitated for 2 h at r.t., then treated with finely ground phthalic anhydride (19 g, 0.128 mol) and stirred for another 45 min. The mixture was charged with a second portion of phthalic anhydride (19 g, 0.128 mol), Et_3N (35.5 mL, 0.255 mol), and MeOH (230 mL) and vigorously stirred for another 24 h, during which it slowly changed from a milky white solution to a thick yellow paste. The intermediate phthalamate (and salts) were precipitated as a white solid by cooling the mixture to – 20 °C for 4 h. These were filtered and washed with cold MeOH, then dried overnight under reduced pressure. The solid was re-dispersed in pyridine (500 mL) and cooled to –5 °C, followed by treatment with Ac_2O (330 mL). The mixture was stirred at r.t. for 48 h, during which it slowly changed from a translucent white to an opaque yellow solution. Cold EtOH (100 mL) was slowly added to quench the excess Ac_2O, which was then reduced by rotary evaporation. This was re-dispersed in toluene (3x100 mL) and concentrated several times for the azeotropic removal of pyridine. The remaining slurry was re-dissolved in $CHCl_3$ (1 L) and washed with distilled H_2O (4x250 mL) and brine (250 mL), then dried (Na_2SO_4) and concentrated The crude product was dissolved in minimal amount of hot EtOAc (100 mL), then diluted with hexanes (400 mL) and left to cool at –5 °C. The recrystallized product was collected by filtration, washed with cold hexanes, and dried to yield the desired tetraacetate **380** as an 8:1 mixture of anomers
Yield: 85.3 g (77%).

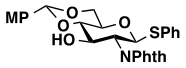
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.1 Hz, 1H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 1H), 6.49 (d, $J_{1,2}$ = 8.9 Hz, 1H, H-1), 5.87 (dd, $J_{2,3}$= 10.6, $J_{3,4}$=9.1 Hz, 1H, H-3), 5.20 (dd, $J_{4,5}$= 10.1, $J_{3,4}$=9.1 Hz, 1H, H-4), 4.45 (dd, $J_{2,3}$= 10.6, $J_{1,2}$=8.9 Hz, 1H, H-2), 4.35 (dd, $J_{6a,6b}$ = 12.5, $J_{5,}$6a=4.4 Hz, 1H, H-6a), 4.20 – 4.06 (m, 1H, H-6b), 4.01 (ddd, $J_{4,5}$ = 10.2, $J_{5,6a}$=4.4, $J_{5,6b}$=2.1 Hz, 1H, H-5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.76, 170.12, 169.57, 168.73, 134.60 (2C), 131.32 (2C), 123.90 (2C), 89.86, 72.73, 70.60, 68.39, 61.63, 53.60, 20.87, 20.84, 20.71, 20.50. **MS** m/z (ESI^+) : 500.4 [$(M+ Na)^+$]

Phenyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (381)



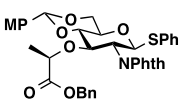
An oven-dried 1 L round-bottomed flask was charged with **380** (43.25 g, 90.9 mmol), thiophenol (28 mL, 272.8 mmol), and anhyd. CH_2Cl_2 (430 mL). The mixture was treated with TMSOTf (20 mL, 109.2 mmol) at rt and stirred for 7 h. The mixture was then quenched with a sat. aq. solution of $NaHCO_3$ (400 mL). The aqueous layer was extracted with additional CH_2Cl_2 (2 x 100 mL); the combined organic phases were then washed with brine (250 mL), dried (Na_2SO_4), and concentrated. The crude product was dissolved in a minimum amount of hot EtOAc (65 mL), then diluted with hexanes (200 mL) and cooled to 0 °C. The recrystallized product was collected by filtration, washed with cold 10% EtOAc in hexanes, and dried to yield the desired thiophenyl glycoside **381**. Yield: 36.5 g (76%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H, ArH), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H, ArH), 7.39 (dd, *J* = 7.7, 1.8 Hz, 2H, ArH), 7.31 – 7.19 (m, 3H, ArH), 5.77 (dd, $J_{2,3}$ = 10.6, $J_{3,4}$=9.3 Hz, 1H, H-3), 5.69 (d, $J_{1,2}$ = 10.6 Hz, 1H, H-1), 5.12 (dd, $J_{4,5}$=10.0, $J_{3,4}$=9.3 Hz, 1H, H-4), 4.33 (t, $J_{1,2}$ =$J_{2,3}$=10.6 Hz, 1H, H-2), 4.27 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$=5.1 Hz, 1H, H-6a), 4.18 (dd, $J_{6a,6b}$ = 12.2, $J_{5,6b}$=2.3 Hz, 1H, H-6b), 3.88 (ddd, $J_{4,5}$ = 10.0, $J_{5,6a}$5.0, $J_{5,6b}$2.3 Hz, 1H, H-5), 2.08 (s, 3H), 2.00 (s, 3H), 1.81 (s, 3H). **^{13}C NMR** (101 MHz,$CDCl_3$): δ 170.70, 170.08, 169.55, 168.71, 167.44, 134.57, 131.26, 123.87, 89.82, 72.67, 70.56, 68.32, 61.58, 53.55, 20.82, 20.68, 20.48.
MS m/z (ESI^+) : 550.5 [$(M+ Na)^+$]

Phenyl 4,6-*O*-(*p*-Methoxybenzylidene)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (382)



To a 100 mL round-bottomed flask was added the triacetate **381** (15.0 g, 28.43 mmol) and a 3:2 mixture of MeOH–CH_2Cl_2 (130 mL). The mixture was cooled to -20 °C, treated with a 0.3 M NaOMe solution in MeOH (37.7 mL, 11.3 mmol) and stirred for 10 min, then warmed to -10 °C and stirred for 2 h. The reaction mixture was warmed to 0 ºC, quenched with Amberlite 120-H^+ resin, filtered and concentrated. The crude was concentrated with toluene three times and left on under vacuum overnight. The crude (11.42 g; 28.45 mmol) was suspended in MeCN (175 ml). (4-OMe)$Ph(OMe)_2$ (6.54 mL; 38.41 mmol) and CSA (0.66 g; 2.84 mmol) was added and the reaction was heated to reflux. 1/3 of the volume was distilled off over 1h after which the mixture was heated to reflux until TLC showed full conversion (2 h). The reaction was quenched by addition of Et_3N (2 mL) and concentrated. The product **382** was purified by flash chromatography (6:1 Tol/EtOAc). R_f 0.5 (4:1 Tol/EtOAc). Yield: 13.0 g (88%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 1H, -Ar-H^{PhTh}), 7.77 – 7.72 (m, 1H, -H^{PhTh}), 7.69 – 7.56 (m, 2H), 7.38 – 7.25 (m, 4H), 7.25 – 7.14 (m, 3H), 6.78 (d, *J* = 8.8 Hz, 2H, H^{MP}), 5.59 (d, $J_{1,2}$ = 10.6 Hz, 1H, H-1), 5.42 (s, 1H, *CH*-MP), 4.51 (ddd, $J_{2,3}$=10.6, $J_{3,4}$= 9.1, $J_{3,OH}$=1.0 Hz, 1H, H-3), 4.27 (dd, $J_{6a,6b}$ = 10.5, $J_{5,6a}$=4.9 Hz, 1H, H-6a), 4.22 (t, $J_{1,2}$ =$J_{2,3}$=10.6 Hz, 1H, H-2), 3.71 (s, 3H, -OCH_3), 3.70 (m, 1H, H-6b), 3.56 (td, $J_{4,5b}$ = 9.1, $J_{5,6a}$=4.9 Hz, 1H, H-5), 3.46 (t, $J_{3,4}$=$J_{4,5}$=9.1 Hz, 1H, H-4), 2.71 (d, *J* = 2.6 Hz, 1H, -OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.35, 167.64, 160.40, 134.33, 132.68 (2C), 131.94, 129.48, 129.07 (2C), 128.19, 127.77 (2C), 123.95, 123.47, 113.84 (2C), 101.97, 84.38, 81.92, 70.40, 69.77, 68.62, 55.64, 55.42. **MS** m/z (ESI^+): 542.5 [$(M+ Na)^+$]

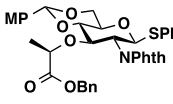
Phenyl 3-*O*-(benzyl (S)-lactate)-4,6-*O*-(*p*-Methoxybenzylidene)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (383)



382 (1.0 g; 1.92 mmol) was dissolved in dry DMF (15 mL). The solution was cooled to 0 °C and treated with NaH (60%)(0.101 g; 2.52 mmol) and stirred for 10 min. Then a solution of **385** (2.34 g; 9.62 mmol) in DMF was added and the solution was stirred at 0 °C until TLC showed full conversion of the starting material (12 h). The solution was diluted with EtOAc (150 mL) and washed with 1N HCl (50 mL) and H_2O (50 mL). The organic layer was dried over MgSO4 and concentrated. The compound was purified by flash chromatography (40:1 Tol/EtOAc) to give **383** as white crystals. R_f 0.75 (5:1 Tol/EtOAc). Yield: 0.44 g (35%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 -6.79 (m, 36H, Ar-H), 5.64 (d, *J* = 10.5 Hz, 1H, H-1a), 5.55 (d, *J* = 10.1 Hz, 1H, H-1b), 5.46 (s, 1H), 4.76 (d, *J* = 3.4 Hz, 2H, $CH_2^{Bn,b}$), 4.69 (d, J_{CH2} = 12.4 Hz, 1H, 0.5x$CH_2^{Bn,a}$), 4.59 (d, J_{CH2} = 12.4 Hz, 1H, 0.5x$CH_2^{Bn,a}$), 4.44 – 4.17 (m, 5H, H-2a, H-2b, H-3^a, H-3^b, CH-CH_3^a, CH-CH_3^b), 3.81 (s, 3H, -OMe^b), 3.79 – 3.72 (m, 2H, H-4^a, H-4^b), 3.71 (s, 3H, -OMe^a), 3.69 – 3.56 (m, 2H, H-5^a, H-5^b), 1.19 (d, *J* = 5.5 Hz, 3H, CH_3-CH^b), 1.18 (d, *J* = 6.9 Hz, 3H, CH_3-CH^a). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.97, 173.70, 172.72, 168.87, 167.64, 164.74, 160.19, 135.66, 135.40, 134.15, 133.94, 132.97, 132.56, 132.46, 132.13, 131.97, 131.76, 130.08, 129.66,

129.09, 129.05, 128.69, 128.65, 128.53, 128.45, 128.23, 128.20, 128.10, 128.02, 127.78, 127.35, 127.11, 123.75, 123.28, 123.07, 114.44, 113.79, 101.40, 84.26, 83.88, 82.99, 79.90, 79.26, 77.36, 76.64, 75.59, 73.80, 71.66, 70.22, 68.72, 66.71, 66.20, 65.48, 62.82, 55.72, 55.40, 54.52, 53.54, 19.33, 19.03. **HRMS**: calc. $[M+H]^+$: 558.1688 found $[M+ H]^+$: 558.1688

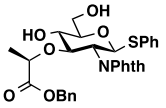
Phenyl 3-*O*-(benzyl (S)-lactate)-4,6-*O*-(*p*-Methoxybenzylidene)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (383_2)



A solution of **382** (10g; 19.25 mmol) in dry THF (180 mL) was treated with NaH (60%) (1.39g; 57.74 mmol) at 22 °C for 15 min. The solution was cooled to 0 °C and a solution of **386** (13.22 g; 42.34 mmol) in dry THF (20 mL) was added slowly. The reaction mixture was stirred at 0 °C until TLC showed full conversion (app. 4h). The reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with sat. aq. NH_4Cl (200mL). The organic phase was dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (40:1 Tol/EtOAc) to give **383** as a white crystalline material. R_f 0.75 (5:1 Tol/EtOAc). Yield: 11.9 g (88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 -6.79 (m, 36H, Ar-H), 5.64 (d, *J* = 10.5 Hz, 1H, H-1a), 5.55 (d, *J* = 10.1 Hz, 1H, H-1b), 5.46 (s, 1H), 4.76 (d, *J* = 3.4 Hz, 2H, $CH_2^{Bn,b}$), 4.69 (d, J_{CH2} = 12.4 Hz, 1H, 0.5x$CH_2^{Bn,a}$), 4.59 (d, J_{CH2} = 12.4 Hz, 1H, 0.5x$CH_2^{Bn,a}$), 4.44 – 4.17 (m, 5H, H-2a, H-2b, H-3^a, H-3^b, CH-CH_3^a, CH-CH_3^b), 3.81 (s, 3H, -OMe^b), 3.79 – 3.72 (m, 2H, H-4^a, H-4^b), 3.71 (s, 3H, -OMe^a), 3.69 – 3.56 (m, 2H, H-5^a, H-5^b), 1.19 (d, *J* = 5.5 Hz, 3H, CH_3-CH^b), 1.18 (d, *J* = 6.9 Hz, 3H, CH_3-CH^a). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.97, 173.70, 172.72, 168.87, 167.64, 164.74, 160.19, 135.66, 135.40, 134.15, 133.94, 132.97, 132.56, 132.46, 132.13, 131.97, 131.76, 130.08, 129.66, 129.09, 129.05, 128.69, 128.65, 128.53, 128.45, 128.23, 128.20, 128.10, 128.02, 127.78, 127.35, 127.11, 123.75, 123.28, 123.07, 114.44, 113.79, 101.40, 84.26, 83.88, 82.99, 79.90, 79.26, 77.36, 76.64, 75.59, 73.80, 71.66, 70.22, 68.72, 66.71, 66.20, 65.48, 62.82, 55.72, 55.40, 54.52, 53.54, 19.33, 19.03. **HRMS**: calc. $[M+H]^+$: 558.1688 found $[M+ H]^+$: 558.1688

Phenyl 3-*O*-(benzyl (S)-lactate)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (384)



383 (6 g; 8.8 mmol) was dissolved in a mixture of MeOH and CH_2Cl_2 (80 mL:20 mL). To the solution was added CSA (204 mg; 0.88 mmol) and the reaction mixture was stirred at 45 °C for 1½h. The reaction mixture was neutralized with Et_3N (0.5 mL) and concentrated. The crude mixture was purified by flash chromatography (2:1 Tol/EtOAc) to afford **384** as a white crystalline material. R_f 0.15 (2:1 Tol/EtOAc). Yield 4.5 g (92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 1H), 7.86 – 7.80 (m, 1H), 7.77 – 7.68 (m, 2H), 7.42 – 7.33 (m, 2H), 7.34 – 7.28 (m, 6H), 7.28 – 7.22 (m, 2H), 7.18 – 7.11 (m, 2H), 5.65 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.81 (m, 2H, CH_2-Ph), 4.48 (d, *J* = 6.8 Hz, 1H, *CH*-CH_3), 4.34 (m, 1H, H-5), 4.33(t, $J_{1,2}$=$J_{2,3}$=9.9, 1H, H-2), 4.11 – 3.81 (m, 2H, H-6a, H-6b), 3.74 (s, 2H, H-3, -OH), 3.57 (m, 1H, H-4), 2.53 (s, 1H, HO-), 1.28 (d, *J* = 6.8 Hz, 3H, *CH_3*-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.51, 168.71(1C), 167.67, 135.32, 134.02, 132.30 (2C), 132.05, 129.00 (2C), 128.51 (2C), 128.29, 128.04 (2C), 127.97, 123.67, 123.13, 83.73, 79.77, 79.29, 77.39, 77.07, 76.75, 74.29, 71.60, 66.47, 62.43, 53.70, 19.17. **HRMS**: calc. $[M+H]^+$: 564.1692 found $[M+ H]^+$: 564.1698

(S)-benzyl 2-bromopropanoate (385)

α-bromopropionic acid (5 g; 32.68 mmol), BnOH (3.54 g; 32.75 mmol) and *p*-TSA (0.053 g; 0.28 mmol) was dissolved in toluene (15 mL) and refluxed for 18 h with a Dean-Stark apparatus for removal of water. The reaction mixture was diluted with Et_2O (50 mL), washed with 5% NaOH (3x), dried over $MgSO_4$, filtered and concentrated. The product **385** was purified by flash chromatography (4% EtOAc/petroleum ether). R_f 0.33 (4% EtOAc/petroleum ether. Yield: 9.87 g (97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 5H, Ar-H), 5.21 (s, 2H, -CH_2Ph), 4.42 (q, *J* = 6.9 Hz, 1H, -*CH*-CH_3), 1.85 (d, *J* = 6.9 Hz, 3H, -*CH_3*-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.08, 135.19, 128.66 (2C), 128.51, 128.21 (2C), 67.61, 40.02, 21.66.

(S)-benzyl 2-(((trifluoromethyl)sulfonyl)oxy)propanoate (386)

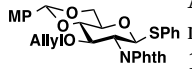
Tf_2O (19.7 mL; 116.54 mmol) was dissolved in dry CH_2Cl_2 (300 mL) and the solution was cooled to -10 °C. Pyridine (13.44 mL; 123.20 mmol) was added and after 5 min a white precipitate was observed. **387** (20 g; 110.99 mmol) was dissolved in CH_2Cl_2 (120 mL) and added slowly to the reaction mixture. The reaction mixture was warmed to 22 °C and stirred for another 10 min. The solid was removed by filtration and washed with CH_2Cl_2. The sample was concentrated at low temperature and purified on a silica plug (10x5cm 4:1 DCM/hexane. The solvent was quickly removed and the clear liquid **386** was stored at -20 °C. Yield: 30.1 g (87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.31 (m, 5H, ArH), 5.69 – 5.13 (m, 3H, *CH_2*Ph, *CH*-CH_3), 1.71 (d, *J* = 7.0 Hz, 3H, *CH_3*-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.25, 134.35, 128.85, 128.74 (2C), 128.43 (2C), 79.95, 68.31, 53.44, 18.05.

(S)-benzyl 2-hydroxypropanoate (387)

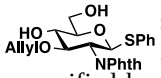
In a 2L flask was placed $Fe(acac)_3$ (4.48 g; 12.7 mmol), benzyl alcohol (31.57 mL; 304.75 mmol) and Na_2CO_3 (1.35 g; 12.70 mmol) in heptane (800 mL). A solution of **385** (30 g; 253.96 mmol) in heptane (200 mL) was added and the resulting mixture was heated to reflux with azeotropic removal of ethanol. After TLC showed full conversion (3 h) the reaction was cooled to 22 °C and quenched with sat. aq. NH_4Cl (500 mL) and extracted with EtOAc (500 mL). The product **387** was purified by flash chromatography (7:1 hexane/EtOAc). R_f 0.33 (7:1 hexane/EtOAc). Yield 40.1 g (88%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H, ArH), 5.12 (s, 2H, *-CH_2*Ph), 4.23 (q, *J* = 6.9 Hz, 1H, *-CH*-CH_3), 2.89 (s, 1H, *-OH*), 1.35 (d, *J* = 6.9 Hz, 3H, *CH_3*-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.57, 135.25, 128.69, 128.57, 128.26, 127.63, 127.00, 67.31, 66.87, 20.38.

Phenyl 3-*O*-allyl-4,6-*O*-(*p*-Methoxybenzylidene)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (388)



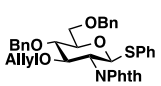
A solution of **382** (11.3 g; 21.75 mmol) and allyl bromide (3.75 mL; 43.49 mmol) in THF (150 mL) was cooled to 0 °C and added drop wise to a flask containing NaH (60% oil dispersion; 1.734 g; 43.49 mmol). The mixture was stirred at 0 °Cfor 2h then Ac_2O (8 mL) was added and the mixture was stirred for another 2 h. The reaction was quenched by addition of MeOH (10 mL) and diluted with Et_2O (250 mL). The organic phase was washed with H_2O(2x100 mL), dried over $MgSO_4$ and concentrated. The product **388** was purified by flash chromatography (9:1 Tol/EtOAc). R_f 0.65 (5:1 Tol/EtOAc). Yield: 9.57 g (79%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 1H, H^{PhTh}), 7.80 – 7.73 (m, 1H, H^{PhTh}), 7.73 – 7.65 (m, 2H), 7.38 – 7.26 (m, 4H), 7.24 – 7.15 (m, 3H), 6.82 (d, *J* = 8.8 Hz, 2H, H^{MP}), 5.60 (d, $J_{1,2}$ = 10.3 Hz, 1H, H-1), 5.46 (s, 1H, *CH*-MP), 5.50 – 5.38 (m, 1H, *-CH*=CH_2), 4.92 (ddd, J_{trans} = 17.2, J_{gem}=3.1, J_{CH2}=1.6 Hz, 1H, trans*CH_2*=CH), 4.76 (dd, *J* = 10.4, 1.5 Hz, 1H, cis*CH_2*=CH), 4.36 – 4.29 (m, 2H, H-3, H-6a), 4.25 (t, $J_{1,2}$ = $J_{2,3}$=10.3 Hz, 1H, H-2), 4.17 (ddt, J_{gem} = 13.1, $J_{CH=CH2}$= 5.1, $J_{CH2=CH}$=1.3 Hz, 1H, CH_2a^{allyl})), 3.86 (dd, J_{gem}= 13.1, $J_{CH=CH2}$=6.3 Hz, 1H, CH_2a^{allyl}), 3.75 (t, *J* = 10.2 Hz, 1H, H-6b), 3.72 (s, 3H, *CH_3*O-), 3.69 – 3.60 (m, 2H, H-4, H-5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.35, 167.31, 160.08, 136.78, 134.26, 132.69 (2C), 131.78, 129.75, 128.96 (2C), 128.10, 127.37 (2C), 123.83, 123.34, 117.17, 113.62 (2C), 101.25, 84.29, 82.42, 76.22, 73.27, 70.55, 68.60, 55.31, 54.91. **MS** m/z (ESI^+): 560.1 [(M+ H)$^+$]

Phenyl 3-*O*-allyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (389)



388 (8.1 g; 14.5 mmol) was dissolved in a mixture of MeOH and CH_2Cl_2 (80 mL:20 mL). To the solution was added CSA (336 mg; 1.45 mmol) and the reaction mixture was stirred at 45 °C for 2½h. The reaction mixture was neutralized with Et_3N (1.5 mL) and concentrated. The crude mixture was purified by flash chromatography (3:2 Tol/EtOAc) to afford **389** as a white crystalline material. R_f 0.23 (2:1 Tol/EtOAc). Yield 6.01 g (94%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 1H), 7.91 – 7.82 (m, 1H), 7.77 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.49 – 7.32 (m, 2H), 7.32 – 7.21 (m, 3H), 5.63 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 5.72 – 5.49 (m, 1H, *-CH*=CH_2), 5.04 (dd, *J* = 17.2, 1.5 Hz, 1H, *-transCH_2*=CH), 4.88 (d, *J* = 10.3 Hz, 1H, *-cisCH_2*=CH), 4.22 (t, $J_{1,2}$=$J_{2,3}$=10.0 Hz, 1H, H-2), 4.20 (dd, $J_{2,3}$=10.0, $J_{3,4}$= 9.4 Hz, H-3), 4.17 (m, 1H, -CH_2^{allyl}) 3.98 (m, 1H, -CH_2^{allyl}), 3.97 (m, 1H, H-6a), 3.89 (m, 1H, H-6b), 3.76 (td, $J_{3,4}$ = 9.4, $J_{4,5}$=4.1 Hz, 1H, H-4), 3.68 – 3.52 (m, 1H, H-5), 3.37 – 3.16 (m, 1H, -OH), 2.52 (d, *J* = 6.7 Hz, 1H, -OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.59, 167.53, 134.44, 134.39, 132.33 (2C), 132.20, 131.68, 129.09 (2C), 128.33, 128.05, 123.93, 123.49, 117.61, 83.80, 80.35, 79.59, 73.53, 71.44, 62.51, 54.77. **HRMS**: calc. [M+H]$^+$: 442.1324 found [M+ H]$^+$: 442.1328

