CHIRAL AUXILIARIES FOR THE STEREOSELECTIVE SYNTHESIS OF GLYCOSIDIC BONDS AND THEIR APPLICATION IN COMPLEX OLIGOSACCHARIDE SYNTHESIS

by

THOMAS J. BOLTJE

(Under the Direction of Geert-Jan Boons)

ABSTRACT

The stereoselective synthesis of 1,2-*cis*-glycosidic bonds using a 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether chiral auxiliary is descrided herein. Activation of a glycosyl donor protected with a 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether chiral auxiliary results in the formation of an anomeric β-sulfonium ion, which can be displaced with sugar alcohols to afford the corresponding α-glycosides. Sufficient deactivation of such glycosyl donors by electron-withdrawing protecting groups is, however, critical to avoid glycosylation of an oxa-carbenium ion intermediate resulting in the formation of mixtures of anomers. The latter type of glycosylation pathway can also be suppressed by adding geminal substituents to the chiral auxiliary to promote the formation of the β-sulfonium ion.

Adhering to these rules, the use of the 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether chiral auxiliary was used to perform Solid Phase Oligosaccharide Synthesis (SPOS). Solid-phase oligosaccharide synthesis offers the promise of providing libraries of oligosaccharides for glycomics research. A major stumbling block to solid-phase oligosaccharide synthesis has been a lack of general methods for the stereoselective installation of 1,2-*cis*-glycosides, and intractable mixtures of compounds are obtained if several such glycosides need to be installed. We have prepared on-resin a biologically important glucoside containing multiple 1,2-*cis*-glycosidic linkages with complete anomeric control by using glycosyl donors having a participating (*S*)-(phenylthiomethyl)benzyl chiral auxiliary at C-2. The synthetic strategy made it possible to achieve partial on-resin deprotection of the completed oligosaccharide, thereby increasing the overall efficiency of the synthesis. The combination of classical and auxiliary-mediated neighboring-group

participation for controlling anomeric selectivity is bringing the promise of routine automated solid-supported oligosaccharide synthesis closer.

The use of the 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether chiral auxiliary was also tested in the synthesis of substructures of the unusual core region of the lipopolysaccharide of *Francisella tularensis*. *F.tularensis* has been classified by the CDC as a Class A bio-terrorism agent. *F. tularensis* is highly virulent, requiring as few as 10-50 cells to cause human infection, which in an urban area would result in thousands of deaths. The lipopolysaccharide of *F. tularensis* is an attractive candidate for vaccine and diagnostic test development to combat such an event. Herein, the synthesis of the inner core hexasaccharide domain of *F. tularensis* is described.

INDEX WORDS: Oligosaccharides, Stereoselectivity, Glycosylation, Chiral Auxiliary, Sulfonium ion, Solid Phase Synthesis, α-Glucans, *Francisella tularensis*, Vaccine.

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DEDICATION

This thesis is dedicated to my parents, Gerard Boltje and Marian Vogt, my brothers, Joost Boltje and Daan Boltje and my wife, Kanar Al-Mafraji for their support, love and encouragement.

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TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF SCHEMES

Page

LIST OF ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic Anhydride
AcOH	Acetic Acid
AgOTf	Silver Trifluoromethanesulfonate
AIBN	Azobisisobutyronitrile
Alloc	Allyloxycarbonyl
AllocCl	Allylchloroformate
ALPH	Antiperiplanar Lone Pair Hypothesis
ATIII	Antithrombin III
BCR	B-Cell Receptor
$BF_3{\cdot}Et_2O$	Boron Trifluoride Diethyl Etherate
Bn	Benzyl
BnBr	Benzyl Bromide
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine Serum Albumin
BSP	1-Benzenesulfinyl Piperidine
Bz	Benzoyl
BzCl	Benzoyl Chloride
CDC	Centers for Disease Control and Prevention
CFG	Consortium of Functional Glycomics
CIP	Contact Ion Pair
COSY	Correlation Spectroscopy
CPS	Capsular Polysaccharide
DBTS	di-*tert*-Butylsilyl
DBU	1,8-Diazabicycloundec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEIPS	Diethylisopropylsilyl

DHB ..... 2,5-Dihydroxybenzoic Acid

DIC ..... *N*,*N*'-Diisopropylcarbodiimide

DIPEA ..... Diisopropylethylamine

DMAP ..... 4-*N*,*N*'-Dimethylaminopyridine

DMB 3,4-Dimethoxybenzyl

DMF ..... *N*,*N*'-Dimetylformamide

DMTST ..... Dimethyl-Thiomethyl Sulfonium Triflate

DNA ..... Deoxyribonucleic Acid

DTBMP 2,6-Di-*tert*-Butyl-4-Methyl-Pyridine

EPO ..... Erythropoietin

Fmoc 9-Fluorenylmethyloxycarbonyl

FmocCl 9-Fluorenylmethylchloroformate

FSH ..... Follicle Stimulating Hormone

GAG ..... Glycosaminoglycan

Gal ..... Galactose

GalN ..... Galactoseamine

Glc ..... Glucose

HIV ..... Human Immunodeficiency Virus

HMBC ..... Heteronuclear Multiple Bond Correlation Spectroscopy

HSQC ..... Heteronuclear Single Quantum Coherence Spectroscopy

IAD ..... Intramolecular Aglycon Derlivery

KDO ..... 3-Deoxy-D-Manno-Octulosonic Acid

KIE ..... Kinetic Isotope Effect

KLH ..... Keyhole Limpet Hemocyanin

Lev ..... Levulinyl

LHMDS ..... Lithium bis(trimethylsilyl)amide

LPS ..... Lipopolysaccharide

LUMO ..... Lowest unoccupied molecular orbital

LVS ..... Life Vaccine Strain

MAB ..... Monoclonal Antibody

MALDI-TOF ..... Matrix Assisted Laser Desorption Ionization Time-Of-Flight

Man ..... Mannose

m-CPBA ..... *meta*-Chloroperbenzoic Acid

Me ..... Methyl

MeOTf ..... Methyl Trifluoromethanesulfonate
MS ..... Molecular Sieves
Nap 2-Methylnaphthyl
Neu5Ac ..... *N*-Acetylneuraminic Acid
Neu5Gc ..... *N*-Glycolylneuraminic Acid
NGP ..... Neighboring Group Participation
NIS ..... *N*-Iodosuccinimide
NMR ..... Nuclear Magnetic Resonance
OMe ..... Methoxy
PBS ..... Phosphate Buffered Saline
*p*ClBn ..... *para*-Chlorobenzyl
Ph ..... Phenyl
Phth ..... Phthalimido
PSA ..... Prostate Specific Antigen
Pyr ..... Pyridine
RNA ..... Ribonucleic Acid
RRV ..... Relative Reactivity Value
Sl-1 ..... Sulfolipid-1
SPOS ..... Solid Phase Oligosaccharide Synthesis
SSIP ..... Solvent Separated Ion Pair
TBAF ..... Tetrabutyl Ammonium Fluoride
TBS ..... *tert*-Butyldimehtylsilyl
TBSOTf ..... *tert*-Butyldimehtylsilyl Trifluoromethanesulfonate
TCA ..... Trichloroacetonitrile
TEA ..... Triethylamine
TEMPO ..... (2,2,6,6-Tetramethyl-Piperidin-1-yl)oxyl
Tf_2O ..... Trifluoromethanesulfonic Anhydride
TFA ..... Trifluoroacetic Acid
TfOH ..... Trifluoromethanesulfonic Acid
THF ..... Tetrahydrofuran
TLC ..... Thin Layer Chromatography
TLR ..... Toll-Like Receptor
TMEDA ..... *N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS ..... Trimethylsilyl

TMSOTf ..... Trimethylsilyl Trifluoromethanesulfonate

TOCSY ..... Total Correlation Spectroscopy

Troc 2,2,2-Trichloroethyloxycarbonyl

CHAPTER 1

INTRODUCTION[1]

Carbohydrates in biology. There is a growing appreciation that post-translational modifications, such as glycosylation, dramatically increase protein complexity and function.[2-7] For example, almost all cell surface and secreted proteins are modified by covalently linked carbohydrate moieties, and the glycan structures on these glycoproteins have been implicated as essential mediators in processes such as protein folding, cell signalling, fertilization, embryogenesis, neuronal development, hormone activity and the proliferation of cells and their organization into specific tissues. In addition, overwhelming data supports the relevance of glycans in pathogen recognition, inflammation, innate immune responses and the development of autoimmune diseases and cancer[8-11]. The importance of protein glycosylation is also underscored by the developmental abnormalities observed in a growing number of human disorders known as congenital disorders of glycosylation, caused by defects in the glycosylation machinery[12]. Polysaccharides are major constituents of the microbial cell surfaces and, for example, the bacterial cell wall can contain relatively large amounts of capsular polysaccharides (CPS) or lipopolysaccharides (LPS).[13] These components are important virulence factors in that they promote bacterial colonization, block phagocytosis and interfere with leukocyte migration and adhesion. CPS and LPS can be recognized by receptors of the innate immune system leading to the production of cytokines, chemokines and cellular adhesion molecules.[14-17] With a few exceptions, bacterial polysaccharides can induce an adaptive immune response and, not surprisingly, bacterial saccharides have been employed for the development of vaccines for several pathogens[18-21].

Synthetic oligosaccharides for glycobiology. A major obstacle in glycobiology and glycomedicine is the lack of pure and structurally well-defined carbohydrates and glycoconjugates.[22] These compounds are

often found in low concentrations and in microheterogeneous forms, greatly complicating their isolation and characterization. In many cases, well-defined oligosaccharides can only be obtained by chemical or enzymatic synthesis[23-29] and such compounds are increasingly used to address important problems in glycobiology research and for vaccine and drug discovery. For example, the Consortium of Functional Glycomics (CFG) has employed a chemoenzymatic approach for the preparation of a library of over 400 oligosaccharides derived from *N*-and *O*-linked glycoproteins and glycolipids.[30-31] These compounds, which are equipped with an artificial aminopropyl spacer, have been covalently attached to *N*-hydroxysuccinimide-activated glass slides and the resulting microrray has found wide use for profiling the specificity of a diverse range of glycan-binding proteins, such as C-type lectins, siglecs, galectins and anticarbohydrate antibodies. Glycan array technology has also been employed for rapid assessment of influenzae virus receptor specificity due to the species-specific nature of the interaction between virus and host glycans.[32]

Synthetic heparin and heparan sulfate fragments. The power of organic carbohydrate synthesis has also been demonstrated by the development of a fully synthetic heparin fragment used for the treatment of deep vein thrombosis in humans.[33-35] Heparin and heparan sulfate are naturally occurring polydisperse linear polysaccharides that are heavily *O*-and *N*-sulfated.[6] For more than eighty years, heparin isolated from porcine mucosal tissue has been used as an anticoagulant drug. It exerts its activity by binding to the plasma protein antithrombin III (ATIII) causing a conformational change that results in its activation through an increase in the flexibility of its reactive site loop. The activated ATIII then inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa. The ATIII-binding region of heparin consists of a unique penta-saccharide domain. A fully synthetic analogue (Arixtra, Figure 1.1A) of this domain has been developed, which is being produced on a multikilogram scale for the treatment of deep vein thrombosis.[33-34] Unlike heparin, the synthetic derivative is easy to characterize and has a much-improved subcutaneous bioavailability.

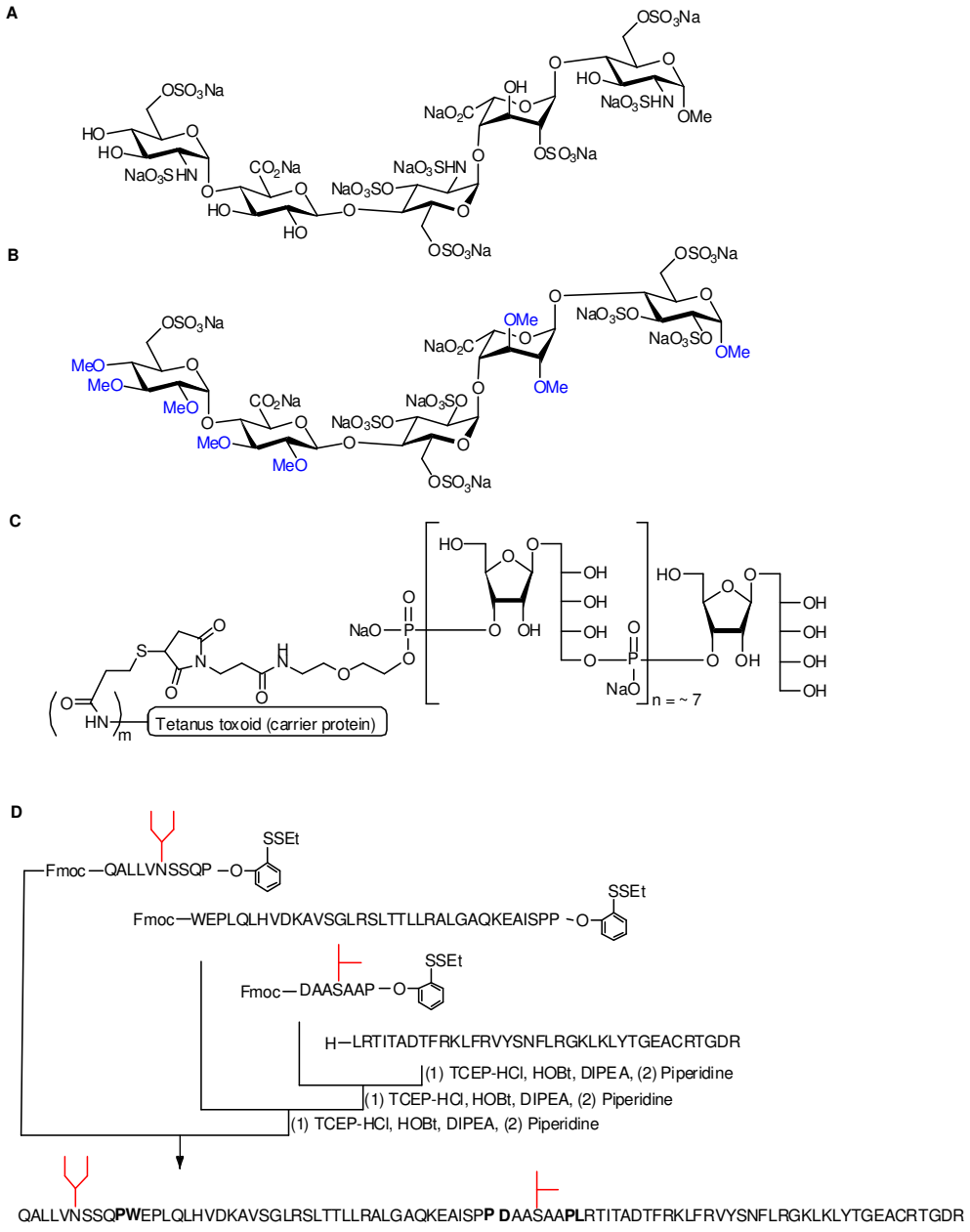


Figure 1.1: Examples of biologically active synthetic oligosaccharide and glycopeptide constructs. A). Structure of the anticoagulant drug Arixtra. B). Structure of the promising anticoagulant candidate drug Idraparinux, in which the methyl ethers are highlighted in blue. C). Synthetic conjugate polysaccharide vaccine against *Haemophilus influenzae* type b. D). Synthesis of the erythropoietin (EPO; from amino acids 78-166) glycopeptide through sequential fragment condensation using auxiliary-based cysteine-free native chemical ligation. Glycans are shown in red and the ligation sites are shown in bold, amino acids are represented by their single-letter codes. DIPEA, *N,N*-diisopropylethylamine; HOBt, 1-hydroxybenzotriazole; TCEP-HCl, *tris*(2-carboxyethyl)phosphine hydrochloride.

Several other synthetic heparin fragments are being developed for anticoagulation therapy, and the most exciting example is Idraparinux (Figure 1.1B).[33] This compound, which contains methyl ethers instead of hydroxyls and *O*-sulfates instead of *N*-sulfates, is much easier to synthesize than Arixtra, has an increased half-life and a much improved potency. The latter property seems to be due to the presence of the methyl ethers, which induce the biologically active $^2S_0$ conformation of the iduronic acid moiety. The importance of synthetic heparin for anticoagulation therapy was recently highlighted by the discovery of batches of heparin that were associated with anaphylactoid-type reactions, leading to hypotension and which resulted in nearly 100 deaths.[36-37] These adverse reactions were traced to contamination with a semi-synthetic over-sulfated chondroitin sulfate, which is a popular shellfish-derived oral supplement for arthritis.

There is a growing body of literature indicating that glycosylaminoglycans (GAGs), such as heparin and heparan sulfate, can have profound physiological effects on lipid transport and adsorption, cell growth and migration and development.[6] Alterations in GAG expression has been associated with cancer and, for example, significant changes in the structure of GAGs has been reported in the stroma surrounding tumours, which is important for tumour growth and invasion. GAGs also have important neurobiological functions and examples include neuroepithelial growth and differentiation, neurite outgrowth, nerve regeneration, axonal guidance and branching, deposition of amyloidotic plaques in Alzheimer's disease, and astrocyte proliferation.[38] It is to be expected that synthetic analogues of heparin may find application in the treatment of several neurodiseases, cancer and infection.[34-35,38-43]

Carbohydrate-based prophylactic and therapeutic vaccines. Synthetic oligosaccharide epitopes offer promising possibilities for the development of vaccines for the prevention of infectious diseases such as *Haemophilus influenzae* type b, HIV, *Plasmodium falciparum*, *Vibrio cholerae*, *Cryptococcus neoformans*, *Streptococcus pneumoniae*, *Shiga toxin*, *Neisseria meningitides, Bacillus anthracis* and *Candida albicans*.[18-19,44-45] Natural polysaccharides conjugated to carrier proteins have been successfully developed as human vaccines, however, their use is associated with problems such as the destruction of

vital immuno-dominant features during the chemical conjugation to a carrier protein.[18] Furthermore, natural polysaccharides show significant heterogeneity, which may compromise the reproducibility of their production and can contain highly toxic components that may be difficult to remove. Fortunately, organic synthesis can provide carbohydrate epitopes in high purity and in relatively large amounts for controlled conjugation to a carrier protein. In such an approach, synthetic saccharides are equipped with an artificial spacer to facilitate selective conjugation to a carrier protein. In general, antibodies recognize epitopes that are no larger than a hexasaccharide. Although challenging, oligosaccharides of this length can be obtained by organic synthesis. The recent approval of a human vaccine based on a synthetic carbohydrate illustrates the potential use of organic synthesis to develop glycoconjugate vaccines.[46] The vaccine prevents infection by *Haemophilus influenzae* type b, a bacterium that causes pneumonia and meningitis in infants and young children. The carbohydrate epitope of this vaccine is an oligo-ribosylribitol phosphate, which was synthesized by a one-pot solution-phase oligomerization process (Figure 1.1C). The synthetic compound is equipped with an artificial spacer that contains a maleimide moiety. The latter functionality enabled a controlled coupling of the synthetic oligosaccharide with a carrier protein that was modified by thiol moieties.

Synthetic oligosaccharides have also been employed for the development of therapeutic vaccines for cancer. The over-expression of oligosaccharides such as Globo-H, LewisY, and Tn antigen is a common feature of oncogenic transformed cells, and a broad and expanding body of preclinical and clinical studies demonstrates[47-49] that naturally acquired, passively administered, or actively induced antibodies against carbohydrate-associated tumour antigens are able to eliminate circulating tumour cells and micro-metastases in cancer patients. The development of tumour-associated saccharides as cancer vaccines has been complicated because they are self-antigens and consequently tolerated by the immune system. The shedding of antigens by the growing tumour reinforces this tolerance. In addition, foreign carrier proteins, such as KLH and BSA, and the linker that attaches the saccharides to the carrier protein can elicit strong B-cell responses, which may lead to the suppression of antibody responses against the carbohydrate epitope. These problems are being addressed by the design, chemical synthesis, and immunological

evaluation of a number of fully synthetic vaccine candidates that have the potential to overcome the poor immunogenicity of tumour-associated carbohydrates and glycopeptides.[50]

Glycopeptide and glycoprotein therapeutics. Synthetic oligosaccharides are also being employed for the preparation of well-defined glycoproteins.[51] Protein-based drugs represent approximately a quarter of new drug approvals with a majority being glycoproteins. The carbohydrate moiety of a glycoprotein is important for its pharmacokinetic properties, is involved in tissue targeting, and can modulate biological activities. Therefore, it is critical to control the exact chemical composition of the oligosaccharide moieties for the development of glycoprotein therapeutics. However, protein glycosylation is not under direct genetic control, and results in the formation of a heterogeneous range of glycoforms that possess the same peptide backbone but differ in the nature and site of glycosylation. Several strategies are being pursued to prepare well-defined mammalian glycoforms of glycoproteins, which include enzymatic remodelling of the oligosaccharide portion of glycoproteins, genetic engineering of the expression host, and the use of an orthogonal synthetase-tRNA pair that genetically encodes a glycosylated amino acid in response to a stop codon (an Amber codon).[52] A combination of site-directed mutagenesis and chemical attachment of synthetic oligosaccharides offers another unique approach for the preparation of well-defined glycoproteins.[53] This strategy involves the introduction of a cysteine in a protein, which can be site-selectively coupled with a synthetic saccharide containing an electrophilic moiety such as glycosyl iodoacetamides, thiols, dithiopyridines and methanethiosulfonates to give a well-defined neoglycoprotein. Recently, it has been demonstrated that the unnatural amino acid azido-homoalanine (Aha) can be incorporated into proteins by employing a Met(-)auxotropic strain, *Escherichia coli* B834(DE3), that is fed the unnatural amino acid instead of methionine.[54] A subsequent "click" reaction between an alkyne-containing glycoside and the azide-modified protein gave triazole-linked glycoproteins in good yields.

The advent of native chemical ligation combined with the ability to prepare complex glycans has made it possible to synthesize glycoproteins. For example, the Danishefsky group has developed a strategy entailing the chemical synthesis of complex carbohydrates in their hemiacetal form, followed

successively by Kochetkov amination, Lansbury amidation of a peptide, and auxiliary-based cysteine-free ligation to merge several glycopeptide and peptide fragments (Figure 1.1D).[55] The approach was applied to the chemical synthesis of glycoproteins that carry multiple *N*-and *O*-linked glycans such as β-human follicle-stimulating hormone (β-hFSH), prostate-specific antigen (PSA) and part of human erythropoietin (EPO; from amino acids 78-166). These impressive syntheses showcase the power of chemical synthesis of carbohydrates and glycopeptides and the impact it can have on large-molecule 'biologicals'.

Multivalent glycomaterials. The ability to synthesize complex oligosaccharides is offers exciting opportunities to prepare glycopolymers, glycodendrimers, and glyconanoparticles.[56-59] These materials are receiving increasing attention because monovalent saccharides often have weak interactions with their protein receptors. However, in nature, carbohydrate-binding proteins often exist as higher-order oligomeric structures presenting multiple binding sites, acting as 'polydentate' donors, thereby circumventing the intrinsic weak binding interactions of monovalent ligands.[60-61] Furthermore, cell-surface glycoproteins can be organized in domains by multivalent interactions with soluble lectins. The formation of lectin–saccharide lattices on the cell surface can thus organize the plasma membrane into specialized domains that perform unique functions.[62] For example, it has been found that Galectin-1, which is a lactoside-binding lectin, can selectively form complexes containing either the cell surface proteins CD45 and CD3 or CD7 and CD43, resulting in segregation of CD3/CD45 from CD7/CD43 complexes.This segregation seems to be essential for mediating controlled cell death.[63]

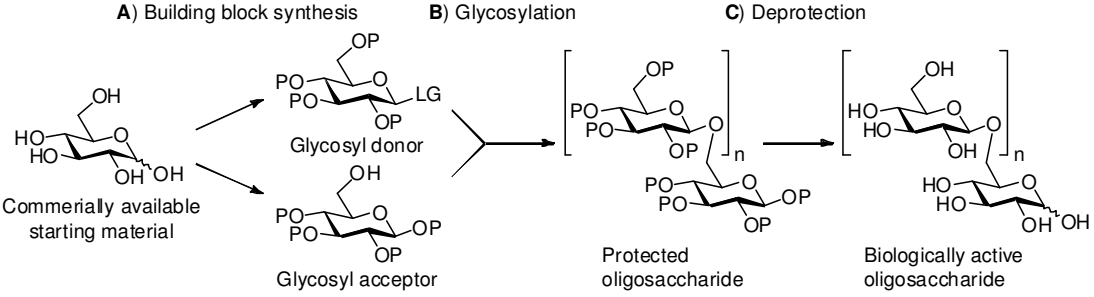
Synthetic multivalent glycomaterials are being examined for antimicrobial therapy, anti-adhesive therapy, targeted drug delivery, cell separation and imaging purposes. One of the most impressive examples involves the design and chemical synthesis of an oligovalent starfish-shaped compound that has subnanomolar inhibitory activity for the B-5 subunit of Shiga-like toxin I.[64] A co-crystal structure of the starfish-shaped saccharide ligand and Shiga-like toxin I showed that two trisaccharides at the tips of each

of five spacer arms simultaneously engage all five B subunits of two toxin molecules. Multivalent carbohydrate ligands have also been used for interfering in cell-signalling events.[60] For example, it has been shown that exposure of B-cells to polymers containing sialylated oligosaccharides and a ligand for B-cell receptor (BCR) attenuates key steps in BCR signalling events compared with a polymer containing BCR ligands alone.[65] The polymer containing BCR ligand alone clusters the BCRs, resulting in cellular activation and immune responses. However, the bifunctional polymer engages both the BCR and the immuno-suppressing co-receptor Siglec-2 (CD22), thereby dampening B-cell activation. Siglec-2 is a member of the sialic acid-binding Ig-like lectin (Siglec) family of receptors, which can interact with glycoconjugates possessing terminal sialic acid residues. The results of this study indicate that *trans*-interactions between Siglec-2 on a B-cell and sialyated oligosaccharides on another cell serves as an innate form of self-regulation thereby preventing auto-immune reactions.