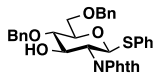
Phenyl 3-*O*-allyl-4,6-*O*-dibenzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (390)



389 (5.85 g; 13.25 mmol) was dissolved in dry THF (120 mL) and cooled to 0 °C. NaH (60%; 2.12 g; 53.0 mmol) was added and the reaction mixture was stirred at 0 °C for 10 min. BnBr (6.30 mL; 53.0 mmol) and TBAI (0.98 g; 2.65 mmol) was then added and the reaction mixture was stirred at 22 °C until TLC showed full conversion (7 h). The reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with NH_4Cl (400 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to give **390** as slightly yellow viscous oil. R_f 0.35 (19:1 Tol/EtOAc). Yield: 8.05 g (97%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.75 (s, 1H), 7.71 – 7.63 (m, 2H), 7.39 – 7.31 (m, 2H), 7.31 – 7.05 (m, 13H), 5.50 (d, *J* = 10.3 Hz, 1H, H-1), 5.58 – 5.35 (m, 1H, *-CH*=CH_2), 4.90 (ddd, J_{trans} = 17.2, 2.9, 1.4 Hz, 1H, *transCH_2*=CH), 4.72 (d, *J* = 10.9 Hz, 1H, -CH_2Ph), 4.71 (dd, J_{cis}= 10.3, 1.4 Hz, 1H, , *-cisCH_2*=CH), 4.60 – 4.40 (m,

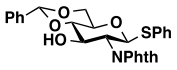
3H, -CH_2Ph), 4.24 – 4.19 (m, 2H, H-2, H-4), 4.13 (ddt, J_{gem} = 12.7, $J_{CH=CH2}$=5.3, $J_{CH2=CH}$=1.2 Hz, 1H, -CH_2^{allyl}), 3.81 (dd, J_{gem} = 12.7, $J_{CH=CH2}$=6.4 Hz, 1H, -CH_2^{allyl}), 3.77 – 3.57 (m, 4H, H-3, H-5, H-6a, H-6b). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.46, 167.39, 138.30, 138.03, 134.22 (2C), 132.53 (2C), 132.29, 131.73, 128.83 (2C), 128.45 (2C), 128.38 (2C), 127.94 (2C), 127.84, 127.79, 127.72 (2C), 127.59, 123.77, 123.29, 117.34, 83.38, 80.46, 79.43, 78.89, 74.94, 73.89, 73.46, 68.93, 55.16. **HRMS**: calc. $[M+Na]^+$: 644.2083 found $[M+ Na]^+$: 644.2078

Phenyl 3-*O*-allyl-4,6-*O*-dibenzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (391)



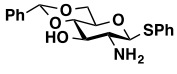
A solution of {Ir(COD)[$PCH_3(C_6H_5)_2$]}PF_6 (286 mg; 0.34 mmol) in dry THF (100 mL) was degassed and then H_2 was bubbled through the solution until it had changed colour from red to pale yellow. It was then purged with N_2 and a solution of **390** (3.5 g; 5.63 mmol) in THF (20 mL) was added. After stirring for 2h the solution was diluted with EtOAc (100 mL) and concentrated. The slurry was re-dissolved in MeOH (120 mL) and amberlite 120-H^+ resin (30 mL) was added. The solution was stirred at 70 °C until full conversion was observed (36h). The reaction mixture was filtered and concentrated. The product was purified by flash chromatography (19:1 Tol/EtOAc) to give **391** as off-white crystals. R_f 0.10 (19:1 Tol/EtOAc). Yield: 2.91 g (88%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H, ArH), 7.81 (s, 1H, ArH), 7.78 – 7.65 (m, 2H, ArH), 7.49 – 7.05 (m, 15H, ArH), 5.60 (d, $J_{1,2}$ = 10.4 Hz, 1H, H-1), 4.71 (s, 2H, CH_2Ph), 4.64 (dd, J = 36.2, 12.0 Hz, 2H, CH_2Ph), 4.48 (ddd, $J_{2,3}$= 10.4, $J_{3,4}$ = 8.4, $J_{3,OH}$=4.7 Hz, 1H, H-3), 4.26 (t, $J_{1,2}$=$J_{2,3}$=10.4 Hz, 1H, H-2), 3.94 – 3.77 (m, 2H, H-6a, H-6b), 3.70 (ddd, $J_{4,5}$ = 9.7, $J_{5,6a}$=3.6, $J_{5,6b}$=2.1 Hz, 1H, H-5), 3.67 – 3.56 (m, 1H, H-4), 2.36 (dd, J = 8.0, 3.7 Hz, 1H, OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.21, 138.10, 134.18, 132.51, 132.28, 129.06, 128.85, 128.61, 128.40, 128.25, 128.01, 127.91, 127.79, 127.65, 83.41, 79.25, 79.11, 74.77, 73.49, 72.88, 68.90, 55.68.
HRMS: calc. $[M+Na]^+$: 604.1770 found $[M+ Na]^+$: 604.1772

Phenyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (392)



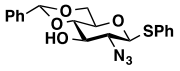
To a 100 mL round-bottomed flask was added the triacetate **381** (15.0 g, 28.43 mmol) and a 3:2 mixture of MeOH–CH_2Cl_2 (130 mL). The mixture was cooled to –20 °C, treated with a 0.3 M NaOMe solution in MeOH (37.7 mL, 11.3 mmol) and stirred for 10 min, then warmed to –10 °C and stirred for 2 h. The reaction mixture was warmed to 0 ºC, quenched with Amberlite 120-H^+ resin, filtered and concentrated. The crude was concentrated with toluene three times and left on under vacuum overnight. To a solution of benzaldehyde dimethyl acetal (7.4 mL; 49.29 mmol) and CSA (0.88 g; 3.79 mmol) in MeCN (250 mL) was added the crude triol (15.2 g; 37.91 mmol). The reaction mixture was heated to reflux for 2h during which app. 1/3 of the solvent was distilled off. The flask was fitted with a condenser and the reaction was refluxed until TLC showed full conversion (2h). The reaction was quenched by addition of Et_3N (2 mL) and concentrated. The product was purified by flash chromatography (16:1 → 9:1 toluene/EtOAc) to give **392** as a white solid. Yield: 17.5 (95%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.71 (m, 2H), 7.71 – 7.60 (m, 2H), 7.45 – 7.33 (m, 2H), 7.36 – 7.23 (m, 4H), 7.23 – 7.16 (m, 4H), 5.61 (d, $J_{1,2}$ = 10.3 Hz, 1H, H-1), 5.48 (s, 1H, , -$CH^{benzylidene}$), 4.58 (t, $J_{2,3}$=$J_{3,4}$ = 10.3 Hz, 1H, H-3), 4.31 (dd, $J_{6a,6b}$= 10.3, $J_{5,6a}$=4.8 Hz, 1H, H-6b), 4.25 (t, $J_{1,2}$=$J_{2,3}$ = 10.3 Hz, 1H, H-2), 3.74 (t, $J_{5,6b}$=$J_{6a,6b}$= 10.3 Hz, 1H, 6b), 3.60 (td, $J_{4,5}$=$J_{5,6b}$=10.3, $J_{5,6a}$=4.8 Hz, 1H, H-5), 3.51 (t, $J_{3,4}$=$J_{4,5}$= 10.3 Hz, 1H, H-4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.28, 167.57, 136.91 (2C), 134.29, 132.69, 131.78, 129.43, 129.07, 129.00 (2C), 128.43 (2C), 128.26, 128.16, 126.35 (2C), 125.33, 123.91, 123.43, 102.00, 84.31, 81.90, 70.32, 69.73, 68.60, 55.54. **HRMS**: calc. $[M+Na]^+$: 512.1143 found $[M+ Na]^+$: 512.1143

Phenyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-glucopyranoside (393)



392 (5 g; 10.21 mmol) was dissolved in ethylendiamine (50 mL) and *n*-BuOH (250 mL) and was heated to 90 °C. The reaction mixture was stirred at 90 °C for 12h and then concentrated. The oily residue was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to give **393** as a white crystalline material. Yield: 3.19 g (86%)
^{1}H NMR (400 MHz, DMSO-d6) δ 7.73 – 7.08 (m, 10H, Ar-H), 5.61 (s, 1H, -$CH^{benzylidene}$), 5.51 – 5.38 (m, 1H, -OH), 4.79 (d, J = 9.8 Hz, 1H, H-1), 4.21 (dd, $J_{6a,6b}$ = 10.1, $J_{5,6a}$ = 4.9 Hz, 1H, H-6a), 3.71 (t, $J_{6a,6b}$ = $J_{5,6b}$ =10.1 Hz, 1H, H-6b), 3.54 (dd, $J_{5,6b}$ = 10.1, $J_{5,6a}$ = 4.9 Hz, 1H, H-5), 3.48 – 3.37 (m, 2H, H-3, H-4), 2.57 (dd, $J_{1,2}$ = 9.8, $J_{2,3}$ = 8.5 Hz, 1H, H-2), 1.73 (s, 2H, -NH_2). **^{13}C NMR** (101 MHz, DMSO) δ 138.22, 133.62, 131.19 (2C), 129.50 (2C), 129.30, 128.48 (2C), 127.60, 126.80 (2C), 101.17, 88.82, 81.14, 74.44, 70.51, 68.24, 57.77. **HRMS**: calc. $[M+H]^+$: 360.1270 found $[M+H]^+$: 360.1275

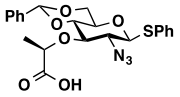
Phenyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-glucopyranoside (394)



To a solution of NaN_3 (7.96 g; 122.4 mmol) in H_2O (20 mL) was added CH_2Cl_2 (25 mL). The mixture was cooled to 0 °C and Tf_2O (4.11 mL; 24.48 mmol) was added drop wise over 15 min. The two-phase mixture was stirred for 2 h at 0 °C after which the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x15mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (40 mL) and H_2O (45 mL), dried over $MgSO_4$ and filtered. The resulting solution was added drop wise to a slurry of **393** (4.4 g; 12.24 mmol) and DMAP (4.55 g; 37.21 mmol) in CH_2Cl_2 (45 mL). The reaction mixture was stirred for 12 h at 22 °C, concentrated and the product **394** was purified by flash chromatography (9:1 toluene/EtOAc). Yield: 4.3 g (91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 2H), 7.44 – 7.35 (m, 2H), 7.36 – 7.23 (m, 6H), 5.46 (s, 1H, -$CH^{benzylidene}$), 4.47 (d, $J_{1,2}$ = 10.2 Hz, 1H, H-1), 4.35 – 4.27 (dd, J = 10.6, 4.6 Hz, 1H, H-4), 3.76 – 3.62 (m, 2H, H-3, H-6a), 3.40 (m, 2H, H-5, H-6b), 3.28 (dd, $J_{1,2}$ = 10.2, $J_{2,3}$ =9.1 Hz, 1H, H-2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.82, 133.80 (2C), 130.93, 129.59, 129.28 (2C), 128.84, 128.55 (2C), 126.38 (2C), 102.06, 86.91, 80.31, 74.16, 70.36, 68.52, 65.23. **HRMS**: calc. $[M+Na]^+$: 408.0994 found $[M+ Na]^+$: 408.0991

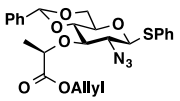
Phenyl 2-Azido-4,6-*O*-benzylidene-3-*O*-[(R)-1-carboxyethyl]-2-deoxy-1-thio-β-D-glucopyranoside (395)



394 (1.5 g; 3.89 mmol) was dissolved in THF (125 mL) and cooled to 0 °C. NaH (60% oil dispersion; 1.55 g; 38.9 mmol) was added and the mixture was stirred at 0 °C for 30 min. (S)-(−)-2-Bromopropionic acid (2.23 mL; 15.56 mmol) was added and the reaction mixture was stirred at 22 °C for 12 h. The reaction was poured into 1M HCl (100 mL) and the aqueous phase was washed with CH_2Cl_2 (3x100 mL). The combined organic phases were washed sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated. The crude was purified by flash chromatography (4:1:0.01 toluene/EtOAc/AcOH) to give **395**. Yield: 1.33 g (75%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.46 (m, 2H), 7.41 – 7.24 (m, 8H), 5.48 (s, 1H), 4.49 (d, $J_{1,2}$ = 10.1 Hz, 1H, H-1), 4.44 (q, J = 6.9 Hz, 1H, *CH*-CH_3), 4.32 (dd, $J_{6a,6b}$ = 10.3, $J_{5,6a}$=5.0 Hz, 1H, H6-a), 3.71 (t, $J_{6a,6b}$ = $J_{5,6b}$ = 10.3 Hz, 1H, H6-b), 3.57 – 3.49 (m, 2H, H-3, H-4), 3.42 – 3.31 (m, 2H, H-2, H-5), 1.38 (d, J = 6.9 Hz, 3H, CH_3-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.95, 136.75, 133.89 (2C), 130.55, 129.23 (3C), 128.85, 128.41 (2C), 125.86 (2C), 101.37, 86.97, 80.95, 80.78, 76.02, 70.31, 68.42, 64.31, 18.96. **HRMS**: calc. $[M+Na]^+$: 480.1205 found $[M+ Na]^+$: 480.1211

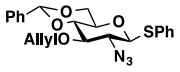
Phenyl 2-Azido-4,6-*O*-benzylidene-3-*O*-[*(R)*-1'-allyloxycarbonylethyl]-2-deoxy-1-thio-β-D-glucopyranoside (396)



To a solution of **395** (1.52 g; 3.32 mmol) in DMF (20 mL) was added allyl bromide (320 μL; 3.65 mmol) and DBU (520 μL; 3.49 mmol). The reaction mixture was stirred at 22 °C for 16 h, diluted by EtOAc (200 mL) and poured into H_2O (200 mL). The aqueous phase was extracted with EtOAc (3x100 mL), dried over $MgSO_4$ and concentrated. The crude was purified by flash chromatography (6:3.5:0.5 Pet. et./toluene/EtOAc) to give **396**. Yield: 1.52 g (92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.40 – 7.34 (m, 2H), 7.33 – 7.25 (m, 6H), 5.85 (ddt, J = 16.3, 10.4, 5.9 Hz, 1H, -*CH*=CH_2), 5.47 (s, 1H, -$CH^{benzylidene}$), 5.25 (ddd, J = 17.2, 2.9, 1.4 Hz, 1H, -CH_2=CH^{trans}), 5.17 (dd, J = 10.4, 1.2 Hz, 1H, -CH_2=CH^{cis}), 4.57 (dt, J = 5.9, 1.2 Hz, 2H, -CH_2^{allyl}), 4.44 (q, J = 6.8 Hz, 1H, *CH*-CH_3), 4.41 (d, $J_{1,2}$ = 10.2 Hz, 1H, H-1), 4.30 (dd, $J_{6a,6b}$= 10.5, $J_{5,6a}$=5.0 Hz, 1H, H-6a), 3.70 (t, $J_{5,6b}$=$J_{6a,6b}$= 10.5 Hz, 1H, H-6b), 3.64 (t, $J_{2,3}$=$J_{3,4}$= 9.2 Hz, 1H, H-3), 3.52 (t, $J_{3,4}$=$J_{4,5}$= 9.2 Hz, 1H, H-4), 3.35 (td, $J_{5,6b}$= 9.7, $J_{5,6a}$=4.9 Hz, 1H, H-5), 3.29 (dd, $J_{1,2}$ = 10.2, $J_{2,3}$ =9.2 Hz, 1H, H-2), 1.35 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.19, 136.91, 133.95 (2C), 131.78, 130.67, 129.17 (2C), 129.14, 128.76, 128.36, 125.88 (2C), 118.82, 101.26, 86.68, 80.98, 76.16, 70.28, 68.47, 65.67, 64.50, 19.05. **HRMS**: calc. $[M+Na]^+$: 520.1518 found $[M+ Na]^+$: 520.1521

Phenyl 2-Azido-3-*O*-allyl-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-glucopyranoside (397)

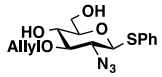


To a solution of NaN_3 (2.03 g; 31.2 mmol) in H_2O (5 mL) was added CH_2Cl_2 (6.25 mL). The mixture was cooled to 0 °C and Tf_2O (1.05 mL; 6.26 mmol) was added drop wise over 15 min. The two-phase mixture was stirred for 2 h at 0 °C after which the the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x3mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over $MgSO_4$ and filtered. The resulting solution was added drop wise to a solution of **394** (1.25 g; 3.12 mmol) and DMAP (1.16 g; 9.51 mmol) in CH_2Cl_2 (12.5 mL). The reaction mixture was stirred for 12 h at 22 °C. The mixture was concentrated and the crude product was purified by flash chromatography (6:3:1 heptane/toluene/EtOAc). Yield: 1.22 g (92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.45 (m, 2H), 7.44 – 7.34 (m, 2H), 7.33 – 7.21 (m, 6H), 5.87 (ddt, J = 16.3, 10.4, 5.9 Hz, 1H, -*CH*=CH_2), 5.47 (s, 1H, -$CH^{benzylidene}$), 5.21 (dq, J = 17.2, 1.5 Hz, 1H, -CH_2=CH^{trans}), 5.12 (ddd, J = 10.4, 2.7, 1.1 Hz, 1H, -CH_2=CH^{cis}), 4.41 (d, J = 10.2 Hz, 1H, H-1), 4.37 – 4.31 (m, 1H, CH_2^{allyl}), 4.30 (dd, J = 10.5, 4.9 Hz, 1H, H-6a), 4.16 (ddt, J = 12.4, 6.0, 1.3 Hz, 1H, CH_2^{allyl}), 3.70 (t, J = 10.3 Hz, 1H, H-6b), 3.54 – 3.44

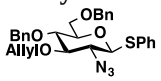
(m, 2H, H-3, H-4), 3.35 (m, 1H, H-5), 3.31 – 3.21 (m, 1H, H-2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.07, 134.30, 133.90 (2C), 130.70, 129.16 (2C), 129.10, 128.75, 128.31 (2C), 125.96 (2C), 117.81, 101.24, 86.58, 81.18, 80.99, 74.12, 70.48, 68.48, 64.57. **HRMS**: calc. $[M+Na]^+$: 448.1307 found $[M+ Na]^+$: 448.1311

Phenyl 2-Azido-3-*O*-allyl-2-deoxy-1-thio-β-D-glucopyranoside (398)



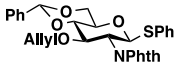
Compound **397** (0.5 g; 1.18 mmol) was dissolved in CH_2Cl_2 (10 mL) at 22 °C. *p*-TSA (0.045 g; 0.24 mmol) was added followed by addition of ethanethiol (0.6 mL; 8.22mmol). The reaction mixture was stirred for 30 min. The mixture was concentrated and the crude product was purified by flash chromatography (2:1 toluene/EtOAc) to give **398**. R_f 0.19 (2:1 Tol/EtOAc). Yield: 0.36 g (90%).

Phenyl 2-Azido-3-*O*-allyl-4,6-di-O-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (398)



Compound **398** (0.4 g; 4.74 mmol) was dissolved in DMF (10 mL) and cooled to 0 °C. NaH (190 mg; 4.74 mmol) was added and the mixture was stirred for 10 min. Then BnBr (0.71 mL; 5.93 mmol) was added and the reaction was allowed to reach 22 °C and stirred overnight. The reaction was quenched by addition of MeOH and poured into sat. aq. $NaHCO_3$ (100 mL). The aqueous phase was extracted with EtOAc (2x50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (9:1 Heptane/EtoAc). R_f 0.78 (19:1 Tol/EtOAc). Yield: 0.54 g (89%).