Synthetic Carbohydrate Chemistry. Although great progress has been made, a major obstacle in glycobiology and glycomedicine research is still the lack of pure and structurally well-defined carbohydrates and glycoconjugates. These compounds are often found in low concentrations and in microheterogeneous forms, thereby greatly complicating their isolation and characterization. In many cases, well-defined oligosaccharides can only be obtained by chemical- or enzymatic synthesis. The chemical synthesis of biomolecules such as peptides and nucleotides has become routine since outstanding automated solid phase synthetic methods have been developed for these classes of molecules. These developments caused a wave of new developments in peptide and DNA biology since these molecules became more easily available. In the case of carbohydrates, such general solid support methods are not available at present since carbohydrates are more difficult to synthesize chemically.

The challenges associated with the chemical synthesis of carbohydrates are a direct result of the diversity and complexity of this class of molecules. Structurally, carbohydrates differ from other biological polymers in two important characteristics: (1) their monomeric constituents can be connected to each other in many different ways, and (2) they can be highly branched molecules. Proteins and nucleic

acids can only be connected in a single way (amide bonds for proteins and [3'-5']-phosphodiester bonds for nucleic acids) and are almost exclusively linear. This complexity enables carbohydrates to provide almost unlimited variations in their structure, making them a tremendous challenge to synthesize chemically. Monosaccharides are connected to each other via the anomeric center by an acetal linkage termed the glycosidic bond. Glycosidic bonds can exist as two anomers (equatorial and axial) and the anomeric stereochemistry is usually defined relative to the C-2 substituent, 1,2-*cis* or 1,2-*trans*, or relative to the last chiral substituent on the carbohydrate chain (α and β) . In addition, monosaccharides can be connected to each other through the different alcohols on the sugar ring which necessitates the use of protecting groups to ensure the remaining alcohols remain unchanged. A typical oligosaccharide synthesis can be divided in three distinct stages (Scheme 1.1). The first stage entails the introduction of the protecting groups onto the monosaccharide building blocks (Scheme 1.1A). Next, a series of stereoselective glycosylations are needed to yield a single protected oligosaccharide (Scheme 1.1B). Finally, the protecting groups are removed to afford the biologically active derivative(Scheme 1.1C).



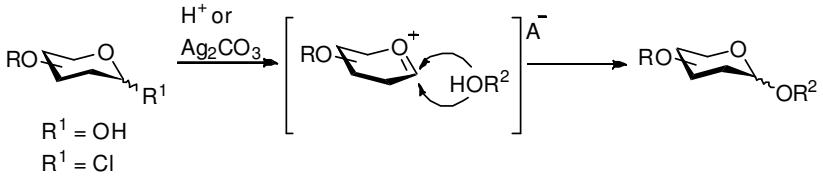
Scheme 1.1:.A Overview of a typical oligosaccharide synthesis) Synthesis of monosaccharide building blocks by the sequential introduction of protecting groups B) Stereoselective glycosylations to afford a single oligosaccharide C) Removal of all the permanent protecting groups to afford a natural oligosaccharide.

One of the challenges in this process is the labor intensive nature of oligosaccharide assembly. Many efforts have been directed at the development of glycosylation strategies to streamline this process.[23,66] For example, one-pot multistep glycosylations have been developed to cut down on intermediate

purification and speed-up oligosaccharide assembly.[67-72] With the same goal in mind, Solid Phase Oligosaccharide Synthesis (SPOS) has come to the fore.[23,73-77] SPOS can be automated[78] which further reduces the time needed for glycosylation, can be performed 24 hours a day and does not require highly skilled personnel to operate. Another elegant way to reduce the time needed to synthesize a collection of oligosaccharide targets is the modular assembly method. In this strategy, a few common modular starting materials are designed which can be used to make multiple targets from common precursors.[79-81] Recently, protocols for the one-pot multi-step introduction of multiple protecting groups have been developed to speed-up monosaccharide building block synthesis.[82-85]

Nevertheless, the second and main challenge in carbohydrate chemistry is still the stereoselective synthesis of the glycosidic bond. The absence of general protocols for stereoselective glycosylation have severely hampered or limited the application of the methods discussed above from being applied in a broad sense. The research presented in this dissertation addresses this critical issue by the development of general stereoselective glycosylation protocols. Thus, the next section of this introductory chapter focuses on the latest developments in this field.

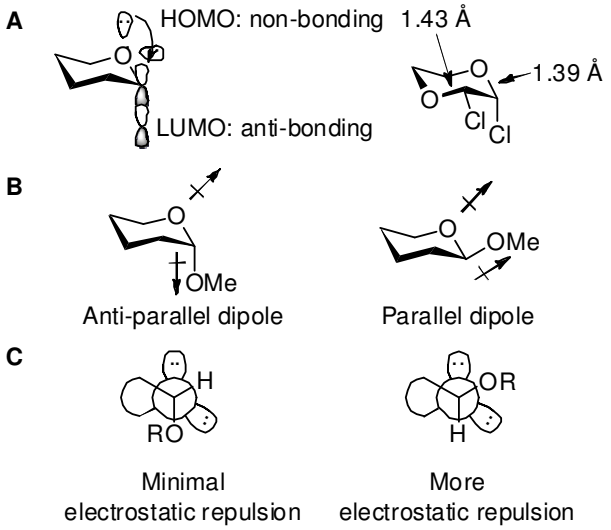
Stereoselective synthesis of the glycosidic bond. The first chemical glycosylation procedure was reported by Emil Fisher in 1893.[86] Fisher discovered the acid catalyzed reaction of an anomic lactol with an alcohol to afford a glycoside product. In 1902, Koenigs and Knorr reported the use of glycosyl halides that could be activated using silver salts.[87]



Scheme 1.2: Fisher glcosylation and Koenigs and Knorr glycosylation.

The terminology of a glycosylation reaction is as follows: the glycosyl donor has a leaving group at its anomeric centre and the glycosyl acceptor bears a nucleophilic hydroxyl group. After promoter assisted

departure of the anomeric leaving group an oxa-carbenium ion intermediate is formed. This is then attacked by the glycosyl acceptor from either the α- or the β-face to afford α- or β-glycosides, respectively. A major determinant of the stereoselectivity of a glycosylation is the anomeric effect.[88] In general it is known that substituents of a cyclic six membered hydrocarbon prefer the energetically more stable equatorial position (β-directed) because this prevents unwanted 1,3-diaxial interactions.



Scheme 1.3: The anomeric effect. A) The antiperiplanar lone pair hypothesis B) Anti-parallel placement of dipoles in the stabilized α-anomer C) Explanation of the anomeric effect by the electrostatic repulsion of lone pair electrons.

However, when an electron-withdrawing substituent is attached to the anomeric centre of a pyranose, the axial α-position is favoured. This phenomenon was first observed by Edward,[89] and defined as the "anomeric effect" by Lemieux.[90] The anomeric effect has been explained in a number of ways. The most widely accepted explanation is by the Antiperiplanar Lone Pair Hypothesis (ALPH). In the α-configuration the HOMO of the endocyclic oxygen is positioned to donate electron density into the LUMO anti-bonding orbital of the C1-O1 bond (Scheme 1.3A). The delocalization of electron density contributes favourably to the stabilization of the α-anomer and is expected to decrease the bond length of the *endo*-O-C1 bond. Compelling evidence for this phenomenon is the measurement of bond lengths of

2,3-dichloro-1,4-dioxane. As expected the bond length of the axial chloride *endo*-O-C1 bond is considerably longer than the equatorial chloride *endo*-O-C1 bond.

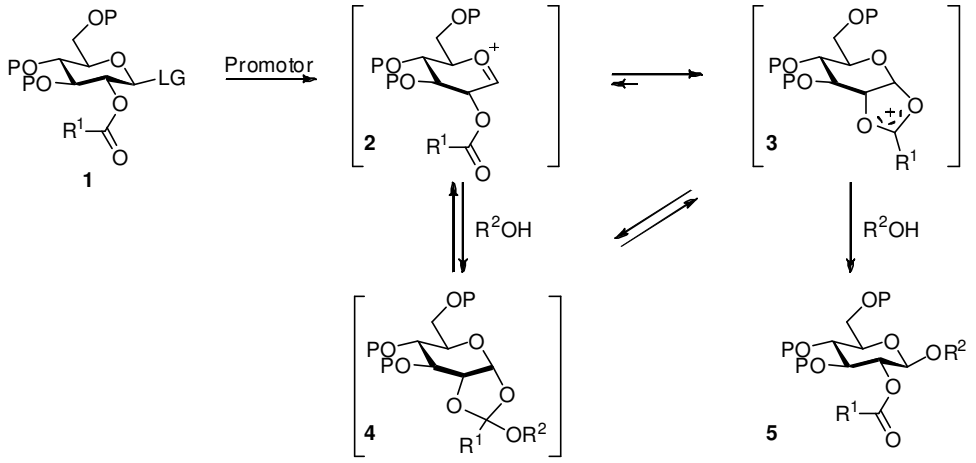
Another explanation considers the direction of the dipoles in case of the α and β-anomers (Scheme 1.3B). The first dipole is along the C1-O1 bond and is a result of the polarisation of this bond. The second dipole is in a bisected position between the two lone pairs of the ring oxygen. When the OMe group is in an equatorial position, the angle between the two dipoles is very small and this results in an unfavoured dipole-dipole interaction. An axial position of the OMe group place the dipoles anti-parallel, resulting in a more favoured dipole-dipole interaction because the two dipoles almost cancel each other out. The beneficial effect of these anti-parallel dipoles is far greater than the loss of stability due to 1,3-diaxial interactions. Finally, the electrostatic repulsion between the lone pair electrons of the endocyclic oxygen and the electronegative anomeric oxygen is minimized in the α-anomer (Scheme 1.3C).

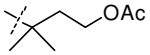
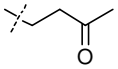
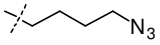
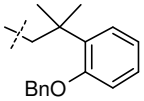
In addition to the anomeric effect, other factors may play an important role in controlling anomeric stereoselectivity and overall efficiency of a glycosylation. Careful selection of reaction parameters such as solvent and temperature is crucial for anomeric selectivity. In addition, mild promoter systems and leaving groups have been developed. The next section will highlight the state-of-the-art methods for the stereoselective glycosylations that do not employ reaction parameters such as solvent and temperature. Instead the use of intrinsic properties of certain carbohydrates and protecting groups as well as purposely designed auxiliaries for stereoselective glycosylation will be discussed.

Neighbouring group participation. The use of protecting groups that can stabilize an intermediate oxa-carbenium ion by anchimeric assistance or neighboring group participation (NGP) is a proven strategy to ensure stereoselective glycosylation. In most cases, the relative configuration of the participating group of the glycosyl donor is the main determinant of the stereochemical outcome of the glycosylation. The next section will discuss NGP by different C-2 functional groups designed to ensure stereoselective 1,2-*cis* and

1,2-*trans* glycosylation as well as remote participation (participation from positions other than C-2) and intramolecular aglycone delivery.

Neighboring group participation of C-2 esters to afford 1,2-*trans* glycosides. The nature of the protecting group at C-2 of a glycosyl donor is a major determinant of anomeric selectivity.[91] After departure of the anomeric leaving group, a 2-*O*-acyl functionality can perform neighboring group participation.



entry	R^1	specific function	conditions for removal
1		Prevent orthoester formation	Concentrated NaOMe/MeOH
2		Prevent orthoester formation Selectively removed in the presence of other esters	DBU, MeOH
3		Selectively removed in the presence of other esters	$H_2NNH_2 \cdot AcOH$, Toluene/Ethanol
4		Selectively removed in the presence of other esters	PPh_3, THF/H_2O
5		Removed under non-basic conditions in concert with benzyl ethers	H_2, Pd/C,

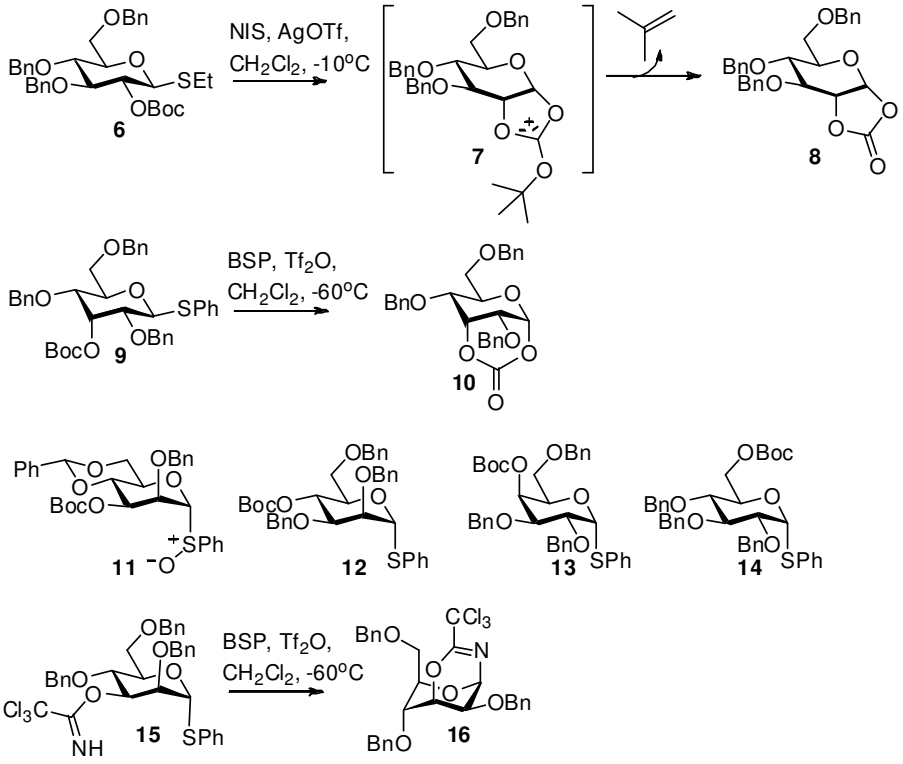
Scheme 1.4: Neighboring group participation of a 2-*O*-acyl functionality to provide 1,2-*trans*-glycosides.[91]

The intermediate oxa-carbenium ion **2** is attacked by the neighboring group to form an intermediate five-membered dioxalenium-ion **3**, which can only be formed as a 1,2-*cis* fused ring system (Scheme 1.4). The intermediate dioxalenium ion has been detected by NMR spectroscopy[92] and its existence has also been

demonstrated by the isolation of crystalline dioxalenium ions.[93] A glycosyl acceptor can attack the dioxalenium ion at the anomeric center only from the β-face leading to the stereoselective formation of 1,2-*trans* glycoside **5**. The glycosyl acceptor can also add directly to the dioxalenium ion leading to the formation of orthoester **4**. The orthoester is not stable under acidic conditions and will rearrange to the desired 1,2-*trans* glycoside. In general, the use of a 2-*O*-acyl functionality to synthesize 1,2-*trans* glycosides is very reliable, highly stereoselective and in the case of glucosyl-type donors, β-linked products will be obtained whereas mannosides will give α-linked products. Numerous 2-*O*-acyl protecting groups have been developed to reduce orthoester formation and/or incorporate a latent nucleophile to enable selective removal in the presence of other esters. For example, the bulky pivaloyl ester (trimethyl acetyl ester) is used to suppress orthoester formation but due to its bulky nature it is also harder to remove except under highly basic conditions (entry 1, Scheme 1.4). The 4-acetoxy-2,2-dimethylbutanoate ester (ADMB) was also developed to suppress orthoester formation and can be selectively removed by deacetylation/cyclization under very mild basic conditions (Scheme 1.4 entry 2).[94] The bulky geminal dimethyl substitution is responsible for suppressing orthoester formation while also promoting cyclization by the "gem-dialkyl" or Thrope-Ingold effect.[95-97]

Similarly, the levulinoyl ester contains a ketone which upon treatment with hydrazinium acetate forms a hydrazone that will cyclize to unmask the alcohol (Scheme 1.4, entry 3).[98] Staudinger reduction of the azidobutyryl ester also leads to selective removal by intramolecular attack of the ester (Scheme 1.4, entry 4).[99] In addition, the dimethylbenzyloxyphenylpropionate (DMPP) ester can be removed under non-basic conditions and in concert with the commonly used benzyl ethers by catalytic hydrogenation using H_2, Pd/C (Scheme 1.4, entry 5).[100] In addition to 2-*O*-glycosides NGP can also be employed to obtain 2-Deoxy-2-amino-glycosides which are common constituents of *N*-and *O*-linked glycoproteins, glycolipids and proteoglycans. Amino-protecting group that can perform NGP comprise phthalimido, tetrachlorophthalimido (TCP), *N*,*N*-dimethyl maleoyl, trichloroacetyl, allyloxycarbonyl, and trichloroethyloxycarbonyl.

Remote neighbouring group participation. In addition to the C-2 position, neighboring group participation from non-vicinal alcohols of the sugar ring has been implied to play a role in determining the stereochemical outcome of a glcosylation.[101-104] In the case of non-vicinal esters, the presence of the intermediate dioxalenium ion, arising from remote participation is controversial and evidence for its existence rarely extends beyond stereochemical arguments.[105-107] Recently, efforts to trap the intermediate dioxalenium ion using a *tert*-butoxycarbonyl (Boc) group have been reported (Scheme 1.5).[108] It was envisioned that upon participation of the Boc group, the intermediate dioxolenium ion **7** would subsequently lose isobutylene, which would lead to the formation of the stable cyclic carbonate **8**.



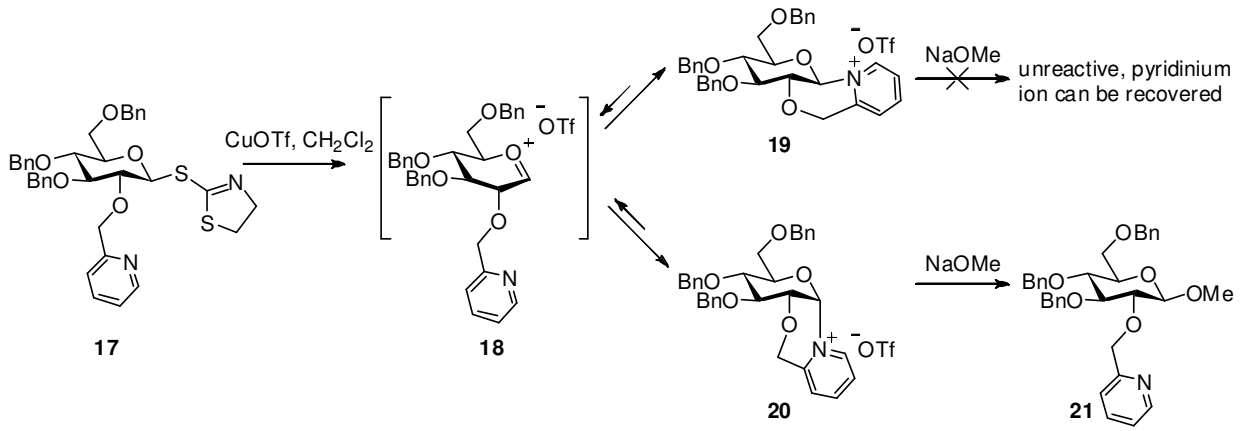
Scheme 1.5: Nucleophilic traps to investigate the possibility for neighboring group participation from non-vicinal positions.[108-109]

Indeed, treatment of thioglycoside **6** with NIS/AgOTf resulted in the formation of 1,2-carbonate **8** in a high yield. Next, a series of glycosyl donors carrying a Boc group at either equatorial or axial C-3, C-4 and C-6 position were prepared and tested. Only in the case of the allose donor **9**, which has an axial C-3 Boc group, the corresponding 1,3-carbonate **10** was formed, thereby confirming that remote participation

had occurred. Thioglycosides **11** and **12** did not form bicyclic carbonates but instead hydrolyzed or glycosylated when glycosyl acceptor was added, however the Boc group remained intact. The same holds true for thioglycosides **13** and **14** and hence it was concluded that no other positions could be involved in remote participation. However, a later report by Kim and co-workers proved that remote participation from and equatorial C-3 position is indeed possible.[110] In this case, a trichloroacetimidate was used as the nucleophilic trap (Scheme 1.5). Upon low-temperature activation of thioglycoside **15** using 1-benzenesulfinyl piperidine (BSP) and trifluoromethanesulfonic anhydride (Tf_2O), bicyclic trichlorooxazine product **16** was formed in 85% yield. However, in the case of a C-4 and C-6 trichloroacetimidoyl group no bicylcic trichlorooxazine products were formed. Therefore, remote participation can play an important role although it seems to depend on the nature of the sugar configuration and conformation as well as the structure of the participating group.

Neighboring group participation by other functional groups. The use of electron withdrawing ester protecting groups reduces the reactivity of a glycosyl donor by destabilization of an intermediate oxa-carbenium ion.[111] This reduced reactivity usually leads to incomplete activation and a lower glycosylation yield. Considerable efforts have been directed at resolving this issue by either modification of the participating group[112] or by the use of reactivity enhancing groups.[113] Demchenko and co-workers reported the use of modified ether groups that can perform NGP to ensure stereoselectivity while not adversely affecting the reactivity of the glycosyl donor. The most promising protecting group to achieve this goal is the 2-pyridylmethylpicolyl ether which was found suitable for selective 1,2-*trans*-glycosylation (Scheme 1.6). Even though the 2-pyridylmethylpicolyl ether is expected to be less electron withdrawing and therefore less deactivating that an ester protecting group, reaction rates were slow and heating was needed to drive the glycosylations to completion.[114] However, the slow reaction rate was not due to a slow activation which occurred readily at low temperature. Activation of thioglycoside donor **17** with $Cu(OTf)_2$ was complete within one hour, but the ensuing glycosylation was found to be sluggish.

NMR studies showed a mixture of two stable pyridinium ions **20** and **19** were formed upon activation and the 1,2-*cis*-pyridinium ion **20** was formed predominantly.

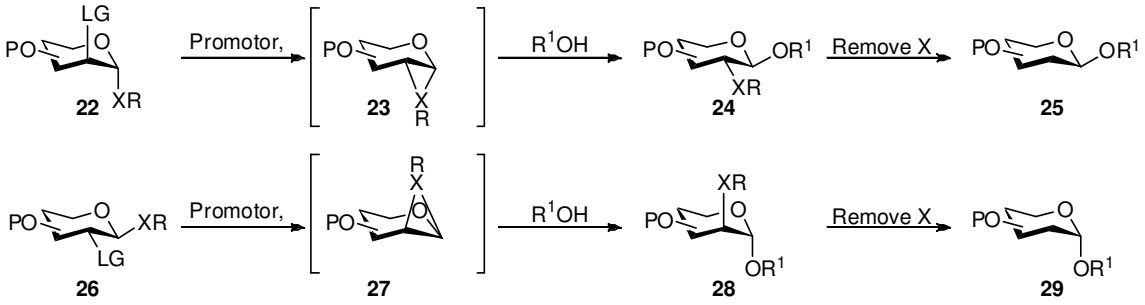


Scheme 1.6: Use of the 2-pyridylmethylpicolyl ether for the stereoselective synthesis of 1,2-*trans*-glycosides.[114]

The pyridinium ions **19** and **20** were found to be remarkably stable and could be isolated by silica gel chromatography. When the purified pyridinium ions were reacted with nucleophiles, the 1,2-*cis*-pyridinium ion **20** reacted smoothly with methanol or sodium methoxide to afford 1,2-*trans*-glycoside **21**. The 1,2-*trans*-pyridinium ion **19** was inert under these conditions and could be reisolated. Although the activation of glycosyl donors proceed readily, to unreactive nature of the intermediate pyridinium ions hamper the broad applicability of this method.

Neighboring group participation followed by migration has received considerable attention and is particularly useful in the stereoselective synthesis of 2-deoxy-glycosides (Scheme 1.7).[115] Typically, the leaving group is situated on the C-2 position while the participating functionality is 1,2-*trans* to the leaving group on the anomeric center (**22**, **26** Scheme 1.7). If a β-anomeric product is desired, the participating group of the glycosyl donor has an α-anomeric configuation, and if an α-anomeric product is desired, the participating group on the glycosyl donor should be placed in an β-anomeric configuration. Upon promoter assisted departure of the leaving group the participating group, a three membered ring

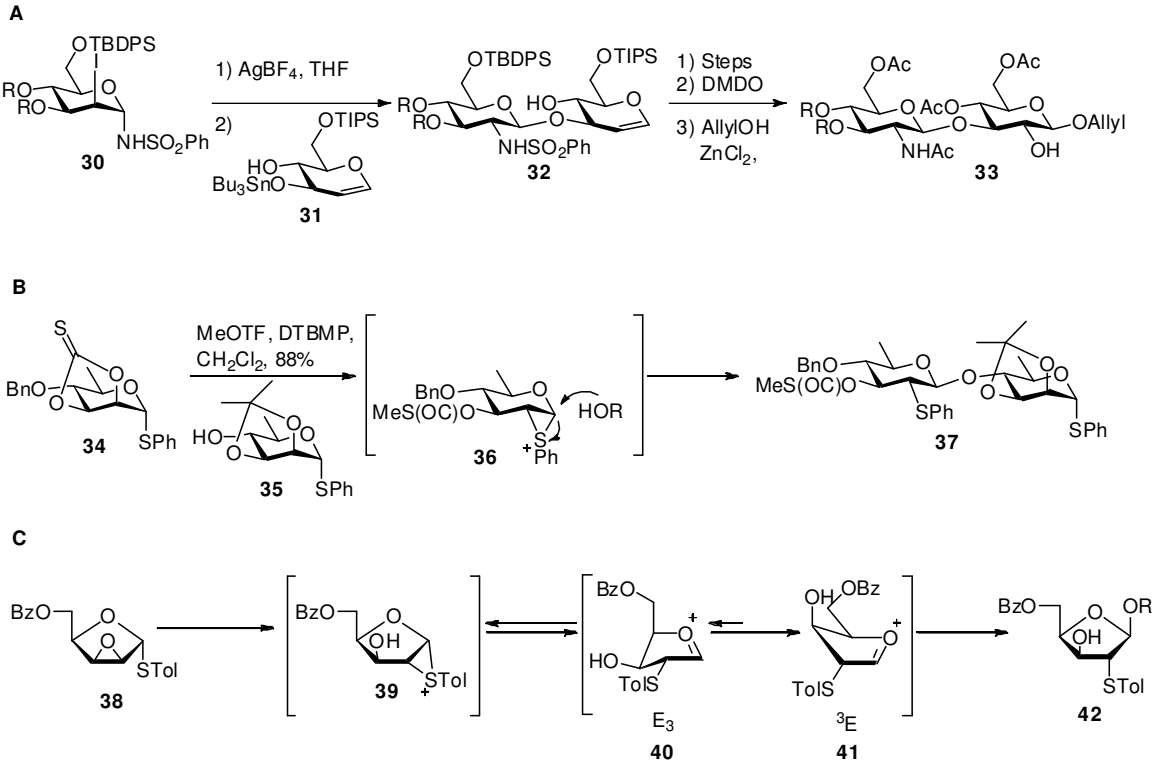
intermediate is formed (**23**,**27**), which after displacement in an S_N2-fashion by the glycosyl acceptor leads to stereoselective formation of disaccharides. The participating group is usually a thio- or seleno ether which can be reduced using Raney nickel to afford 2-deoxy-glycosides (**25**,**29**). In addition, three membered halonium intermediates can also be used which afford halogycosides that can be reduced to 2-deoxy-glycosides or used to incorporate additional functionalities.



Scheme 1.7: The 1,2-migration of an anomeric participating group to afford α- or β-(deoxy)-glycosides.[115]

An early example of the 1,2-participation-migration strategy was developed by Danishefsky and co-worker and was coined the glycal assembly method (Scheme 1.8A).[116] In this approach, the double bond of a glycal is reacted to afford an epoxide or 1,2-*trans*-diaxyl iodosulfonamide. Subsequent opening of the epoxide with an aglycone affords 1,2-*trans*-glycosides. Reaction of the 1,2-*trans*-diaxyl iodosulfonamide with a strong base affords a 1,2-*N*-sulfonylaziridine which can be reacted an aglycone to afford 1,2-*trans*-aminoglycosides. This method was applied to the synthesis of Le^y and Le^b neoglycoconjugates.[117] Key steps involved the preparation of a glycal intermediate which was reacted with iodonium di-*sym*-collidine perchloride and benzenesulfonamide to afford 1,2-*trans*-diaxyl iodosulfonamide **30** in a stereoselective manner.[118] Activation of **30** with silver tetrafluoroborate led to the intermediate 1,2-*N*-sulfonylaziridine which was reacted with tributyltin ether glycal **31** to afford 1,2-*trans*-glucosamine **32**. The second glycal was activated with dimethyldioxirane to afford the intermediate epoxide which was reacted with $ZnCl_2$ and allyl alcohol to afford Le^y pentasaccharide **33**.

Recently, Yu and co-worker reported the use of 2,3-*O*-thionocarbonyl-1-thioglycosides as viable glycosyl donors for the construction of 2-deoxy- β-glycosides.[119] This method was applied to the synthesis of the Landomycin A hexasaccharide which contains two β-D-olivose-(1→4)-β-D-olivose disaccharides.[120] The 2,3-*O*-thionocarbonate of olivosyl donor **34** was activated with methyltrifluoromethanesulfonate, which led to the 1,2-migration of the thiophenyl moiety to provide the corresponding episulfonium ion **36**. The latter reaction intermediate was displaced by olivose acceptor **35** to afford the β-linked disaccharide **37** with absolute control of stereoselectivity.



Scheme 1.8 : 1,2-migration reactions in the stereoselective synthesis of 1,2-*trans*-(amino)-glycosides and 2-deoxy-glycosides. [120-122]

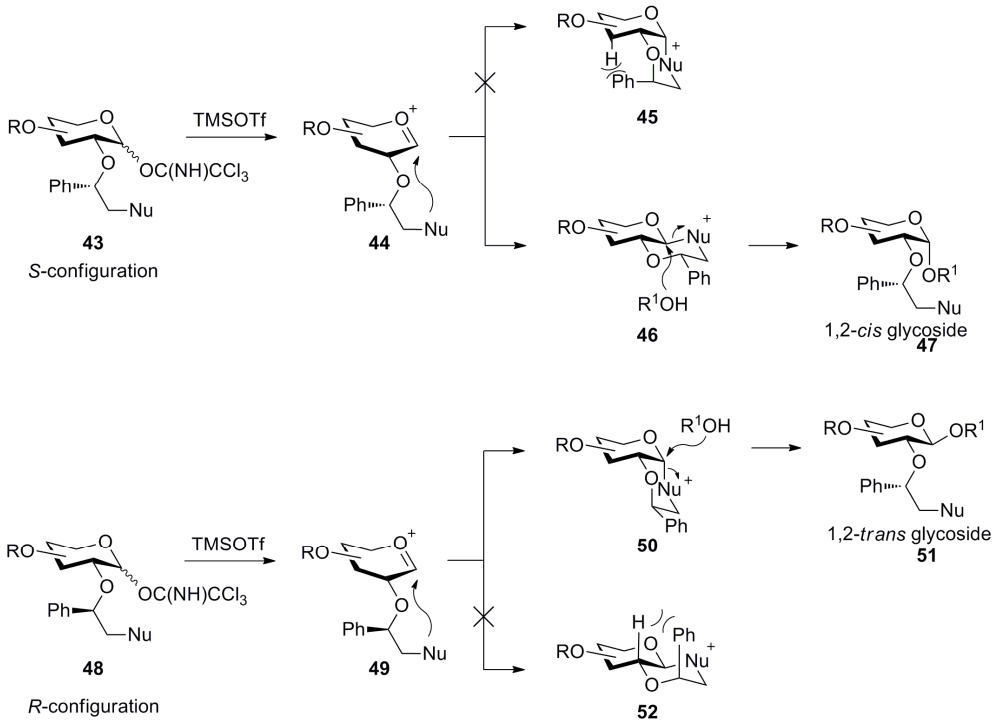
This type of participation/migration has also been extended to the stereoselective synthesis of furanosides. Lowary and co-workers reported the use of 2,3-anhydrothioglycosides which upon activation with $Cu(OTf)_2$ led to the formation of 1,2-*trans*-glycosides (Scheme 1.8C). This type of reaction is assumed to

proceed through an episulfonium intermediate **39**. However, a detailed investigation showed that oxa-carbenium ions **40** and **41** were the predominant intermediates.[122] The kinetic isotope effect (KIE) was determined to be within 1.17-1.20, a value which is more consistent with an oxa-carbenium ion intermediate *vs* an episulfonium ion. Furthermore, computational experiments also indicated that the ^{3}E oxa-carbenium ion **41** is considerably more stable than the strained epi-sulfonium ion **39**. The observed stereoselectivity can be explained by an inside attack on the ^{3}E oxa-carbenium ion (*vide infra*).

Neighbouring group participation using chiral auxiliaries to obtain 1,2-*cis* glycosides. Until recently, 1,2-*cis*-glycosides could only be obtained employing glycosyl donors that have a non-assisting functionality at C-2. In this type of glycosylation reaction, parameters such as the anomeric effect and reaction conditions such as solvent, temperature, and promoter, as well as the constitution of the glycosyl donor and acceptor (for example, type of saccharide, leaving group at the anomeric centre, protection and substitution pattern) control anomeric selectivity. The introduction of 1,2-*cis* glycosides often leads to mixtures of anomers despite extensive efforts to optimize conditions.

A new approach to the synthesis of 1,2-*cis*-glycosides was reported using NGP by a chiral auxiliary at C-2 of the glycosyl donor.[123] In the approach, the chiral auxiliary is designed to trap the oxa-carbenium-ion from the β-face therefore blocking it and hence displacement of this intermediate should result in the formation of 1,2-*cis*-glycosides. To achieve this, a nucleophilic group is distanced to form a six membered ring system upon participation which either results in a *cis* (**45**,**50**) or *trans*-decalin (**46**,**52**) system (Scheme 1.9). It was envisioned that a chiral substituent could be used to favor the formation of the *cis* or *trans*-decalin system leading to 1,2-*trans* or 1,2-*cis* glycosides, respectively. In case of an *S*-configured auxiliary, formation of the *cis*-decaling intermediate **45** results in axial placement of the chiral subsituent which in turn leads to an unfavorable 1,4-diaxial steric interaction. In contrast, formation of the *trans*-decalin intermediate **46** leads to a more favorable equatorial substitution and is hence preferred. In addition, the *trans*-decalin system will have less unfavorable gauche interactions than the *cis*-decalin system. Therefore, the *S*-configuration is expected to favor 1,2-*cis*-glycoside formation by selectively

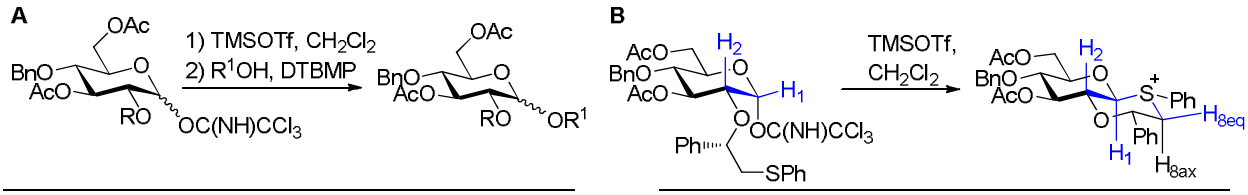
forming the *trans*-decalin intermediate (Scheme 1.9, top). Similarly, the *R*-configured auxiliary was expected to favor 1,2-*trans* glycoside formation, since the 1,2-*cis*-decalin intermediate **50** leads to equatorial placement of the phenyl substituent and prevents the 1,3-diaxial steric interaction that the *trans*-decalin experiences (Scheme 1.9 bottom).

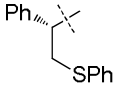
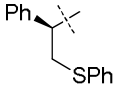


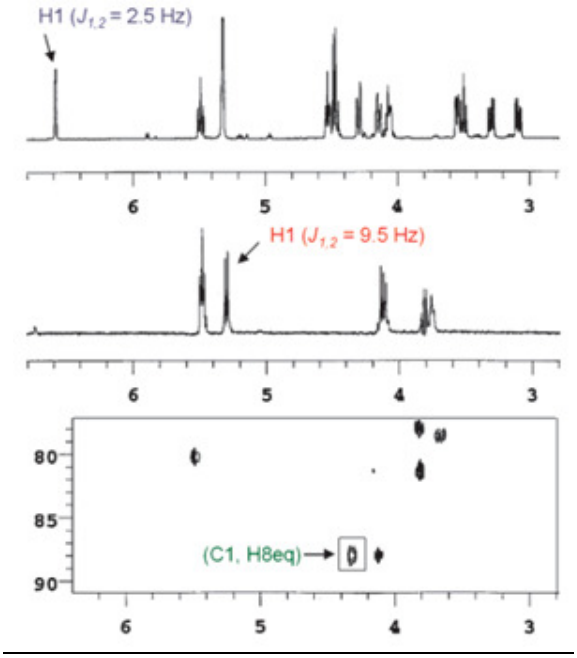
Scheme 1.9: Chiral auxiliaries designed to form *cis* or *trans*-decalin oxonium intermediates to afford 1,2-*trans* of 1,2-*cis*-glycosides, respectively.[123-124]

The first generation of chiral auxiliaries employed an (*S*)-ethoxycarbonylbenzyl moiety as the nucleophilic head group since esters are proven to perform NGP.[123,125] As expected, the use of the *S*-configured-auxiliary lead to the selective, formation of 1,2-*cis* glycosides with the α/β selectivity ranging from 20/1 to 4/1 depending on the nature of glycosyl acceptor (Scheme 1.10A, entry 1). As expected, the use of the *R*-auxiliary led to the predominate formation of 1,2-*trans*-glycosides (Scheme 1.10A, entry 2) albeit with lower selectivity (α/β selectivity between 1/8 and 1/1 depending on the glycosyl acceptor). These results clearly demonstrated that the chirality of the auxiliary controls the anomeric selectivity

albeit that in some cases modest selectivity was achieved. The lack of absolute anomeric stereoselectivity was attributed to the sp^2 character of the (*S*)-ethoxycarbonylbenzyl moiety which does not allow the formation of a perfect *trans*-decalin system. The second generation of chiral auxiliary, employed a more nucleophilic thiophenyl ether.[124]



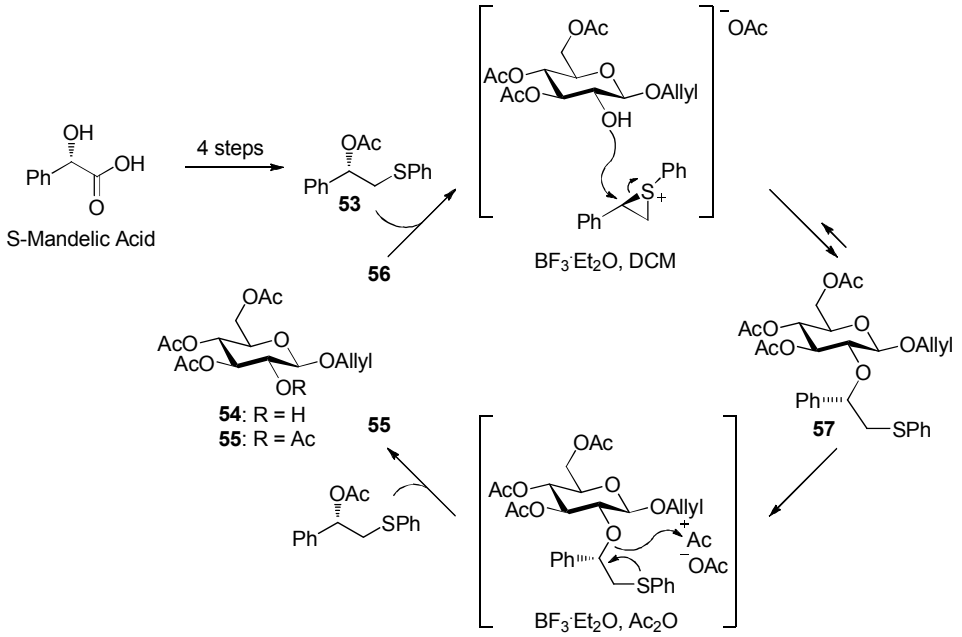
entry	R	α/β	yield
1		20/1 - 4/1	92% - 94%
2		1/8 - 1/1	88% - 94%
3		α - only	95%
4		1/1	88%
5		8/1	86%
6		3/1	94%



Scheme 1.10: C-2 Chiral axiliaries. A) (*R*/*S*)-Ethyl mandelate auxiliaries and (*S*)-(phenylthiomethyl) benzyl ethers in stereoselective glycosylation. B) NMR identification of the trans-sulfonium ion using HMBC correlation spectroscopy.[123-124]

This modification significantly improved 1,2-*cis*-stereoselectivities and provided exclusively 1,2-*cis*-glycosides (Scheme 1.10A, entry 3). In general, glycosylations using the (*S*)-(phenylthiomethyl) benzyl moiety were observed to be slower than normal indicating the presence of a stable, slow-reacting intermediate. Low temperature NMR experiments convincingly showed the selective formation of a β-linked sulfonium ion intermediate (Scheme 1.10B).[124] The characteristic anomeric signal of the

glycosyl donor was shifted upfield after addition of TMSOTf and its coupling constant went from 2.5 Hz to 9.5 Hz indicating the formation of the expected β-linked decalin system. Furthermore, through bond coupling was observed between C-1 and $H8_{eq}$ using an HMBC experiment. An auxiliary lacking the chiral substituent was less selective than the (*S*)-(phenylthiomethyl) benzyl moiety (Scheme 1.10A, entry 5), but still more selective than a non-participating functionality (Scheme 1.10A, entry 6). Since the 1,2-*cis*-decalin system experiences more unfavorable gauche interactions than the 1,2-*trans*-decalin system 1,2-*cis*-glycosides are still formed predominantly even though no chiral substituent is present (Scheme 1.10A, entry 5). The loss of 1,2-*cis* selectivity compared to the (*S*)-(phenylthiomethyl) benzyl moiety can be explained by the fact that a more substituted ring system is more stable and that additional substituents also promote cyclization (the Thorpe-Ingold effect).

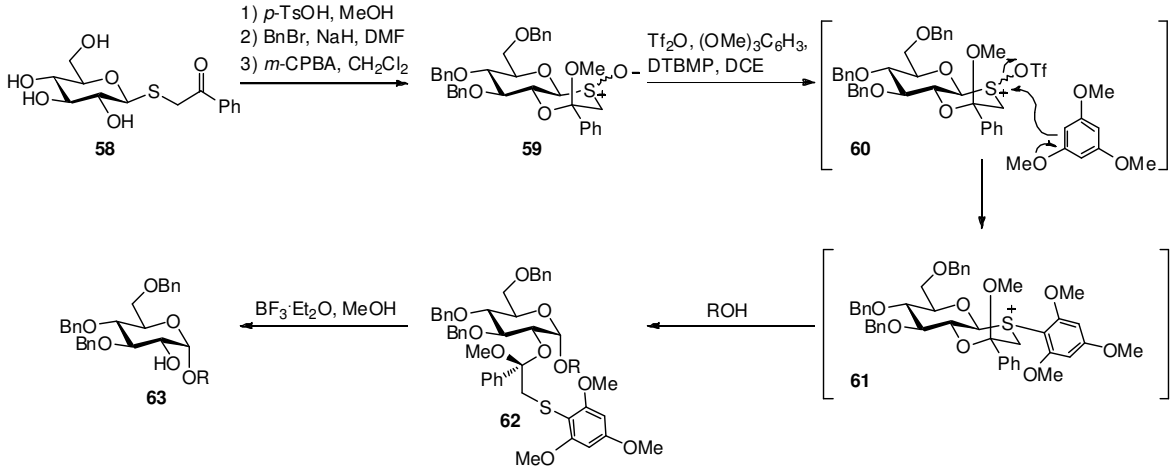


Scheme 1.11: Lewis acid catalyzed stereoselective introduction and removal of the (*S*)-(phenylthiomethyl) benzyl moiety.[124]

The (*S*)-(phenylthiomethyl) benzyl moiety could readily be introduced by reaction of sugar alcohol **54** with (*S*)-(phenylthiomethyl)benzyl acetate **53** in the presence of $BF_3{\cdot}OEt_2$ (Scheme 1.11). Removal was

achieved by conversion into acetyl ester **55** by treatment of **57** with $BF_3{\cdot}OEt_2$ in acetic anhydride. Both reactions proceed through an intermediate episulfonium ion with overall retention of configuration.

Recently, Turnbull and co-workers have reported an elegant modification of the (*S*)-(phenylthiomethyl) benzyl auxiliary that involved the use of a prearranged oxathiane glycosyl donors (Scheme 1.12).[126-127] The intramolecular reaction of glycosyl ketone **58** in acidic methanol afforded the corresponding oxathiane **59** derivative in high yield and absolute stereoselecivity.

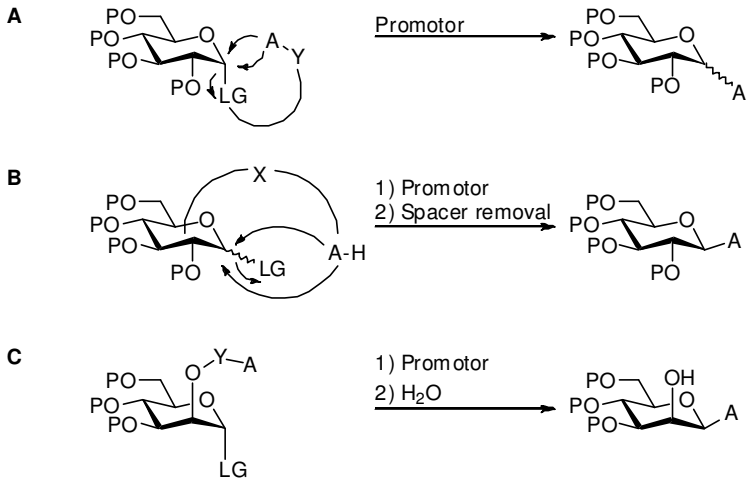


Scheme 1.12: Generation of sulfonium ions using the electrophilic aromatic substitution of oxathiane glycosyl donors.[126-127]

The desired configuration of methoxy group in **59** is stabilized by the anomeric effect and the equatorial placement of the biggest substituent. A major benefit of this approach is that no chiral starting material other than glucose is needed and that the O-2 position if selectively modified without the use of protecting groups. Protection of the remaining hydroxyl groups and oxidation of the thioether using *m*-CPBA afforded sulfoxide **59**. Activation of oxathiane donor **59** was performed using Tf_2O and 1,3,5-trimethoxy benzene in the presence of DTBMP. The triflation of the sulfoxide led to the formation of sulfonium ion **60** which reacted with 1,3,5-trimethoxy benzene by an electrophilic aromatic substitution to afford sulfonium ion **61**. Addition of various glycosyl acceptors led to the corresponding 1,2-*cis*-glycosides with

absolute selectivity in moderate to high yield. The acyclic acetal **62** proved to be very labile and was cleaved during the glycosylation leading to the formation of side-products.

Intramolecular aglycon delivery. Another innovative approach, which utilizes the relative configuration of (remote) substituents of the glycosyl donor is termed intramolecular aglycon delivery.[128-129] Intramolecular aglycon delivery (IAD) through tethering of the glycosyl donor and acceptor by a spacer has been extensively researched. The tether can be used to prearrange the donor and acceptor in such a way that it directs the stereochemical outcome of the ensuing glycosylation. Tethering at reactive and non-reactive centers has been successfully implemented although the installation and removal of the tether involves additional steps (Scheme 1.13A-C).

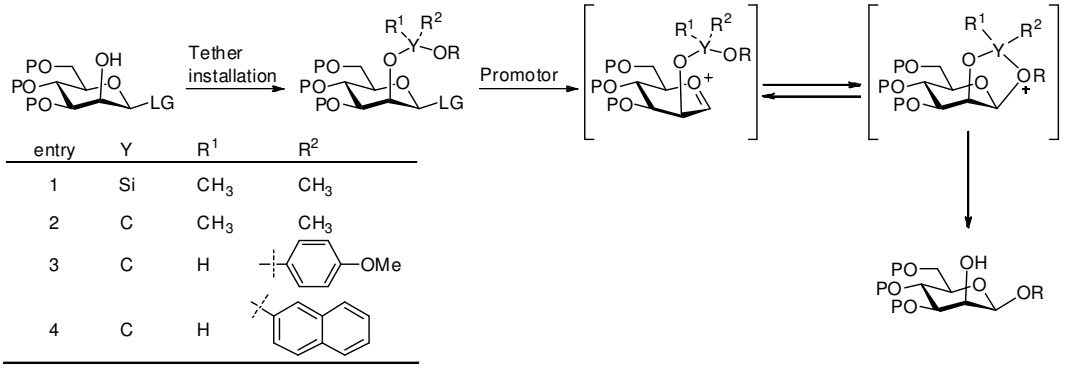


Scheme 1.13: Intramolecular aglycon delivery (IAD). A) IAD by the use of anomeric linkers. B) IAD by the use of rigid spacers at non-reacting centers. C) IAD by tethering from C-2 to 1,2-*cis*-glycosides.

Anomeric tethers have been successfully implemented; however the anomeric selectivity is difficult to control since this type of tether needs to be broken in order for the glycosylation to take place (Scheme 1.13A). This leads to competition of intra- and intermolecular reaction pathways usually resulting in a loss of stereoselectivity. Therefore, linking monosaccharides prior to glycosylation through a non-reactive center is more suitable to ensure a stereoselective glycosylation. The ability of an enzyme to prearrange the glycosyl donor and acceptor has inspired the use of rigid spacers (Scheme 1.13B). The use of such

spacers non-reacting centers require additional steps for the introduction of removal and the stereoselectivity can be hard to predict.

Another version of IAD and arguably the most successful to date involves a tether between the O-2 of the glycosyl donor and a hydroxyl of an acceptor (Scheme 1.13C, Scheme 1.14). This type of IAD is distinct from the prearranging strategy since the acceptor alchol is directly connected to the tether usually resulting in a five membered transition state and formation of a 1,2-*cis*-glycoside. Tethers are designed to stabilize a positive charge and fragment upon glycosylation. The silylacetal-tether which can be installed using dichlorodimethylsilane is suitable for this purpose in addition to mixed acetals. The mixed isopropylidene acetal can be readily obtained under mild acidic conditions from an isopropenyl functionalized sugar and a glycosyl acceptor. The isopropenyl functionality can be obtained from the acetyl precursor upon treatment with Tebbe's reagent. The latter step somewhat limits this technology since no other ester can be present.