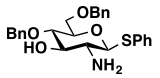
Phenyl 3-allyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (400)



A solution of **392** (15.4 g; 31.49 mmol) and allyl bromide (5.5 mL; 62.97 mmol) in THF (200 mL) was cooled to 0 °C and added drop wise to a flask containing NaH (60%) (2.5 g; 62.97 mmol). The mixture was stirred at 0 °Cfor 2h then Ac_2O (8 mL) was added and the mixture was stirred for another 2 h. The reaction was quenched by addition of MeOH (10 mL) and diluted with Et_2O (350 mL). The organic phase was washed with H_2O (2x200 mL), dried over $MgSO_4$ and concentrated. The crude was purified by flash chromatography (9:1 Tol/EtOAc), R_f 0.55 (5:1 Tol/EtOAc) to afford **400**. Yield: 13.8 g; (83%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.75 (m, 2H, Ar-H), 7.71 – 7.63 (m, 2H, Ar-H), 7.48 – 6.96 (m, 10H, Ar-H), 5.60 (d, $J_{1,2}$ = 10.3 Hz, 1H, H-1), 5.51 (s, 1H, $CH^{benzylidene}$), 5.45 (ddd, J_{trans} = 16.9, J_{cis} =10.3, J_{CH2} =6.3, 1H, C*H*=CH_2), 4.93 (dd, J_{trans} = 17.2, J_{CH2} =1.6 Hz, 1H, CH_2=CH^{trans}), 4.76 (dd, J_{cis} = 10.4, J_{CH2} =1.5 Hz, 1H, CH_2=CH^{trans}), 4.39 – 4.30 (m, 2H, H-6a, H-3), 4.26 (t, $J_{1,2}$ = $J_{2,3}$ =10.2 Hz, 1H, H-2), 4.18 (ddt, J_{CH2} = 13.1, $J_{CH=CH2}$ = 5.1, $J_{CH2=CH}$ =1.6 Hz, 1H, 0.5xCH_2^{allyl}), 3.87 (ddt, J_{CH2} = 13.1, $J_{CH=CH2}$ = 6.3, $J_{CH2=CH}$ =1.6 Hz, 1H, 0.5xCH_2^{allyl}), 3.76 (t, $J_{6a,6b}$ = $J_{5,6b}$ = 10.0 Hz, 1H, H-6b), 3.71 – 3.56 (m, 2H, H-4, H-5), 2.27 (s, 1H, -OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.33, 167.29, 137.24, 134.27, 134.22, 132.71 (2C), 131.74, 129.05, 129.02, 128.95 (2C), 128.26 (2C), 128.24, 128.11, 126.04 (2C), 125.31, 123.83, 123.32, 117.20, 101.25, 84.29, 82.47, 76.20, 73.28, 70.51, 68.65, 54.90. **HRMS**: calc. $[M+Na]^+$: 552.1457 found $[M+ Na]^+$: 552.1457

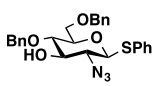
Phenyl 2-Amino-4,6-*O*-dibenzyl-2-deoxy-1-thio-β-D-glucopyranoside (401)



391 (3.4 g; 5.85 mmol) was dissolved in 213thylenediamine (22.5 mL) and n-BuOH (105 mL) and was heated to 90 °C. The reaction mixture was stirred at 90 °C for 14h and then concentrated. The oily residue was purified by flash chro-matography (9:1 CH_2Cl_2/MeOH) to give **401** as a white crystalline material. Yield: 2.19 g (83%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.41 (m, 2H, Ar-H), 7.35 – 7.09 (m, 13H, Ar-H), 4.68 (d, J_{CH2} = 11.3 Hz, 1H, 0.5xCH_2^{Bn}), 4.58 – 4.52 (m, 2H, CH_2^{Bn}), 4.48 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}), 4.33 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 3.79 – 3.62 (m, 2H, H-6), 3.47 – 3.29 (m, 3H, H-3, H-4, H-5), 2.60 (dd $J_{1,2}$ =9.8 Hz, $J_{2,3}$ = 9.2 Hz, 1H, H-2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.38 (2C), 132.72, 132.42 (2C), 129.02 (2C), 128.63 (2C), 128.45 (2C), 128.07 (2C), 128.00, 127.87, 127.79 (2C), 127.68, 89.48, 79.15, 78.40, 77.89, 74.64, 73.54, 69.33, 56.30. **HRMS**: calc. $[M+H]^+$: 452.1896 found $[M+ H]^+$: 452.1899

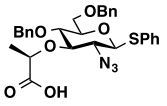
Phenyl 2-Azido-4,6-*O*-dibenzyl-2-deoxy-1-thio-β-D-glucopyranoside (402)



To a solution of NaN_3 (2.3 g; 35.4 mmol) in H_2O (6 mL) was added CH_2Cl_2 (7.5 mL). The mixture was cooled to 0 °C and Tf_2O (1.2 mL; 7.08 mmol) was added drop wise over 15 min. The two-phase mixture was stirred for 2 h at 0 °C after which the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x5mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over $MgSO_4$ and filtered. The resulting solution was added drop wise to a solution of **401** (1.6 g; 3.54 mmol) and DMAP (1.32 g; 10.77 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred for 12 h at 22 °C. The mixture was concentrated and the product was purified by flash chromatography (20:1 toluene/EtOAc). Yield: 1.34 g (79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.41 (m, 2H), 7.37 – 7.08 (m, 13H), 4.61 (d, *J* = 9.8 Hz, 2H, -CH_2^{Bn1}), 4.54 (d, *J* = 11.4 Hz, 2H, -CH_2^{Bn2}), 4.37 (d, $J_{1,2}$ = 10.1 Hz, 1H, H-1), 3.74 (dd, $J_{6a,6b}$ = 11.0, $J_{5,6a}$ = 2.0 Hz, 1H, H-6a), 3.69 (dd, $J_{6a,6b}$=11.0, $J_{5,6b}$ = 3.8 Hz, 1H, H-6b), 3.51 (t, $J_{2,3}$=$J_{3,4}$= 9.0 Hz, 1H, H-3), 3.44 (t, $J_{3,4}$=$J_{4,5}$= 9.0 Hz, 1H, H-4), 3.38 (ddd, $J_{4,5}$=9.5, $J_{5,6b}$=3.8, $J_{5,6a}$ = 2.0 Hz, 1H, H-5), 3.22 (dd, $J_{1,2}$ = 10.0, $J_{2,3}$=9.0 Hz, 1H, H-2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.14, 137.97, 133.39 (2C), 131.48, 129.03 (2C), 128.69 (2C), 128.44 (2C), 128.33, 128.15, 128.03 (2C), 127.73 (3C), 86.08, 79.07, 77.30, 77.20, 74.82, 73.52, 68.79, 64.98. **HRMS**: calc. $[M+Na]^+$: 500.1620 found $[M+ Na]^+$: 500.1645

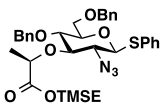
Phenyl 2-Azido-4,6-*O*-dibenzyl-3-*O*-[(R)-1-carboxyethyl]-2-deoxy-1-thio-β-D-glucopyranoside (403)



A solution of **402** (4.50 g; 9.43 mmol) in dry THF (300 mL) was treated with NaH (60% oil dispersion; 3.77 g; 94.31 mmol) at 0 °C for 15 min. Then (S)-(−)-2-Bromopropionic acid (9.17 g; 37.72 mmol) was added and the reaction was stirred at 22 °C for 12h. The reaction mixture was poured into 1M HCl and extracted with CH_2Cl_2 (3x200 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (4:1:0.01 toluene/EtOAc/AcOH) to give **403** as a white crystalline solid. Yield: 4.1 (78%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.33 – 7.11 (m, 13H), 4.68 (d, J_{CH2} = 10.9 Hz, 1H, -CH_2^{Bn1}), 4.55 (d, J_{CH2} = 11.9 Hz, 1H, -CH_2^{Bn2}), 4.52 (d, J_{CH2} = 10.9 Hz, 1H, -CH_2^{Bn1}), 4.47 (d, J_{-CH2}= 11.9 Hz, 1H, -CH_2^{Bn2}), 4.42 (q, *J* = 7.0 Hz, 1H, *CH*-CH_3), 4.37 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 3.69 (m, 2H, H-6a, H-6b), 3.57 (dd, $J_{2,3}$= 9.8 Hz, $J_{3,4}$= 9.1, 1H, H-3), 3.36 (m, 1H, H-5), 3.35 (t, $J_{1,2}$=$J_{2,3}$ = 9.8 Hz, 1H, H-2), 3.28 (t, $J_{3,4}$ = 9.1 Hz, 1H, H-4), 1.36 (d, *J* = 7.0 Hz, CH_3-CH, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.70, 138.19, 137.71, 133.67 (2C), 131.12 (2C), 129.17 (2C), 128.64 (2C), 128.52 (2C), 128.09, 127.88 (2C), 127.79 (2C), 127.72 (2C), 86.67, 85.09, 79.25, 76.99, 76.86, 75.27, 73.55, 68.72, 64.92, 19.30. **HRMS**: calc. $[M+Na]^+$: 572.1831 found $[M+Na]^+$: 572.1842

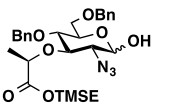
Phenyl 2-Azido-4,6-*O*-benzylidene-3-*O*-[*(R)*-1'-((2-trimethylsilyl)-ethyloxycarbonyl)ethyl]-2-deoxy-1-thio-β-D-glucopyranoside (404)



To a solution of **403** (2.28 g; 4.14 mmol) in CH_2Cl_2 (50 mL) was added 2-(trimethylsilyl)ethanol (980 mg; 8.28 mmol), DMAP (76 mg; 0.62 mmol) and EDCl (836 mg; 5.39 mmol). The reaction mixture was stirred at 22 °C until TLC showed full conversion (4h). The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (6:3.5:0.5 Pet. et. /toluene/EtOAc). Yield: 2.44 (91%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.49 (m, 2H), 7.38 – 7.10 (m, 13H), 4.75 (d, *J* = 10.9 Hz, 1H, -CH_2^{Bn1}), 4.57 (d, *J* = 11.9 Hz, 1H, -CH_2^{Bn2}), 4.53 (d, *J* = 10.9 Hz, 1H, -CH_2^{Bn1}), 4.49 (d, *J* = 11.9 Hz, 1H, -CH_2^{Bn2}), 4.42 – 4.31 (m, 2H, H-1, *CH*-CH_3), 4.28 – 4.13 (m, 2H, CH_2-CH_2-TMS), 3.76 – 3.65 (m, 2H, H-6a, H-6b), 3.57 (m, 1H, H-3), 3.43 – 3.33 (m, 3H, H-2, H-4, H-5), 1.35 (d, *J* = 6.8 Hz, 3H, CH-CH_3), 0.97 (t, *J* = 8.7 Hz, 2H, CH_2-CH_2-TMS), 0.00 (s, 9H, 3xCH_3^{TMS}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.37, 139.67, 139.27, 135.05 (2C), 132.64, 130.54, 130.50, 129.98, 129.89 (2C), 129.83 (2C), 129.73, 129.39, 129.28 (2C), 129.12, 129.06 (3C), 87.87, 86.42, 80.68, 78.77, 78.37, 76.60, 74.92, 70.20, 66.39, 64.91, 20.65, 18.79, 0.00 (3C). **HRMS**: calc. $[M+Na]^+$: 672.2540 found $[M+ Na]^+$: 672.2521

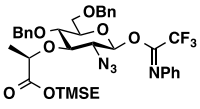
2-Azido-4,6-*O*-benzylidene-3-*O*-[*(R)*-1'-((2-trimethylsilyl)-ethyloxycarbonyl)ethyl]-2-deoxy-β-D-glucopyranose (405)



404 (2.3 g; 3.54 mmol) was dissolved in acetone/H_2O (50 mL). NBS (2.84 g; 15.94 mmol) was added and the solution was stirred at 22 °C until TLC showed full conversion (1h). The reaction mixture was poured into 10% NaS_2O_3 (200 mL), extracted with CH_2Cl_2 (2x100 mL), dried over $MgSO_4$, filtered and concentrated. The product **405** was purified by flash chromatography (9:1 toluene/EtOAc). Yield: 1.92 (97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 6.95 (m, 20H, Ar-H), 5.28 (d, $J_{1,2}$ = 3.5 Hz, 1H, H-1α), 4.78 (d, J_{CH2} = 10.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.76 (d, J_{CH2} = 10.9 Hz, 1H, 0.5xCH_2^{Bn}), 4.62 – 4.37 (m, 8H, 3xCH_2^{Bn}, H-1β, $CH^{lactate}$α/β), 4.35 – 4.15 (m, 5H, -OCH_2^{TMSE}α, -OCH_2^{TMSE}β, $CH^{lactate}$α/β), 3.99 (ddd, $J_{4,5}$ = 10.1, $J_{5,6a}$ = 4.4, $J_{5,6a}$ = 2.1 Hz, 1H, H-5α), 3.87 (dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 8.8 Hz, 1H, H-3α), 3.68 – 3.24 (m, 8H, H-2α, H-2β, H-3β, H-4α, H-4β, H-5β, H-6β, H-6α,), 1.37 (m, 4H, 2x$CH_2^{lactate}$), 1.00 (m, 4H, 2xCH_2^{TMSE}), 0.01 (m, 18H, 2xTMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.25, 173.06, 137.83, 137.74, 137.71, 128.57, 128.34, 128.13, 128.04, 128.00, 127.96, 127.85, 96.48, 92.07, 83.31, 79.48, 78.24, 77.21, 76.60, 75.28, 75.12, 74.80, 73.60, 70.50, 68.74, 68.64, 67.34, 64.05, 63.51, 63.46, 19.30, 19.27, 17.50, 17.38, -1.38.

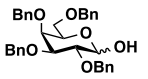
2-Azido-4,6-*O*-benzylidene-3-*O*-[*(R)*-1'-((2-trimethylsilyl)-ethyloxycarbonyl)ethyl]-2-deoxy-β-D-glucopyranose *N*-phenyl trifluoroacetimidate (406)



To a solution of **405** (600 mg; 1.08 mmol) in CH_2Cl_2 (15 mL) was added PTFAICl (447 mg; 2.15 mmol) and Cs_2CO_3 (701 mg; 2.15 mmol) at 0 °C. The reaction was stirred at 0 °C until TLC showed full conversion (2.5h). The reaction was filtered, concentrated and the crude was purified by flash chromatography (19:1 Pet. et./EtOAc) to give **406** as a viscous oil. Yield: 637 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.09 (m, 12H, 2x*Bn*, N-*Ph*), 7.04 (t, *J* = 7.5 Hz, 1H, N-*Ph*), 6.76 (d, *J* = 7.6 Hz, 2H, N-*Ph*), 4.76 (d, *J* = 11.0 Hz, 1H, -CH_2^{Bn1}), 4.57 (d, *J* = 12.0 Hz, 1H, -CH_2^{Bn2}), 4.49 (d, *J* = 11.0 Hz, 2H, -CH_2^{Bn1}), 4.46 (d, *J* = 12.0 Hz, 1H, -CH_2^{Bn2}), 4.31 (dt, *J* = 9.7, 4.8 Hz, 1H, *CH*-CH_3), 4.27 – 4.18 (m, 2H, *CH_2*-CH_2-TMS), 4.27 – 4.17 (m, 2H,), 3.70 (t, *J* = 9.3 Hz, 1H), 3.63 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 3H, CH-*CH_3*), 0.99 (t, *J* = 8.7 Hz, 2H, CH_2-*CH_2*-TMS), 0.00 (s, *J* = 3.3 Hz, 9H, 3xCH_3^{TMS}).

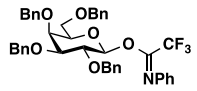
2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (407)



33 (8 g; 12.64 mmol) was dissolved in acetone/H_2O (9:1) (200 mL). NBS (2.77 g; 15.55 mmol) was added and the reaction mixture was stirred at 22 °C for 4h. The reaction mixture was then diluted with H_2O (200 mL) and extracted with Et_2O (3x100 mL). The combined organic phases where washed with sat. aq. $NaHCO_3$ (150 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (9:1 Tol/EtOAc) to give **407** as white crystals. R_f 0.1 (20:1 Tol/EtOAc). Yield: 6.82 g (98%).

^{1}H NMR (400 MHz, CDCl3) δ = 7.40-7.25 (m, 33H, Ph), 5.29 (d, $J_{1,2}$=3.5 Hz, 1H, H-1α), 4.95 (d, *J*=11.4 Hz, 0.65H, CH_2Phβ), 4.94 (d, *J*=11.7 Hz, 1H, CH_2Phα), 4.92 (d, *J*=10.5 Hz, 0.65H, CH_2Phβ), 4.71-4.56 (m, 5.95H, 4xCH_2Phα, 3xCH_2Phβ), 4.66 (d, $J_{1,2}$=7.4 Hz, 0.65H, H-1β), 4.61 (d, *J*=11.4 Hz, 0.65H, CH_2Phβ), 4.58 (d, *J*=11.7 Hz, 1H, CH_2Phα), 4.48 (d, *J*=11.7Hz, 1.65H, CH_2Phα, CH_2Phβ), 4.41 (d, *J*=11.7 Hz, 1H, CH_2Phα), 4.41 (d, *J*=11.7 Hz, 0.65H, CH_2Phβ), 4.16 (dd, *J*=6.8, 6.2 Hz, 1H, H-5α), 4.04 (dd, *J*=9.9, 3.5 Hz, 1H, H-2α), 3.97 (d, *J*=2.8 Hz, 1H, H-4α), 3.91(dd, *J*=9.9, 2.8 Hz, 1H, H-3α), 3.89 (d, *J*=1.7 Hz, 0.65H, H-4β), 3.77 (dd, *J*=9.6, 7.5 Hz, 0.65H, H-2β), 3.61-3.52 (m, 3.6H, 2xH-6β, H-5β, H-3β, H-6α), 3.52-3.48 (dd, *J*=9.4, 6.8 Hz, 1H,H-6α), 3.31 (d, *J*=6.5 Hz, 0.65H, OHβ), 2.99 (s, 1H, OHα). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.72 (1.65C), 138.64, 138.57 (0.65C), 138.49 (0.65C), 138.34(1C), 137.93(1C), 137.83 (0.65C) 128.53-127.61 (33C), 97.88 (0.65C), 91.97, 82.28 (0.65C), 80.81 (0.65C), 78.83, 76.67, 75.18 (0.65C), 74.83 (0.65C), 74.75, 74.65 (0.65C), 73.70 (0.65C), 73.64 (0.65C), 73.56, 73.04, 69.57, 69.16, 69.02 (0.65C). **HRMS**: calc. $[M+ Na]^+$: 563.6358 found $[M+ Na]^+$: 563.6355

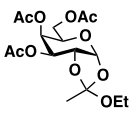
2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (408)



To a solution of **407** (400 mg; 0.74 mmol) in CH_2Cl_2 (7.5 mL) was added PTFAICl (383 mg; 1.85 mmol) and Cs_2CO_3 (602 mg; 1.85 mmol) at 0 °C. The reaction was stirred at 0 °C until TLC showed full conversion (2.5h). The reaction was filtered, concentrated and the crude was purified by flash chromatography (19:1 Pet. et./EtOAc) to give **408** as a viscous oil. Yield: 460 mg (88%).

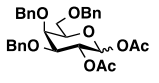
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.10 (m, 22H, N-*Ph*), 6.99 (t, *J* = 7.4 Hz, 1H, N-*Ph*), 6.69 (d, *J* = 7.7 Hz, 2H, N-*Ph*), 5.77 – 5.40 (m, 1H), 4.88 (d, *J* = 11.5 Hz, 1H, -CH_2^{Bn}), 4.80 – 4.71 (m, 2H, -CH_2^{Bn}), 4.66 (s, 2H, -CH_2^{Bn}), 4.55 (d, *J* = 11.5 Hz, 1H, -CH_2^{Bn}), 4.36 (q, *J* = 11.7 Hz, 2H, -CH_2^{Bn}), 3.99 (t, *J* = 8.6 Hz, 1H), 3.87 (s, 1H), 3.54 (d, *J* = 6.6 Hz, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.56, 138.41, 138.16, 138.03, 137.77, 128.66, 128.49, 128.45 (2C), 128.32, 128.27 (2C), 127.97, 127.89, 127.86, 127.78, 127.73, 127.58, 124.15, 119.33, 97.37, 82.10, 78.16, 75.59, 74.78, 74.42, 73.53, 73.23, 73.02, 68.16.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(exo-ethoxyethylidene)-α-D-galactopyranose (409)



Galactose pentaacetate (20 g; 51.2 mmol) was dissolved in CH_2Cl_2 under N_2-atmosphere. A 30% solution of HBr in AcOH (40 mL) was added and the reaction mixture was stirred at 22 °C overnight. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and poured over ice. The organic layer was separated and washed with H_2O (2x75 mL) and cold sat. aq. $NaHCO_3$ (2x120 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to give the glycosyl bromide. The crude product was used directly in the next step without further purification. To a solution of crude product in s-collidine (70 mL) was added dry ethanol (5 mL) and TBAB (5.0 g; 15.5 mmol) and the mixture was stirred at 50 °C for 12 h. During this period the reaction mixture went from a solution to almost solid due to precipitated s-collidinium bromide salts. The reaction mixture was diluted with chloroform (150 mL) and washed with 2N HCl (70 mL), sat. aq. $NaHCO_3$ (70 mL) and H_2O (70 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated.

1,2-*O*-diacetyl-3,4,6-tri-*O*-benzyl-D-galactopyranose (411)

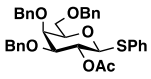


The syrupy ortho ester **409** (20 g; 51.81 mmol) was dissolved in MeOH (330 mL) and a freshly prepared 0.1M solution if NaOMe in MeOH (55 mL) was added. The reaction mixture was stirred at 22 °C for 2 h after followed by removal of MeOH *in vacuo* and co-distillation with toluene (2x100 mL). R_f 0.6 (9:1 CH_2Cl_2/ MeOH). To the oily residue was added DMF (200 mL), NaH (60%; 5.49 g; 228.7 mmol) and benzyl bromide (27.06 mL; 126.94 mmol). After stirring for 10 h at 22 °C the reaction mixture was diluted with EtOAc (750 mL) and washed with sat. aq. $NaHCO_3$ and water (500 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. R_f 0.2 (9:1 Pet. Ether/EtOAc)

The crude orthoester **410** (26.1 g; 51.81 mmol) was dissolved in 60% AcOH (500 mL) and was stirred at 22 °C for 16 h. The reaction mixture was co-evaporated with toluene (2x200 mL) and left under high vacuum.The crude was purified by flash chromatography (4:1 Tol/EtOAc) to give a viscous oil. R_f 0.3 (4:1 Tol/EtOAc). The oil (22.6 g; 45.88 mmol) and DMAP (0.56 g; 4.59 mmol) was dissolved in dry pyridine (150 mL) and cooled to 0 °C. Ac_2O (8.67 mL; 91.77 mmol) was added and the reaction was allowed to reach 22 °C. After 3h the reaction was quenched with MeOH (15 mL), diluted with ether (300 mL) and washed with 1M HCl (300 mL) and sat. aq. $NaHCO_3$ (300 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (19:1 Tol/EtOAc) to give **411** as white crystals. R_f 0.45 (9:1 Tol/EtOAc). Yield: 23.30 g (9:1α/β mixture) (82% over four steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.10 (m, 18H), 6.35 (d, $J_{1,2}$= 3.7 Hz, 1H, H-1), 5.53 (dd, $J_{2,3}$= 10.5, $J_{1,2}$=3.7 Hz, 1H, H-2), 4.96 (d, J = 11.4 Hz, 1H, -CH_2Ph), 4.70 (dd, J = 12.1 Hz, 2H, -CH_2Ph), 4.59 (d, J = 11.4 Hz, 1H, -CH_2Ph), 4.46 (dd, J = 11.7 Hz, 2H, -CH_2Ph), 4.08 (m, 2H, H-4, H-5), 3.93 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$=2.7 Hz, 1H, H-3), 3.59 (ddd, $J_{6a,6b}$ = 14.6, $J_{5,6a}$=9.1, $J_{5,6b}$=6.6 Hz, 2H, H6a,), 2.11 (s, 3H), 2.03 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.95, 169.25, 138.26, 138.11, 137.69, 128.47 (2C), 128.44 (2C), 128.30 (2C), 128.15 (2C), 128.00 (2C), 127.90, 127.74, 127.69, 127.30 (2C), 90.49, 76.50, 74.88, 73.92, 73.62, 72.55, 72.03, 69.37, 68.25, 21.04, 20.78.
MS m/z (ESI^+): 535.2 [$(M+H)^+$]

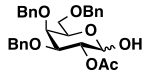
Phenyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (412)



411 (7 g; 13.09 mmol) was dissolved in CH_2Cl_2 (150 mL) under N_2-atmosphere. Thiophenol (2.02 mL; 19.64 mmol) was added and the reaction mixture was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (1.93 mL; 15.71 mmol) was added drop wise. The mixture was allowed to warm to 22 °C and the reaction was monitored by TLC. After 4h the reaction was diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. $NaHCO_3$ (200 mL), dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography (9:1 Pet. Ether/EtOAc) to give **412** as a white powder. R_f 0.75 (9:1 Tol/EtOAc). Yield: 5.43 g (71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H, Ar-H), 7.43 – 7.19 (m, 18H, Ar-H), 5.46 (dd $J_{1,2}$=$J_{2,3}$= 9.8 Hz, 1H, H-2), 4.97 (d, J = 11.6 Hz, 1H, CH_2^{Bn}), 4.77 – 4.53 (m, 4H, H-1, CH_2^{Bn}, CH_2^{Bn}), 4.47 (dd, J_{CH2} = 11.6 Hz, 2H, -CH_2^{Bn}), 4.02 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-4), 3.76 – 3.63 (m, 3H, H-5, H-6^{a,b}), 3.59 (dd, $J_{2,3}$= 9.6, $J_{3,4}$=2.7 Hz, 1H, H-3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.52, 138.47, 137.88, 137.84, 133.72-127.37 (17C), 86.69, 81.47, 77.61, 74.38, 73.62, 72.79, 72.00, 69.71, 68.80, 21.10. **MS** m/z (ESI^+): 585.2 [$(M+H)^+$]

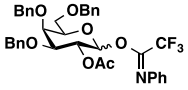
2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-D-galactopyranose (413)



A solution of **411** (5.0 g; 9.35 mmol) in Et_2O (125 mL) and benzyl amine (20 mL) was stirred at 22 °C for 5 h and then concentrated. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with 1M HCl (100 mL), sat. aq. NH_4Cl (100 mL) and H_2O, dried over $MgSO_4$ and concentrated. The product **413** was purified by column chromatography (4:1 Tol/EtOAc). R_f 0.4 (4:1 Tol/EtOAc). Yield: 3.0 g (66%).