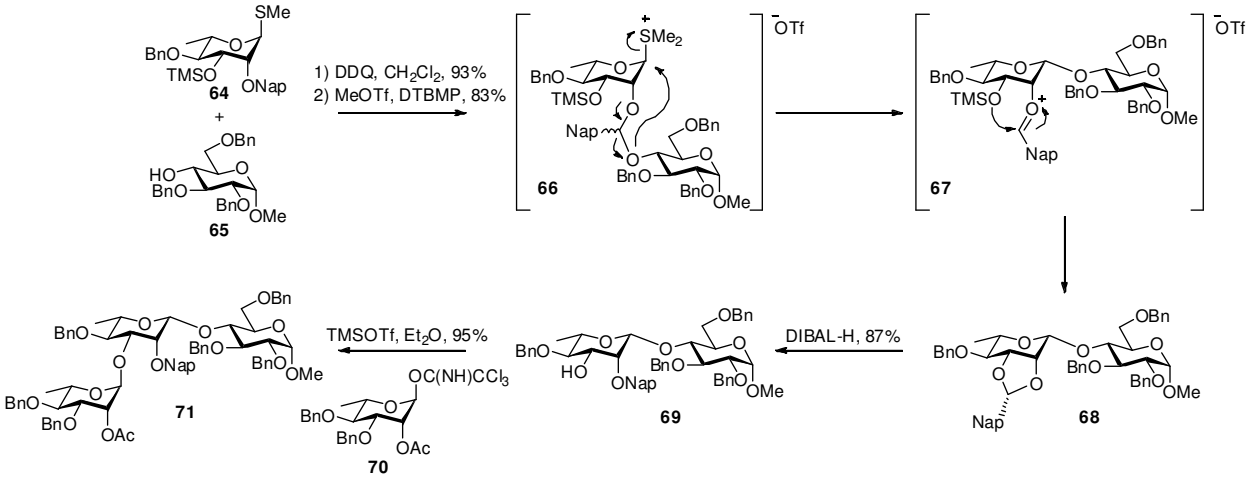


entry	Y	R^1	R^2
1	Si	CH_3	CH_3
2	C	CH_3	CH_3
3	C	H	
4	C	H	

Scheme 1.14: IAD by acetal tethering to afford 1,2-*cis*-glycosides.

Another approach to prepare a mixed acetal exploits the oxidation of an electron-rich aryl ether in the presence of an alcohol acceptor. The mixed acetal is usually prepared by DDQ oxidation of an glycosyl donor carrying an 2-naphtylmethyl, 4-methoxybenzyl or 3,4-dimethoxybenzyl ether at C-2 under dry conditions in the presence of an glycosyl acceptor. The position of the substituted aryl ether can also be switched from the acceptor to the donor, and this approach is referred to as inverse tethering, which can improve the yield of mixed acetal formation in some cases. Upon activation of the glycosyl donor, the

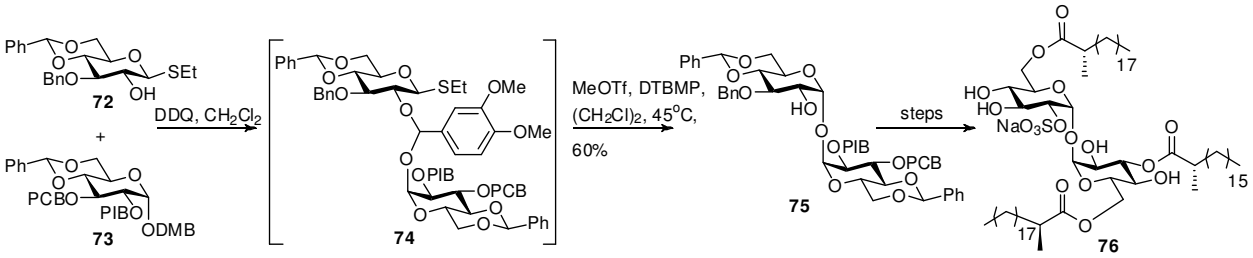
mixed aryl acetal ensures the acceptor oxygen is delivered from the same face as the 2-*O* substituent (1,2-*cis*) on the glycosyl donor since it forms a five membered ring in the proposed transition state. Usually, the product disaccharide is isolated as a free 2-OH′ which can directly serve as a glycosyl acceptor. However, the oxa-carbenium reaction intermediate arising from the substituted aryl ether can also be trapped using Et_3SiH, succinimide (formed when using NIS as promotor) or a 3-*O*-TMS ether affording an 2-*O*-aryl ether, 2-*O*-succinyl mixed-acetal or 2,3-*O*-aryl acetal, respectively.



Scheme 1.15: Trapping of the intermediate oxa-carbenium ion using an 3-*O*-TMS ether in the synthesis of β-L-rhamnosides.[130]

The benefits of trapping the intermediate oxa-carbenium ion using a neighboring protecting group was demonstrated by Ito and co-workers in the elegant synthesis of β-L-rhamnosides (Scheme 1.15).[131] Mixed acetal **66** was prepared using a 2-methylnaphthyl protected rhamnosyl donor **64** and glucosyl acceptor **65** upon oxidation with DDQ. Activation of the thiomethyl leaving group of **66** with methyltriflate led to the formation of an oxonium ion intermediate **67** which was trapped by the O-3 position leading to the formation of a naphthyl acetal **68**. Selective reductive opening of the acetal using DIBAL-H unmasked the C-3 alcohol for an ensuing glycosylation (**69**). Finally, an α-L-rhamnoside was installed by glycosylation of **69** with **70** using a catalytic amount of TMSOTf to afford trisaccharide **71**. Intramolecular aglycon delivery has been used to prepare other 1,2-*cis*-pyranosides and furanosides such

as α-D-glucose, β-D-mannose, β-L-rhamnopyranoside, β-D-arabinofuranoside, β-D-fructofuranoside and β-D-fucofuranoside. Furthermore, IAD was used to prepare α,α trehaloses such as Sulfolipid-1 (SL-1), which are saccharides which are linked through their anomeric centers (Scheme 1.16). The key step in the synthesis of SL-1 analogues by Bertozzi and co-workers involved intermolecular aglycon delivery mediated by a 3,4-dimethoxybenzyl mixed acetal.[132] The synthesis of α/α threhaloses is difficult since two anomeric centers need to be controlled and the anomeric hydroxyl cannot be used as an acceptor since it can mutarotate and convert to the unwanted β-anomer.

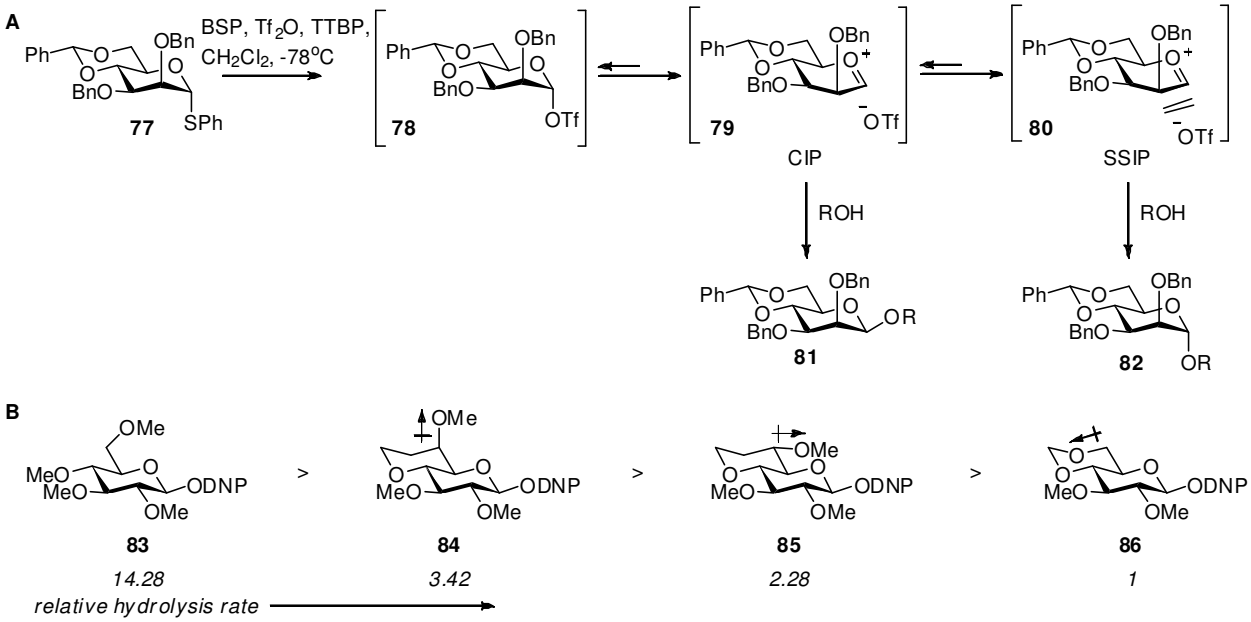


Scheme 1.16: Dual stereocontrol using IAD in the synthesis of α,α-trehalose sulfolipid-1.[132]

Therefore, IAD lends itself well since the anomeric hydroxyl can be masked as a stable α-anomeric ether and directly transferred unto the donor anomeric center. Thus, glucose acceptor **73** carrying an α-anomeric 3,4-dimethoxybenzyl (DMB) ether, which was obtained using altered Gervay-Hague glycosylation conditions with DMB-OH, upon oxidation with DDQ in the presence of thioglycoside donor **72** afforded mixed acetal **74** (inverse tethering). Ensuing glycosylation using MeOTf as promoter afforded only the α,α trehalose product in good yield **75**. Subsequent selective removal of the protecting groups and installation of the lipid chains followed by deprotection afforded SL-1 (**76**).

Anomeric control by electronic and steric effects. Crich and co-workers discovered that pre-activation of 4,6-*O*-benzylidene protected mannosyl sulfoxide donors at low temperature followed by addition of a glycosyl acceptor leads to the stereoselective formation of β-mannosides (Scheme 1.17A). The necessity

for pre-activation at low temperature to obtain good β-selectivity led to the notion that first a stable intermediate is formed which than reacts in a stereoselective manner with the nucleophile to form β-mannosides.



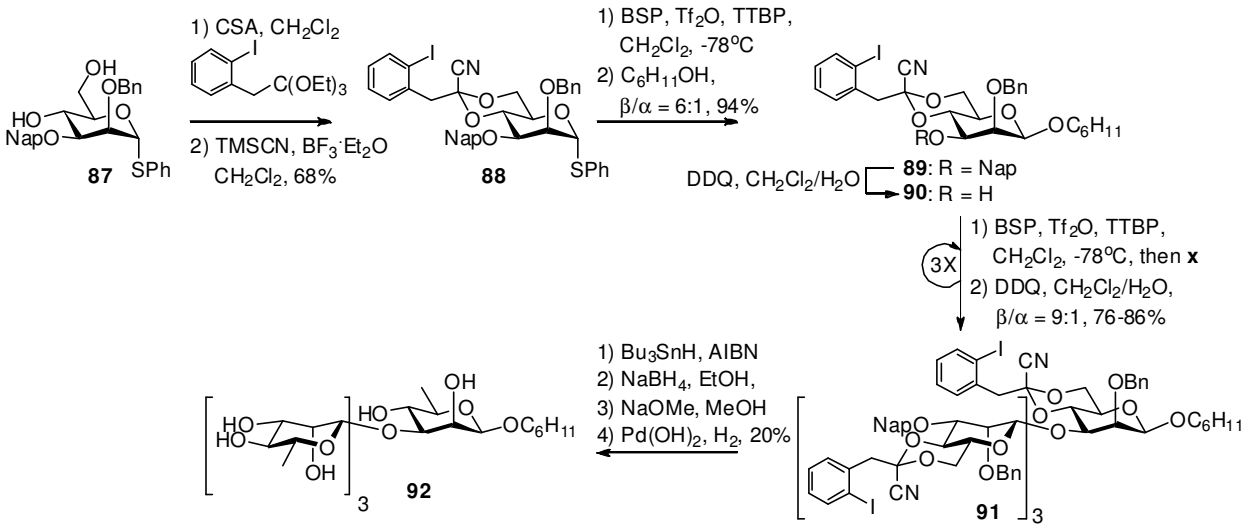
Scheme 1.17: β-mannosylations. A) Torsional and electronic disarming of mannosyl donors using the 4,6-*O*-benzylidene acetal, leading to the preferential formation of an α-triflate intermediate. B) A systematic study of the nature of the disarming ability of 4,6-*O*-acetals.[133-134]

In addition to pre-activation, the 4,6-*O*-benzylidene acetal was found to be indispensable for high β-selectivity. Crich and co-workers have proposed that under pre-activation conditions, the oxacarbenium ion is trapped by a triflate anion which would lead to the formation of the more stable α-triflate **78** (Scheme 1.17A). This α-triflate intermediate can then be displaced after addition of the acceptor in an S_N2-like manner to afford the β-mannoside product (**81**). To support this hypothesis ^{1}H, ^{13}C and ^{19}F NMR spectra of the activated mannosyl donor were recorded at low temperature.[135] These experiments unambiguously confirmed the presence of α-glycosyl triflates but could not establish the exact reaction path of the ensuing displacement. To investigate the mechanism of α-triflate displacement, kinetic isotope effects (KIE) were determined.[136] A mannosyl donor was synthesized which had 50% deuterium content

at H-1 and H-7 to determine the KIE and as internal standard, respectively.The experimental KIE was ~1.12 and consistent with an oxacarbenium transition state. It was hypothesized that the α-triflate converts into contact ion pair (CIP) **79** where the triflate anion remains on the α-face therefore blocking it, or that an exploded transition state is formed where the nulceophile has a loose association with the oxacarbenium ion as the triflate departs. The formation of α-product **82** can be explained by the formation of solvent separated ion pair (SSIP) **80** where the counter-ion is solvated and facial selectivity is lost. The necessity of the 4,6-*O*-benzylidene acetal was believed to be due to its torsional disarming effect. In earlier work, Fraser-Reid and co-workers had found that a 4,6-*O*-benzylidene acetal is torsionally disarming by locking the pyranose ring in a stable chair conformation.[137] In doing so, it disfavors the formation of an intermediate oxacarbenium ion since it requires rehybridization and flattening of the sugar ring which usually results in a half-chair conformation. Due to this torsional effect combined with the strong endo-anomeric effect in mannose, the α-triflate is the favored intermediate. Bols and co-workers reported a comprehensive study to dissect the electronic and torsional effects of 4,6-cyclic acetals on the hydrolysis rate of anomeric dinitrophenyl glycosides (Scheme 1.17B).[134] It was established that the donor can be deactivated by torsional effects however, in addition the electronic influence the 4,6-*O*-acetal has on the O-6 substituent was investigated and found to be significant. The additional electronic effect is caused by the fixed arrangement of the O-6 substituent.

Dinitrophenyl glycosides **83**-**86** were prepared and their relative hydrolysis rates were determined (Scheme 1.17B). **84**-**86** are all torsionally deactivated since they all have a fused bycyclic ring system. However, the orientation of the O-6 substituent was altered to be *tg* **(86)**, *gt* **(85)** and *gg* **(84)**. A marked difference in the hydrolysis rate was observed and can de explained by direction of the O-6 dipole. A 4,6-acetal forces the O-6 substituent to adopt the *tg* (**86**) conformation which places its dipole approximately anti parallel to the electron deficient center which is formed in the transition state, thereby destabilizing it. In the *gg* (**84**) and *gt* (**85**) conformation, the dipoles are more or less perpendicular to the developing positive charge and thus less destabilizing. This electronic disarming effect was found to be approximately equal to the torsional disarming effect of a 4,6-acetal. The use of a 4,6-acetal to ensure 1,2-

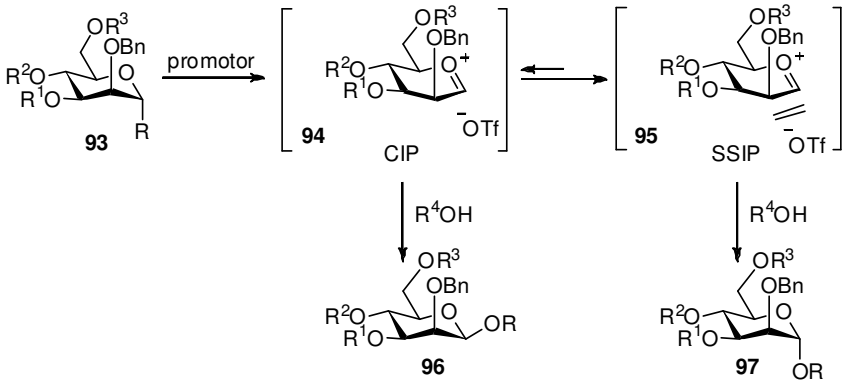
cis-glycosylation, has been extended to the synthesis of L-glycero-β-D-manno-hepropyranoses[138] and the synthesis of β-D-rhamnose (β-D-6-deoxy-mannose) derivatives.[139]



Scheme 1.18: Application of the [1-cyano-2(2-iodophenyl)-ethylidene] acetal to the synthesis of a β-(1→3)-D-rhamnotetraose.[139]

To this end, the [1-cyano-2(2-iodophenyl)-ethylidene] acetal was developed[140] to ensure stereoselective β-mannosylation as well as to perform a radical fragmentation/reduction to finally afford a β-(1→3)-D-rhamnotetraose (Scheme 1.18). The [1-cyano-2(2-iodophenyl)-ethylidene] acetal was installed in two steps. First, the 4,6-ethoxy-orthoester was prepared using D/L-10-camphorsulfonic acid (CSA) in CH_2Cl_2. Lewis acid promoted cyanation using TMSCN and $BF_3{\cdot}Et_2O$ afforded [1-cyano-2(2-iodophenyl)-ethylidene] acetal **88** in high yield.[141] Ensuing cycles of BSP/Tf_2O promoted glycosylation and oxidative naphthylether removal gave β-(1→3)-D-rhamnotetraose **91** in high yield and with high stereoselectivity. Treatment with tributyltinhydride and radical initiator AIBN led to the radical fragmentation[142-143] of the [1-cyano-2(2-iodophenyl)-ethylidene] acetal and C-6 deoxygenation of the tetrasaccharide. Sodium borohydride was used to remove any tin residues followed by transesterification and hydrogenation to afford deprotected β-(1→3)-D-rhamnotetraose **92**. In addition to the disarming effect of the 4,6-benzylidene acetal, highly electron withdrawing protecting groups have also been shown to improve 1,2-

cis-stereoselectivity (Scheme 1.19).[144-148] It had been noted that a highly electron withdrawing group at C-2 of mannosyl donor led to the selective formation of β-mannosides. Recently, Kim and co-workers reported a systematic study of the influence of highly electron withdrawing protecting groups at positions other than C-2 on β-mannosylation.[109]



entry	leaving group	R^1	R^2	R^3	promotor	α/β ratio
1	R = $OC(NH)CCl_3$	SO_2Bn	Bn	Bn	TMSOTf	1/15.9
2	R = $OC(NH)CCl_3$	Bn	SO_2Bn	Bn	TMSOTf	1/10.7
3	R = $OC(NH)CCl_3$	Bn	Bn	SO_2Bn	TMSOTf	1/13.8
4	R = Br	SO_2Bn	Bn	Bn	AgOTf	1/3.9
5	R = Br	SO_2Bn	Bn	Bn	$AgClO_4$	2.1/1

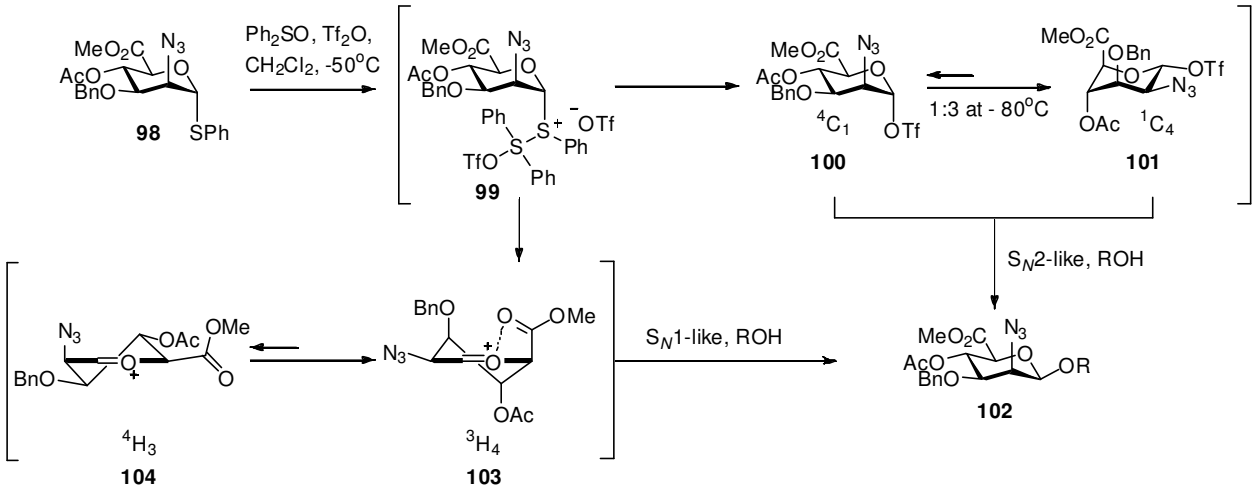
Scheme 1.19: The use of highly electron withdrawing groups to promote α-triflate formation and ensure β-mannosylation.[110]

A series of mannosyl donors carrying a variety of electron withdrawing protecting groups at different positions were investigated. A clear correlation between the electron withdrawing capacity and the β-selectivity was observed regardless of the position on the sugar ring. The highest selectivity was observed when the benzylsulfonate ester was at C-3 (Scheme 1.19, entry 2). Since the possibility of remote participation is often suggested (*vide supra*) the authors performed low temperature NMR experiments to identify reaction intermediates. Upon activation, the α-triflate intermediate **94** was observed for the mannosyl donors in entry 1-3, Scheme 1.19. Furthermore, remote participation from C-3 would lead to α-glycosylation, however β-selectivity was observed which together with the NMR experiments excludes

remote participation of the electron withdrawing protecting groups. These observations led the authors to conclude that S_N2-like displacement of α-triflate intermediate **94** is responsible for the high β-selectivity. The α-triflate intermediate is expected to be more stable than an oxa-carbenium ion intermediate since it is electronically destabilized by a highly electron withdrawing protecting group. To further demonstrate the importance of the counterion, a mannosylbromide donor was prepared (Scheme 1.19, entry 4,5). When glycosylations were performed using silver trifluoromethanesulfonate (AgOTf) β-mannosides were selectively formed whereas silver perchlorate, which has a non-participating counterion, gave mainly α-mannosides.

Uronic acids are an important class of glycans that carry a C-5 carboxyl group and are notoriously difficult to glycosylate due to the electron withdrawing C-5 carboxy group.[149] Thioglycoside derivatives of uronic acids (thiouronic acid donors) however can be can be activated under mild conditions however thiouronic acid donors are difficult to prepare due to the sensitivity of the thioether functionality toward oxidative conditions. Van der Marel and co-workers reported the use of 2,2,6,6-tertramethyl-piperidinyloxy (TEMPO) and [bis(acetoxy)iodo]benzene (BAIB) as a highly regio- and chemoselective selective oxidation method for the preparation of thioglycouronic acids.[150] This reagent combination selectively oxidized primary sugar alcohols without affecting the anomeric thioether. Furthermore, these highly disarmed glycosyl donors could be activated using the highly thiophilic Ph_2SO/Tf_2O promoter system (Scheme 1.20). Interestingly, thio mannuronic acid donors exhibited high β-selectivity although a 3-*O*-acetyl seemed to diminish the β-selectivity presumably through participation.[151] This methodology was later extended to the stereoselective synthesis of β-D-manno- and its C-5 epimer, α-L-guluronic acid alganites.[152] The unexpected high 1,2-*cis*-selectivity was attributed to a unique combination of factors.[153] Firstly, the orientation of the C-5 carboxylate ester in the presumed oxacarbenium ion transition state (**104**,**103**) was proposed to be a dominating factor in influencing the stereoselectivity.[154-155] It is suggested that in a half-chair oxacarbenium transition state, the $^3H_4$ conformation **103** is favored since it places the C-5 methyl ester in an axial orientation and can donate electron density into the anomeric oxacarbenium

ion. In addition, the axial orientation of the C-5 places its dipole orthogonal to the oxa-carbenium ion therefore minimizing its destabilizing effect. Computational experiments indicated that the $^3H_4$ conformer **103** was more stable by 3.4 kcal/mol.

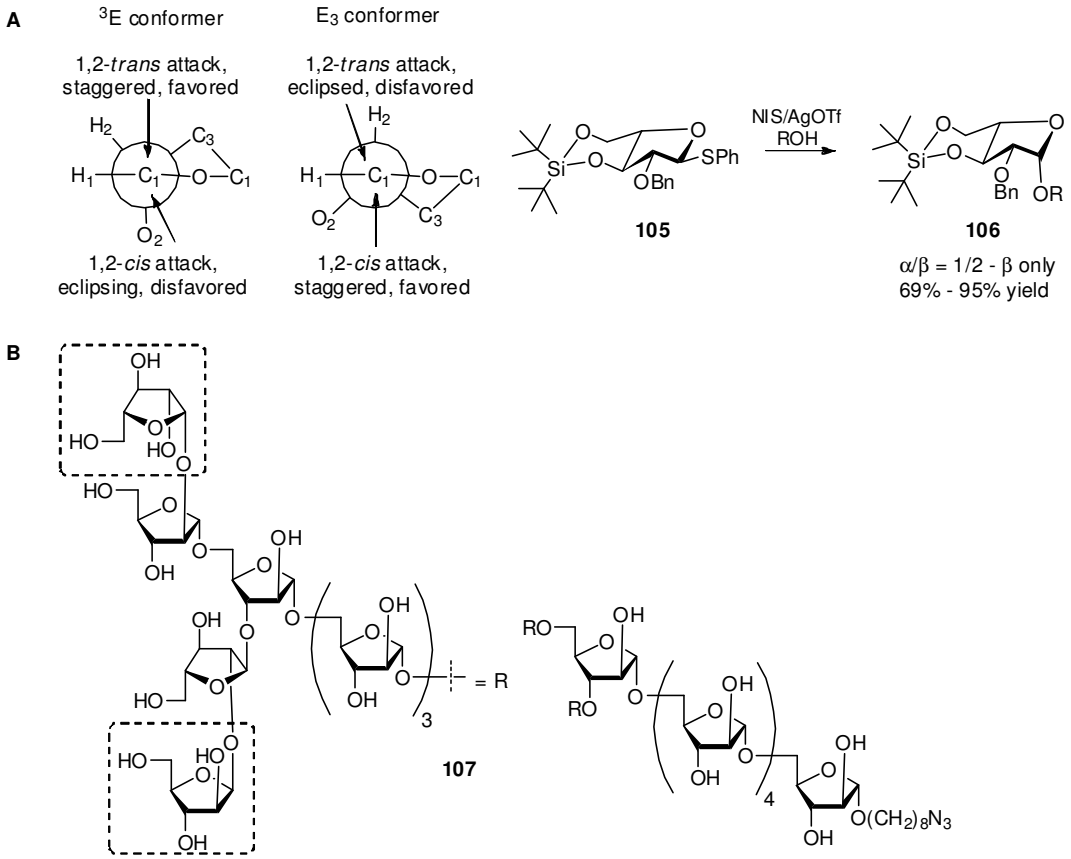


Scheme 1.20: The origin of β-selectivity in the glycosylation of disarmed manuronate esters. [153]

The nucleophile attacks this stabilized oxacarbenium ion with facial selectivity to form the lower energy chair β-product as opposed to the twist-boat α-adduct. Since L-Gulose is the C-5 epimer of D-Mannose it prefers the $^4H_3$ conformation due to the axial orientation of the C-5 carboxylate ester leading to the stereoselective formation of α-L-Gulose products[152]. Secondly, low temperature NMR experiments revealed the presence of two anomeric α-triflate species **100** and **101** as a mixture of $^1C_4$ and $^4C_1$ conformers.[156] The electronic disarming effects of the C-2 azide and C-5 methylester and the strong endo-anomeric effect in mannose are thought to be responsible for the preferential formation of these triflate intermediates. Thus, the nucleophilicity of the glycosyl acceptor probably determines which reaction-path is taken. Highly nucleophilic acceptors are expected in a S_N2-like mechanism whereas acceptors of reduced nucleophilicity will react in a S_N1-like manner, however both will lead to 1,2-*cis*-glycosides.

Conformational selection using the 3,5-O-(di-tert-butylsilane) protecting group. Factors such as small differences between anomeric effect of α- and β-anomers and the inherent ring flexibilities have

complicated the development of a general method for the stereoselective introduction of 1,2-*cis*-furanosides. It has been reasoned that by examining possible conformers of the arabinofuranosyl oxa-carbenium ion, it might be possible to identify one that favours attack from the β-face (a 1,2-*cis* attack). In this respect, oxa-carbenium ions of furanosides can adopt two possible low-energy conformations in which C-3 is either above (^{3}E) or below the plane (E_3) of C-4, O-(endo), C-1 and C-2 (Scheme 1.21A).

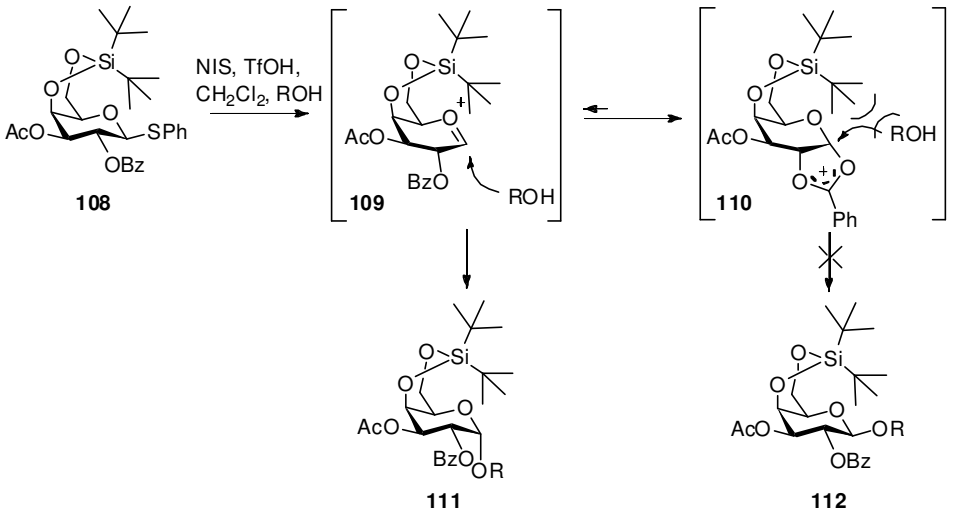


Scheme 1.21: Selection of the E_3 conformer using the 3,5-*O*-(di-*tert*-butylsilane)- protecting group to ensure 1,2-*cis*-glycosylation.[157-158]

The Newman projection of the E^3 conformer of D-arabinofuranose showed that nucleophilic attack from the α-face is disfavored because an eclipsed H-2 will be encountered. On the other hand, an approach from the β-face was expected to be more favorable because it will experience only staggered substituents. Computational studies have indicated that the arabinofuranosyl oxa-carbenium ion can be locked in the E^3 conformation by employing a 3,5-*O*-(di-*tert*-butylsilane)- protecting group, which places O-5 and O-3 in

a pseudo-equatorial orientation resulting in a perfect chair conformation of the protecting group.[157] Indeed, an arabinofuranosyl donor **105**, which is protected with a DTBS group gave excellent β-selectivities in a range of glycosylations with glycosyl acceptors having primary and secondary alcohols. In addition to the 3,5-*O*-(di-*tert*-butylsilane)- protecting group, selection of the promoter system proved to be very important in order to obtain good 1,2-*cis*-selectivity.

Crich and co-workers showed that pre-activation of the DTBS protected arabinofuranosyl donor followed by addition of the glycosyl acceptor led to non-selective reactions.[159] NMR experiments confirmed that these reactions did not proceed by S_N1-like attack of the oxacarbenium-ion but other intermediates such as glycosyl triflates. Furthermore, this method has been successfully employed for the synthesis of an arabinogalactan fragment derived from plant cell walls and for the preparation of arabinogalactan and lipoarabinomannan domains of *Mycobacteria*. Lowary and co-workers have prepared octadecasaccharide arabinan domain **107** found in *Mycobacterium Tuberculosis*, containing four 1,2-*cis*-linked arabinofuranosides using this method (Scheme 1.21B).[158]



Scheme 1.22: The use of the DTBS group in α-galactosylation.[160]

Glycosylations with galactosyl donor **108** which is protected with a 4,6-*O*-di-*tert*-butylsilyl (DTBS) group gave the corresponding α-galactosides (**111**) with very high α-anomeric selectivities, even in the presence of a C-2 benzoyl ester that can perform NGP (Scheme 1.22).[160] In stark contrast, the 4,6-*O*-benzylidene

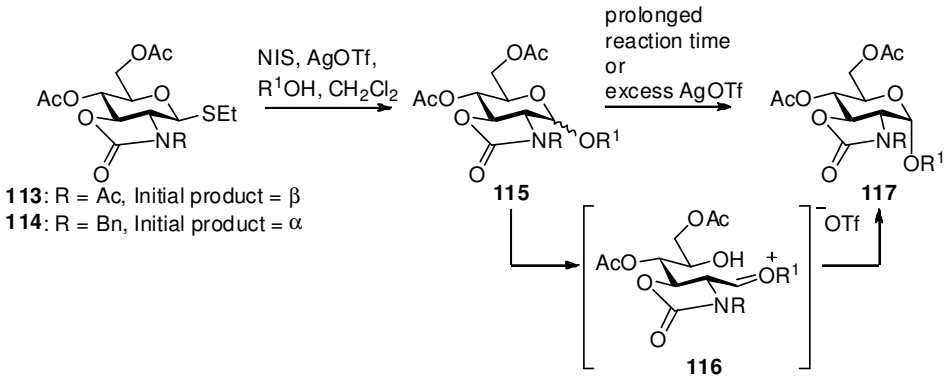
derivative of **108** showed only β-glycosylation when a participating protecting group at C-2 was present and only moderate α-selectivity when a non-participating protecting group at C-2 was employed. The crystal structure of the glycosyl donor **108** revealed that the silydene ring is in the boat conformation placing one of the *tert*-butyl groups directly over the β-face of the molecule therefore blocking from attack of a glycosyl acceptor if it approaches from this face. In the presence of a participating protecting group at C-2 dioxolenium ion intermediate **110** is expected to be more stable than oxa-carbenium ion **109**. However, the Curtin-Hammet principle can be at work when the interconversion of dioxolenium and oxa-carbenium ion is faster than glycosylation and thus α-selective glycosylation of the oxa-carbenium ion can predominate.

Sialic acid glycosylations. Sialic acids are a family of naturally occurring 2-keto-3-deoxy-nononic acids that are involved in a wide range of biological processes and thus far 50 different derivatives have been reported. The C-5-amino derivative represents the long-known neuraminic acid and its amino function can either be acetylated (Neu5Ac) or glycolylated (Neu5Gc). The hydroxyls of these derivatives can be further acetylated, most commonly at C-9 but di- and tri-*O*-acetylated derivatives are also known. The use of glycosyl donors of sialic acid is complicated by the fact that no C-3 functionality is present to direct the stereochemical outcome of glycosylations.[161] The deoxy moiety in combination with the electron-withdrawing carboxylic acid at the anomeric centre makes these derivatives prone to elimination. Also, glycosylations of Neu5Ac take place at a sterically hindered tertiary oxa-carbenium ion intermediate.

Recently, the direct and stereoselective introduction of α-sialosides has been achieved by acylation of the acetamido group of a corresponding donor. This modification results in dramatic increases in reactivity and α-anomeric selectivity (Fig. 4c). The first compound of this class was a 2-thioglycosyl donor of Neu5Ac bearing a di-*N*-acetyl (*N*-acetylacetamido) functionality at C-5.[162] Further improvements came with the use of azido, *NH*-trifluoroacetyl (TFA), *NH*-2,2,2-trichloroethoxycarbonyl (Troc), *NH*-Fmoc, *NH*-trichloroacetyl, *N*-phthalimide (Phth) and 5*N*,4*O*-carbonyl groups, and it has been shown that this type of protection improved the efficiency of α-selective sialylation providing easy access to various

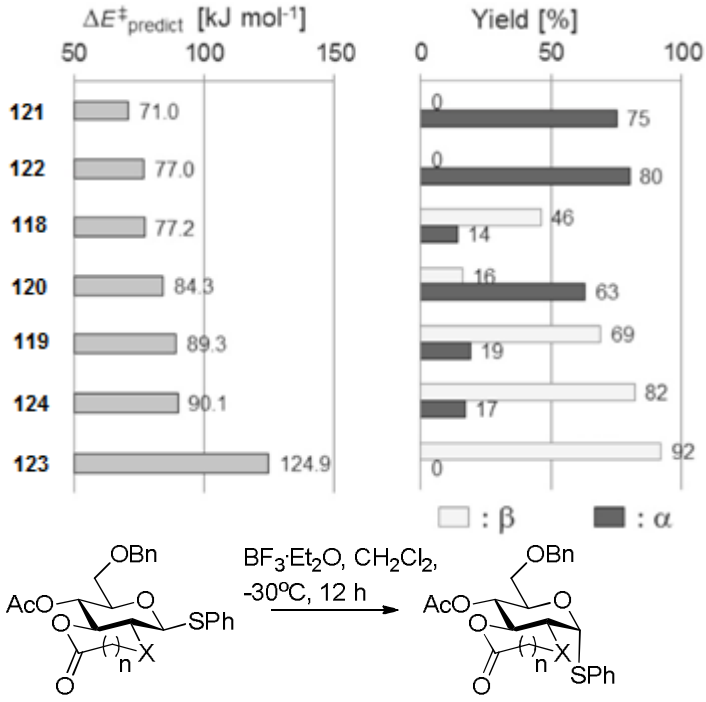
α(2,3), α(2,6)-, α(2,8)- and α(2,9)-linked sialosides.[163] The introduction of 5*N*,4*O*-carbonyl-protected sialyl donors have made it feasible to prepare sialosides by one-pot multistep glycosylation protocols.[164-166]

Stereoselective introduction of 2-deoxy-2-amino-glycosides. 2-Deoxy-2-azido-glucosides and galactosides are commonly employed for the introduction of 1,2-*cis*-glycosides. In this respect, the azido moiety is a non-participating functionality that is stable under a wide variety of reaction conditions but can readily be reduced to an amine with reagents such as phosphines and thiols, and by catalytic hydrogenation. Invariably, the use of 2-azido-2-deoxy-glycosyl donors leads to the formation of mixtures of anomers, which requires time-consuming purification protocols resulting in loss of material. 2,3-*N*,*O*-oxazolidone-protected glucosamine derivatives have been developed in an effort to improve its acceptor properties (Scheme 1.22).[167-169] It was found that these derivatives were also very α-selective glycosyl donors. Oscarson and co-workers investigated the nature of this unexpected selectivity using an *N*-benzyl and *N*-acetyl protected 2,3-*N*,*O*-oxazolidone protected glycosyl donors. As expected *N*-benzyl derivative **114** provided the α-product whereas *N*-acetyl derivative **113** produced the β-anomer.[167] However, when prolonged reaction times or higher concentrations of AgOTf were employed, the β-anomer was converted into α-anomer **117** over time. NMR studies showed that the β-anomer was stable for approximately 30 min at low concentration of AgOTf (0.1 eq) and was completely anomerized in 4 hrs. With excess AgOTf, the anomerization was complete in under 1 hr.



Scheme 1.23: Anomerization of 2,3-*N*,*O*-oxazolidinone protected glycosides.

The anomerization proceeds by an intramolecular reaction involving an endocyclic C-O bond cleavage, to give mainly or exclusively an α-glucoside. Evidence for endocyclic cleavage was provided by intra- and intermolecular Friedel-Crafts reactions, chloride addition, and reduction of cation **116**.[170] Interestingly, it is important that pyranosides are locked in a chair conformation for endocyclic opening because furanosides with the distorted conformations do not undergo this reaction.



118: n = 0, X = O
119: n = 0, X = NH
120: n = 0, X = NBn
121: n = 0, X = NAc
122: n = 0, X = NCO_2Me
123: n = 1, X = NH
124: n = 1, X = NAc

125: n = 0, X = O
126: n = 0, X = NH
127: n = 0, X = NBn
128: n = 0, X = NAc
129: n = 0, X = NCO_2Me
130: n = 1, X = NH
131: n = 1, X = NAc

Scheme 1.24: Correlation of the calculated activation energies and the expermintal results.[171]

A very recent study by Ito and co-workers explored the driving force for the C-O bond cleavage using computational and experimental methods.[171] It was found that the 2,3-*trans*-fused protecting group induce ring strain that lower the transition state (TS) energy of endocyclic cleavage. The trend between the calculated TS energy and degree of anomerization (α/β ratio) were found to be in accordance (Scheme

1.24). Thioglycosides **118**-**124** were prepared and anomerized using $BF_3{\cdot}Et_2O$ at -30°C. Five membered ring oxazolidinones **118**-**122** all showed anomerization (Scheme 1.24, Top right) which was predicted by the calculated activation energies (Scheme 1.24, Top left). Less strained six membered ring derivatives **123** and **124** only anomerized to a small extent, consistent with the ring strain hypothesis. Furthermore, the TS energy was found to correlate directly to the ring strain. It takes much less computing time to calculate the ring strain than to calculate the TS energy and therefore it can be used to rapidly predict the degree of anomerization in a virtual screening.

In general, the methods described above to prepare 1,2-*cis*-glycosides are limited to a specific type of carbohydrate or protecting group and are not widely applicable. However, the use of chiral auxiliaries has the potential to become a general method for the preparation of 1,2-*cis*-glycosides. The aim of the work described in this dissertation is to further develop chiral auxiliary mediated 1,2-cis-glycosylation to prepare 1,2-*cis*-gluco, 1,2-*cis*-galacto, and 1,2-*cis*-mannoglycosides and to apply this technology to complex oligosaccharide synthesis in solution and on solid support.

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CHAPTER 2

STEREOELECTRONIC EFFECTS DETERMINE OXA-CARBENIUM *vs* β-SULFONIUM ION MEDIATED GLYCOSYLATIONS[†]

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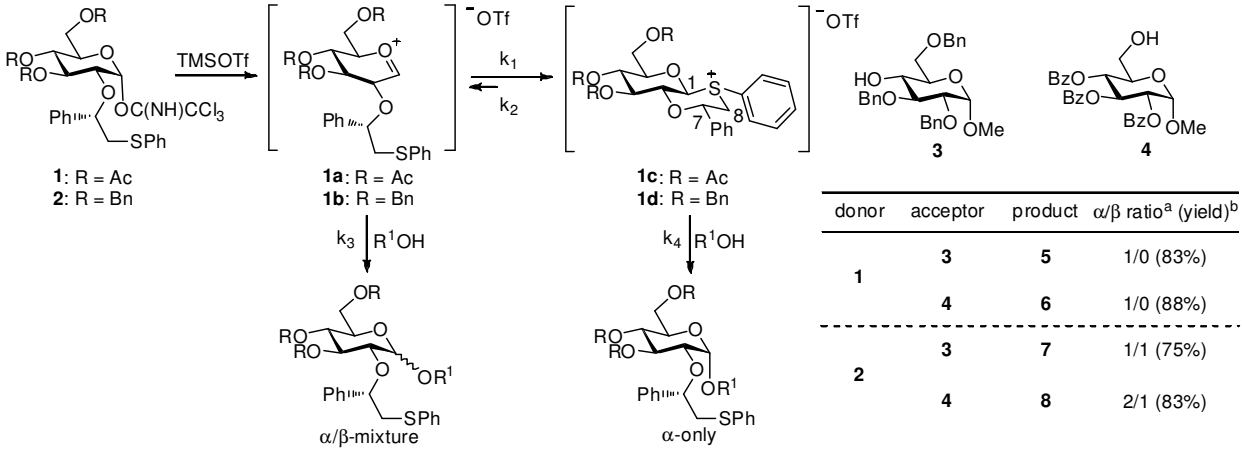
Abstract. Activation of a glycosyl donor protected with a 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether chiral auxiliary results in the formation of an anomeric β-sulfonium ion, which can be displaced with sugar alcohols to afford the corresponding α-glycosides. Sufficient deactivation of such glycosyl donors by electron withdrawing protecting groups is, however, critical to avoid glycosylation of an oxa-carbenium ion intermediate resulting in the formation of mixtures of anomers. The latter type of glycosylation pathway can also be suppressed by adding geminal substituents to the chiral auxiliary to promote the formation of the β-sulfonium ion.

Introduction. The stereoselective introduction of glycosidic linkages is one of the most challenging aspects in the chemical synthesis of biologically important complex oligosaccharides.[1-2] In general, 1,2-*trans* glycosides can reliably be introduced by exploiting neighboring group participation of a 2-*O*-acyl group and this approach has, for example, been exploited in the automated solid phase synthesis of several complex oligosaccharides using a modified peptide synthesizer.[3-4] The introduction of 1,2-*cis* glycosidic linkages, such as α-glucosides and α-galactosides, requires glycosyl donors having a non-assisting functionality at C-2.[5] In general, these glycosylations require extensive optimization of reaction conditions to achieve acceptable anomeric ratios. Recent advances in anomeric control include the use of protecting groups that sterically shield the β-face of galactosyl donors[6] or locking a glycosyl donor in a conformation that allows nucleophilic attack from only one face of an anomeric oxa-carbenium ion.[7]

We have shown that a glycosyl donor substituted at C-2 with a (*S*)-(phenylthiomethyl)benzyl ether can be employed for the stereoselective introduction of 1,2-*cis* glycosides such as α-glucosides and α-galactosides.[8] Neighboring group participation by the chiral auxiliary leads to a quasi-stable anomeric sulfonium ion (Scheme 2.1), which due to steric and electronic factors is formed as a *trans*-decalin ring system. Nucleophilic displacement of the sulfonium ion by a hydroxyl leads then to the stereoselective formation of α-glycosides. Recently, the attractiveness of chiral auxiliary mediated glycosylations was shown by solid phase synthesis of several branched pentasaccharides having only 1,2-*cis*-glycosidic linkages.[9] As part of a program to utilize auxiliary mediated glycosylations for complex oligosaccharide

synthesis, we observed that protecting groups and constitution of the C-2 auxilary can have a profound influence on the pathway and hence anomeric outcome of glycosylations. Herein, we report clear rules for the reliable installation of 1,2-*cis* glycosidic linkages.

Results and Discussion. TMSOTf promoted glycosylations[10] of glycosyl donor **1**, having an (*S*)-(phenylthiomethyl)benzyl ether at C-2 and acetyl esters at C-3, C-4 and C-6, with glycosyl acceptors **3**[11] and **4**[12] gave the corresponding glucosides as only the α-anomer. However, similar glycosylations with glucosyl donor **2**, having benzyl ethers instead of acetyl esters, gave no or poor anomeric selectivity.



donor	acceptor	product	α/β ratio[a] (yield)[b]
1	3	5	1/0 (83%)
	4	6	1/0 (88%)
2	3	7	1/1 (75%)
	4	8	2/1 (83%)

Scheme 2.1: The dynamic equilibrium between an oxacarbenium and β-sulfonium ion. [a] The α/β ratios were determined by integration of key signals in the ^{1}H NMR spectrum of the disaccharides products after purification by size exclusion chromatography over LH-20. [b] Isolated yields of the α/β mixture of disaccharide products.

To examine whether glycosyl donor **2** can form an intermediate sulfonium ion, it was dissolved in CD_2Cl_2 and treated with one equivalent of TMSOTf at –50 °C. After raising the temperature to 0 °C and cooling to –20 °C, ^{1}H and HMBC NMR spectra were recorded (Figure 2.1). Upon activation, the anomeric proton of **2** (δ 6.56 ppm, $J_{1,2}$ = 2.5 Hz) shifted up field (δ 5.52, $J_{1,2}$ = 8.5 Hz) and its large vicinal coupling constant established an equatorial orientation of the anomeric substituent. The coupling constants of the other saccharide protons showed that no conformational distortion of the saccharide ring had occurred. The HMBC spectrum, which allows the determination of three bond heteronuclear

couplings, showed a correlation between C-1 and H8-eq, indicating that the *trans*-decalin system had been formed. No oxa-carbenium ion, anomeric triflate or α-sulfonium ion was detected and hence the NMR data indicate that the β-substituted sulfonium ion is the main reaction intermediate. Addition of an alcohol resulted, however, in the formation of a mixture of anomers.

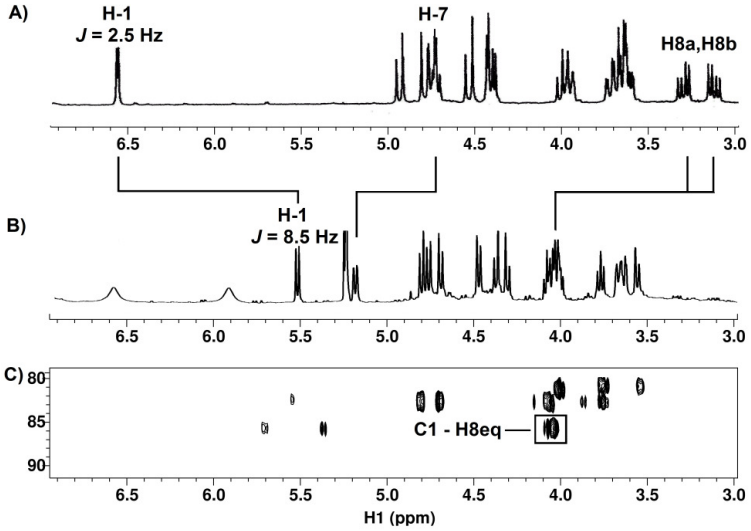


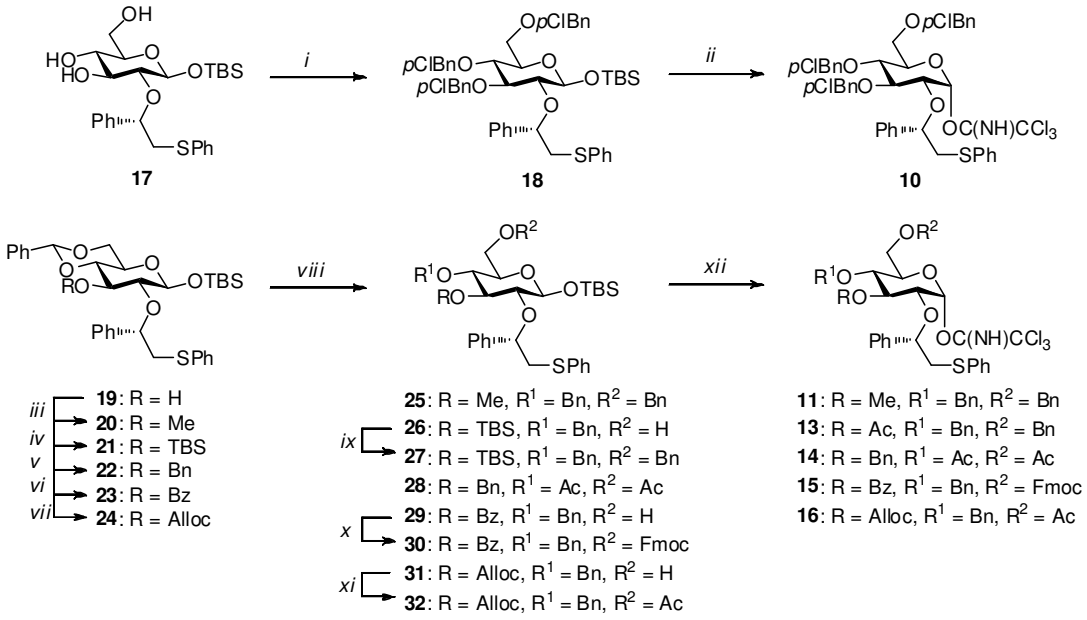
Figure 2.1: ^{1}H and ^{13}C NMR detection of the β-sulfonium ion intermediate **1d**. A) ^{1}H NMR spectrum of glucosyl donor **2** in CD_2Cl_2. B) ^{1}H NMR spectrum of **2** after addition of TMSOTf at (-20 ^{o}C). c) HMBC spectrum of the β-sulfonium ion at -20 ^{o}C. A cross-peak was observed between C-1 and H8-eq.