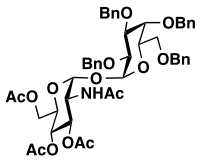
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.14 (m, 6H), 6.20 (d, J = 3.9 Hz, 1H), 5.37 (t, J = 3.3 Hz, 1H), 5.31 – 5.22 (m, 1H), 5.16 – 5.07 (m, 1H), 4.85 (dd, J = 11.5, 2.4 Hz, 1H), 4.77 – 4.25 (m, 2H), 4.25 (dt, J = 10.0, 4.0 Hz, 1H), 4.08 (t, J = 6.3 Hz, 1H), 4.02 (d, J = 1.6 Hz, 1H), 3.88 (td, J = 10.2, 2.3 Hz, 1H), 3.69 (dd, J = 10.1, 2.7 Hz, 1H), 3.64 – 3.52 (m, 1H), 3.51 – 3.43 (m, 1H), 3.37 (dd, J = 9.5, 6.0 Hz, 1H), 3.14 (t, J = 10.4 Hz, 1H), 2.00 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.41, 169.75, 138.32, 138.24, 137.89, 137.75, 137.70, 129.07, 128.61, 128.48, 128.45, 128.31, 128.29, 128.02, 127.92, 127.87, 127.86, 127.72, 127.69, 127.51, 127.41, 96.33, 90.90, 79.66, 77.38, 77.06, 76.74, 76.45, 74.85, 74.77, 74.64, 74.60, 74.25, 73.73, 73.61, 73.56, 73.00, 72.82, 72.38, 71.26, 69.48, 69.29, 68.34, 21.07. **MS** m/z (ESI^+) : 493.2 [$(M+H)^+$]

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-D-galactopyranose *N*-phenyltrifluoroacetimidate(414)



Hemiacetal **413** (300 mg; 0.61 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. PTAICl (253 mg; 1.22 mmol) and CsCO3 (397 mg; 1.22 mmol) were added and the reaction was stirred at 0 °C for 4 h. The reaction mixture was then filtered and concentrated. The crude product was purified by flash chromatography (7:2:1 heptane/toluene/EtOAc) to give **414**. Yield: 310 mg (76%).

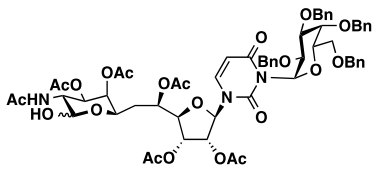
2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1→1)-2,3,4,6-*O*-tetrabenzyl-α-D-galactopyranosyl (415)



373 (52 mg; 0.15 mmol) and **408** (160 mg; 0.22 mmol) were mixed and dried azeotropically with toluene (2x5 mL) and dried under high vacuum overnight. The mixture was dissolved in CH_2Cl_2 (3 mL), freshly dried 4Å **MS** were added, and the mixture was cooled to 0 °C. TMSOTf (3 mg; 0.015 mmol) was added and the reaction was stirred at 0 °C until TLC showed full conversion (0.5h). The reaction was quenched with Et_3N (100 μL), concentrated and purified by flash chromatography (4:1 toluene/EtOAc) to give **415** as a colorless crystalline material. Yield: 79 mg (61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.08 (m, 20H, Ar-H), 5.73 (d, $J_{2,NH}$ = 8.8 Hz, 1H, NH^{Ac}), 5.17 (dd, $J_{3,4}$ = 9.8, $J_{2,3}$ =9.5 Hz, 1H, H-3'), 5.095 (d, $J_{1,2}$ = 3.9 Hz, 1H, H-1), 5.09 (d, $J_{1,2}$ = 3.7 Hz, 1H, H-1'), 5.05 (t, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, 1H, H-4'), 4.85 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.79 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.75 (m, 2H, CH_2^{Bn}), 4.56 (d, J_{CH2} = 11.6 Hz, 1H, 0.5xCH_2^{Bn}), 4.48 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.34 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.27 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.24 (ddd, $J_{2,3}$ = 9.5 $J_{2,NH}$ = 8.8, $J_{1,2}$ = 3.1 Hz, 1H, H-2'), 4.15 (ddd, $J_{4,5}$ = 10.2, $J_{5,6a}$ =3.5, $J_{5,6b}$ =2.3 Hz, 1H, H-5'), 4.05 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 3.9 Hz, 1H, H-2), 3.98 (dd, $J_{3,4}$ = 2.7, $J_{4,5}$ = 1.2 Hz, 1H, H-4), 3.91 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 2.7 Hz, 1H, H-3), 3.88 – 3.79 (m, 2H, H-6a', H-5), 3.64 (dd, $J_{6a,6b}$ = 12.6, $J_{5,6b}$ = 2.3 Hz, 1H, H-6b'), 3.45 (dd, $J_{6a,6b}$ = 9.1, $J_{5,6a}$ = 7.3 Hz, 1H, H-6a), 3.37 (dd, $J_{6a,6b}$ = 9.1, $J_{5,6a}$ = 5.5 Hz, 1H, H-6b), 1.96 (s, 3H, CH_3^{Ac}), 1.96 (s, 3H, CH_3^{Ac}), 1.93 (s, 3H, CH_3^{Ac}), 1.76 (s, 3H, CH_3^{Ac}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.96, 170.76, 170.23, 169.31, 138.40 (2C), 138.24, 137.59, 128.55-127.62 (20C), 94.93, 94.31, 78.95, 75.58, 74.92, 74.23, 74.02, 73.70, 72.69, 71.15, 70.97, 68.59, 67.84, 67.75, 61.46, 52.31, 22.87, 20.92, 20.80, 20.72. **HRMS**: calc. $[M+ Na]^+$: 892.3520 found $[M+ Na]^+$: 892.3524

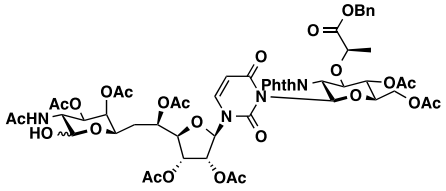
2,3,4,6-*O*-tetrabenzyl-α-D-galactopyranosyl-(1→N-3)-hexaacetyl-tunicaminyl-uracil (416)



374 (90 mg; 0.14 mmol) and **408** (195 mg; 0.27 mmol) was dried azeotropically with toluene (2x5 mL) and dried under high vacuum overnight. The mixture was dissolved in dry CH_2Cl_2 (4 mL) and freshly dried 4Å MS (200 mg) was added. The reaction mixture was stirred for 20 min at -20 °C after which TMSOTf (3 mg; 0.014 mmol) was added. After 30 min at -20 °C another round of TMSOTf (3 mg; 0.014 mmol) was added. The reaction was allowed to reach 0 °C and stirred until TLC showed full conversion (1.5h). The reaction was quenched with Et_3N (100 μL) and concentrated. The product **416** was purified by flash chromatography (40:1 EtOAc/MeOH). Yield: 103 mg (65%).

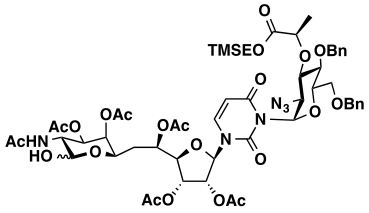
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 20H, Ar-H), 7.12 (d, $J_{5,6}$ = 8.1 Hz, 1H, H-6^{uracil}), 6.96 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1''), 5.94 (d, $J_{1,2}$ = 5.5 Hz, 1H, H-1'), 5.75 (d, $J_{5,6}$ = 8.1 Hz, 1H, H-5^{uracil}), 5.44 (dd, $J_{2,3}$ = 5.5, $J_{3,4}$ = 2.0 Hz, 1H, H-3'), 5.38 – 5.31 (m, 1H, H-5'), 5.26 – 5.13 (m, 4H, H-2', H'8, H-9', H-11'), 4.96 (d, J_{CH2} = 11.4 Hz, 1H, 0.5xCH_2^{Bn}), 4.83 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.75 (d, J_{CH2} = 11.7 Hz, 1H, 0.5xCH_2^{Bn}), 4.69 – 4.35 (m, 7H, H-2'', H-3'', H-5'', H-10', 1.5xCH_2^{Bn}), 4.39 (d, J_{CH2} = 12.0 Hz, 1H, 0.5xCH_2^{Bn}) 4.17 – 4.11 (m, 1H, H-7'), 4.11 – 4.01 (m, 2H, H-4', H-4''), 3.51 (m, 2H, H-6''), 2.17 (s, 3H, CH_3^{Ac}), 2.14 (s, 3H, CH_3^{Ac}), 2.11 (s, 3H, CH_3^{Ac}), 2.11 (s, 3H, CH_3^{Ac}), 2.00 (s, 3H, CH_3^{Ac}), 1.96 (s, 3H, CH_3^{Ac}), 1.94 – 1.88 (m, 1H, H-6a'), 1.58 (ddd, $J_{6a,6b}$ = 14.7, $J_{5,6b}$ = 9.5, $J_{7,6b}$ = 2.2 Hz, 1H, H-6b'). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.11, 170.91, 170.84, 170.33, 169.62, 169.36, 163.07, 139.24, 138.87, 138.11, 138.01, 137.75, 128.45, 128.37, 128.34, 128.29, 128.16, 127.96, 127.79, 127.66, 127.59, 127.58, 127.48, 127.40, 92.02, 88.55, 82.72, 81.24, 77.36, 75.88, 75.82, 74.78, 74.56, 74.15, 73.54, 73.14, 70.22, 69.92, 69.69, 69.57, 68.67, 64.68, 47.99, 31.05, 23.45, 21.19, 20.92, 20.88, 20.62, 20.39. **HRMS**: calc. $[M+ Na]^+$: 1202.4321 found $[M+ Na]^+$: 1202.4322

4,6-*O*-diacetyl-3-*O*-(benzyl (S)-lactate)-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→N-3)-hexaacetyl-tunicaminyl-uracil (417)



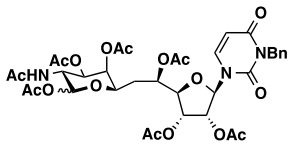
374 (120 mg; 0.18 mmol) and **376** (331 mg; 0.46 mmol) was dried azeotropically with toluene (2x5 mL) and left under high vacuum overnight. The mixture was dissolved in CH_2Cl_2 (5 mL) and freshly dried 4Å MS were added. The mixture was stirred at -20 °C for 15 min. TMSOTf (4 mg; 0.018 mmol) was added and the reaction was stirred at 0 °C until TLC showed full conversion of the acceptor (5h). The reaction was quenched with Et_3N, filtered and concentrated. The residue was purified by flash chromatography (40:1 EtOAc/MeOH) to afford **417** as colorless crystals. Yield: 97 mg (45%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, $J_{Ar\text{-}H}$ = 5.4, $J_{Ar\text{-}H}$ = 3.0 Hz, 2H, H^{Phth}), 7.69 (dd, $J_{Ar\text{-}H}$ = 5.4, $J_{Ar\text{-}H}$ = 3.0 Hz, 2H, H^{Phth}), 7.39 (d, $J_{5,6}$ = 7.4 Hz, 1H, H-6^{uracil}), 7.33 – 7.24 (m, 3H, Ar-H), 7.10 (m, 2H, Ar-H), 6.73 (d, $J_{1,2}$= 8.8 Hz, 1H, H-1''), 5.90 (d, $J_{1,2}$ = 5.2 Hz, 1H, H-1'), 5.87 (d, $J_{5,6}$ = 7.4 Hz, 1H, H-5^{uracil}), 5.48 (d, $J_{10,NH}$ = 9.3 Hz, 1H, N*H*^{Ac}), 5.37 (t, $J_{2,3}$ = $J_{3,4}$ = 5.6 Hz, 1H, H-3'), 5.26 – 5.22 (m, 1H, H-4''), 5.20 (dd, $J_{2,3}$ = 5.6 Hz, $J_{1,2}$ = 5.2 Hz, 1H, H-2'), 5.18 – 5.13 (m, 3H, H-9', H-11', H-8'), 5.09 (dt, $J_{5,6b}$ = 7.8 Hz, $J_{4,5}$ = $J_{5,6a}$ = 4.0 Hz, 1H, H-5'), 4.71 (d, J_{CH2} = 12.2 Hz, 1H, CH_2^{Bn}), 4.64 (d, J_{CH2} = 12.2 Hz, 1H, CH_2^{Bn}), 4.59 – 4.53 (m, 2H, H-2'', H-3''), 4.44 (td, $J_{9,10}$ = $J_{10,NH}$ = 10.5, $J_{10,11}$ = 3.5, 1H, H-10'), 4.30 (dd, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6a}$ = 4.3 Hz, 1H, H-6a''), 4.15 (dd, $J_{3,4}$ = 5.6, $J_{4,5}$ = 4.0 Hz, 1H, H-4'), 4.13 – 4.04 (m, 3H, C*H*-$CH_3^{lactate}$, H-6b'', H-7'), 3.96 (ddd, $J_{4,5}$ =10.0 Hz, $J_{5,6a}$ = 4.3 Hz, $J_{5,6b}$ = 2.3 Hz, 1H, H-5''), 2.16 (s, 3H, CH_3^{Ac}), 2.09 (s, 6H, 2xCH_3^{Ac}), 2.08 (s, 3H, CH_3^{Ac}), 2.06 (s, 3H, CH_3^{Ac}), 2.05 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}), 1.94 (s, 3H, CH_3^{Ac}), 1.92 – 1.85 (m, 1H, H-6a'), 1.58 (ddd, $J_{6a,6b}$ = 14.8, $J_{5,6b}$ = 7.9, $J_{6b,7}$ = 2.5 Hz, 1H, H-6b'), 1.21 (d, $J_{CH,CH3}$ = 6.9 Hz, 3H, *CH*$_3$-CH^{lactate}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.00, 171.19, 170.83, 170.67, 169.96, 169.92, 169.78, 169.49, 169.24, 169.11, 154.55, 143.53, 135.18, 133.89, 133.87, 128.47, 128.30, 128.11, 123.35, 96.46, 92.11, 91.48, 88.98, 82.54, 77.23, 75.99, 73.20, 72.33, 71.20, 70.02, 69.88, 69.48, 68.11, 66.36 (2C), 65.54, 61.40, 54.20, 48.78, 31.97, 23.27, 21.01, 20.86, 20.80, 20.76, 20.72, 20.46, 20.42, 18.92.
HRMS: calc. $[M+Na]^+$: 1071.3308 found $[M+Na]^+$: 1071.3312

2-Azido-4,6-*O*-dibenzyl-3-*O*-[*(R)*-1'-((2-trimethylsilyl)-ethyloxycarbonyl)ethyl]-2-deoxy-β-D-glucopyranosyl-(1→N-3)-hexaacetyl-tunicaminyl-uracil (418)



374 (110 mg; 0.17 mmol) and **406** (365 mg; 0.50 mmol) was dried azeotropically with toluene (2x5 mL) and left under high vacuum overnight. The mixture was dissolved in CH_2Cl_2 (5 mL) and freshly dried 4Å MS were added. The mixture was stirred at -20 °C for 15 min. TMSOTf (4 mg; 0.017 mmol) was added and the reaction was stirred at 0 °C until TLC showed full conversion of the acceptor (5h). The reaction was quenched with Et_3N, filtered and concentrated. The residue was purified by flash chromatography (40:1 EtOAc/MeOH) to afford **418** as colorless crystals. Yield: 120 mg (59%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.4 Hz, 1H, H-6^{uracil} β), 7.48 (d, $J_{5,6}$ = 7.4 Hz, 1H, H-6^{uracil}α), 7.38 – 7.05 (m, 15H, Ar-H), 6.74 (d, $J_{1,2}$ = 8.6 Hz, 1H, H-1''β), 6.71 (d, $J_{1,2}$ = 3.6 Hz, 1H, H-1''α), 6.00 (d, $J_{5,6}$ = 7.4 Hz, 1H, H-5^{uracil}β), 5.99 (d, J = 4.9 Hz, 1H, H-1'α), 5.98 (d, $J_{1,2}$ = 5.3 Hz, 1H, H-1'β), 5.91 (d, $J_{5,6}$ = 7.4 Hz, 1H, H-5^{uracil}α), 5.82 (d, $J_{10,NH}$ = 9.6 Hz, 1H, N*H*^{Ac}), 5.40 (td, $J_{2,3}$ = 6.0, $J_{3,4}$ = 3.7 Hz, 2H, H-3'α, H-3'β), 5.36 – 5.06 (m, 10H, H-2'α, H-2'β, H-5'α, H-5'β, H-11'α, H-11'β, H-8'α, H-8'β, H-9'α, H-9'β), 4.77 (d, J_{CH2} = 10.9 Hz, 1H, 0.5xCH_2^{Bn}α) 4.76 (d, J = 10.9 Hz, 1H, 0.5xCH_2β), 4.63 – 4.31 (m, 14H, H-3''α, H-3''β, H-7'α, , H-7'β, H-10'α, H-10'β, 3xCH_2^{Bn}, O-C*H*-CH_3α, O-C*H*-CH_3β), 4.30 – 4.05 (m, 8H, H-2''β, H-4'α, O-C*H*$_2$-CH_2^{TMS}, O-C*H*$_2$-CH_2^{TMS}), 3.94 – 3.84 (m, 2H, H-5''α, H-5''β), 3.83 – 3.49 (m, 4H, H-2''α, H-4''β, H-6a'', H-6b''), 2.13 (s, 6H, 2xCH_3^{Ac}), 2.08 (s, 3H, 2xCH_3^{Ac}), 2.07 (s, 6H, 2xCH_3^{Ac}), 2.04 (s, 6H, 2xCH_3^{Ac}), 1.95 (s, 6H, 2xCH_3^{Ac}), 1.93 (s, 6H, 2xCH_3^{Ac}), 1.90 – 1.86 (m, 2H, H-6a'α, H-6a'β), 1.56 (ddd, $J_{6a,6b}$ = 14.5, $J_{5,6b}$ = 8.5, $J_{7,6b}$ =2.1 Hz, 1H, H-6b'α, H-6b'β), 1.39 (d, J = 6.9 Hz, 3H, C*H*$_3$-CH-α), 1.37 (d, J = 6.9 Hz, 3H, C*H*$_3$-CH-β), 1.05 – 0.93 (m, 4H, TMS-C*H*$_2$-CH$_2$-Oα, TMS-C*H*$_2$-CH$_2$-Oβ), 0.03 (s, 9H, TMSα). 0.00 (s, 9H, TMSβ) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.43, 174.21, 172.47, 172.45, 172.38, 172.36, 172.22, 171.80, 171.55, 171.50, 171.23, 171.15, 170.87, 156.46, 145.27, 139.25, 139.23, 139.12, 130.02, 129.98, 129.96, 129.90, 129.86, 129.83, 129.44, 129.40, 129.35, 129.32, 129.30, 129.26, 129.24, 129.21, 129.13, 98.21, 98.11, 95.92, 94.13, 93.43, 90.46, 84.33, 84.28, 84.12, 81.08, 78.99, 78.75, 78.47, 78.38, 78.01, 77.97, 76.82, 76.58, 76.53, 75.07, 75.02, 74.97, 74.78, 74.73, 74.69, 71.68, 71.65, 71.58, 71.47, 71.34, 71.14, 70.04, 69.35, 69.31, 66.74, 66.21, 66.10, 64.85, 64.71, 64.36, 49.42, 33.82, 31.17, 24.81, 24.69, 22.59, 22.57, 22.55, 22.48, 22.38, 22.30, 22.29, 22.26, 22.21, 22.02, 21.98, 21.96, 21.84, 20.75, 20.64, 20.62, 18.84, 18.78, 18.76, 2.51, -0.00.
HRMS: calc. $[M+Na]^+$: 1219.4367 found $[M+Na]^+$: 1219.4361

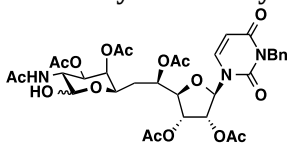
3-*N*-benzyl-heptaacetyl-tunicaminyl uracil (419)