This unexpected observation can be rationalized by the classical Curtin-Hammett principle in which an equilibrium exists between the sulfonium and oxa-carbenium ions (Scheme 2.1). This equilibrium is shifted strongly in the direction of the sulfonium ion as shown by the NMR studies. A glycosylation can, however, take place from the much more reactive oxa-carbenium ion when the rates of inter-conversion (k_1 and k_2) are faster than that of glycosylation (k_4). Previously, relative reactivity values (RRVs) of differentially protected glycosyl donors have been determined and for example, it was found that a 2,3,4,6-tetra-*O*-benzyl protected glucosyl donor is 980 times more reactive than its tetra-*O*-acetylated counterpart.[13] This difference in reactivity has been attributed to inductive destabilization of the positively charged transition state by the electron withdrawing acetyl esters. The ester protecting groups of an anomeric sulfonium ion are more remote from the positive charge than that of the oxa-carbenium and

hence such electron withdrawing protecting groups are expected to widen the energy difference between sulfonium and oxa-carbenium ion. Thus, strongly electron withdrawing groups such as the acetyl esters of **1** are expected to disfavor oxacarbenium ion formation and hence glycosylations takes place by an S_N2 like displacement of the β-anomeric sulfonium ion leading to the formation of α-glycosides. On the other hand, glycosylations with donors having electron donating protecting groups, such as the benzyl protected glycosyl donor **2**, involve an equilibrium between the corresponding sulfonium and oxa-carbenium ions, and glycosylations take place mainly through the latter intermediate thereby diminishing the α-selectivity. Previously, it has been noted that care has to be taken in implying reaction mechanisms of glycosylations based on the detection of reaction intermediates.[14-20] We have performed numerous glycosylations with donors such as **1** and in general isolated only α-anomeric products implying S_N2 displacement of intermediate sulfonium ions. Furthermore, glycosylations of **2** (Scheme 2.1) and **9**[21] (Table 2.1), which have a chiral auxiliary or benzyl ether at C-2, both gave poor anomeric selectivities indicating that the nature of the C-2 substituent has only a small influence on the selectivity of glycosylations by oxa-carbenium ions. On the other hand, glycosylations with **1** proceeded with α-selectivity whereas similar couplings with a C-2 benzyl protected glycosyl donor[8] led to the formation of mixtures of anomers (α/β = 3/1) indicating a difference in reaction pathway.

In order to establish how many, what type and at which position electron withdrawing protecting groups are needed to ensure α-selectivity, a number of differentially protected glycosyl donors (**10**-**16**, Table 2.1) were synthesized. Disarming *p*-chlorobenzyl protecting groups increases the stability of fucosides by destabilizing the corresponding oxa-carbenium ion.[22] Therefore, it was expected that the use of this protecting group would increase the α-anomeric selectivity of auxiliary mediated glycosylations. Thus, glycosyl donor **10** was prepared from compound **17**[8] by tri *O*-benzylation using sodium hydride and *p*-chlorobenzyl bromide in DMF (Scheme 2.2). The anomeric TBS ether was removed using HF·Pyridine and the resulting lactol was converted into trichloroacetimidate donor **10** using trichloroacetonitrile and DBU in CH_2Cl_2. To investigate the influence of the structure of the electron donating protecting group, C-3 methyl derivative **11** was prepared. Reaction of **19** with iodomethane and sodium hydride in DMF

afforded metyl derivative **20**. Acid hydrolysis of the benzylidene acetal and dibenzylation of the 4,6-diol yielded **25**. The anomeric TBS ether was removed using HF·Pyridine and the resulting lactol was then reacted with trichloroacetonitrile and DBU to afford trichloroacetimidate donor **11**.



Scheme 2.2: Synthesis of glycosyl donors **10**-**16**. Reagents and conditions; *i) p*ClBnBr, NaH, DMF, rt, 16 hrs, 77%. *ii)* 1). HF·Pyr, THF, rt, 16 hrs. 2). TCA, DBU, CH_2Cl_2, 0°C, 10 min, 91%. *iii)* MeI, NaH, THF, rt, 3 hrs, 95%. *iv)* TBSOTf, 2,6-Lutidine, CH_2Cl_2, -78°C→0°C, 30 min. *v)* BnBr, NaH, DMF, rt, 3 hrs, 95%. *vi)* BzCl, pyridine, CH_2Cl_2, rt, 16 hrs, 96%. *vii)* AllocCl, TMEDA, CH_2Cl_2, rt, 4 hrs, 81%. *viii)* AcOH/H_2O, 2 hrs, 60°C, 92%, 2). BnBr, NaH, DMF, rt, 2 hrs, 74% for **25**. Cl_2PhB, Et_3SiH, CH_2Cl_2, 15 min, -78°C, for **26** (90%), **29** (91%) and **31** (86%). AcOH/H_2O, 60°C, 4 hrs, 92% 2). Pyr, Ac_2O, rt, 16 hrs, 98% for **28**. *ix*) NaH, BnBr, DMF, rt, 1hr, 85%. *x*) FmocCl, Pyr, CH_2Cl_2, rt, 2 hrs, 87%. *xi*) Ac_2O, Pyr, rt, 6 hrs, 98%. *xii*) 1). TBAF, THF, 20 min, 0°C, 96% 2). TCA, DBU, CH_2Cl_2, 1 hr, 0°C, 91% for **12**. 1). TBAF, THF, 0°C, 1 hr, 97% 2). Ac_2O, Pyr, rt, 16 hrs. 3). N_2H_4·AcOH, DMF, rt, 16 hrs, 89% 4). TCA, DBU, CH_2Cl_2, 1 hr, 0°C, 88% for **13**. 1). TBAF, THF, 0°C, 20 min, 96%, 2). TCA, DBU, CH_2Cl_2, 1hr, 0°C, 91% for **14**. HF·Pyridine, THF, rt, 16 hrs, 2). TCA, NaH, CH_2Cl_2, 10 min, 0°C, 81% for **15**. 1) HF·Pyridine, THF, rt, 16 hrs, 2). TCA, DBU, CH_2Cl_2, 10 min, 0°C, 93% for **16**.

To compare the importance of the relative position of the acetyl esters in **1**, three structural isomers containing two acetyl ester and one benzyl ether, **12**[8], **13** and **14** were prepared from starting material **19**[9].

Glycosyl donor **13** was prepared by TBS protection of **19** using TBSOTf and 2,6-Lutidine in CH_2Cl_2. Selective ruductive opening of the benzylidene acetal and benzylation of the resulting 6-OH afforded intermediate **27**. The TBS ethers were removed using TBAF in THF. The intermediate diol was acetylated, followed by selective removal of the anomeric acetyl ester using hydrazinium acetate in DMF. The lactol was then reacted with trichloroacetonitrile and DBU to afford trichloroacetimidate donor **13**. Isomer **14** was prepared by benzylation of the C-3 alcohol of **19**, followed by acid hydrolysis of the benzylidene acetal and acetylation to afford **28**. Removal of the anomeric TBS ether using HF·Pyridine and installation of the imidate leaving group using aforementioned conditions afforded **14**. To investigate the influence of the structure of the electron withdrawing group, glycosyl donors **15** and **16** were prepared. Benzoylation or reaction with allylchloroformate of **19** afforded **23** and **24**, respectively. Selective opening of the benzylidene acetal followed by protection with an acetyl ester of Fmoc carbonate afforded **30** and **32**. Finally, removal of the anomeric TBS ether and installation of the trichloroacetimidate under aforementioned conditions afforded **15** and **16**.

The differentially protected glycosyl donors (**10-16**) were investigated to establish the influence of protecting groups on the anomeric selectivity of auxiliary mediated glycosylations (Table 2.1). As expected, anomeric selectivities improved when chiral auxiliary containing glucosyl donors were employed having electron withdrawing protecting groups. The *p*-chlorobenzyl protected glycosyl donor **10** showed a small but significant improvement complared to donor **2** indicating that the effect is indeed of electronic nature. To ascertain that the bulk of the C-3 protecting group does not play a major role in controlling anomeric selectivities, glycosylations with glycosyl donor **11** were performed, which has a methyl ether at C-3, and in this case the glycoside products (**37** and **38**) were obtained as mixtures of anomers. However, the presence of two acetyl esters at C-3 and C-6 (**12**), C-3 and C-4 (**13**) or C-4 and C-6 (**14**) drastically improved α-selectivity although the latter still gave an α/β mixture when coupled to **4** (**44**).

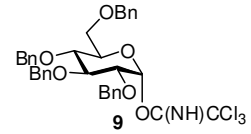
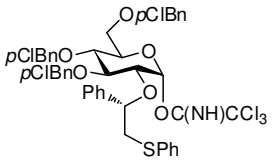
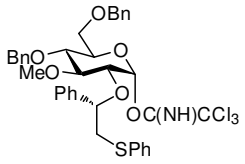
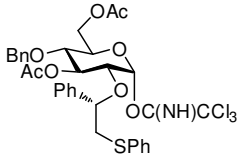
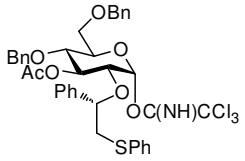
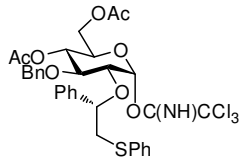
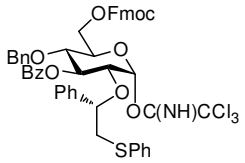
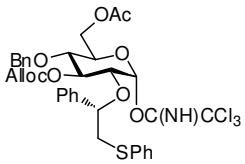
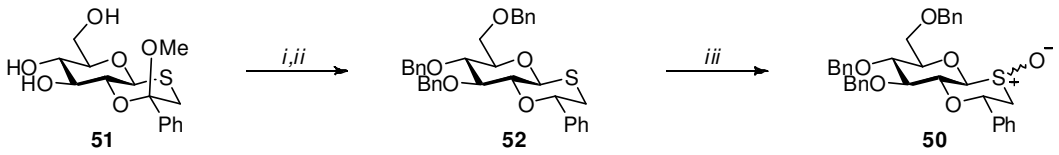
entry	glycosyl donor	glycosyl acceptor	product	yield[a]	α/β ratio[b]
1	 **9**	**3**	**33**	73%	1.7/1
		4	**34**	85%	2.5/1
2	 **10**	**3**	**35**	70%	1.4/1
		4	**36**	78%	4.1/1
3	 **11**	**3**	**37**	70%	1/1
		4	**38**	84%	6/1
4	 **12**	**3**	**39**	85%	1/0
		4	**40**	93%	1/0
5	 **13**	**3**	**41**	77%	1/0
		4	**42**	86%	1/0
6	 **14**	**3**	**43**	74%	1/0
		4	**44**	82%	10/1
7	 **15**	**3**	**45**	76%	1/0
		4	**46**	82%	1/0
8	 **16**	**3**	**47**	73%	1/0
		4	**48**	85%	1/0

Table 2.1: Glycosylation results for glycosyl donors **9**-**16**.[a] The α/β ratios were determined by the integration of key signals in the ^{1}H NMR spectra of the disaccharide products after purification by LH-20 size exclusion chromatography.[b] Isolated yields of the α/β mixture of disaccharide products.

The coupling of glycosyl donor **13**, which has an acetyl ester at C-3 and benzyl ethers at C-4 and C-6, with glycosyl acceptors **3** and **4** gave only α-linked products. Hence, the electronic withdrawing nature of the C-3 protecting group appears to be critical to achieve absolute α-anomeric selectivity. To further support the latter observation, glycosyl donors **15** and **16** were examined which have a C-3 benzoyl ester and allyloxycarbonate, respectively and as expected, the use of these compounds led to the selective formation of α-anomeric products (**45**-**48**).

Next, attention was focused on examining the importance of the constitution of the chiral auxiliary for controlling anomeric selectivity (Scheme 2.4). Recently, oxathiane donor **49** was introduced, which can be activated by triflation of the sulfoxide followed by electrophilic aromatic substitution with 1,3,5-trimethoxy benzene to form an intermediate sulfonium ion, which can then react with alcohols to give glycoside products.[23]

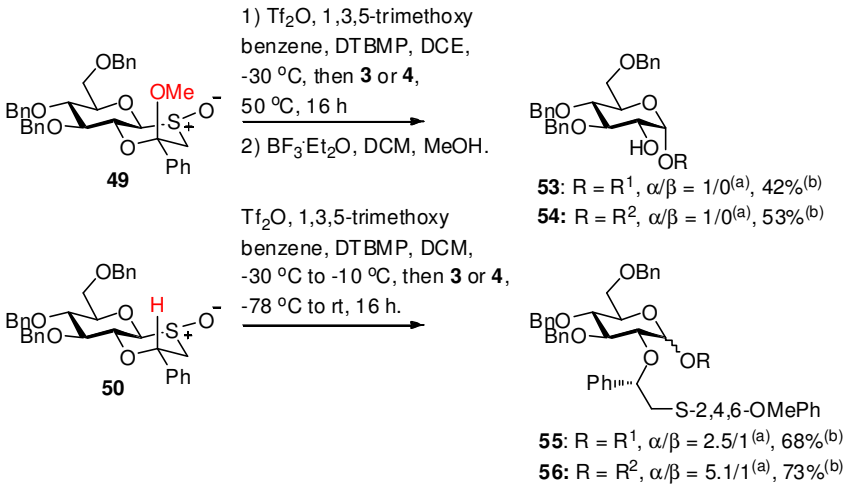


Scheme 2.3: Synthesis of glycosyl donor **50**. Reagents and conditions; *i)* TMSOTf, Et_3SiH, CH_2Cl_2, 0°C. *ii)* BnBr, NaH, DMF, rt, 3 hrs, 84%. *iii*) *m*-CPBA, CH_2Cl_2, 30 min, -78°C, 74%.

In addition, we investigated similar glycosylations with donor **50**, which is the reduced form of **49**. To this end, precursor **51** was reduced with TMSOTf and Et_3SiH to afford a single thiane product[24] which was benzylated using benzyl bromide and sodium hydride in DMF (Scheme 2.3).

Next, oxathiane **49** was activated by addition of trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 1,3,5-trimethoxy benzene in 1,2-dichloroethane (DCE) at -35°C (Scheme 2.4). After completion of the electrophilic aromatic substitution and formation of the intermediate sulfonium ion, alcohols **3** or **4** were added and after a reaction time of 16 h at 50°C the disaccharides **53** and **54**, respectively were formed as only the α-anomers albeit in moderate yields. On the other hand, similar glycosylations with **49** led to the formation of disaccharides **55** and **56** as mixtures of anomers. Although **49** is protected with benzyl ethers at C-3, C-4 and C-6, glycosylation with this compound took place with

inversion of anomeric configuration leading to selective formation of α-glucosides. The geminal OMe substituent of **49** was critical since glycosyl donor **50** exhibited compromised α-anomeric selectivities.



Scheme 2.4: Effects of substitution pattern of the C-2 auxiliary.[a] The α/β ratios were determined by the integration of key signals in the ^{1}H NMR spectra of the disaccharide products after purification by LH-20 size exclusion chromatography.[b] Isolated yields of the α/β mixture of disaccharide products.

It is well known that substituents can enhance ring stability and this observation is, for example, embodied in the "gem-dialkyl" or Thorpe-Ingold effect.[25-27] Substitutions can also promote the rate of ring formation by increasing the probability of correct alignment for ring formation.[28] Saccharides also respond to these effects and, alkylation of the aldofuranose ring shifts the equilibrium between aldofuranoses and the corresponding acyclic aldehydes in the direction of the cyclic forms.[29] Thus, it is likely that the additional substituent of the auxiliary of **49** selectively increased the stability of the sulfonium ion thereby promoting glycosylations by an S_N2-like mechanism. The latter is supported by our observation that a glycosyl donor that has no substituent at the auxiliary (2-*O*-phenylsulfanyl-ethyl substituent) forms an intermediate β-sulfonium ion but upon glycosylation gives mixtures of anomers.[8]

Previously, it has been reported that anomeric sulfonium ion intermediates may not necessarily be the species that undergo glycosylation and parameters such as the potency of the nucleophile may determine whether a reaction proceeds through S_N2 displacement of a sulfonium ion or by substitution of an oxacarbenium ion.[30]

Conclusions. We demonstrated that protecting groups and the chemical nature of the sulfonium ion can have a profound influence on the stereochemical outcome of glycosylations and it has been found that by disfavoring oxacarbenium ion formation by electronic or stereoelectronic effects, exclusive α-anomeric selectivity can be accomplished. These observations can be used as a guide to select glycosyl donors that are expected to give exclusive 1,2-*cis* stereoselectivity and be employed for further improvement of chiral auxiliary mediated glycosylation methodology.

Experimental Section:

General procedures: ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz, 500 MHz or a 600 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. NMR data is presented as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration. All NMR signals were assigned on the basis of ^{1}H NMR, ^{13}C NMR, COSY and HSQC experiments. Mass spectra were recorded on an MALDI-TOF mass spectrometer. The matrix used was 2,5-dihydroxy-benzoic acid (DHB) and Ultamark 1621 as the internal standard. Column chromatography was performed on silica gel G60 (Silicycle, 60-200 μm, 60 Å). TLC-analysis was conducted on Silicagel 60 F_{254} (EMD Chemicals inc.) with detection by UV-absorption (254nm) were applicable, and by spraying with 20% sulfuric acid in ethanol followed by charring at ~150^{o}C or by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (25 g/L) in 10% sulfuric acid in ethanol followed by charring at ~150^{o}C. CH_2Cl_2 was freshly distilled from calcium hydride under nitrogen prior to use. Molecular sieves (4Å) were flame activated under vacuum prior to use. All reactions were carried out under an argon atmosphere. Compounds **1**[8], **3**[11], **4**[12], **5**[8], **6**[8], **9**[21], **12**[8], **17**[9], **39**[8], **40**[8], **49**[23] and **51**[23] were prepared following literature procedures.

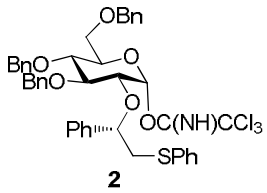
General Procedure for the Glycosylation Reaction Employing Glycosyl Donors 1,2 and 10-16.

A mixture of glycosyl donor (0.1 mmol) and activated molecular sieves (4Å) in CH_2Cl_2 (3 mL) was stirred for 10 min under an atmosphere of argon at room temperature. After cooling to -78 °C, trimethylsilyl trifluoromethanesulfonate (18 μL, 0.1 mmol) was added and the reaction mixture was allowed to warm to 0 °C over a period of 40 min. After cooling the reaction mixture to -78 °C, a solution of glycosyl acceptor **3** or **4** (0.12 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (41 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added. The reaction mixture was allowed to warm to room temperature over 5 h, and stirred for 11 h at room temperature. After diluting with CH_2Cl_2 (10 mL), aqueous saturated $NaHCO_3$ (5 mL) was added and the organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 20% - EtOAc in PE) or sephadex® LH20 size exlusion chromatography (CH_2Cl_2/MeOH, 1/1) to afford the pure disaccharide.

Procedure for low-temperature NMR experiments. ^{1}H NMR spectrum of **2** (16 mg, 0.02 mmol) in CD_2Cl_2 (0.5 mL) was recorded; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.54 (s, 1H, N*H*), 7.33-7.06 (m, 25H, CH Ar), 6.61 (d, 1H, *J* = 2.5 Hz, H-1), 4.97 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.83 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.78 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.74 (t, 1H, *J* = 6.5 Hz, H-7), 4.57 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.44 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.43 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.00 (t, 1H, *J* = 9.5 Hz, H-3), 3.99-3.94 (m, 1H, H-5), 3.74-3.58 (m, 4H, H-6a, H-6b, H-2, H-4), 3.30 (dd, 1H, *J* = 13.5, 6.5 Hz, H-8a), 3.12 (dd, 1H, *J* = 13.5, 6.5 Hz, H-8b). Trimethylsilyl trifluoromethanesulfonate (3.6 μL, 0.02 mmol) was added to the solution at -50 °C. The reaction mixture was allowed to warm to 0 °C over 40 min. NMR spectra of **1d** (^{1}H, HSQC and HMBC) were recorded at -20 °C, **1d**; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.05-7.11 (m, 25H, CH Ar), 5.59 (d, 1H, *J* = 8.5 Hz, H-1)**,** 5.25 (d, 1H, *J* = 9.5 Hz, H-7), 4.86 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.82 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.75 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.52 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.42 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.35 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.13-4.02 (m, 4H, H-2, H-3, H-8ax, H-8eq), 3.79 (t, 1H, *J* = 9.5 Hz, H-4), 3.70-3.64 (m, 2H, H-5, H-6a), 3.59 (d, 1H, *J* = 10.5 Hz, H-6b).

The ^{1}H NMR spectrum of **1d** showed that the anomeric proton (H-1) signal of **2** (δ 6.61, d, $J_{1,2}$ = 2.5 Hz, α-configuration) had shifted upfield to (δ 5.59, d, $J_{1,2}$ = 8.5 Hz, α-configuration) for **1d**. The change of anomeric configuration indicates that the α-imidate donor **2** was completely transformed to a new intermediate (**1d**) after activation. H-1, H-7, H8-eq and H8-ax signals of **1d** were assigned from ^{1}H COSY 2D data. The anomeric carbon signal (C-1, δ 88.0 ppm) of **1d** was assigned from HSQC data. The HMBC spectrum of **1d** showed the three-bond coupling between C-1 (δ 88.0 ppm) and H8-eq (δ 4.04 ppm), which confirmed the presence of C-1-H8-eq bond.