371 (110 mg; 0.15 mmol) was dissolved in DMF (4 mL). BnBr (40 mg; 0.24 mmol) and Cs_2CO_3 (54 mg; 0.17 mmol) was added and the reaction was stirred at 50 °C for 1h. The mixture was poured into water (50 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were concentrated and the crude was purified by flash chromatography to give **419** as an off-white solid (40:1 EtOAc/MeOH). Yield: 109 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H, Ar-H), 7.34 – 7.23 (m, 3H, Ar-H), 7.21 – 7.15 (m, 1H, H-6^{uracil}), 6.14 (d, $J_{10,11}$ = 3.7 Hz, 1H, H-11'), 6.00 (d, $J_{1,2}$ = 5.8 Hz, 1H, H-1'), 5.88 (d, $J_{5,6}$ = 8.1 Hz, 1H, H-5^{uracil}), 5.48 (d, $J_{10,NH}$ = 9.4 Hz, 1H, NH^{Ac}), 5.35 (dd, $J_{2,3}$ = 5.9 Hz, $J_{3,4}$ = 4.3 Hz, 1H, H-3'), 5.30 – 5.17 (m, 3H, H-2', H-8', H-9'), 5.12 (m, 1H, H-5'), 5.10 – 5.07 (m, 2H, CH_2^{Bn}), 4.71 (ddd, $J_{9,10}$ = 10.8, $J_{10,NH}$ = 9.4, $J_{10,11}$ = 3.7 Hz, 1H, H-10'), 4.08 – 4.02 (m, 2H, H-4', H-7').18 (s, 3H, CH_3^{Ac}), 2.17 (s, 3H, CH_3^{Ac}), 2.11 (s, 3H, CH_3^{Ac}), 2.06 (s, 3H, CH_3^{Ac}), 2.03 (s, 3H, CH_3^{Ac}), 2.02 (s, 3H, CH_3^{Ac}), 1.96 (s, 3H, CH_3^{Ac}), 1.94 – 1.84 (m, 1H, H-6a'), 1.56 (ddd, $J_{6a,6b}$ = 15.0, $J_{5,6b}$ = 8.3, $J_{6b,7}$ = 2.1 Hz, 1H, H-6b'). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.32, 170.68, 170.18, 170.13, 169.66, 169.40, 169.21, 162.24, 151.08, 137.98, 137.38, 136.55, 129.15, 128.96, 128.94, 128.53, 128.34, 127.74, 125.41, 103.26, 91.16, 87.99, 82.47, 77.36, 72.60, 69.67, 69.64, 69.50, 68.27, 67.72, 46.85, 44.46, 32.90, 29.82, 23.34, 21.58, 21.04, 21.01, 20.89, 20.83, 20.64, 20.47. **HRMS**: calc. $[M+ Na]^+$: 812.2490 found $[M+ Na]^+$: 812.2499

3-*N*-benzyl-hexaacetyl-tunicamine uracil (420)



419 (200 mg; 0.25 mmol) was dissolved in THF (3 mL). A solution of ethylene diamine (18.3 mg; 0.30 mmol) and AcOH (21.3 mg; 0.35 mmol) in THF was added and the reaction was stirred for 18h at 22 °C. The reaction mixture was poured into 0.5M HCl (50 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were dried over $MgSO_4$, and concentrated. The crude was purified by flash chro-matography (50:1 EtOAc/MeOH) to afford **420** as colorless crystals. Yield: 56 mg (30 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H, Ar-H), 7.34 – 7.22 (m, 3H, Ar-H), 7.16 (d, $J_{5,6}$ = 8.1 Hz, 1H, H-6^{uracil}), 5.95 (d, J = 5.7 Hz, 1H, H-1'), 5.85 (d, J = 8.1 Hz, 1H, H-5^{uracil}), 5.77 (d, $J_{\text{N-H, 10}}$ = 9.7 Hz, 1H, N-H^{Ac}), 5.40 (dd, $J_{2,3}$ = 6.1, $J_{3,4}$ = 4.6 Hz, 1H, H-3'), 5.34 – 5.24 (m, 2H, H-2', H-5') 5.26 (d, $J_{10,11}$ = 3.6 Hz, 1H, H-11'), 5.23 – 5.16 (m, 2H, H-9', H-8'), 5.12 – 5.02 (m, 2H, CH_2^{Bn}), 4.53 (ddd, $J_{9,10}$ = 10.5, $J_{NH,10}$ = 9.7, $J_{10,11}$ = 3.5, 1H, H-10'), 4.14 (dd, $J_{6b,7}$ = 10.0 Hz, $J_{6a,7}$ = 3.1 Hz 1H, H-7'), 4.09 (t, $J_{3,4}$ = $J_{4,5}$ = 4.6 Hz, 1H, H-4'), 2.17 (s, 3H, CH_3^{Ac}), 2.11 (s, 3H, CH_3^{Ac}), 2.08 (s, 3H, CH_3^{Ac}), 2.03 (s, 3H, CH_3^{Ac}), 2.00 (s, 3H, CH_3^{Ac}), 1.97 (s, 3H, CH_3^{Ac}), 1.90 (ddd, $J_{6a,6b}$ = 14.3 Hz, $J_{5,6a}$ = 11.0 Hz, $J_{6a,7}$ = 3.1 Hz, 2H, H-6a'), 1.58 (ddd, $J_{6a,6b}$ = 14.6 Hz, $J_{6b,7}$ = 9.4 Hz, $J_{5,6b}$ = 2.2 Hz, 1H, H-6b'). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.13, 171.05, 170.79, 170.38, 169.80, 169.48, 162.24, 150.95, 137.57, 136.49, 129.15, 128.97 (2C), 128.55 (2C), 128.34, 127.80, 103.24, 92.08, 88.32, 82.52, 77.36, 72.51, 70.22, 69.69, 69.50, 68.60, 64.72, 48.05, 44.50, 32.37, 29.82, 23.46, 21.16, 20.93 (2C), 20.62, 20.49. **HRMS**: calc. $[M+ Na]^+$: 770.2385 found $[M+ Na]^+$: 770.2387.

11 References

1. Carpita, N. C. *et al.* Cell Wall Architecture of the Elongating Maize Coleoptile. *Plant Physiol.* **127 ,** 551–565 (2001).
2. Burton, R. A., Gidley, M. J. & Fincher, G. B. Heterogeneity in the chemistry, structure and function of plant cell walls. *Nat. Chem. Biol.* **6,** 724–732 (2010).
3. Bacic, A., Harris, P. J. & Stone, B. A. in *Biochem. plants. A Compr. treatise. Vol. 14. Carbohydrates.* 297–372 (1988). at <http://web.ebscohost.com/ehost/detail?sid=3db72644-2262-4d71-b8d4-2f70a8fe6c8c@-sessionmgr11&vid=9&bk=1&hid=8&bdata=JnNpdGU9ZWhvc3QtbGl2ZQ==#db=lah&AN=19900738383>
4. Cosgrove, D. J. Growth of the plant cell wall. *Nat. Rev. Mol. Cell Biol.* **6,** 850–861 (2005).
5. Doblin, M. S., Pettolino, F. & Bacic, A. : Plant cell walls: the skeleton of the plant world. *Funct. Plant Biol.* **37,** 357 (2010).
6. Basic, A., Harris, P. & Stone, B. in *Biochem. Plants* **14,** 297–369 (Academic Press, 1988).
7. Somerville, C. Cellulose synthesis in higher plants. *Annu. Rev. Cell Dev. Biol.* **22,** 53–78 (2006).
8. Peña, M. J., Darvill, A. G., Eberhard, S., York, W. S. & O'Neill, M. A. Moss and liverwort xyloglucans contain galacturonic acid and are structurally distinct from the xyloglucans synthesized by hornworts and vascular plants. *Glycobiology* **18,** 891–904 (2008).
9. Fincher, G. B. Exploring the evolution of (1,3;1,4)-beta-D-glucans in plant cell walls: comparative genomics can help! *Curr. Opin. Plant Biol.* **12,** 140–7 (2009).
10. York, W. S. & O'Neill, M. A. Biochemical control of xylan biosynthesis - which end is up? *Curr. Opin. Plant Biol.* **11,** 258–265 (2008).
11. Matheson, N. K. *Carbohydrates*. *Methods Plant Biochem.* **2,** 371–413 (Elsevier, 1990).
12. Ridley, B. L., O'Neill, M. A. & Mohnen, D. Pectins: structure, biosynthesis, and oligogalacturonide-related signaling. *Phytochemistry* **57,** 929–967 (2001).
13. Caffall, K. H. & Mohnen, D. The structure, function, and biosynthesis of plant cell wall pectic polysaccharides. *Carbohydr. Res.* **344,** 1879–1900 (2009).
14. Carpita, N. C. & Gibeaut, D. M. Structural models of primary cell walls in flowering plants: consistency of molecular structure with the physical properties of the walls during growth. *Plant J.* **3,** 1–30 (1993).
15. Mossine, V. V, Glinsky, V. V & Mawhinney, T. P. Food-related carbohydrate ligands for galectins. in *Sect. Title Food Feed Chem.* 235–270 (2008).
16. Brull, L. *et al.* Rapid molecular mass and structural determination of plant cell wall-derived oligosaccharides using off-line high-performance anion-exchange chromatography/mass spectrometry. *J. Mass Spectrom.* **33,** 713–720 (1998).
17. Luonteri, E. *et al.* Purification and characterization of Aspergillus β-D-galactanases acting on β-1,4- and β-1,3/6-linked arabinogalactans. *Carbohydr. Polym.* **53,** 155–168 (2003).
18. Nakamura, A., Furuta, H., Maeda, H., Takao, T. & Nagamatsu, Y. Structural studies by stepwise enzymatic degradation of the main backbone of soybean soluble polysaccharides consisting of galacturonan and rhamnogalacturonan. *Biosci. Biotechnol. Biochem.* **66,** 1301–1313 (2002).
19. Engelsen, S. B., Cros, S., Mackie, W. & Perez, S. A molecular builder for carbohydrates: application to polysaccharides and complex carbohydrates. *Biopolymers* **39,** 417–433 (1996).
20. Rose, J. K. C. *The Plant Cell Wall*. (Blackwell Publishing Ltd, 2003).
21. Motose, H., Sugiyama, M. & Fukuda, H. A proteoglycan mediates inductive interaction during plant vascular development. *Nature* **429,** 873–878 (2004).
22. Schultz, C., Gilson, P., Oxley, D., Youl, J. & Bacic, A. GPI-anchors on arabinogalactan-proteins: implications for signalling in plants. *Trends Plant Sci.* **3,** 426–431 (1998).
23. Van Hengel, A. J. & Roberts, K. AtAGP30, an arabinogalactan-protein in the cell walls of the primary root, plays a role in root regeneration and seed germination. *Plant J.* **36,** 256–270 (2003).
24. Van Hengel, A. J. & Roberts, K. Fucosylated arabinogalactan-proteins are required for full root cell elongation in arabidopsis. *Plant J.* **32,** 105–113 (2002).
25. Gao, M. & Showalter, A. M. Yariv reagent treatment induces programmed cell death in Arabidopsis cell cultures and implicates arabinogalactan protein involvement. *Plant J.* **19,** 321–331 (1999).
26. Seifert, G. J. & Roberts, K. The biology of arabinogalactan proteins. *Annu. Rev. Plant Biol.* **58,** 137–161 (2007).
27. Nothnagel, E. A. Proteoglycans and related components in plant cells. *Int. Rev. Cytol.* **174,** 195–291 (1997).
28. Knox, J. P. The use of antibodies to study the architecture and developmental regulation of plant cell walls. *Int. Rev. Cytol.* **171,** 79–120 (1997).

29. Gane, A. M. *et al.* Structural analysis of the carbohydrate moiety of arabinogalactan-proteins from stigmas and styles of Nicotiana alata. *Carbohydr. Res.* **277,** 67–85 (1995).
30. Ellis, M., Egelund, J., Schultz, C. J. & Bacic, A. Arabinogalactan-proteins: key regulators at the cell surface? *Plant Physiol.* **153,** 403–419 (2010).
31. Churms, S. C., Stephen, A. M. & Siddiqui, I. R. Evidence for repeating sub-units in the molecular structure of the acidic arabinogalactan from rapeseed (Brassica compestris). *Carbohydr. Res.* **94,** 119–122 (1981).
32. Bacic, A., Churms, S. C., Stephen, A. M., Cohen, P. B. & Fincher, G. B. Fine structure of the arabinogalactan-protein from Lolium multiflorum. *Carbohydr. Res.* **162,** 85–93 (1987).
33. Goodrum, L. J., Patel, A., Leykam, J. F. & Kieliszewski, M. J. Gum arabic glycoprotein contains glycomodules of both extensin and arabinogalactan-glycoproteins. *Phytochemistry* **54,** 99–106 (2000).
34. Tan, L., Qiu, F., Lamport, D. T. A. & Kieliszewski, M. J. Structure of a hydroxyproline (Hyp)-arabinogalactan polysaccharide from repetitive Ala-Hyp expressed in transgenic Nicotiana tabacum. *J. Biol. Chem.* **279,** 13156–13165 (2004).
35. Edman, P. Method for Determination of the Amino Acid Sequence in Peptides. *Acta Chem. Scand.* **4,** 283–293 (1950).
36. Chen, C. G. *et al.* Molecular cloning of a gene encoding an arabinogalactan-protein from pear (Pyrus communis) cell suspension culture. *Proc. Natl. Acad. Sci. U. S. A.* **91,** 10305–10309 (1994).
37. Schultz, C. J. *et al.* Using genomic resources to guide research directions. The arabinogalactan protein gene family as a test case. *Plant Physiol.* **129,** 1448–1463 (2002).
38. Johnson, K. L., Jones, B. J., Bacic, A. & Schultz, C. J. The fasciclin-like arabinogalactan proteins of Arabidopsis. A multigene family of putative cell adhesion molecules. *Plant Physiol.* **133,** 1911–1925 (2003).
39. Hill, K. L., Harfe, B. D., Dobbins, C. A. & L'Hernault, S. W. dpy-18 encodes an alpha-subunit of prolyl-4-hydroxylase in caenorhabditis elegans. *Genetics* **155,** 1139–1148 (2000).
40. Kieliszewski, M. J. & Shpak, E. Synthetic genes for the elucidation of glycosylation codes for arabinogalactan-proteins and other hydroxyproline-rich glycoproteins. *Cell. Mol. Life Sci.* **58,** 1386–1398 (2001).
41. Barondes, S. H. *et al.* Galectins: a family of animal β-galactoside-binding lectins. *Sect. Title Gen. Biochem.* **76,** 597–598 (1994).
42. Nesmelova, I. V, Dings, R. P. M. & Mayo, K. H. Understanding galectin structure-function relationships to design effective antagonists. in *Sect. Title Gen. Biochem.* 33–69, 4 plates (2008).
43. Klyosov, A. A. Galectins and their functions in plain language. in *Sect. Title Gen. Biochem.* 9–31 (2008).
44. Teichberg, V. I., Silman, I., Beitsch, D. D. & Resheff, G. A β-D-galactoside binding protein from electric organ tissue of Electrophorus electricus. *Proc. Natl. Acad. Sci. U. S. A.* **72,** 1383–1387 (1975).
45. Cooper, D. N. W. Galectinomics: finding themes in complexity. *Biochim. Biophys. Acta* **1572,** 209–231 (2002).
46. Leffler, H. Galectins structure and function--a synopsis. *Results Probl. Cell Differ.* **33,** 57–83 (2001).
47. Kasai, K. & Hirabayashi, J. Galectins: a family of animal lectins that decipher glycocodes. *Sect. Title Gen. Biochem.* **119,** 1–8 (1996).
48. Rapoport, E. M., Kurmyshkina, O. V & Bovin, N. V. Mammalian galectins: Structure, carbohydrate specificity, and functions. *Sect. Title Gen. Biochem.* **73,** 393–405 (2008).
49. Leffler, H., Carlsson, S., Hedlund, M., Qian, Y. & Poirier, F. Introduction to galectins. *Glycoconj. J.* **19,** 433–440 (2004).
50. López-Lucendo, M. F. *et al.* Growth-regulatory Human Galectin-1: Crystallographic Characterisation of the Structural Changes Induced by Single-site Mutations and their Impact on the Thermodynamics of Ligand Binding. *J. Mol. Biol.* **343,** 957–970 (2004).
51. Seetharaman, J. *et al.* X-ray crystal structure of the human galectin-3 carbohydrate recognition domain at 2.1-A resolution. *J. Biol. Chem.* **273,** 13047–13052 (1998).
52. Sujatha, M. S., Sasidhar, Y. U. & Balaji, P. V. MP2/6-311++G(d,p) study on galactose-aromatic residue analog complexes in different position-orientations of the saccharide relative to aromatic residue. *J. Mol. Struct. THEOCHEM* **814,** 11–24 (2007).
53. Walser, P. J. *et al.* Structure and Functional Analysis of the Fungal Galectin CGL2. *Structure* **12,** 689–702 (2004).
54. Leonidas, D. D. *et al.* Structural Basis for the Recognition of Carbohydrates by Human Galectin-7. *Biochemistry* **37,** 13930–13940 (1998).
55. Massa, S. M., Cooper, D. N. W., Leffler, H. & Barondes, S. H. L-29, an endogenous lectin, binds to glycoconjugate ligands with positive cooperativity. *Biochemistry* **32,** 260–267 (1993).

56. Yoshii, T. *et al.* Galectin-3 phosphorylation is required for its anti-apoptotic function and cell cycle arrest. *J. Biol. Chem.* **277,** 6852–6857 (2002).
57. Hsu, D. K. & Liu, F.-T. Regulation of cellular homeostasis by galectins. *Glycoconj. J.* **19,** 507–515 (2002).
58. Takenaka, Y., Fukumori, T. & Raz, A. Galectin-3 and metastasis. *Glycoconj. J.* **19,** 543–549 (2002).
59. Liu, F.-T. Regulatory Roles of Galectins in the Immune Response. *Int. Arch. Allergy Immunol.* **136,** 385–400 (2005).
60. Ochieng, J., Furtak, V. & Lukyanov, P. Extracellular functions of galectin-3. *Glycoconj. J.* **19,** 527–535 (2002).
61. Dumic, J., Dabelic, S. & Flogel, M. Galectin-3: An open-ended story. *BBA - Gen. Subj.* **1760,** 616–635 (2006).
62. Lefranc, F., Le Mercier, M., Mathieu, V. & Kiss, R. Galectin-1, cancer cell migration, angiogenesis, and chemoresistance. in *Sect. Title Mamm. Pathol. Biochem.* 157–191 (2008).
63. Bacac, M. & Stamenkovic, I. Metastatic Cancer Cell. *Annu. Rev. Pathol. Mech. Dis.* **3,** 221–247 (2008).
64. Klein, C. A. Cancer. The metastasis cascade. *Science (80-.).* **321,** 1785–1787 (2008).
65. Byrd, J. C. & Bresalier, R. S. in *Sect. Title Mamm. Pathol. Biochem.* 193–221, 2 plates (2008).
66. Nangia-Makker, P. *et al.* Galectin-3 induces endothelial cell morphogenesis and angiogenesis. *Am. J. Pathol.* **156,** 899–909 (2000).
67. Nangia-Makker, P. *et al.* Galectin-3 induces endothelial cell morphogenesis and angiogenesis. *Am. J. Pathol.* **156,** 899–909 (2000).
68. Fukushi, J., Makagiansar, I. T. & Stallcup, W. B. NG2 Proteoglycan Promotes Endothelial Cell Motility and Angiogenesis via Engagement of Galectin-3 and a3β1 Integrin. *Mol. Biol. Cell* **15,** 3580 (2004).
69. Kim, H.-R. C., Lin, H.-M., Biliran, H. & Raz, A. Cell cycle arrest and inhibition of anoikis by galectin-3 in human breast epithelial cells. *Cancer Res.* **59,** 4148–4154 (1999).
70. Elola, M. T., Wolfenstein-Todel, C., Troncoso, M. F., Vasta, G. R. & Rabinovich, G. A. Galectins: matricellular glycan-binding proteins linking cell adhesion, migration, and survival. *Cell. Mol. Life Sci.* **64,** 1679–1700 (2007).
71. Warfield, P. R., Makker, P.-N., Raz, A. & Ochieng, J. Adhesion of human breast carcinoma to extracellular matrix proteins is modulated by galectin-3. *Invasion and Metastasis* **17,** 101–112 (1997).
72. Le Marer, N. & Hughes, R. C. Effects of the carbohydrate-binding protein galectin-3 on the invasiveness of human breast carcinoma cells. *J. Cell. Physiol.* **168,** 51–58 (1996).
73. Ochieng, J., Warfield, P., Green-Jarvis, B. & Fentie, I. Galectin-3 regulates the adhesive interaction between breast carcinoma cells and elastin. *J. Cell. Biochem.* **75,** 505 (1999).
74. Glinsky, V. V *et al.* Intravascular metastatic cancer cell homotypic aggregation at the sites of primary attachment to the endothelium. *Cancer Res.* **63,** 3805–3811 (2003).
75. Nakahara, S., Oka, N. & Raz, A. On the role of galectin-3 in cancer apoptosis. *Apoptosis* **10,** 267–275 (2005).
76. Yang, R.-Y., Hsu, D. K. & Liu, F.-T. Expression of Galectin-3 Modulates T-Cell Growth and Apoptosis. *Proc. Natl. Acad. Sci. U. S. A.* **93,** 6737; 39379–6742 (1996).
77. Akahani, S., Nangi-Makker, P., Inohara, H., Kim, H.-R. C. & Raz, A. Galectin-3: A novel antiapoptotic molecule with a functional BH1 (NWGR) domain of Bcl-2 family. *Cancer Res.* **57,** 5272–5276 (1997).
78. Fukumori, T. *et al.* Galectin-3 Regulates Mitochondrial Stability and Antiapoptotic Function in Response to Anticancer Drug in Prostate Cancer. *Cancer Res.* **66,** 3114 (2006).
79. Chauhan, D. *et al.* A Novel Carbohydrate-Based Therapeutic GCS-100 Overcomes Bortezomib Resistance and Enhances Dexamethasone-Induced Apoptosis in Multiple Myeloma Cells. *Cancer Res.* **65,** 8350 (2005).
80. Johnson, K. D. *et al.* Galectin-3 as a potential therapeutic target in tumors arising from malignant endothelia. *Neoplasia* **9,** 662–670 (2007).
81. Yu, F., Finley Jr., R. L., Raz, A. & Kim, H.-R. C. Galectin-3 translocates to the perinuclear membranes and inhibits cytochrome c release from the mitochondria. A role for synexin in galectin-3 translocation. *J. Biol. Chem.* **277,** 15819–15827 (2002).
82. Lavi, I. *et al.* Chemical characterization, antiproliferative and antiadhesive properties of polysaccharides extracted from Pleurotus pulmonarius mycelium and fruiting bodies. *Appl. Microbiol. Biotechnol.* **85,** 1977–1990 (2010).
83. Barondes, S. H. & Leffler, H. Multiple soluble beta galactoside-binding lectins from rat intestine. *J. Cell. Biochem. Suppl.* 59 (1989).
84. Platt, D. & Raz, A. Modulation of the lung colonization of B16-F1 melanoma cells by citrus pectin. *Sect. Title Pharmacol.* **84,** 438–442 (1992).
85. Pienta, K. J. *et al.* Inhibition of spontaneous metastasis in a rat prostate cancer model by oral administration of modified citrus pectin. *J. Natl. Cancer Inst.* **87,** 348–353 (1995).