3,4,6-Tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl



2

trichloroacetimidate (2). Boron trifluoride diethyl etherate (0.38 mL, 3.0 mmol) was added to a solution of allyl 3,4,6-tri-*O*-benzyl-*α*-D-glucopyranose[31] (0.98 g, 2.0 mmol), acetic acid (1*S*)-phenyl-2-phenylsulfanyl-ethyl ester[8] (0.81 g, 3.0 mmol) and activated molecular sieves (4Å) in CH_2Cl_2 (10 mL) at 0 °C. After 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 15% - EtOAc in PE) to afford Allyl 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranoside (0.98 g, 70%) as a colorless syrup. TLC: (EtOAc/PE, 25/75 v/v): R_f = 0.44; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.07 (m, 25H, CH Ar), 5.91-5.83 (m, 1H, CH Allyl), 5.27-5.13 (m, 2H, CH_2 Allyl), 5.05 (dd, 1H, *J* = 8.0, 5.0 Hz, H-7), 5.02 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.69 (d, 1H, *J* = 3.0 Hz, H-1), 4.61 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.57 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.48 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.38 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.27 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.08 (dd, 1H, *J* = 12.5, 5.0 Hz, H-6a), 4.02 (t, 1H, *J* = 9.5 Hz, H-3), 3.91 (dd, 1H, *J* = 12.5, 7.0 Hz, H-6b), 3.78-3.61 (m, 4H, Allyl, H-4, H-5), 3.54 (dd, 1H, *J* = 12.5, 5.0 Hz, H-8a), 3.40 (dd, 1H, *J* = 9.5, 3.0 Hz, H-2), 3.13 (dd, 1H, *J* = 12.5, 8.0 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.64, 138.46, 138.42, 138.12, 137.22, 134.00, 128.94, 128.64, 128.62, 128.62, 128.57, 128.48, 128.39, 128.26, 128.18, 128.08, 127.95, 127.90,

127.33, 125.71, 118.24, 95.88, 82.04, 80.31, 80.12, 75.39, 73.77, 73.13, 70.44, 68.80, 68.45, 40.37; HR MALDI-TOF MS: m/z: calcd for $C_{44}H_{46}O_6S$ $[M+Na]^+$: 725.2913; found: 725.2955. Tetrakis(triphenylphosphine) palladium (1.60 g, 1.40 mmol) was added to a solution of Allyl 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranoside (0.98 g, 1.40 mmol) in acetic acid (20 mL) at room temperature. The reaction mixture was stirred for 16 h, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 25% - EtOAc in PE) to afford 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.90 g, 97%). Trichloroacetonitrile (1.36 mL, 13.6 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (81 µL, 0.54 mmol) were added to a solution of 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.90 g, 1.36 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and was then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 10% - EtOAc in PE) to afford **2** (1.06 g, 97%): TLC: (EtOAc/PE, 25/75 v/v): R_f = 0.37; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H, N*H*), 7.33-7.06 (m, 25H, CH Ar), 6.61 (d, 1H, *J* = 3.3 Hz, H-1), 4.97 (d, 1H, *J* = 11.1 Hz, C*H*HPh), 4.83 (d, 1H, *J* = 11.1 Hz, C*H*HPh), 4.78 (d, 1H, *J* = 10.8 Hz, C*H*HPh), 4.74 (t, 1H, *J* = 6.6 Hz, H-7), 4.57 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.44 (d, 1H, *J* = 10.8 Hz, C*H*HPh), 4.43 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.00 (t, 1H, *J* = 9.1 Hz, H-3), 3.99-3.94 (m, 1H, H-5), 3.74-3.58 (m, 4H, H-6a, H-6b, H-2, H-4), 3.30 (dd, 1H, *J* = 13.5, 6.6 Hz, H-8a), 3.12 (dd, 1H, *J* = 13.5, 6.6 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.12, 139.13, 138.77, 138.03, 137.74, 136.74, 129.20, 128.86, 128.54, 128.37, 128.26, 128.04, 127.99, 127.77, 127.73, 127.46, 125.92, 93.64, 80.94, 79.09, 76.75, 76.22, 75.49, 75.31, 73.48, 73.04, 67.93; HR MALDI-TOF MS: m/z: calcd for $C_{43}H_{42}Cl_3NO_6S$ $[M+Na]^+$: 828.1696; found: 828.1690.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (7α); Compound **7** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-6.92 (m, 40H, CH Ar), 5.77 (d, 1H, *J* = 3.5 Hz, H-1'), 5.16 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.97 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.89 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.72-4.46 (m, 8H, H-1, H-7', C*H*HPh × 6), 4.35-4.07 (m, 4H, C*H*HPh × 3, H-3), 3.87-3.63 (m, 6H, H-6a', H-6b', H-5', H-5, H-6a, H-3'), 3.50-3.32 (m, 6H, H-6b, H-4, H-4', H-2', H-2, H-8a'), 3.39 (s, 3H, OMe), 3.01 (dd, 1H, *J* = 12.5, 6.5 Hz, H-8b'); HR MALDI-TOF MS: m/z: calcd for $C_{69}H_{72}O_{11}S$ $[M+Na]^+$: 1131.4693; found: 1131.4698. **Methyl 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (7β);** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.12 (m, 40H, CH Ar), 5.11 (t, 1H, *J* = 7.0 Hz, H-7'), 4.90 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.86 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.79 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.77 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.72 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.69 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.64 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.60 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.59 (d, 1H, *J* = 3.5 Hz, H-1), 4.50-4.45 (m, 3H, C*H*HPh × 3), 4.38 (d, 1H, *J* = 8.5 Hz, H-1'), 4.36 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.10 (t, 1H, *J* = 9.5 Hz), 4.01 (dd, 1H, *J* = 11.0, 2.0 Hz), 3.83 (t, 1H, *J* = 9.5 Hz), 3.68 (d, 2H, *J* = 11.0 Hz), 3.56 (d, 1H, *J* = 11.0 Hz), 3.46-3.32 (m, 5H), 3.34 (s, 3H, OMe), 3.22-3.19 (m, 2H), 3.10 (dd, 1H, *J* = 13.0, 5.0 Hz, H-8b'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.91, 139.63, 139.00, 138.87, 138.67, 138.54, 137.95, 128.78, 128.54, 128.51, 128.47, 128.42, 128.36, 128.28, 128.25, 128.14, 128.03, 127.90, 127.78, 127.72, 127.64, 127.60, 127.44, 127.30, 125.79, 102.07, 98.74, 84.62, 81.02, 78.99, 78.54, 78.46, 77.42, 75.80, 75.51, 74.97, 73.87, 73.75, 73.58, 70.11, 69.05, 68.44, 55.74, 41.10; HR MALDI-TOF MS: m/z: calcd for $C_{69}H_{72}O_{11}S$ $[M+Na]^+$: 1131.4693; found: 1131.4698.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (8*α*); Compound **8** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.86 (m, 6H, CH Ar), 7.53-7.05 (m, 34H, aromatic), 6.18 (t, 1H, *J* = 10.0 Hz, H-3), 5.62 (t, 1H, *J* = 10.0 Hz, H-4), 5.30 (dd, 1H, *J* = 10.0, 4.0 Hz, H-2), 5.21 (d, 1H, *J* = 4.0 Hz, H-1), 4.98 (d, 1H, *J* = 3.5 Hz, H-1'), 4.86 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.74 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.72 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.64 (dd, 1H, *J* = 7.5, 7.0 Hz, H-7'), 4.52 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.40-4.34 (m, 3H, H-5, 2 x C*H*HPh), 3.95-3.90 (m, 2H, H-3', H-6a), 3.84-3.81 (m, 1H, H-5'), 3.76 (dd, 1H, *J* = 11.0, 2.0 Hz, H-6b), 3.60 (dd, 1H, *J* = 10.5, 3.5 Hz, H-6a'), 3.52-3.44 (m, 3H, H-6b', H-4', H-2'), 3.48 (s, 3H, OMe), 3.37 (dd, 1H, *J* = 13.5, 7.5 Hz, H-8a'), 3.16 (dd, 1H, *J* = 13.5, 5.0 Hz, H-8b'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.01, 165.45, 140.00, 139.19, 138.72, 138.02, 137.07, 133.46, 133.17, 130.09, 129.95, 129.84, 129.46, 129.29, 129.17, 129.13, 129.01, 128.80, 128.63, 128.55, 128.46, 128.40, 128.34, 128.30, 128.08, 127.98, 127.86, 127.80, 127.77, 127.57, 127.39, 127.23, 126.90, 125.96, 96.97, 96.58, 81.18, 79.38, 77.36, 75.43, 74.91, 73.54, 72.44, 70.85, 70.36, 69.79, 68.96, 68.39, 66.87, 55.81, 41.89; HR MALDI-TOF MS: m/z: calcd for $C_{69}H_{66}O_{14}S$ $[M+Na]^+$: 1173.4071; found: 1173.4076. **Methyl 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (8β);** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.85 (m, 6H, CH Ar), 7.53-7.06 (m, 34H, CH Ar), 6.17 (t, 1H, *J* = 10.0 Hz, H-3), 5.48 (t, 1H, *J* = 10.0 Hz, H-4), 5.33 (t, 1H, *J* = 7.0 Hz, H-7'), 5.27 (dd, 1H, *J* = 10.0, 3.5 Hz, H-2), 5.19 (d, 1H, *J* = 3.5 Hz, H-1), 4.88 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.73 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.69 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.48-4.35 (m, 5H, H-5, H-1', C*H*HPh × 3), 4.04 (dd, 1H, *J* = 11.0, 2.0 Hz, H-6a), 3.84 (dd, 1H, *J* = 11.0, 3.0 Hz, H-6b), 3.57-3.31 (m, 7H, H-5', H-6a', H-6b', H-4', H-3', H-2', H-8a'), 3.47 (s, 3H, OMe), 3.22 (dd, 1H, *J* = 13.0, 6.0 Hz, H-8b'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.79, 165.49, 140.12, 138.73, 138.08, 137.44, 133.02, 129.94, 129.88, 129.67, 129.27, 129.16, 129.01, 128.77, 128.41, 128.31, 128.25, 128.20, 127.92, 127.71, 127.54, 127.48, 127.32, 125.59, 104.20, 96.87, 84.34,

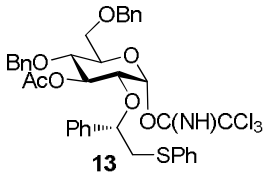
80.16, 77.86, 77.21, 75.57, 74.86, 73.38, 72.13, 70.59, 69.99, 68.91, 68.54, 55.86, 41.11; HR MALDI-TOF MS: m/z: calcd for $C_{69}H_{66}O_{14}S$ $[M+Na]^+$: 1173.4071; found:1173.4083.

3,4,6-tri-*O*-*p*-chlorobenzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl trichloroacetimidate (10). To a cooled (0°C) solution of **18** (0.45 g, 0.51 mmol) in THF (8 mL), 70% HF.Pyridine (2 mL) was added and the resulting mixture was stirred on at rt. The mixture was diluted with EtOAc (30 mL) and was poured into sat. aq. $NaHCO_3$ (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded the pure lactol. The lactol was dissolved in a mixture of CH_2Cl_2 (5 mL) and trichloroacetonitrile (2 mL), cooled (0°C) and DBU (16 μL, 0.10 mmol) was added. The resulting mixture was stirred for 10 min and concentrated *in vacuo.* Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **10** (0.42 g, 0.46 mmol, 91%) as a white foam. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.71; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H, N*H*), 7.20-6.88 (m, 22H, CH Ar), 6.53 (d, 1H, *J* = 3.0 Hz, H-1), 4.82 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.65 (t, 1H, *J* = 6.0 Hz, H-7), 4.63-4.26 (m, 5H, CH*H*Ph, 2 x CH_2 Bn), 3.89-3.84 (m, 2H, H-3, H-5), 3.60-3.46 (m, 4H, H-2, H-4, H-6a/b), 3.22 (dd, 1H, *J* = 13.5 Hz, *J* = 6.5 Hz, H-8a), 3.04 (dd, 1H, *J* = 13.0 Hz, *J* = 6.0 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 139.0, 137.1, 136.5, 136.3, 136.1, 133.5, 133.1, 129.2-125.9, 93.4, 91.2, 80.7, 79.2, 76.6, 76.3, 74.4, 74.2, 72.9, 72.6, 67.9, 41.6; HR MALDI-TOF MS: m/z: calcd for $C_{43}H_{39}Cl_6NO_6$ $[M+Na]^+$: 930.0527; found: 930.0519.

4,6-Di-*O*-benzyl-3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl trichloroacetimidate (11). 1M Solution of tetrabutylammonium fluoride in THF (1.2 mL) was added to a solution of **25** (0.64 g, 0.92 mmol) in THF (10 mL) at 0 °C. After stirring for 1 h at the same temperature, the reaction mixture was diluted with dichloromethane (20 mL), and then quenched with saturated aqueous $NaHCO_3$ (20 mL). The

organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 25% - EtOAc in PE) to afford 4,6-di-*O*-benzyl-3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.52 g, 97%). Trichloroacetonitrile (0.89 mL, 8.9 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (53 µL, 0.35 mmol) were added to a solution of 4,6-di-*O*-benzyl-3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.52 g, 0.89 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 15% - EtOAc in PE) to afford **11** (0.61 g, 94%): TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.57; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H, N*H*), 7.38-7.14 (m, 20H, CH Ar), 6.57 (d, 1H, *J* = 3.5 Hz, H-1), 4.77 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.71 (t, 1H, *J* = 6.5 Hz, H-7), 4.56 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.43 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.41 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 3.93-3.90 (m, 1H, H-5), 3.71 (dd, 1H, *J* = 10.0, 3.3 Hz, H-6a), 3.67 (d, 1H, *J* = 10.0 Hz, H-6b), 3.61-3.52 (m, 3H, H-4, H-3, H-2), 3.58 (s, 3H, OCH_3), 3.30 (dd, 1H, *J* = 12.5, 6.5 Hz, H-8a), 3.13 (dd, 1H, *J* = 12.5, 6.5 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.35, 139.82, 138.40, 137.98, 136.97, 129.39, 129.09, 128.75, 128.62, 128.60, 128.29, 128.24, 128.02, 127.96, 127.55, 126.14, 93.98, 83.21, 79.79, 77.00, 75.39, 73.69, 73.11, 68.09, 61.47, 42.02; HR MALDI-TOF MS: m/z: calcd for $C_{37}H_{38}Cl_3NO_6S$ $[M+Na]^+$: 752.1383; found: 752.1389.

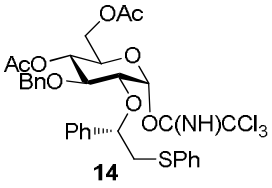
4,6-Di-*O*-benzyl-3-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl trichloroacetimidate (13).



13

1M Solution of tetrabutylammonium fluoride in THF (1.7 mL) was added to a solution of **27** (0.70 g, 0.87 mmol) in THF (10 mL) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was diluted with dichloromethane (20 mL), and then quenched with saturated aqueous $NaHCO_3$ (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 25% -

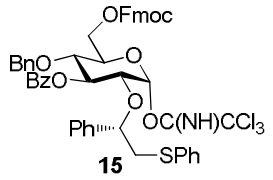
EtOAc in PE) to afford 4,6-di-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.48 g, 97%). Acetic anhydride (4 mL) was added to a solution of 4,6-di-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.48 g, 0.84 mmol) in Pyridine (10 mL) at room temperature. After stirring for 16 h, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF (10 mL) and hydrazinium acetate (0.147 g, 1.60 mmol) was added. The reaction mixture was stirred overnight, then quenched with saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic phase was washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 20% - EtOAc in PE) to afford 3-*O*-acetyl-4,6-di-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.438 g, 89%). Trichloroacetonitrile (0.71 mL, 7.1 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (42 µL, 0.28 mmol) were added to a solution of 3-*O*-acetyl-4,6-di-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.438 g, 0.71 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 20% - EtOAc in PE) to afford **13** (0.47 g, 88%). TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H, N*H*), 7.34-7.09 (m, 20H, CH Ar), 6.64 (d, 1H, *J* = 3.5 Hz, H-1), 5.52 (t, 1H, *J* = 10.0 Hz, H-3), 4.59 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.49 (t, 1H, *J* = 7.0 Hz, H-7), 4.45-4.38 (m, 3H, 3 × C*H*HPh), 4.02-3.99 (m, 1H, H-5), 3.74 (dd, 1H, *J* = 11.5, 3.0 Hz, H-6a), 3.66 (t, 1H, *J* = 10.0 Hz, H-4), 3.65 (dd, 1H, *J* = 11.5, 2.0 Hz, H-6b), 3.57 (dd, 1H, *J* = 10.0, 3.5 Hz, H-2), 3.25 (dd, 1H, *J* = 13.5, 7.0 Hz, H-8a), 3.05 (dd, 1H, *J* = 13.5, 7.0 Hz, H-8b), 1.77 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.63, 161.22, 139.82, 137.66, 137.62, 136.28, 129.37, 128.95, 128.48, 128.43, 128.41, 128.11, 127.92, 127.86, 127.83, 127.26, 126.07, 93.52, 80.76, 75.51, 74.60, 73.59, 72.69, 67.70, 41.23, 20.94; HR MALDI-TOF MS: m/z: calcd for $C_{38}H_{38}Cl_3NO_7S$ $[M+Na]^+$: 780.1332; found: 780.1366.

4,6-Di-*O*-acetyl-3-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl trichloroacetimidate (14). 

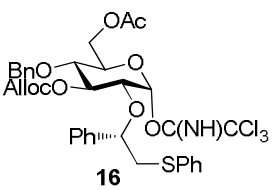
14

1M Solution of tetrabutylammonium fluoride in THF (1.1 mL) was added to a solution of **28** (0.75 g, 1.10 mmol) in THF (10 mL) at 0 °C. After stirring for 20 min at the same temperature, the reaction mixture was diluted with dichloromethane (20 mL), and then quenched with saturated aqueous $NaHCO_3$ (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 25% - EtOAc in PE) to afford 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.65 g, 96%). Trichloroacetonitrile (1.05 mL, 10.5 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (63 μL, 0.42 mmol) were added to a solution of 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-D-glucopyranose (0.65 g, 1.05 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 15% - EtOAc in PE) to afford **14** (0.72 g, 91%): TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.48; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H, N*H*), 7.32-7.16 (m, 15H, CH Ar), 6.60 (d, 1H, *J* = 3.5 Hz, H-1), 4.96 (t, 1H, *J* = 10.0 Hz, H-4), 4.81 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.75 (t, 1H, *J* = 6.0 Hz, H-7), 4.64 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.15 (dd, 1H, *J* = 12.0, 4.0 Hz, H-6a), 4.06-4.03 (m, 1H, H-5), 4.01 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 3.95 (t, 1H, *J* = 10.0 Hz, H-3), 3.69 (dd, 1H, *J* = 10.0, 3.5 Hz, H-2), 3.31 (dd, 1H, *J* = 13.5, 6.0 Hz, H-8a), 3.15 (dd, 1H, *J* = 13.5, 6.0 Hz, H-8b), 2.01 (s, 3H, CH_3), 1.90 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.62, 169.45, 160.75, 138.89, 138.23, 136.60, 129.19, 129.04, 128.91, 128.78, 128.65, 128.53, 128.43, 128.27, 127.87, 127.59, 127.28, 126.01, 93.14, 79.48, 77.71, 76.17, 75.16, 70.39, 68.79, 61.78, 41.71, 20.71, 20.67; HR MALDI-TOF MS: m/z: calcd for $C_{33}H_{34}Cl_3NO_8S$ $[M+Na]^+$: 732.0968; found: 732.0987.

3-*O*-benzoyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl trichloroacetimidate (15). To a cooled (0°C) solution of **30** (0.45 g, 0.48 mmol) in THF (8 mL), 70% HF.Pyridine (2 mL) was added and the resulting mixture was stirred on at rt. The mixture was diluted with EtOAc (30 mL) and was poured into sat. aq. $NaHCO_3$ (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded the pure lactol. The lactol was dissolved in a mixture of CH_2Cl_2 (5 mL) and trichloroacetonitrile (2 mL), cooled (0°C) and 60% NaH in mineral oil (4 mg, 0.09 mmol) was added. The resulting mixture was stirred for 10 min and filtered through a short silica gel column which was subsequently washed with EtOAc (10 mL). The filtrate was concentrated *in vacuo* and silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **15** (0.38 g, 0.39 mmol, 81%) as a white foam. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H, N*H*), 7.85-6.95 (m, 28H, CH Ar), 6.61 (d, 1H, *J* = 3.0 Hz, H-1), 5.81 (t, 1H, *J* = 9.5 Hz, H-3), 4.46 (t, 1H, *J* = 6.5 Hz, H-7), 4.45-4.25 (m, 6H, CH_2 Bn, CH_2 Fmoc, H-6a/b), 4.17-4.11 (m, 2H, H-5, CH Fmoc), 3.66-3.62 (m, 2H, H-2, H-4), 3.15 (dd, 1H, *J* = 6.5 Hz, *J* = 14.0 Hz, H-8a), 2.89 (dd, 1H, *J* = 7.0 Hz, *J* = 14.0 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 161.0, 154.7, 143.3, 143.1, 14.12, 139.2, 136.7, 136.3, 133.1, 129.9-125.0, 120.0, 92.8, 91.0, 80.2, 75.1, 74.7, 74.6, 73.1, 71.0, 70.0, 65.6, 46.6, 41.1; HR MALDI-TOF MS: m/z: calcd for $C_{51}H_{44}Cl_3NO_9S$ $[M+Na]^+$: 974.1700; found: 974.1769.

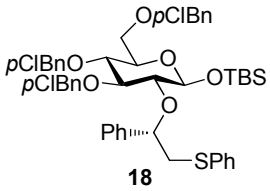


6-*O*-acetyl-3-*O*-allyloxycarbonyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl trichloroacetimidate (16). To a cooled (0°C) solution of **32** (0.42 g, 0.58 mmol) in THF (8 mL), 70% HF.Pyridine (2 mL) was added and the resulting mixture was stirred on at rt. The mixture was diluted with EtOAc (30 mL) and was poured into sat. aq. $NaHCO_3$ (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded the pure



lactol. The lactol was dissolved in a mixture of CH_2Cl_2 (5 mL) and trichloroacetonitrile (2 mL), cooled (0°C) and DBU (18 µL, 0.11 mmol) was added. The resulting mixture was stirred for 10 min and concentrated *in vacuo.* Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **16** (0.40 g, 0.54 mmol, 93%) as a white foam. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.65; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H, N*H*), 7.29-7.07 (m, 15H, CH Ar), 6.54 (d, 1H, *J* = 3.0 Hz, H-1), 5.85-5.78 (m, 1H, CH Alloc), 5.32-5.17 (m, 3H, H-3, CH_2 Alloc), 4.53-4.36 (m, 5H, H-7, CH_2 Alloc, CH_2 Bn), 4.19-4.11 (m, 2H, H-6a/b), 4.02-4.00 (m, 1H, H-5), 3.55 (dd, 1H, *J* = 10.0 Hz, *J* = 3.0 Hz, H-2), 3.46 (t, 1H, J = 9.5 Hz, H-4), 3.17 (dd, 1H, *J* = 14.0 Hz, *J* = 6.5 Hz, H-8a), 2.98 (dd, 1H, *J* = 13.5 Hz, *J* = 6.0 Hz, H-8b)1.92 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 160.9, 154.1, 139.3, 136.9, 136.3, 131.4, 129.4-126.0, 119.1, 93.0, 90.8, 80.5, 77.7, 75.1, 75.0, 74.8, 71.0, 68.2, 41.5, 20.7; HR MALDI-TOF MS: m/z: calcd for $C_{35}H_{36}Cl_3NO_9S$ $[M+Na]^+$: 774.1074; found: 774.1065.

***t*-Butyldimethylsilyl 3,4,6-tri-*O*-*p*-chlorobenzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (18).** To a cooled (0°C) solution of *t*-butyldimethylsilyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*β*-D-glucopyranoside[9] (0.35 g, 0.7 mmol) and *p*-chlorobenzyl bromide (0.50 g, 2.42 mmol) in DMF (5 mL), NaH (0.1 g, 2.42 mmol) was added. The reaction mixture was stirred at rt for 16 h and quenched upon addition of EtOAc (50 mL) and water (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 10% - EtOAc in PE) of the residue afforded **18** (0.47 g, 77 %) as a colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.14 (m, 20H, CH Ar), 7.00 (d, 2H, *J* = 8.0 Hz, CH Ar), 5.29 (t, 1H, *J* = 6.5 Hz, H-7), 4.86 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.68-4.58 (m, 3H, CH*H*Ph, C*H*HPh, H-1), 4.51-4.40 (m, 3H, CH*H*Ph, CH_2 Bn) 3.58 (s, 2H, H-6a/b), 3.48-3.36 (m, 4H, H-3, H-4, H-5, H-8a), 3.28 (t, 1H, *J* = 8.5 Hz, H-2), 3.14 (dd, 1H, *J* = 6.0 Hz, *J* = 13.0 Hz, H-8b), 0.97 (s, 9H, *t*-Bu), 0.19 (s, 3H, CH_3), 0.18 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 137.2, 137.2, 136.5, 133.4, 133.3, 132.9, 129.0-127.6, 125.7, 98.6, 84.2, 80.2, 79.3, 77.7, 74.5,



18

74.5, 73.8, 72.6, 68.9, 41.4, 25.9, 18.0, -4.1, -4.6; HR MALDI-TOF MS: m/z: calcd for $C_{47}H_{53}Cl_3O_6S$ $[M+Na]^+$: 901.2295; found: 901.2301.

***t*-Butyldimethylsilyl 4,6-*O*-benzylidene-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (19).** Sodium methoxide (3.2 mg, 0.06 mmol) was added to a solution of *t*-butyldimethylsilyl 3,4,6-tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*β*-D-glucopyranose[7] (0.72 g, 1.14 mmol) in methanol (20 mL). After stirring for 3 h at room temperature, the reaction mixture was quenched by Amberlite IRC-50 H^+ resin. After filtration, the filtrate was concentrated *in vacuo* and the residue was dissolved in acetonitrile (10 mL). Benzaldehyde dimethyl acetal (0.34 mL, 2.24 mmol) and *p*-toluenesulfonic acid monohydrate (7.0 mg, 0.04 mmol) were added and after 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with ethyl acetate (2 x 20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 10% - EtOAc in PE) to afford **19** (0.57 g, 86%) as a colorless syrup. TLC: (EtOAc/PE, 25/75 v/v): R_f = 0.36; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.11 (m, 15H, CH Ar), 5.41 (s, 1H, benzylidene), 5.11 (t, 1H, *J* = 7.5 Hz, H-7), 4.76 (d, 1H, *J* = 7.5 Hz, H-1), 4.23 (dd, 1H, *J* = 5.5, 3.5 Hz, H-6a), 3.71-3.64 (m, 2H, H-3, H-5), 3.49 (dd, 1H, *J* = 12.5, 7.5 Hz, H-8a), 3.38-3.34 (m, 2H, H-6b, H-4), 3.21 (dd, 1H, *J* = 12.5, 7.5 Hz, H-8b), 3.16 (dd, 1H, *J* = 8.5, 7.5 Hz, H-2), 0.95 (s, 9H, *t*-Bu), 0.17 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.10, 137.07, 136.78, 129.32, 129.10, 128.81, 128.79, 128.73, 128.24, 127.61, 126.24, 125.95, 101.69, 98.46, 81.29, 80.98, 80.39, 77.22, 72.65, 68.67, 66.09, 40.78, 25.88, 18.02, -4.16, -4.59; HR MALDI-TOF MS: m/z: calcd for $C_{33}H_{42}O_6SSi$ $[M+Na]^+$: 617.2369; found: 617.2342.

***t*-Butyldimethylsilyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (20).** Methyl iodide (44 μL, 0.71 mmol) and sodium hydride (60% dispersion in mineral oil, 21 mg, 0.53 mmol) were added to a solution of **19** (0.21 g, 0.35 mmol) in THF (10 mL) at 0°C. After stirring for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with ethyl acetate (2 x 20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 15% - EtOAc in PE) to afford **20** (0.20 g, 95%) as a colorless syrup; TLC: (EtOAc/PE, 25/75 v/v): R_f = 0.49; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.11 (m, 15H, CH Ar), 5.44 (s, 1H, benzylidene), 5.11 (t, 1H, *J* = 6.9 Hz, H-7), 4.76 (d, 1H, *J* = 6.9 Hz, H-1), 4.23 (dd, 1H, *J* = 10.2, 4.5 Hz, H-6a), 3.67 (t, 1H, *J* = 10.2 Hz, H-6b), 3.50-3.22 (m, 5H, H-8a, H-5, H-4, H-3, H-2), 3.43 (s, 3H, OCH_3), 3.17 (dd, 1H, *J* = 12.6, 6.9 Hz, H-8b), 0.95 (s, 9H, *t*-Bu), 0.17 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.28, 137.39, 137.11, 129.07, 128.88, 128.75, 128.18, 128.15, 128.12, 127.77, 126.01, 125.75, 101.10, 98.67, 82.46, 81.41, 81.31, 80.30, 77.21, 68.73, 66.01, 60.87, 41.07, 25.87, 18.06, -4.19, -4.61; HR MALDI-TOF MS: m/z: calcd for $C_{34}H_{44}O_6SSi$ $[M+Na]^+$: 631.2526; found: 631.2521.