86. Nangia-Makker, P. *et al.* Inhibition of human cancer cell growth and metastasis in nude mice by oral intake of modified citrus pectin. *Sect. Title Pharmacol.* **94,** 1854–1862 (2002).
87. Sathisha, U. V, Jayaram, S., Harish Nayaka, M. A. & Dharmesh, S. M. Inhibition of galectin-3 mediated cellular interactions by pectic polysaccharides from dietary sources. *Glycoconj. J.* **24,** 497–507 (2007).
88. Inohara, H. & Raz, A. Effects of natural complex carbohydrate (citrus pectin) on murine melanoma cell properties related to galectin-3 functions. *Glycoconj. J.* **11,** 527–532 (1994).
89. Johnson, K. D. *et al.* Galectin-3 as a potential therapeutic target in tumors arising from malignant endothelia. *Neoplasia* **9,** 662–670 (2007).
90. Glinskii, O. V *et al.* Mechanical entrapment is insufficient and intercellular adhesion is essential for metastatic cell arrest in distant organs. *Neoplasia* **7,** 522–527 (2005).
91. Colnot, C., Fowlis, D., Ripoche, M.-A., Bouchaert, I. & Poirier, F. Embryonic implantation in galectin 1/galectin 3 double mutant mice. *Dev. Dyn.* **211,** 306–313 (1998).
92. Arnusch, C. J. *et al.* Interference of the galactose-dependent binding of lectins by novel pentapeptide ligands. *Ther. Interv. Target. Protein-Protein Interact.* **14,** 1437–1440 (2004).
93. Zou, J., Glinsky, V. V, Landon, L. A., Matthews, L. & Deutscher, S. L. Peptides specific to the galectin-3 carbohydrate recognition domain inhibit metastasis-associated cancer cell adhesion. *Carcinogenesis* **26,** 309–318 (2005).
94. Sorme, P., Qian, Y., Nyholm, P.-G., Leffler, H. & Nilsson, U. J. Low Micromolar Inhibitors of Galectin-3 Based on 3'-Derivatization of N-Acetyllactosamine. *ChemBioChem* **3,** 183 (2002).
95. Delaine, T. *et al.* Galectin-Inhibitory Thiodigalactoside Ester Derivatives Have Antimigratory Effects in Cultured Lung and Prostate Cancer Cells. *J. Med. Chem.* **51,** 8109–8114 (2008).
96. Salameh, B. A., Cumpstey, I., Sundin, A., Leffler, H. & Nilsson, U. J. 1H-1,2,3-triazol-1-yl thiodigalactoside derivatives as high affinity galectin-3 inhibitors. *Bioorg. Med. Chem.* **18,** 5367–78 (2010).
97. Renard, C. M. G. C. & Thibault, J.-F. Degradation of pectins in alkaline conditions: kinetics of demethylation. *Carbohydr. Res.* **286,** 139–150 (1996).
98. Thibault, J.-F., Renard, C. M. G. C., Axelos, M. A. V, Roger, P. & Crépeau, M.-J. Studies of the length of homogalacturonic regions in pectins by acid hydrolysis. *Carbohydr. Res.* **238,** 271–286 (1993).
99. Beuth, J., Ko, H. L., Schirrmacher, V., Uhlenbruck, G. & Pulverer, G. Inhibition of liver tumor cell colonization in two animal tumor models by lectin blocking with D-galactose or arabinogalactan. *Clin. Exp. Metastasis* **6,** 115–120 (1988).
100. Sathisha, U., Jayaram, S., Harish Nayaka, M. & Dharmesh, S. Inhibition of galectin-3 mediated cellular interactions by pectic polysaccharides from dietary sources. *Glycoconj. J.* **24,** 497–507 (2007).
101. Timell, T. E., Glaudemans, C. P. J. & Gillham, J. K. Recent studies on polysaccharides of white birch and other hardwoods. *Tappi* **42,** 623–634 (1959).
102. R, T., S, K. & M, K. Studies on the pectin present in the bark of white willow Salix-alba fractionation and acidic depolymerization of the water soluble pectin. *Carbohydr. Res.* **43,** 111–116 (1975).
103. Farkas, E. & Thiem, J. Enzymatic Synthesis of Galactose-Containing Disaccharides Employing β-Galactosidase from Bacillus circulans. *European J. Org. Chem.* 3073 (1999).
104. El-Shenawy, H. & Schuerch, C. Synthesis and characterization of propyl O-β-d-galactopyranosyl-(1→4)-O-β-d-galactopyranosyl-(1→4)-α-d-galactopyranoside. *Carbohydr. Res.* **131,** 239–246 (1984).
105. Kováč, P. & Taylor, R. B. Alternative syntheses and related N.M.R. studies of precursors for internal β-d-galactopyranosyl residues in oligosaccharides, allowing chain extension at O-4. *Carbohydr. Res.* **167,** 153–173 (1987).
106. Lichtenthaler, F. W., Oberthur, M. & Peters, S. Directed and Efficient Syntheses of β-(1->4)-Linked Galacto-Oligosaccharides. *European J. Org. Chem.* 3849 (2001).
107. Komba, S., Terauchi, T. & Machida, S. A regio- and stereo-selective parallel synthesis of five types of trigalactoses on a solid support as a model of a combinatorial oligosaccharide library. *J. Appl. Glycosci.* **58,** 1–12 (2011).
108. Oberthür, M., Peters, S., Kumar Das, S. & Lichtenthaler, F. W. Synthesis of linear β-(1→4)-galacto-hexa- and heptasaccharides and studies directed towards cyclogalactans. *Carbohydr. Res.* **337,** 2171–2180 (2002).
109. Wang, Z. in *Compr. Org. Name React. Reagents* (John Wiley & Sons, Inc., 2010). doi:10.1002/9780470638859.conrr691
110. Xu, J. & Vasella, A. Oligosaccharide Analogues of Polysaccharides, Part 19, Synthesis of 2-(Naphthalen-1-yl)ethyl Cellooligoglycosides and [(Naphthalene-1,8-diyl)di(ethane-2,1-diyl)] Bis[cellooligoglycosides]. *Helv. Chim. Acta* **82,** 1728–1752 (1999).
111. Ohara, K. *et al.* Synthesis and Bioactivity of β-(1→4)-Linked Oligomannoses and Partially Acetylated Derivatives. *J. Org. Chem.* **78,** 6390–6411 (2013).

112. Van Steijn, A. M. P., van der Ven, J. G. M., van Seeventer, P., Kamerling, J. P. & Vliegenthart, J. F. G. Synthesis of a repeating pentasaccharide fragment of the capsular polysaccharide of Streptococcus pneumoniae type 18C. *Carbohydr. Res.* **229,** 155–160 (1992).
113. Evans, D. A., Kim, A. S., Metternich, R. & Novack, V. J. General strategies toward the syntheses of macrolide antibiotics. The total syntheses of 6-deoxyerythronolide B and oleandolide. *J. Am. Chem. Soc.* **120,** 5921–5942 (1998).
114. Lipták, A., Borbás, A., Jánossy, L. & Szilágyi, L. Preparation of (2-naphthyl)methylene acetals of glycosides and their hydrogenolytic transformation into 2-naphthylmethyl (NAP) ethers. *Tetrahedron Lett.* **41,** 4949–4953 (2000).
115. Kaburagi, Y., Osajima, H., Shimada, K., Tokuyama, H. & Fukuyama, T. 4-(tert-butyldimethylsilyloxy)benzylidene acetal: a novel benzylidene-type protecting group for 1,2-diols. *Tetrahedron Lett.* **45,** 3817–3821 (2004).
116. K, H., T, Y., T, T., Y, O. & O, Y. On the selectivity of deprotection of benzyl 4-methoxybenzyl and 3,4-dimethoxybenzyl protecting group for hydroxy functions. *Tetrahedron* **42,** 3021–3028 (1986).
117. Georg, G. I., Mashava, P. M., Akgun, E. & Milstead, M. W. Asymmetric synthesis of β-lactams and N-benzoyl-3-phenylisoserines via the Staudinger reaction. *Tetrahedron Lett.* **32,** 3151–3154 (1991).
118. Yan, L. & Kahne, D. p-Methoxybenzyl Ethers as Acid-Labile Protecting Groups in Oligosaccharide Synthesis. *Synlett* (1995).
119. Misra, A. K., Mukherjee, I., Mukhopadhyay, B. & Roy, N. Notes - A simple method for the removal of 4-methoxybenzoyl group. *Indian J. Chem. - Part B Org. Incl. Med.* **38,** (1999).
120. Gaunt, M. J., Yu, J. & Spencer, J. B. Rational Design of Benzyl-Type Protecting Groups Allows Sequential Deprotection of Hydroxyl Groups by Catalytic Hydrogenolysis. *J. Org. Chem.* **63,** 4172–4173 (1998).
121. Xia, J. Use of 1,2-dichloro 4,5-dicyanoquinone (DDQ) for cleavage of the 2-naphthylmethyl (NAP) group. *Tetrahedron Lett.* **41,** 169–173 (2000).
122. Sugimura, H. & Watanabe, K. Formal Synthesis of Cytosamine-A Component of Nucleoside Antibiotics, the Amicetin Family. *Synth. Commun.* **31,** 2313–2322 (2001).
123. Clausen, M. H., Jørgensen, M. R., Thorsen, J. & Madsen, R. A strategy for chemical synthesis of selectively methyl-esterified oligomers of galacturonic acid. *Perkin 1* **1,** 543–551 (2001).
124. Clausen, M. H. & Madsen, R. Synthesis of hexasaccharide fragments of pectin. *Chemistry* **9,** 3821–32 (2003).
125. Ratcliffe, A. J. & Fraser-Reid, B. Generation of α-D-glucopyranosylacetonitrilium ions. Concerning the reverse anomeric effect. *J. Chem. Soc., Perkin Trans. 1* 747–750 (1990).
126. Garegg, P. J., Hultberg, H. & Wallin, S. A novel, reductive ring-opening of carbohydrate benzylidene acetals. *Carbohydr. Res.* **108,** 97–101 (1982).
127. Xie, J., Molina, A. & Czernecki, S. Alkylidenation of Sugar Lactones and Further Transformation to C-Glycosides. *J. Carbohydr. Chem.* **18,** 481 (1999).
128. Schmidt, R. R., Behrendt, M. & Toepfer, A. Nitriles as solvents in glycosylation reactions highly selective beta glycoside synthesis. *Synlett* 694–696 (1990).
129. Herczeg, M. *et al.* Novel syntheses of Idraparinux, the anticoagulant pentasaccharide with indirect selective factor Xa inhibitory activity. *Tetrahedron* **69,** 3149–3158 (2013).
130. Liao, W., Locke, R. D. & Matta, K. L. Selectin ligands: 2,3,4-tri-acetyl-6-(2-naphthyl)methyl (NAP) α-D-galactopyranosyl imidate as a novel glycosyl donor for the efficient total synthesis of branched mucin core 2-structure containing the NeuAc α-2,3(SONa-6)Gal-β-1,3GalNAc alpha sequence. *Chem. Commun.* 369–370 (2000). doi:10.1039/A908511D
131. Clausen, M. H. & Madsen, R. Synthesis of hexasaccharide fragments of pectin. *Chem. Eur. J.* **9,** 3821–3832 (2003).
132. Mootoo, D. R., Konradsson, P., Udodong, U. & Fraser-Reid, B. Armed and disarmed n-pentenyl glycosides in saccharide couplings leading to oligosaccharides. *J. Am. Chem. Soc.* **110,** 5583–5584 (1988).
133. Konradsson, P., Udodong, U. E. & Fraser-Reid, B. Iodonium promoted reactions of disarmed thioglycosides. *Tetrahedron Lett.* **31,** 4313–4316 (1990).
134. Codée, J. D. C., Litjens, R. E. J. N., Van, den B., Overkleeft, H. S. & Van, der M. Thioglycosides in sequential glycosylation strategies. *Chem. Soc. Rev.* **34,** 769–782 (2005).
135. Veeneman, G. H. & van Boom, J. H. An efficient thioglycoside-mediated formation of α-glycosidic linkages promoted by iodonium dicollidine perchlorate. *Tetrahedron Lett.* **31,** 275–278 (1990).
136. Schmidt, T. H. & Madsen, R. Glycosylations Directed by the Armed-Disarmed Effect with Acceptors Containing a Single Ester Group. *European J. Org. Chem.* **2007,** 3935–3941 (2007).

137. Deng, S., Yu, B., Guo, Z. & Hui, Y. Chemical Synthesis of (4,6-Pyr)-Gal β1→4GlcNAcβ1→3Fucβ1→OMe: A Pyruvated Trisaccharide Related to the Cell Aggregation of the Sponge Microciona Prolifera. *J. Carbohydr. Chem.* **17,** 439 (1998).
138. Li, C. *et al.* Synthesis of 6′-acylamido-6′-deoxy-α-d-galactoglycerolipids. *Carbohydr. Res.* **376,** 15–23 (2013).
139. Jensen, H. H., Nordstrøm, L. U. & Bols, M. The disarming effect of the 4,6-acetal group on glycoside reactivity: Torsional or electronic? *J. Am. Chem. Soc.* **126,** 9205–9213 (2004).
140. Zhang, Z. *et al.* Programmable One-Pot Oligosaccharide Synthesis. *J. Am. Chem. Soc.* **121,** 734–753 (1999).
141. Lahmann, M. & Oscarson, S. Investigation of the reactivity difference between thioglycoside donors with variant aglycon parts. *Can. J. Chem.* 889–893 (2002). doi:10.1139/V02-101
142. Lindhorst, T. K. Essential[s] of carbohydrate chemistry and biochemistry. (2008).
143. Aversa, M. C., Barattucci, A. & Bonaccorsi, P. Glycosulfoxides in carbohydrate chemistry. *Tetrahedron* **64,** 7659–7683 (2008).
144. Kahne, D., Walker, S., Cheng, Y. & Van Engen, D. Glycosylation of unreactive substrates. *J. Am. Chem. Soc.* **111,** 6881–6882 (1989).
145. Yan, L. & Kahne, D. Generalizing Glycosylation: Synthesis of the Blood Group Antigens Lea, Leb, and Lex Using a Standard Set of Reaction Conditions. *J. Am. Chem. Soc.* **118,** 9239–9248 (1996).
146. Nicolaou, K. C., Dolle, R. E., Papahatjis, D. P. & Randall, J. L. Practical synthesis of oligo saccharides partial synthesis of avermectin b-1a. *J. Am. Chem. Soc.* **106,** 4189–4192 (1984).
147. Nicolaou, K. C., Chucholowski, A., Dolle, R. E. & Randall, J. L. Reactions of glycosyl fluorides. Synthesis of O-, S-, and N-glycosides. *J. Chem. Soc., Chem. Commun.* 1155–1156 (1984).
148. Okagawa, T. & Takahashi, Y. Total synthesis of alpha cyclodextrin. *Carbohydr. Res.* **138,** C5–C9 (1985).
149. Matsumoto, T., Maeta, H., Suzuki, K. & Tsuchihashi, late G. New glycosidation reaction - Combinational use of Cp2ZrCl2-AgClO4 for activation of glycosyl fluorides and application to highly β-selective glycosidation of D-mycinose. *Tetrahedron Lett.* **29,** 3567–3570 (1988).
150. Suzuki, K., Maeta, H., Matsumoto, T. & Tsuchihashi, late G. New glycosidation reaction 2. preparation of 1-fluoro-d-desosamine derivative and its efficient glycosidation by the use of Cp2HfCl2-AgClO4 as the activator. *Tetrahedron Lett.* **29,** 3571–3574 (1988).
151. Mukaiyama, T., Murai, Y. & Shoda, S. An efficient method for glucosylation of hydroxy compounds using glucopyranosyl fluoride. *Chem. Lett.* 431–432 (1981). doi:10.1246/cl.1981.431
152. Schmidt, R. R. New Methods for the Synthesis of Glycosides and Oligosaccharides - Are There Alternatives to the Koenigs-Knorr Method? [New Synthetic Methods (56)]. *Angew. Chemie Int. Ed. English* **25,** 212–235 (1986).
153. Schmidt, R. R. & Michel, J. Direct o-glycosyl trichloroacetimidate formation, nucleophilicity of the anomeric oxygen atom. *Tetrahedron Lett.* **25,** 821–824 (1984).
154. Schmidt, R. R. & Toepfer, A. Glycosylation with highly reactive glycosyl donors: efficiency of the inverse procedure. *Tetrahedron Lett.* **32,** 3353–3356 (1991).
155. Yu, B. & Sun, J. Glycosylation with glycosyl N-phenyltrifluoroacetimidates (PTFAI) and a perspective of the future development of new glycosylation methods. *Chem. Commun.* **46,** 4668–79 (2010).
156. Hanashima, S., Castagner, B., Esposito, D., Nokami, T. & Seeberger, P. H. Synthesis of a sialic acid alpha(2-3) galactose building block and its use in a linear synthesis of sialyl Lewis X. *Org. Lett.* **9,** 1777–1779 (2007).
157. Ueki, A., Takano, Y., Kobayashi, A., Nakahara, Y. & Hojo, H. Solid-phase synthesis of glycopeptide carrying a tetra-N-acetyllactosamine-containing core 2 decasaccharide. *Tetrahedron* **66,** 1742–1759 (2010).
158. Peng, W., Han, X. & Yu, B. Synthesis of a Typical Glucuronide-Containing Saponin, 28-O-β-d-Glucopyranosyl Oleanate 3-O-β-d-Galactopyranosyl-(1→2)-[β- d -glucopyranosyl-(1→3)]-β- d -glucuronopyranoside. *Synthesis (Stuttg).* **2004,** 1641–1647 (2004).
159. Pastore, A., Adinolfi, M., Iadonisi, A. & Valerio, S. One-Pot Catalytic Glycosidation/Fmoc Removal - An Iterable Sequence for Straightforward Assembly of Oligosaccharides Related to HIV gp120. *European J. Org. Chem.* **2010,** 711–718 (2010).
160. Adinolfi, M., Iadonisi, A., Ravida, A. & Schiattarella, M. Effect of dimethoxyethane in Yb(OTf)(3)-promoted glycosidations. *Tetrahedron Lett.* **45,** 4485–4488 (2004).
161. Tanaka, H., Iwata, Y., Takahashi, D., Adachi, M. & Takahashi, T. Efficient Stereoselective Synthesis of gamma-N-Glycosyl Asparagines by N-Glycosylation of Primary Amide Groups. *J. Am. Chem. Soc.* **127,** 1630–1631 (2005).
162. Tamura, K., Mizukami, H., Maeda, K., Watanabe, H. & Uneyama, K. One-pot synthesis of trifluoroacetimidoyl halides. *J. Org. Chem.* **58,** 32–35 (1993).

163. Li, Z. & Gildersleeve, J. C. Mechanistic Studies and Methods To Prevent Aglycon Transfer of Thioglycosides. *J. Am. Chem. Soc.* **128,** 11612–11619 (2006).
164. Pedersen, C. M., Nordstrøm, L. U. & Bols, M. "Super Armed" Glycosyl Donors: Conformational Arming of Thioglycosides by Silylation. *J. Am. Chem. Soc.* **129,** 9222–9235 (2007).
165. Smith, M., Rammler, D. H., Goldberg, I. H. & Khorana, H. G. Studies on Polynucleotides. XIV.1 Specific Synthesis of the C3"-C5" Interribonucleotide Linkage. Syntheses of Uridylyl-(3"→5")-Uridine and Uridylyl-(3"→5")-Adenosine2. *J. Am. Chem. Soc.* **84,** 430–440 (1962).
166. Corey, E. J. & Venkateswarlu, A. Protection of hydroxyl groups as tert-butyldimethylsilyl derivatives. *J. Am. Chem. Soc.* **94,** 6190–6191 (1972).
167. Lafont, D., Boullanger, P., Cadas, O. & Descotes, G. A mild procedure for the preparation of 1,6-anhydro-β-D-hexapyranoses and derivatives. *Synthesis (Stuttg).* 191–194 (1989).
168. Shibagaki, M., Takahashi, K., Kuno, H., Honda, I. & Matsushita, H. Synthesis of Levoglucosenone. *Chem. Lett.* **19,** 307–310 (1990).
169. Blanc-Muesser, M., Defaye, J. & Driguez, H. Stereoselective thioglycoside syntheses. Part 4. A new approach to 1,4-linked 1-thio-disaccharides and a synthesis of thiomaltose. *J. Chem. Soc. Perkin Trans. 1* 15–18 (1982). doi:10.1039/P19820000015
170. Paulsen, H. & Lockhoff, O. Bausteine von Oligosacchariden. Neue effektive β-Glycosidsynthese für Mannose-Glycoside Synthesen von Mannose-haltigen Oligosacchariden. *Chem. Ber.* **114,** 3102–3114 (1981).
171. Hung, S.-C. *et al.* Synthesis of heparin oligosaccharides and their interaction with eosinophil-derived neurotoxin. *Org. Biomol. Chem.* **10,** 760–772 (2012).
172. Ogawa, S. & Sugizaki, H. Synthesis of N-[(1R)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl] derivatives of 4′-amino-4′-deoxy- and 4′-amino-4′,6′-dideoxy-cellobiose. *Carbohydr. Res.* **156,** 264–272 (1986).
173. Mannerstedt, K., Segerstedt, E., Olsson, J. & Oscarson, S. Synthesis of a common tetrasaccharide motif of Haemophilus influenzae LPS inner core structures. *Org. Biomol. Chem.* **6,** 1087–1091 (2008).
174. Wang, L., Sakairi, N. & Kuzuhara, H. 1,6-anhydro-B-D-glucopyranose derivatives as glycosyl donors for thioglycosylation reactions. *J. Am. Chem. Soc. perkin Trans. 1* 1677–1682 (1990).
175. Hanessian, S. & Guindon, Y. Chemistry of the glycosidic linkage - direct conversion of glycosides into 1-thioglycosides by use of [alkyl(oraryl)thio]trimethylsilanes. *Carbohydr. Res.* **86,** C3–C6 (1980).
176. Van den Bos, L. J., Litjens, R. E. J. N., van den Berg, R. J. B. H. N., Overkleeft, H. S. & van der Marel, G. A. Preparation of 1-Thio Uronic Acid Lactones and Their Use in Oligosaccharide Synthesis. *Org. Lett.* **7,** 2007–2010 (2005).
177. Crich, D. & Sun, S. Formation of β-Mannopyranosides of Primary Alcohols Using the Sulfoxide Method. *J. Org. Chem.* **61,** 4506–4507 (1996).
178. Cao, S., Hernandez-Mateo, F. & Roy, R. Scope and applications of "active and latent" thioglycosyl donors. Part 4. *J. Carbohydr. Chem.* **17,** 609–631 (1998).
179. Boss, R. & Scheffold, R. Cleavage of allyl ethers with Pd-C. *Angew. Chem. Int. Ed. Engl.* **15,** 558–559 (1976).
180. Chiesa, M. V. & Schmidt, R. R. Synthesis of an Asparagine-Linked Heptasaccharide − Basic Structure of N-Glycans. *European J. Org. Chem.* **2000,** 3541–3554 (2000).
181. Zhiyuan, Z. & Magnusson, G. Conversion of p-methoxyphenyl glycosides into the corresponding glycosyl chlorides and bromides, and into thiophenyl glycosides. *Carbohydr. Res.* **295,** 41–55 (1996).
182. Grundler, G. & Schmidt, R. R. Glycosylimidates 13. application of the trichloroacetimidate procedure to 2-azidoglucose and 2-azidogalactose derivatives. *Liebigs Ann. der Chemie* 1826–1847 (1984).
183. Hashimoto, S., Honda, T., Yanagiya, Y., Nakajima, M. & Ikegami, S. Highly selective glycosidation reactions on phosphorus-containing leaving groups. *J. Synth. Org. Chem. JAPAN* **53,** 620–632 (1995).
184. Li, Y. *et al.* Gold(I)-Catalyzed Glycosylation with Glycosyl ortho-Alkynylbenzoates as Donors: General Scope and Application in the Synthesis of a Cyclic Triterpene Saponin. *Chem. – A Eur. J.* **16,** 1871–1882 (2010).
185. Lemieux, R. U., Hendriks, K. B., Stick, R. V & James, K. Halide ion catalyzed glycosidation reactions syntheses of alpha-linked disaccharides. *J. Am. Chem. Soc.* **97,** 4056–4062 (1975).
186. Ohashi, I., Lear, M. J., Yoshimura, F. & Hirama, M. Use of polystyrene-supported DBU in the synthesis and alpha-selective glycosylation study of the unstable Schmidt donor of L-kedarosamine. *Org. Lett.* **6,** 719–722 (2004).
187. Weingart, R. & Schmidt, R. R. Can preferential beta-mannopyranoside formation with 4,6-O-benzylidene protected mannopyranosyl sulfoxides be reached with trichloroacetimidates? *Tetrahedron Lett.* **41,** 8753–8758 (2000).

188. Schmidt, R. R. & Michel, J. Facile Synthesis of a- and b-0-Glycosyl Imidates ; Preparation of Glycosides and Disaccharides. *Angew. Chem. Int. Ed. Engl.* **19,** 731–732 (1980).
189. Adinolfi, M., Barone, G., Iadonisi, A., Mangoni, L. & Schiattarella, M. Activation of disarmed 2-O-alkoxycarbonylated glycosyl trichloroacetimidates with lanthanide triflates: an efficient approach for the synthesis of 1,2-trans glycosides. *Tetrahedron Lett.* **42,** 5967–5969 (2001).
190. Rajput, V. K. & Mukhopadhyay, B. Concise Synthesis of a Pentasaccharide Related to the Anti-Leishmanial Triterpenoid Saponin Isolated from Maesa balansae†. *J. Org. Chem.* **73,** 6924–6927 (2008).
191. Yang, Z., Lin, W. & Yu, B. Rearrangement of sugar 1,2-orthoesters to glycosidic products: a mechanistic implication. *Carbohydr. Res.* **329,** 879–884 (2000).
192. Demchenko, A. V. Handbook of chemical glycosylation : advances in stereoselectivity and therapeutic relevance. (2008).
193. Van Boeckel, C. A. A. & van Boom, J. H. Synthesis of glucosylphosphatidylglycerol via a phosphotriester intermediate. *Tetrahedron Lett.* **20,** 3561–3564 (1979).
194. Oltvoort, J. J., Van Boeckel, C. A. A., De Koning, J. H. & Van Boom, J. H. Use of the Cationic Iridium Complex 1,5-Cyclooctadiene-bis[methyldiphenylphosphine]-iridium Hexafluorophosphate in Carbohydrate Chemistry: Smooth Isomerization of Allyl Ethers to 1-Propenyl Ethers. *Synthesis (Stuttg).* **1981,** 305–308 (1981).
195. Nakayama, K., Uoto, K., Higashi, K., Soga, T. & Kusama, T. A Useful Method for Deprotection of the Protective Allyl Group at the Anomeric Oxygen of Carbohydrate Moieties Using Tetrakis(triphenylphosphine)palladium. *Chem. Pharm. Bull. (Tokyo).* **40,** 1718–1720 (1992).
196. Lohman, G. J. S. & Seeberger, P. H. A stereochemical surprise at the late stage of the synthesis of fully N-differentiated heparin oligosaccharides containing amino, acetamido, and N-sulfonate groups. *J. Org. Chem.* **69,** 4081–93 (2004).
197. Hanessian, S. & Lavallee, P. The Preparation and Synthetic Utility of tert-Butyldiphenylsilyl Ethers. *Can. J. Chem.* **53,** 2975–2977 (1975).
198. Nicolaou, K. C., Seitz, S. P., Pavia, M. R. & Petasis, N. A. Synthesis of macrocycles by intramolecular ketophosphonate reactions. Stereoselective construction of the "left-wing" of carbomycin B and a synthesis of dl-muscone from oleic acid. *J. Org. Chem.* **44,** 4011–4013 (1979).
199. Wuts, P. G. M. & Greene, T. W. in *Prot. Groups Org. Synth.* **Fourth,** 84 (John Wiley & Sons, 2007).
200. Hummel, G. & Schmidt, R. A Versatile Synthesis of the lactoneo-Series Antigens - Synthesis of Sialyl Dimer Lewis X and of Dimer Lewis y1. *Tetrahedron Lett.* **38,** 1173–1176 (1997).
201. Chen, J., Zhou, Y., Chen, C., Xu, W. & Yu, B. Synthesis of a tetrasaccharide substrate of heparanase. *Carbohydr. Res.* **343,** 2853–2862 (2008).
202. Lassaletta, J. M., Meichle, M., Weiler, S. & Schmidt, R. R. Silyl Group Migration in 1-O-Silyl Protected Sugars-Convenient Synthesis of 2-O-Unprotected Sugars. *J. Carbohydr. Chem.* **15,** 241–254 (1996).
203. Kværnø, L., Ritter, T., Werder, M., Hauser, H. & Carreira, E. M. An In Vitro Assay for Evaluation of Small-Molecule Inhibitors of Cholesterol Absorption. *Angew. Chemie Int. Ed.* **43,** 4653–4656 (2004).
204. Pohi, N. L. & Kiessling, L. L. Para-chlorobenzyl protecting groups as stabilizers of the glycosidic linkage: Synthesis of the 3′-O-sulfated Lewis x trisaccharide. *Tetrahedron Lett.* **38,** 6985–6988 (1997).
205. Adinolfi, M., Barone, G., Guariniello, L. & Iadonisi, A. An easy and efficient approach for the installation of alkoxycarbonyl protecting groups on carbohydrate hydroxyls. *Tetrahedron Lett.* **41,** 9305–9310 (2000).
206. Higashibayashi, S. *et al.* Letters - Selective Deprotection of t-Butyldiphenylsilyl Ethers in the Presence of t-Butyldimethylsilyl Ethers by Tetrabutylammonium Fluoride, Acetic Acid, and Water. *Synlett* (2000).
207. Yu, B. & Tao, H. Glycosyl trifluoroacetimidates. Part 1: Preparation and application as new glycosyl donors. *Tetrahedron Lett.* **42,** 2405–2407 (2001).
208. Hoffmann, R. W. & Ditrich, K. Total synthesis of mycinolide-V. *Liebigs Ann. der Chemie* **1990,** 23–29 (1990).
209. Zhang, H. X., Guibe, F. & Balavoine, G. Selective palladium-catalyzed deprotection of the allyl and allyloxycarbonyl groups in phosphate chemistry and in the presence of propargyl and propargyloxycarbonyl groups. *Tetrahedron Lett.* **29,** 623–626 (1988).
210. Branden, C. & Tooze, J. Introduction to protein structure. (1999).
211. Danishefsky, S. & Hungate, R. The total synthesis of octosyl acid A: a new departure in organostannylene chemistry. *J. Am. Chem. Soc.* **108,** 2486–2487 (1986).
212. David, S., Thieffry, A. & Veyrières, A. A mild procedure for the regiospecific benzylation and allylation of polyhydroxy-compounds via their stannylene derivatives in non-polar solvents. *J. Chem. Soc. Perkin Trans. I* 1796–1801 (1981). doi:10.1039/P19810001796
213. DeNinno, M. P., Etienne, J. B. & Duplantier, K. C. A method for the selective reduction of carbohydrate 4,6-O-benzylidene acetals. *Tetrahedron Lett.* **36,** 669–672 (1995).

214. Yuan, Y. *et al.* Dimethyl Sulfoxide/Potassium Hydroxide: A Superbase for the Transition Metal Free Preparation of Cross Coupling Products. *Adv. Synth. Catal.* **352,** 2892–2898 (2010).
215. Rao, K. V., Patil, P. R., Atmakuri, S. & Kartha, K. P. R. Iodine-sodium cyanoborohydride-mediated reductive ring opening of 4,6-O-benzylidene acetals of hexopyranosides. *Carbohydr. Res.* **345,** 2709–13 (2010).
216. Shie, C.-R., Tzeng, Z.-H., Wang, C.-C. & Hung, S.-C. Metal Trifluoromethanesulfonate-Catalyzed Regioselective Reductive Ring Opening of Benzylidene Acetals. *J. Chinese Chem. Soc.* **56,** 510–523 (2009).
217. Wu, X., Cui, L., Lipinski, T. & Bundle, D. R. Synthesis of Monomeric and Dimeric Repeating Units of the Zwitterionic Type 1 Capsular Polysaccharide from Streptococcus pneumoniae. *Chem. – A Eur. J.* **16,** 3476–3488 (2010).
218. Sakairi, N. & Kuzuhara, H. Chemical behavior of benzylidene acetal groups bridging the contiguous glucose residues in malto-oligosaccharide derivatives. *Carbohydr. Res.* **246,** 61–73 (1993).
219. Card, P. J. Fluorinated carbohydrates. Use of DAST in the synthesis of fluorinated sugars. *J. Org. Chem.* **48,** 393–395 (1983).
220. Subotkowski, W., Friedrich, D. & Weiberth, F. J. Syntheses and NMR characterizations of epimeric 4-deoxy-4-fluoro carbohydrates. *Carbohydr. Res.* **346,** 2323–2326 (2011).
221. Cumpstey, I. *et al.* Synthesis of fluorescence-labelled disaccharide substrates of glucosidase II. *Carbohydr. Res.* **338,** 1937–1949 (2003).
222. Wilson, B. G. & Fraser-Reid, B. n-Pentenyl Glycoside Based Methodology for Determining the Relative Reactivities of Variously Protected Pairs of Glycosides. *J. Org. Chem.* **60,** 317–320 (1995).
223. Greene, E. A., Drian, C. L. E. & Crabbe, P. An efficient total synthesis of racemic Brefeldin A. *J. Am. Chem. Soc.* **102,** 7583–7584 (1980).
224. Marshall, J. A. & XIE, S. P. Syntheis of a C22-34 subunit of the immunosupressant FK-506. *J. Org. Chem.* **60,** 7230–7237 (1995).
225. Paterson, I. & Coster, M. J. Total synthesis of altohyrtin A (spongistatin 1): an alternative synthesis of the CD-spiroacetal subunit. *Tetrahedron Lett.* **43,** 3285–3289 (2002).
226. Yu, B. & Tao, H. Glycosyl Trifluoroacetimidates. 2. Synthesis of Dioscin and Xiebai Saponin I. *J. Org. Chem.* **67,** 9099–9102 (2002).
227. Clausen, M. H. Synthesis and Application of Pectic Oligosaccharides. (2002).
228. Naruto, M., Ohno, K., Naruse, N. & Takeuchi, H. Synthesis of Prostaglandins and their congeners I. (+)-11-deoxy-11α-hydroxymethyl prostaglandin F2α from aucubin. *Tetrahedron Lett.* **20,** 251–254 (1979).
229. Nicolaou, K. C., Caulfield, T. J., Kataoka, H. & Stylianides, N. A. Total synthesis of the tumor-associated Lex family of glycosphingolipids. *J. Am. Chem. Soc.* **112,** 3693–3695 (1990).
230. Griffin, B. E., Jarman, M. & Reese, C. B. The synthesis of oligoribonucleotides-iV Preparation of dinucleoside phosphates from 2',5'-protected ribonucleoside derivatives. *Tetrahedron* **24,** 639–662 (1968).
231. Trost, B. M., Godleski, S. A. & Belletire, J. L. Synthesis of (+/-)-Catharanthine via organopalladium chemistryCATHARANTHINE VIA ORGANOPALLADIUM CHEMISTRY. *J. Org. Chem.* **44,** 2052–2054 (1979).
232. Nicolaou, K. C. & Webber, S. E. Stereocontrolled toatl synthesis of Lipoxins-B. *Synthesis (Stuttg).* 453–461 (1986).
233. Birch, A. J. 117. Reduction by dissolving metals. Part I. *J. Chem. Soc.* 430–436 (1944). doi:10.1039/JR9440000430
234. Fuwa, H., Fujikawa, S., Tachibana, K., Takakura, H. & Sasaki, M. Convergent synthesis of the ABCDE ring fragment of ciguatoxins. *Tetrahedron Lett.* **45,** 4795–4799 (2004).
235. Boltje, T. J., Li, C. & Boons, G.-J. Versatile Set of Orthogonal Protecting Groups for the Preparation of Highly Branched Oligosaccharides. *Org. Lett.* **12,** 4636–4639 (2010).
236. Fischer, E. Ueber die Glucoside der Alkohole. *Chem. Ber.* **26,** 2400–2412 (1893).
237. Callam, C. S. & Lowary, T. L. Synthesis of Methyl 2,3,5-Tri-O-benzoyl-alpha-D-arabinofuranoside in the Organic Laboratory. *J. Chem. Educ.* **78,** 73–74 (2001).
238. Liang, X.-Y., Deng, L.-M., Liu, X. & Yang, J.-S. Efficient one-pot syntheses of α-d-arabinofuranosyl tri- and tetrasaccharides present in cell wall polysaccharide of Mycobacterium tuberculosis. *Tetrahedron* **66,** 87–93 (2010).
239. Mbadugha, B. N. A. & Menger, F. M. Sugar/Steroid/Sugar Conjugates: Sensitivity of Lipid Binding to Sugar Structure. *Org. Lett.* **5,** 4041–4044 (2003).
240. Burton, B. A. & Brant, D. A. Comparative flexibility, extension, and conformation of some simple polysaccharide chains. *Biopolymers* **22,** 1769–1792 (1983).
241. Szpilman, A. M. & Carreira, E. M. β-Glycosidation of Sterically Hindered Alcohols. *Org. Lett.* **11,** 1305–1307 (2009).

242. Paulsen, H. Advances in Selective Chemical Syntheses of Complex Oligosaccharides. *Angew. Chemie Int. Ed. English* **21,** 155–173 (1982).
243. Komba, S. & Machida, S. UCHP method for oligosaccharide combinatorial library synthesis. *J. Carbohydr. Chem.* **28,** 369–393 (2009).
244. Ziegler, T., Adams, B., Kovac, P. & Glaudemans, C. P. J. Alternative syntheses of (1→3)-β-D-galacto-oligosaccharides. *J. Carbohydr. Chem.* **9,** 135–158 (1990).
245. Fenger, T. H. & Madsen, R. Regioselective Glycosylation of Unprotected Phenyl 1-Thioglycopyranosides with Phenylboronic Acid as a Transient Masking Group. *European J. Org. Chem.* **2013,** 5923–5933 (2013).
246. Kovac, P., Taylor, R. B. & Glaudemans, C. P. J. General synthesis of (1-3)-beta-D-galacto oligosaccharides and their methyl beta-glycosides by a stepwise approach. *J. Org. Chem.* **50,** 5323–5333 (1985).
247. McGill, N. W. & Williams, S. J. 2,6-Disubstituted benzoates as neighboring groups for enhanced diastereoselectivity in beta-galactosylation reactions: synthesis of beta-1,3-linked oligogalactosides related to arabinogalactan proteins. *J. Org. Chem.* **74,** 9388–98 (2009).
248. Chowdary, S. M., Navia, L. J. & Anderson, L. The assembly of oligosaccharides from standardized intermediates beta-1-3-linked oligomers of D-galactose. *Carbohydr. Res.* **150,** 173–186 (1986).
249. Ellervik, U. & Magnusson, G. A High Yielding Chemical Synthesis of Sialyl Lewis x Tetrasaccharide and Lewis x Trisaccharide; Examples of Regio- and Stereodifferentiated Glycosylations. *J. Org. Chem.* **63,** 9314–9322 (1998).
250. Misra, A. K. & Agnihotri, G. Chloramine-T-mediated chemoselective hydrolysis of thioglycosides into glycosyl hemiacetals under neutral conditions. *Carbohydr. Res.* **339,** 885–890 (2004).
251. Xu, Y. C., Bizuneh, A. & Walker, C. Selective deprotection of alkyl esters using magnesium methoxide. *Tetrahedron Lett.* **37,** 455–458 (1996).
252. Neilson, T. & Werstiuk, E. S. Oligoribonucleotide synthesis 3. Synthesis of trinucleotides using a stepwise phosphotriester method. *Can. J. Chem.* **49,** 3004–3011 (1971).
253. Leys, V. *et al.* Total synthesis of the anthelmintic macrolide Avermectin B1A. *J. Chem. Soc. Perkin Trans. I* 667–692 (1991).
254. Li, A. & Kong, F. Syntheses of beta-(1->6)-branched beta-(1->3)-linked d-galactans that exist in the rhizomes of Atractylodes lancea DC. *Carbohydr. Res.* **340,** 1949–62 (2005).
255. Cunico, R. F. & Bedell, L. The triisopropylsilyl group as a hydroxyl-protecting function. *J. Org. Chem.* **45,** 4797–4798 (1980).
256. Lakhmiri, R., Lhoste, P. & Sinou, D. Allyl ethyl carbonate/palladium (0), a new system for the one step conversion of alcohols into allyl ethers under neutral conditions. *Tetrahedron Lett.* **30,** 4669–4672 (1989).
257. Crich, D. & Smith, M. 1-Benzenesulfinyl piperidine/trifluoromethanesulfonic anhydride: a potent combination of shelf-stable reagents for the low-temperature conversion of thioglycosides to glycosyl triflates and for the formation of diverse glycosidic linkages. *J. Am. Chem. Soc.* **123,** 9015–20 (2001).
258. Codee, J. D. C. *et al.* Ph2SO/Tf2O: a powerful promotor system in chemoselective glycosylations using thioglycosides. *Org. Lett.* **5,** 1519–1522 (2003).
259. Tatai, J. & Fügedi, P. A new, powerful glycosylation method: activation of thioglycosides with dimethyl disulfide-triflic anhydride. *Org. Lett.* **9,** 4647–4650 (2007).
260. Valdor, J.-F. & Mackie, W. Synthesis of a Trisaccharide Repeating Unit Related to Arabinogalactan-Protein (AGP) Polysaccharides 1. *J. Carbohydr. Chem.* **16,** 429–440 (1997).
261. Kartha, R. K. P., Kiso, M., Hasegawa, A. & Jennings, H. J. Simple and efficient strategy for making β-(1→6)-linked galactooligosaccharides using "naked" galactopyranosides as acceptors. *J. Chem. Soc. Perkin Trans. 1 Org. Bio-Organic Chem.* 3023–3026 (1995).
262. Kovac, P. Systematic chemical synthesis of (1 → 6)-β-D-galactooligosaccharides and related compounds. *Carbohydr. Res.* **144,** C12–C14 (1985).
263. Kovac, P., Yeh, H. J. C. & Glaudemans, C. P. J. Synthesis of specifically fluorinated methyl β-glycosides of (1 → 6)-β-D-galactooligosaccharides. Part III. Synthesis of methyl O-(3-deoxy-3-fluoro-β-D-galactopyranosyl)-(1 → 6)-β-D-galactopyranoside and methyl O-(3-deoxy-3-fluoro-β-D-galactopyranosyl)-(1. *Carbohydr. Res.* **140,** 277–288 (1985).
264. Ziegler, T., Pavliak, V., Lin, T. H., Kovac, P. & Glaudemans, C. P. J. Synthesis of specifically deoxygenated ligands related to (1→6)-β-D-galacto-oligosaccharides, and studies on their binding to monoclonal antigalactan antibodies. *Carbohydr. Res.* **204,** 167–186 (1990).
265. Srivastava, V. K., Sondheimer, S. J. & Schuerch, C. Synthesis and characterization of methyl 6-O-β-D-galactopyranosyl-β-D-galactopyranoside and methyl O-β-D-galactopyranosyl-(1→6)-O-β-D-galactopyranosyl-(1→6)-β-D-galactopyranoside. *Carbohydr. Res.* **86,** 203–214 (1980).

266. Nashed, E. M. & Glaudemans, C. P. J. Synthesis of 2,3-epoxypropyl-beta-glycosides of 1-6-beta-D-galactopyranooligosaccharides and their binding to monoclonal anti-galactan IGA J539 and IGA X. *Carbohydr. Res.* **158,** 125–136 (1986).
267. Kovac, P. Efficient chemical synthesis of methyl β-glycosides of (1 → 6)-β-linked D-galacto-oligosaccharides by a stepwise and a blockwise approach. *Carbohydr. Res.* **153,** 237–251 (1986).
268. Ekborg, G., Vranesić, B., Bhattacharjee, A. K., Kovác, P. & Glaudemans, C. P. Synthesis of p-nitrophenyl beta-glycosides of (1----6)-beta-D-galactopyranosyl-oligosaccharides. *Carbohydr. Res.* **142,** 203–211 (1985).
269. Bhattacharjee, A. K., Zissis, E. & Glaudemans, C. P. J. Synthesis of 6-O-(6-O-β-D-galactopyranosyl-β-D-galactopyranosyl)-D-galactopyranose by use of 2,3,4-tri-O-acetyl-6-O-(chloroacetyl)-α-D-galactopyranosyl bromide, a key intermediate for the solid-phase synthesis of β-(1 → 6)-linked D-galactopyranans. *Carbohydr. Res.* **89,** 249–254 (1981).
270. Liang, X.-Y., Liu, Q.-W., Bin, H.-C. & Yang, J.-S. One-pot synthesis of branched oligosaccharides by use of galacto- and mannopyranosyl thioglycoside diols as key glycosylating agents. *Org. Biomol. Chem.* **11,** 3903–3917 (2013).
271. Ning, J., Wang, H. & Yi, Y. A simple approach to 3,6-branched galacto-oligosaccharides and its application to the syntheses of a tetrasaccharide and a hexasaccharide related to the arabinogalactans (AGs). *Tetrahedron Lett.* **43,** 7349–7352 (2002).
272. Du, Y., Zhang, M., Yang, F. & Gu, G. A simple access to 3,6-branched oligosaccharides: Synthesis of a glycopeptide derivative that relates to Lycium barbarum L. *J. Chem. Soc. Perkin Trans. 1* 3122–3127 (2001). doi:10.1039/b108399f
273. Fekete, A., Borbas, A., Antus, S. & Liptak, A. Synthesis of 3,6-branched arabinogalactan-type tetra- and hexasaccharides for characterization of monoclonal antibodies. *Carbohydr. Res.* **344,** 1434–1441 (2009).
274. Yang, B., Jing, Y. & Huang, X. Fluorous-Assisted One-Pot Oligosaccharide Synthesis. *European J. Org. Chem.* 1290–1298, S1290/1–S1290/45 (2010). doi:10.1002/ejoc.200901155
275. Huang, L., Wang, Z. & Huang, X. One-pot oligosaccharide synthesis: reactivity tuning by post-synthetic modification of aglycon. *Chem. Commun. (Cambridge, United Kingdom)* 1960–1961 (2004). doi:10.1039/b405886k
276. Zhu, Y. & Kong, F. Regio- and stereoselective synthesis of 1→6 linked manno-, gluco-, and galactopyranose di-, tri-, and tetrasaccharides via orthoester intermediates. *J. Carbohydr. Chem.* **19,** 837–848 (2000).
277. Du, Y., Pan, Q. & Kong, F. Synthesis of a tetrasaccharide representing a minimal epitope of an arabinogalactan. *Carbohydr. Res.* **323,** 28–35 (2000).
278. Timmers, C. M., Wigchert, S. C. M., Leeuwenburgh, M. a., van der Marel, G. a. & van Boom, J. H. Synthesis of Tetrameric Arabinogalactans Based on 1,2-Anhydrosugars. *European J. Org. Chem.* **1998,** 91–97 (1998).
279. Ziegler, T., Kovac, P. & Glaudemans, C. P. J. A synthetic heptasaccharide reveals the capability of a monoclonal antibody to read internal epitopes of a polysaccharide antigen. *Carbohydr. Res.* **203,** 253–263 (1990).
280. Nashed, E. M. & Glaudemans, C. P. J. Selective silylation of β-D-galactosides. A new approach to the synthesis of (1 → 6)-β-D-galactopyranooligosaccharides. *J. Org. Chem.* **52,** 5255–5260 (1987).
281. Srivastava, V. K. & Schuerch, C. Synthesis and characterization of a tetramer, propyl 6-O-β-D-galactopyranosyl-(1→6)-β-D-galactopyranosyl-(1→6)-O-β-D-galactopyranosyl-(1→6)-β-D-galactopyranoside. *Carbohydr. Res.* **106,** 217–224 (1982).
282. Pan, Q., Du, Y., Kong, F., Pan, J. & Lu, M. Synthesis of 3-O-arabinosylated (1→6)-β-D-galactan epitopes. *J. Carbohydr. Chem.* **20,** 297–306 (2001).
283. Zeng, Y., Li, A. & Kong, F. A concise synthesis of arabinogalactan with β-(1→6) galactopyranose backbone and α-(1→2) arabinofuranose side chains. *Tetrahedron Lett.* **44,** 8325–8329 (2003).
284. Miura, T. *et al.* Rapid Oligosaccharide Synthesis Using a Fluorous Protective Group. *J. Org. Chem.* **69,** 5348–5353 (2004).
285. Li, A. & Kong, F. Concise syntheses of arabinogalactans with β-(1→6)-linked galactopyranose backbones and α-(1→3)- and α-(1→2)-linked arabinofuranose side chains. *Bioorg. Med. Chem.* **13,** 839–853 (2005).
286. Gu, G., Yang, F., Du, Y. & Kong, F. Synthesis of a hexasaccharide that relates to the arabinogalactan epitope. *Carbohydr. Res.* **336,** 99–106 (2001).
287. Csavas, M., Borbas, A., Janossy, L. & Liptak, A. Synthesis of an arabinogalactan-type octa- and two isomeric nonasaccharides. Suitable tuning of protecting groups. *Tetrahedron Lett.* **44,** 631–635 (2003).
288. Li, A., Zeng, Y. & Kong, F. An effective synthesis of an arabinogalactan with a β-(1→6)-linked galactopyranose backbone and α-(1→2) arabinofuranose side chains. *Carbohydr. Res.* **339,** 673–681 (2004).

289. Li, A. & Kong, F. Syntheses of arabinogalactans consisting of β-(1→6)-linked D-galactopyranosyl backbone and α-(1→3)-linked L-arabinofuranosyl side chains. *Carbohydr. Res.* **339,** 1847–1856 (2004).
290. Li, A.-X. & Kong, F.-Z. Concise syntheses of arabinogalactans with β-(1→6)-linked galactopyranosyl backbone and α-(1→3)-linked arabinofuranosyl side chains. *Chinese J. Chem.* **23,** 7–10 (2005).
291. Liao, W., Lu, D., Li, A. & Kong, F. Synthesis of a tetra- and a hexasaccharide donor corresponding to the non-reducing termini of mycobacterial 3-O-methylmannose polysaccharide (MMP). *J. Carbohydr. Chem.* **16,** 877–890 (1997).
292. Wang, Z. in *Compr. Org. Name React. Reagents* (John Wiley & Sons, Inc., 2010). doi:10.1002/9780470638859.conrr304
293. Jiang, L. & Chan, T.-H. Regioselective Acylation of Hexopyranosides with Pivaloyl Chloride. *J. Org. Chem.* **63,** 6035–6038 (1998).
294. Sakagami, M. & Hamana, H. A selective ring opening reaction of 4,6-O-benzylidene acetals in carbohydrates using trialkylsilane derivatives. *Tetrahedron Lett.* **41,** 5547–5551 (2000).
295. Hernández-Torres, J. M., Achkar, J. & Wei, A. Temperature-Controlled Regioselectivity in the Reductive Cleavage of p-Methoxybenzylidene Acetals. *J. Org. Chem.* **69,** 7206–7211 (2004).
296. Jiang, L. & Chan, T. H. Borane/Bu2BOTf: A mild reagent for the regioselective reductive ring opening of benzylidene acetals in carbohydrates. *Tetrahedron Lett.* **39,** 355–358 (1998).
297. Liwanag, A. J. M. *et al.* Pectin biosynthesis: GALS1 in Arabidopsis thaliana is a β-1,4-galactan β-1,4-galactosyltransferase. *Plant Cell* **24,** 5024–5036 (2012).
298. Suzuki, N. & Yamamoto, K. Molecular cloning of pigeon UDP-galactose:beta-D-galactoside alpha1,4-galactosyltransferase and UDP-galactose:beta-D-galactoside beta1,4-galactosyltransferase, two novel enzymes catalyzing the formation of Gal alpha1-4Gal beta1-4Gal beta1-4GlcNAc sequence. *J. Biol. Chem.* **285,** 5178–5187 (2010).
299. Viborg, A. H. *et al.* Distinct substrate specificities of three glycoside hydrolase family 42 β-galactosidases from Bifidobacterium longum subsp. infantis ATCC 15697. *Glycobiol.* (2013). doi:10.1093/glycob/cwt104
300. Zakharova, A. N., Madsen, R. & Clausen, M. H. Synthesis of a Backbone Hexasaccharide Fragment of the Pectic Polysaccharide Rhamnogalacturonan I. *Org. Lett.* **15,** 1826–1829 (2013).
301. Clausen, M. H. & Madsen, R. Synthesis of hexasaccharide fragments of pectin. *Chem. - A Eur. J.* **9,** 3821–3832 (2003).
302. Søensen, I., Pedersen, H. L. & Willats, W. G. T. An array of possibilities for pectin. *Carbohydr. Res.* **344,** 1872–1878 (2009).
303. Willats, W. G. T., Rasmussen, S. E., Kristensen, T., Mikkelsen, J. D. & Knox, J. P. Sugar-coated microarrays: A novel slide surface for the high-throughput analysis of glycans. *Proteomics* **2,** 1666–1671 (2002).
304. Pedersen, H. L. *et al.* Versatile High Resolution Oligosaccharide Microarrays for Plant Glycobiology and Cell Wall Research. *J. Biol. Chem.* **287,** 39429–39438 (2012).
305. Jones, L., Seymour, G. B. & Knox, J. P. Localization of Pectic Galactan in Tomato Cell Walls Using a Monoclonal Antibody Specific to (1→4)-β-D-Galactan. *Plant Physiol.* **113,** 1405; 4277663–1412 (1997).
306. Verhertbruggen, Y. *et al.* Developmental complexity of arabinan polysaccharides and their processing in plant cell walls. *PLANT J.* **59,** 413–425 (2009).
307. Thibault, J. F., Ralet, M. C., Quéméner, B. & André-Leroux, G. Erratum to "Sugar beet (Beta vulgaris) pectins are covalently cross-linked through diferulic bridges in the cell wall."*Phytochemistry* **67,** 2800–2814 (2006).
308. Cooper, D. N. W. & Barondes, S. H. God must love galectins; He made so many of them. *Glycobiology* **9,** 979–984 (1999).
309. Takatsuki, A., Arima, K. & Tamura, G. Tunicamycin, a new antibiotic. I. Isolation and characterization of tunicamycin. *J. Antibiot.* **24,** 215 (1971).
310. Keenan, R. W., Hamill, R. L., Occolowitz, J. L. & Elbein, A. D. Biological activities of isolated tunicamycin and streptovirudin fractions. *Biochemistry* **20,** 2973 (1981).
311. Danishefsky, S. J., Deninno, S. L., Chen, S., Boisvert, L. & Barbachyn, M. Fully Synthetic Stereoselective Routes to the Differentially Protected Subunits of the Tunicamycins. *J. Am. Chem. Soc.* **111,** 5810–5818 (1989).
312. Mahoney, W. C. & Duksin, D. Separation of tunicamycin homologues by reversed-phase high-performance liquid chromatography. *J. Chromatogr. A* **198,** 506–510 (1980).
313. Wyszynski, F. J., Hesketh, A. R., Bibb, M. J. & Davis, B. G. Dissecting tunicamycin biosynthesis by genome mining: cloning and heterologous expression of a minimal gene cluster. *Chem. Sci.* **1,** 581–589 (2010).

314. Tkacz, J. S. & Lampen, J. O. Tunicamycin Inhibition of Polyisoprenyl N-Acetylglucosaminyl Pyrophosphate Formation in Calf-Liver Microsomes. *Biochem. Biophys. Res. Commun.* **65,** 248–257 (1975).
315. Myers, A. G., Gin, D. Y. & Widdowson, K. L. Silicon-Mediated Reductive Coupling of Aldehydes and Allylic Alcohols - a Stereoselective Synthesis of Tunicaminyluracil. *J. Am. Chem. Soc.* **113,** 9661–9663 (1991).
316. Suami, T. *et al.* Synthetic Approach Toward Antibiotic Tunicamycins .6. Total Synthesis of Tunicamycins. *Tetrahedron Lett.* **25,** 4533–4536 (1984).
317. Ichikawa, S. & Matsuda, A. Nucleosides and nucleotides: Part 225. Synthesis of tunicaminyluracil derivatives. *Nucleosides Nucleotides & Nucleic Acids* **23,** 239–253 (2004).
318. Tamura, G. *Tunicamycin*. **1,** (Japan Scientific Societies Press, 1982).
319. Johansson, L. *et al.* Hydrolysis of beta-glucan. *Food Chem.* **97,** 71–79 (2006).
320. Vermeer, H. J., Halkes, K. M., van Kuik, J. A., Kamerling, J. P. & Vliegenthart, J. F. G. Synthesis and conjugation of oligosaccharide fragments related to the immunologically reactive part of the circulating anodic antigen of the parasite Schistosoma mansoni. *J. Chem. Soc. Trans. 1* 2249–2263 (2000). doi:10.1039/b002083o
321. Kartha, K. P. R., Mukhopadhyay, B. & Field, R. A. Practical de-O-acylation reactions promoted by molecular sieves. *Carbohydr. Res.* **339,** 729–732 (2004).
322. Zhang, J. & Kovac, P. An alternative method for regioselective, anomeric deacylation of fully acylated carbohydrates. *J. Carbohydr. Chem.* **18,** 461–469 (1999).
323. Nishimura, S.-I., Hato, M., Hyugaji, S., Feng, F. & Amano, M. Glycomics for Drug Discovery: Metabolic Perturbation in Androgen-Independent Prostate Cancer Cells Induced by Unnatural Hexosamine Mimics. *Angew. Chemie-International Ed.* **51,** 3386–3390 (2012).
324. Wang, C., Ying, F., Wu, W. & Mo, Y. How Solvent Influences the Anomeric Effect: Roles of Hyperconjugative versus Steric Interactions on the Conformational Preference. *J. Org. Chem.* **79,** 1571–1581 (2014).
325. Ryan, K. J., Ray, C. G. & Sherris, J. C. *Sherris medical microbiology: an introduction to infectious diseases*. **4th,** (McGraw-Hill Companies, The, 2004).
326. Hernandez-Torres, J. M., Liew, S. T., Achkar, J. & Wei, A. Optimized synthesis of an orthogonally protected glucosamine. *Synthesis (Stuttg).* 487–490 (2002).
327. Shih, H.-W., Chen, K.-T., Cheng, T.-J. R., Wong, C.-H. & Cheng, W.-C. A New Synthetic Approach toward Bacterial Transglycosylase Substrates, Lipid II and Lipid IV. *Org. Lett.* **13,** 4600–4603 (2011).
328. Zhang, Y. *et al.* Synthesis of heptaprenyl-lipid IV to analyze peptidoglycan glycosyltransferases. *J. Am. Chem. Soc.* **129,** 3080–+ (2007).
329. Termin, A. & Schmidt, R. R. Glycosylimidates, 54. Synthesis of the Glcnac-β(1->4)murnac-β(1->4)glcnac-β(1->4)murnac Tetrasaccharide of Bacterial Peptidoglycan. *Liebigs Ann. der Chemie* 527–533 (1992).
330. Weng, S.-S., Ke, C.-S., Chen, F.-K., Lyu, Y.-F. & Lin, G.-Y. Transesterification catalyzed by iron(III) beta-diketonate species. *Tetrahedron* **67,** 1640–1648 (2011).
331. Hoye, R. C., Baigorria, A. S., Danielson, M. E., Pragman, A. A. & Rajapakse, H. A. Synthesis of elenic acid, an inhibitor of topoisomerase II. *J. Org. Chem.* **64,** 2450–2453 (1999).
332. Agoston, K. *et al.* Synthesis of fragments of the glycocalyx glycan of the parasite Schistosoma mansoni. *Chem. Eur. J.* **8,** 151–161 (2002).
333. Boons, G.-J., Burton, A. & Isles, S. A new procedure for the isomerisation of substituted and unsubstituted allyl ethers of carbohydrates. *Chem. Commun.* 141–142 (1996). doi:10.1039/CC9960000141
334. Matsuo, I. *et al.* Synthesis of monoglucosylated high-mannose-type dodecasaccharide, a putative ligand for molecular chaperone, calnexin, and calreticurin. *J. Am. Chem. Soc.* **125,** 3402–3403 (2003).
335. Liu, J. *et al.* Synthesis and High-Throughput Screening of N-Acetyl-β-hexosaminidase Inhibitor Libraries Targeting Osteoarthritis. *J. Org. Chem.* **69,** 6273–6283 (2004).
336. Nyffeler, P. T., Liang, C.-H., Koeller, K. M. & Wong, C.-H. The Chemistry of Amine−Azide Interconversion: Catalytic Diazotransfer and Regioselective Azide Reduction. *J. Am. Chem. Soc.* **124,** 10773–10778 (2002).
337. Lindberg, J., Öhberg, L., Garegg, P. J. & Konradsson, P. Efficient routes to glucosamine-myo-inositol derivatives, key building blocks in the synthesis of glycosylphosphatidylinositol anchor substances. *Tetrahedron* **58,** 1387–1398 (2002).
338. Yan, R.-B., Yang, F., Wu, Y., Zhang, L.-H. & Ye, X.-S. An efficient and improved procedure for preparation of triflyl azide and application in catalytic diazotransfer reaction. *Tetrahedron Lett.* **46,** 8993–8995 (2005).
339. Effenberger, F. & Jäger, J. Synthesis of the Adrenergic Bronchodilators (R)-Terbutaline and (R)-Salbutamol from (R)-Cyanohydrins1. *J. Org. Chem.* **62,** 3867–3873 (1997).

340. Gent, P. A. & Gigg, R. The allyl ether as a protecting group in carbohydrate chemistry. Isomerisations with tristriphenylphosphinerhodium(I) chloride. *J. Chem. Soc. Chem. Commun.* 277–278 (1974). doi:10.1039/C39740000277
341. Sefler, A. M., Kozlowski, M. C., Guo, T. & Bartlett, P. A. Design, Synthesis, and Evaluation of a Depsipeptide Mimic of Tendamistat. *J. Org. Chem.* **62,** 93–102 (1997).
342. Roush, W. R., Coffey, D. S. & Madar, D. J. Total Synthesis of (+)-Damavaricin D. *J. Am. Chem. Soc.* **119,** 11331–11332 (1997).
343. Dinkelaar, J. *et al.* Stereodirecting Effect of the Pyranosyl C-5 Substituent in Glycosylation Reactions. *J. Org. Chem.* **74,** 4982–4991 (2009).
344. Motawia, M. S., Olsen, C. E., Denyer, K., Smith, A. M. & Moller, B. L. Synthesis of 4 ’-O-acetyl-maltose and alpha-D-galactopyranosyl-(1 -> 4)-D-glucopyranose for biochemical studies of amylose biosynthesis. *Carbohydr. Res.* **330,** 309–318 (2001).
345. Pozsgay, V. *et al.* Synthetic Oligosaccharides as Tools to Demonstrate Cross-Reactivity between Polysaccharide Antigens. *J. Org. Chem.* **77,** 5922–5941 (2012).
346. Furstner, A. & Konetzki, I. Total synthesis of caloporoside. *J. Org. Chem.* **63,** 3072–3080 (1998).
347. Premathilake, H. D., Mydock, L. K. & Demchenko, A. V. Superarming common glycosyl donors by simple 2-O-benzoyl-3,4,6-tri-O-benzyl protection. *J. Org. Chem.* **75,** 1095–100 (2010).
348. Still, W. C., Kahn, M. & Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **43,** 2923–2925 (1978).
349. Wei, J. *et al.* Glycosynthase with Broad Substrate Specificity – an Efficient Biocatalyst for the Construction of Oligosaccharide Library. *European J. Org. Chem.* **2013,** 2414–2419 (2013).
350. Sarkar, A. K. & Matta, K. L. 2,3,4,6-Tetra-O-benzyl-β--galactopyranosyl phenyl sulfoxide as a glycosyl donor. Synthesis of some oligosaccharides containing and α--galactopyranosyl group. *Carbohydr. Res.* **233,** 245–250 (1992).
351. Turvey, J. R. & Williams, T. P. 407. Sulphates of monosaccharides and derivatives. Part IV. Galactose 4-sulphate. (1962).
352. Vidadala, S. R., Thadke, S. A., Hotha, S. & Kashyap, S. Synthesis of Thioglycosides from Propargyl Glycosides Exploiting Alkynophilic Gold Catalyst. *J. Carbohydr. Chem.* **31,** 241–251 (2012).
353. Tiwari, P. & Misra, A. K. Acylation of carbohydrates over Al2O3: preparation of partially and fully acylated carbohydrate derivatives and acetylated glycosyl chlorides. *Carbohydr. Res.* **341,** 339–350 (2006).
354. Timmer, M. S. M., Stocker, B. L., Northcote, P. T. & Burkett, B. a. Az—a colourful azulene-derived protecting group. *Tetrahedron Lett.* **50,** 7199–7204 (2009).
355. Gan, Z., Cao, S., Wu, Q. & Roy, R. Regiospecific Syntheses of N-Acetyllactosamine Derivatives and Application Toward a Highly Practical Synthesis of Lewis X Trisaccharide. *J. Carbohydr. Chem.* **18,** 755 (1999).
356. Rodrigue, J. *et al.* Aromatic thioglycoside inhibitors against the virulence factor LecA from Pseudomonas aeruginosa. *Org. Biomol. Chem.* **11,** 6906–6918 (2013).
357. Agnihotri, G. & Misra, A. K. Fast and selective oxidation of thioglycosides to glycosyl sulfoxides using KF/m-CPBA. *Tetrahedron Lett.* **46,** 8113–8116 (2005).
358. Tanaka, T., Huang, W. C., Noguchi, M., Kobayashi, A. & Shoda, S. Direct synthesis of 1,6-anhydro sugars from unprotected glycopyranoses by using 2-chloro-1,3-dimethylimidazolinium chloride. *Tetrahedron Lett.* **50,** 2154–2157 (2009).
359. Junot, N., Meslin, J. C. & Rabiller, C. Regioselective acylation of 1,6-anhydro-β-D-manno and galactopyranose catalysed by lipases. *Tetrahedron: Asymmetry* **6,** 1387–1392 (1995).
360. Jimeno, M. L., Fernandez-Mayoralas, A., Martin-Lomas, M. & Alemany, A. 13C-N.m.r. studies of peracetylated derivatives of O-α- and O-β-d-galactopyranosyl-(1→3)- and -(1→4)-α-d-galactopyranose. *Carbohydr. Res.* **161,** 144–149 (1987).
361. Ley, S. V. *et al.* The Synthesis of Azadirachtin: A Potent Insect Antifeedant. *Chem. – A Eur. J.* **14,** 10683–10704 (2008).
362. Kobayashi, Y., Shiozaki, M. & Ando, O. Syntheses of Trehazolin Derivatives and Evaluation as Glycosidase Inhibitors. *J. Org. Chem.* **60,** 2570–2580 (1995).
363. Stübs, G., Rupp, B., Schumann, R. R., Schröder, N. W. J. & Rademann, J. Chemoenzymatic Synthesis of a Glycolipid Library and Elucidation of the Antigenic Epitope for Construction of a Vaccine Against Lyme Disease. *Chem. – A Eur. J.* **16,** 3536–3544 (2010).
364. Fernandez-Mayoralas, A., Marra, A., Trumtel, M., Veyrières, A. & Sinaÿ, P. Preparation of pyranoid glycal derivatives from phenyl thioglycosides and glycosyl phenyl sulphones. *Carbohydr. Res.* **188,** 81–95 (1989).

365. Osswald, M., Lang, U., Friedrich-Bochnitschek, S., Pfrengle, W. & Kunz, H. Regioselective Glycosylation of Glucosamine and Galactosamine Derivates Using O-Pivaloyl Galactosyl Donors. *ZEITSCHRIFT FUR Naturforsch. B* **58,** 764–774 (2003).
366. Kanaya, T., Schweizer, F., Takeda, T., Kiuchi, F. & Hada, N. Synthetic studies on glycosphingolipids from protostomia phyla: synthesis of glycosphingolipids and related carbohydrate moieties from the parasite Schistosoma mansoni. *Carbohydr. Res.* **361,** 55–72 (2012).