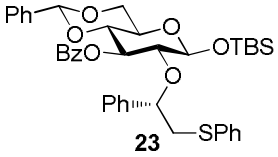
***t*-Butyldimethylsilyl 4,6-*O*-benzylidene-3-*O*-*t*-butyldimethylsilyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (21).** *t*-Butyldimethylsilyl triflate (0.36 mL, 1.57 mmol) and 2,6-lutidine (0.25 mL, 2.15 mmol) were added to a solution of **19** (0.85 g, 1.43 mmol) in dichloromethane (10 mL) at -78°C. The reaction mixture was warmed gradually to 0°C over a period of 30 min, and then quenched with methanol (1 mL). After washing with saturated aqueous $NaHCO_3$ (20 mL), the organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 5% - EtOAc in PE) to afford **21** (0.85 g, 84%) as a colorless syrup; TLC: (EtOAc/PE, 20/80 v/v): R_f = 0.62; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.15 (m, 15H, aromatic), 5.38 (s, 1H, benzylidene), 5.36 (dd,

1H, *J* = 7.2, 6.0 Hz, H-7), 4.81 (d, 1H, *J* = 7.2 Hz, H-1), 4.23 (dd, 1H, *J* = 10.2, 4.5 Hz, H-6a), 3.77 (t, 1H, *J* = 8.4 Hz, H-3), 3.64 (t, 1H, *J* = 10.2 Hz, H-6b), 3.48-3.33 (m, 3H, H-8a, H-5, H-4), 3.25 (dd, 1H, *J* = 8.4, 7.2 Hz, H-2), 3.11 (dd, 1H, *J* = 13.2, 6.0 Hz, H-8b), 0.92 (s, 9H, *t*-Bu), 0.86 (s, 9H, *t*-Bu), 0.14 (s, 3H, CH_3), 0.13 (s, 3H, CH_3), 0.12 (s, 3H, CH_3), 0.01 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.23, 137.58, 137.51, 129.35, 129.20, 129.02, 128.43, 128.31, 128.15, 126.57, 125.98, 102.25, 99.25, 81.81, 79.96, 79.15, 74.09, 69.02, 66.33, 42.04, 26.15, 18.47, 18.26, -3.24, -4.08, -4.17, -4.25; HR MALDI-TOF MS: m/z: calcd for $C_{39}H_{56}O_6SSi_2$ $[M+Na]^+$: 731.3234; found: 731.3221.

***t*-Butyldimethylsilyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (22).** Benzyl bromide (0.30 mL, 2.52 mmol) and sodium hydride (60% dispersion in mineral oil, 76 mg, 1.89 mmol) were added to a solution of **19** (0.75 g, 1.26 mmol) in DMF (20 mL) at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with ethyl acetate (2 x 20 mL), and the combined organic phases were washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 15% - EtOAc in PE) to afford **22** (0.82 g, 95%) as a colorless syrup; TLC: (EtOAc/PE, 25/75 v/v): R_f = 0.67; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.12 (m, 20H, aromatic), 5.47 (s, 1H, benzylidene), 5.20 (t, 1H, *J* = 7.0 Hz, H-7), 4.84 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.79 (d, 1H, *J* = 7.5 Hz, H-1), 4.64 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.25 (dd, 1H, *J* = 10.5, 5.5 Hz, H-6a), 3.69 (t, 1H, *J* = 10.5 Hz, H-6b), 3.61 (t, 1H, *J* = 9.0 Hz, H-3), 3.54 (t, 1H, *J* = 9.0 Hz, H-4), 3.46 (dd, 1H, *J* = 13.0, 7.0 Hz, H-8a), 3.39-3.35 (m, 1H, H-5), 3.16 (dd, 1H, *J* = 9.0, 7.5 Hz, H-2), 3.13 (dd, 1H, *J* = 13.0, 7.0 Hz, H-8b), 0.94 (s, 9H, *t*-Bu), 0.17 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.03, 138.57, 137.38, 137.18, 129.08, 128.88, 128.76, 128.41, 128.19, 128.17, 128.14, 128.09, 128.05, 127.77, 127.46, 125.99, 125.75, 101.11, 98.88, 81.58, 80.75,

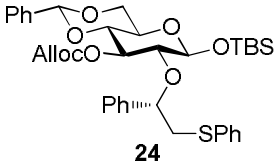
80.72, 79.75, 77.22, 75.10, 68.75, 66.07, 41.23, 25.89, 18.05, -4.19, -4.53; HR MALDI-TOF MS: m/z: calcd for $C_{40}H_{48}O_6SSi$ $[M+Na]^+$: 707.2839; found: 707.2886.

***t*-Butyldimethylsilyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (23).** Benzoyl chloride (0.1 mL, 0.8 mmol) was added to a cooled (0°C) solution of **19** (0.40 g, 0.67 mmol) in a mixture of DCM (5 mL) and pyridine (0.5 mL). The reaction mixture was stirred at room temperature for 16 h and was diluted with MeOH (0.1 mL), EtOAc (50 mL) and water (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in PE) of the residue afforded **23** (0.47 g, 96 %) as a colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.65; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, 1H, *J* = 7.5 Hz, CH Ar), 7.90 (d, 2H, *J* = 8.0 Hz, CH Ar), 7.67-6.95 (m, 17H, aromatic), 5.50 (t, 1H, *J* = 9.0 Hz, H-3), 5.37 (s, 1H, benzylidene), 5.12 (t, 1H, *J* = 7.0 Hz, H-7), 4.93 (d, 1H, *J* = 7.0 Hz, H-1), 4.27 (dd, 1H, *J* = 5.0 Hz, *J* = 11.0 Hz, H-5), 3.70 (t, 1H, *J* = 10.0 Hz, H-6a), 3.59-3.50 (m, 2H, H-6b, H-4), 3.44-3.37 (m, 2H, H-2, H-8a), 3.06 (dd, 1H, *J* = 7.0 Hz, *J* = 13.0 Hz, H-8b), 0.97 (s, 9H, *t*-Bu), 0.18 (s, 3H, CH_3), 0.17 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 139.5, 136.9, 136.9, 134.4, 132.8, 130.5-125.6, 101.2, 99.1, 80.7, 78.9, 78.2, 72.7, 68.6, 66.0, 40.7, 25.8, 17.9, -4.2, -4.6; HR MALDI-TOF MS: m/z: calcd for $C_{40}H_{46}O_7SSi$ $[M+Na]^+$: 721.2631; found: 721.2649.



23

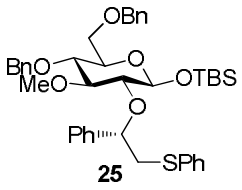
***t*-Butyldimethylsilyl 3-*O*-allyloxycarbonyl-4,6-*O*-benzylidene-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (24). 19** (2.87 g, 4.83 mmol) was dissolved in CH_2Cl_2 (40 mL) and the mixture was cooled to 0°C, followed by the addition of allylchloroformate (0.61 mL, 5.73 mmol) and tetramethylethylenediamine (1.10 mL. 7.17 mmol). The reaction mixture was stirred for 4 h at rt. The mixture was diluted with CH_2Cl_2 (50 mL) and sat. aq. NaCl (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and



24

the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **24** (2.63 g, 3.87 mmol, 81%) as a white solid. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12-7.40 (m, 15H), 5.95 (m, 1H, CH_2CH=CH_2), 5.36 (m, 2H, C-7′, CH_2CH=CH_2), 5.27 (d, J = 10.0 Hz, 1H, CH_2CH=CH_2), 5.09 (t, $J_{7,8a/b}$ = 6.5 Hz, 1H, H-7), 4.99 (t, $J_{3,2}$ = 9.0 Hz, 1H, H-3), 4.85 (d, $J_{1,2}$ = 7.0 Hz, 1H, H-1), 4.59 (d, J = 5.5 Hz, 2H, CH_2CH=CH_2), 3.68 (dd, $J_{6b,6a}$ = 11.0 Hz, $J_{6b,5}$ = 5.0 Hz, 1H, H-6b), 3.68 (t, $J_{6b,6a}$ = 9.5 Hz, 1H, H-6b), 3.43-3.48 (m, 3H, H-4, H-5, H-8b), 3.31 (dd, $J_{2,1}$ = 7.5 Hz, $J_{2,3}$ = 9.0 Hz, 1H, H-2), 3.17 (dd, $J_{8a,7}$ = 7.0 Hz, $J_{8a,8b}$ = 12.5 Hz, 1H, H-8a), 0.96 (s, 9H, 3 x CH_3), 0.17 (s, 3H, CH_3), 0.16 (s, 3H, CH_3); ^{13}C {^{1}H} NMR(APT) (75 MHz, $CDCl_3$): δ 154.1, 139.4, 137.0, 136.9, 131.4, 125.7-129.1, 118.9, 101.3, 98.8, 81.3, 78.7, 78.3, 76.6, 68.6, 68.6, 65.8, 40.9, 25.8, 17.9, -4.2, -4.6. HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{37}H_{46}O_8SSi$, 701.2580; found, 701.2523.

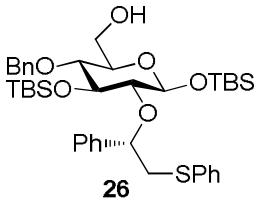
***t*-Butyldimethylsilyl 4,6-di-*O*-benzyl-3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (25).** A solution of **20** (0.82 g, 1.35 mmol) in 80% aq. acetic acid (20 mL) was stirred for 2 h at 60 °C. The reaction mixture was concentrated *in vacuo* and the residue was redissolved in CH_2Cl_2 (20 mL). After washing with saturated aqueous $NaHCO_3$ (3 x 20 mL), the reaction mixture was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 25% - EtOAc in PE) to afford *t*-butyldimethylsilyl 3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*β*-D-glucopyranose (0.65 g, 92%). Benzyl bromide (0.44 mL, 3.72 mmol) and sodium hydride (60% dispersion in mineral oil, 0.15 g, 3.72 mmol) were added to a solution of *t*-butyldimethylsilyl 3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*β*-D-glucopyranose (0.65 g, 1.24 mmol) in DMF (20 mL) at 0°C. After stirring for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with ethyl acetate (2 x 20 mL), and the combined organic phases were washed with saturated aqueous NH_4Cl (20



25

mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 15% - EtOAc in PE) to afford **25** (0.64 g, 74%) as a colorless syrup; TLC: (EtOAc/PE, 25/75 v/v): R_f = 0.59; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.10 (m, 20H, CH Ar), 5.21 (t, 1H, *J* = 7.0 Hz, H-7), 4.76 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.61 (d, 1H, *J* = 7.5 Hz, H-1), 4.54 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.49 (d, 2H, *J* = 12.0 Hz, 2 × C*H*HPh), 3.59-3.55 (m, 2H), 3.52 (s, 3H, OCH_3), 3.46 (dd, 1H, *J* = 12.5, 7.0 Hz, H-8a), 3.37-3.34 (m, 2H), 3.20-3.17 (m, 2H), 3.17 (dd, 1H, *J* = 12.5, 7.0 Hz, H-8b), 0.95 (s, 9H, *t*-Bu), 0.16 (s, 6H, 2 × CH_3); ^{13}C NMR (HSQC, 125 MHz, $CDCl_3$) δ 129.9, 129.3, 129.0, 128.7, 128.5, 128.2, 127.9, 127.0, 125.9, 98.8, 86.8, 80.9, 80.2, 78.1, 75.1, 75.0, 74.8, 73.8, 69.4, 61.6, 41.9, 26.4, -3.4; HR MALDI-TOF MS: m/z: calcd for $C_{41}H_{52}O_6SSi$ $[M+Na]^+$: 723.3152; found: 723.3177.

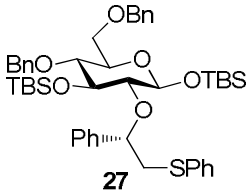
***t*-Butyldimethylsilyl 4-*O*-benzyl-3-*O*-*t*-butyldimethylsilyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (26).** Triethyl silane (0.56 mL, 3.54 mmol) and dichlorophenyl borane (0.46 mL, 3.54 mmol) were added to a solution of **21** (0.84 g, 1.18 mmol) in dichloromethane (10 mL) at -78°C. After stirring for 15 min at the same temperature, the reaction mixture was quenched with methanol (2 mL) and triethylamine (2 mL), and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 5% - EtOAc in PE) to afford **26** (0.75 g, 90%) as a colorless syrup; TLC (EtOAc:PE, 20:80 v/v): R_f = 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.11 (m, 15H, CH Ar), 5.41 (dd, 1H, *J* = 8.1, 6.0 Hz, H-7), 4.83 (d, 1H, *J* = 11.7 Hz, C*H*HPh), 4.75 (d, 1H, *J* = 7.5 Hz, H-1), 4.54 (d, 1H, *J* = 11.7 Hz, C*H*HPh), 3.74-3.66 (m, 2H, H-6a, H-3), 3.59-3.51 (m, 1H, H-5), 3.46 (dd, 1H, *J* = 12.9, 8.1 Hz, H-8a), 3.35-3.24 (m, 2H, H-6b, H-4), 3.15 (dd, 1H, *J* = 8.7, 7.5 Hz, H-2), 3.11 (dd, 1H, *J* = 12.9, 6.0 Hz, H-8b), 0.97 (s, 9H, *t*-Bu), 0.91 (s, 9H, *t*-Bu), 0.21 (s, 3H, CH_3), 0.12 (s, 3H, CH_3), 0.11 (s, 3H, CH_3), 0.06 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.05, 138.28, 137.33, 128.97, 128.81, 128.30, 128.27, 127.89, 127.49, 127.25, 125.71, 98.59, 79.10, 78.51, 77.79, 76.10, 75.18, 74.55, 62.09, 41.83, 26.41,



26

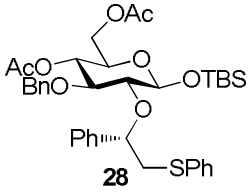
25.91, 18.11, 18.02, -2.80, -4.25, -4.27, -4.35; HR MALDI-TOF MS: m/z: calcd for $C_{39}H_{58}O_6SSi_2$ $[M+Na]^+$: 733.3390; found: 733.3376.

***t*-Butyldimethylsilyl 4,6-di-*O*-benzyl-3-*O*-*t*-butyldimethylsilyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (27).** Benzyl bromide (0.19 mL, 1.58 mmol) and sodium hydride (60% dispersion in mineral oil, 63 mg, 1.58 mmol) were added to a solution of **26** (0.75 g, 1.05 mmol) in DMF (10 mL) at 0°C. After stirring for 1 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with ethyl acetate (2 x 20 mL), and the combined organic phases were washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 30% - CH_2Cl_2 in PE) to afford **27** (0.72 g, 85%) as a colorless syrup; TLC (EtOAc:PE, 60:40 v/v): R_f = 0.37; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.13 (m, 20H, CH Ar), 5.50 (dd, 1H, *J* = 8.1, 6.0 Hz, H-7), 4.84 (d, 1H, *J* = 11.7 Hz, C*H*HPh), 4.72 (d, 1H, *J* = 7.5 Hz, H-1), 4.56 (d, 1H, *J* = 11.7 Hz, C*H*HPh), 4.48 (s, 2H, CH_2Ph), 3.69 (t, 1H, *J* = 8.4 Hz, H-3), 3.58-3.33 (m, 5H, H-5, H-6a, H-8a, H-6b, H-4), 3.23 (dd, 1H, *J* = 8.4, 7.5 Hz, H-2), 3.12 (dd, 1H, *J* = 12.9, 6.0 Hz, H-8b), 1.01 (s, 9H, *t*-Bu), 0.95 (s, 9H, *t*-Bu), 0.25 (s, 3H, CH_3), 0.16 (s, 6H, 2 × CH_3), 0.07 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.22, 138.59, 138.11, 137.44, 128.92, 128.76, 128.23, 128.18, 127.87, 127.79, 127.59, 127.45, 127.25, 127.11, 125.61, 98.85, 78.93, 78.84, 77.77, 76.32, 74.70, 74.32, 73.37, 69.06, 41.86, 26.41, 26.00, 18.10, 18.06, -2.77, -4.25, -4.47; HR MALDI-TOF MS: m/z: calcd for $C_{46}H_{64}O_6SSi_2$ $[M+Na]^+$: 823.3860; found: 823.3854.



27

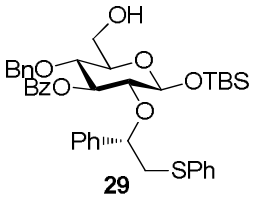
***t*-Butyldimethylsilyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (28).** A solution of **22** (0.81 g, 1.18 mmol) in 80% aq. acetic acid (20 mL) was stirred for 4 h at 60°C. The reaction mixture was concentrated *in vacuo* to remove acetic acid under reduced pressure, and then diluted with



28

dichloromethane (20 mL). After washing with saturated aqueous $NaHCO_3$ (3 x 20 mL), The reaction mixture was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 25% - EtOAc in PE) to afford *t*-butyldimethylsilyl 3-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*β*-D-glucopyranose (0.68 g, 97%). Acetic anhydride (4 mL) was added to a solution of *t*-butyldimethylsilyl 3-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*β*-D-glucopyranose (0.68 g, 1.14 mmol) in pyridine (20 mL) at room temperature. After stirring for 16 h, the reaction mixture was concentrated *in vacuo*, and then diluted with dichloromethane (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo* to afford **28** (0.76 g, 98%) as a colorless syrup; TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.13 (m, 15H, CH Ar), 5.26 (t, 1H, *J* = 7.0 Hz, H-7), 4.81 (t, 1H, *J* = 10.0 Hz, H-4), 4.76 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.70 (d, 1H, *J* = 8.0 Hz, H-1), 4.54 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.03-4.02 (m, 2H, H-6a, H-6b), 3.53-3.45 (m, 2H, H-5, H-3), 3.44 (dd, 1H, *J* = 13.0, 7.0 Hz, H-8a), 3.31 (dd, 1H, *J* = 10.0, 8.0 Hz, H-2), 3.12 (dd, 1H, *J* = 13.0, 7.0 Hz, H-8b), 2.02 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 0.95 (s, 9H, *t*-Bu), 0.17 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.69, 169.63, 139.74, 138.39, 137.27, 129.09, 128.78, 128.32, 128.28, 128.17, 127.66, 127.51, 125.78, 98.49, 81.50, 80.48, 79.23, 77.22, 75.35, 71.87, 70.34, 62.93, 41.47, 25.90, 20.75, 18.06, -4.24, -4.67; HR MALDI-TOF MS: m/z: calcd for $C_{37}H_{48}O_8SSi$ $[M+Na]^+$: 703.2737; found: 703.2738.

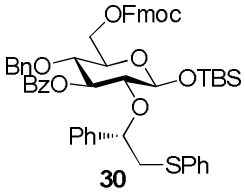
***t*-Butyldimethylsilyl 3-*O*-benzoyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (29).** Compound **29** was prepared following the same procedure for the synthesis of **26**. Silica gel column chromatography (0% → 20% - EtOAc in PE) afforded **29** (0.41 g, 91 %) as a colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 2H, *J* = 7.2 Hz, CH Ar), 7.38 (t, 1H, *J* = 7.5 Hz, CH Ar), 7.24 (t, 2H, *J* = 7.5 Hz, CH Ar), 7.04-6.74 (m, 15H, CH Ar), 5.29 (t, 1H, *J* = 9.6 Hz, H-3), 4.93 (t, 1H, *J* = 6.6 Hz, H-7), 4.68 (d, 1H, *J* = 6.9 Hz, H-1), 4.26 (s, 2H, CH_2 Bn), 3.66-3.44 (m,



29

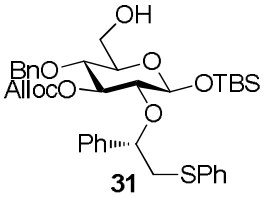
2H, H-6a,b), 3.41 (t, 1H, *J* = 9.3 Hz, H-4), 3.28-3.09 (m, 3H, H02, H-5, H-8a), 2.87 (dd, 1H, *J* = 7.5 Hz, *J* = 12.9 Hz, H-8b), 0.80 (s, 9H, *t*-Bu), 0.10 (s, 3H, CH_3), 0.10 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 139.4, 137.2, 136.8, 132.9, 129.9-125.5, 98.4, 80.4, 77.4, 75.6, 75.5, 74.7, 74.2, 61.6, 40.6, 25.7, 17.8, -4.2, -4.6; HR MALDI-TOF MS: m/z: calcd for $C_{40}H_{48}O_7SSi$ $[M+Na]^+$: 723.2787; found: 723.2781.

***t*-Butyldimethylsilyl 3-*O*-benzoyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (30).** To a cooled (0°C) solution of **29** (0.40 g, 0.57 mmol) in DCM (5 mL) and pyridine (0.5 mL), 9-fluorenylmethyl chloroformate (0.18 g, 0.68 mmol) was added. The reaction mixture was stirred at rt for 2 h and was diluted with EtOAc (50 mL) and water (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in PE) of the residue afforded **30** (0.46 g, 87 %) as a colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.6; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, 2H, *J* = 7.5 Hz, CH Ar), 7.78 (d, 2H, *J* = 7.5 Hz, CH Ar), 7.61 (t, 3H, CH Ar), 7.48-6.95 (m, 21H, CH Ar) 5.50 (t, 1H, *J* = 9.5 Hz, H-3), 5.14 (t, 1H, *J* = 6.5 Hz, H-7), 4.82 (d, 1H, *J* = 7.5 Hz, H-1), 4.47-4.34 (m, 5H, CH_2 Bn, CH_2 Fmoc, H-6a), 4.26 (t, 1H, *J* = 7.0 Hz, CH Fmoc), 4.20 (dd, 1H, *J* = 6.0 Hz, *J* = 11.5 Hz, H-6b), 3.66-3.63 (m, 1H, H-5), 3.55 (t, 1H, *J* = 10.0 Hz, H-4), 3.41-3.33 (m, 2H, H-8a, H-2), 3.06 (dd, 1H, *J* = 7.5 Hz, *J* = 13.0 Hz, H-8b), 0.96 (s, 9H, *t*-Bu), 0.18 (s, 3H, CH_3), 0.18 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 154.8, 143.3, 143.2, 141.2, 141.2, 139.6, 137.0, 136.9, 133.0, 130.0-125.1, 120.0, 98.6, 80.5, 77.4, 76.1, 75.6, 74.3, 72.5, 69.9, 66.4, 46.6, 40.7, 25.8, 17.9, -4.2, -4.7; HR MALDI-TOF MS: m/z: calcd for $C_{55}H_{58}O_9SSi$ $[M+Na]^+$: 945.3468; found: 945.3456.



30

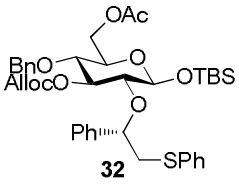
***t*-Butyldimethylsilyl 3-*O*-allyloxycarbonyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (31).** Compound **31** was prepared following the same procedure for the synthesis of **26**. Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **31** (1.42 g, 2.1 mmol, 86%) as a colorless oil. TLC



31

(EtOAc:PE, 30:70 v/v): R_f = 0.40; $[\alpha]^{D}_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +57.2 (*c* = 0.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.10-7.32 (m, 15H), 5.93 (m, 1H, CH_2CH=CH_2), 5.36 (d, *J* = 17.4 Hz, 1H, CH_2CH=CH_2), 5.26 (d, *J* = 10.2 Hz, 1H, CH_2CH=CH_2), 5.06 (t, $J_{7,8a/b}$ = 7.2 Hz, 1H, H-7), 4.93 (t, $J_{3,2}$ = 9.3 Hz, 1H, H-3), 4.74 (d, $J_{1,2}$ = 7.2 Hz, 1H, H-1), 4.55 (m, 4H, CH_2Ph, CH_2CH=CH_2), 3.77 (m, 1H, H-6a), 3.60 (m, 1H, H-6b), 3.43 (m, 3H, H-4, H-5, H-8b), 3.20 (dd, $J_{2,1}$ = 7.5 Hz, $J_{2,3}$ = 9.6 Hz, 1H, H-2), 3.14 (dd, $J_{8a,7}$ = 7.2 Hz, $J_{8a,8b}$ = 12.9 Hz, 1H, H-8a), 1.78 (bt, $J_{OH\text{-}6,6a/b}$ = 5.7 Hz, 1H, OH-6), 0.94 (s, 9H, 3 x CH_3), 0.15 (s, 3H, CH_3), 0.14 (s, 3H, CH_3); ^{13}C {^1H} NMR(APT) (75 MHz, $CDCl_3$): δ 154.4, 139.6, 137.5, 136.9, 131.4, 125.6-129.3, 119.1, 98.1, 81.0, 80.0, 77.8, 76.5, 75.7, 74.5, 68.5, 61.7, 40.9, 25.8, 17.9, -4.3, -4.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{37}H_{48}O_8SSi$, 703.2737; found, 703.2765.

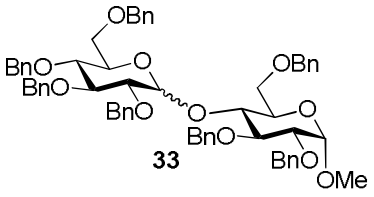
***t*-Butyldimethylsilyl 6-*O*-acetyl-3-*O*-allyloxycarbonyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (32).** **31** (0.40 g, 0.59 mmol) was dissolved in pyridine (3 mL) and Ac_2O (2 mL) was added. The reaction mixture was stirred at rt for 6 h and was concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in PE) of the residue afforded **32** (0.42 g, 98%) as a colorless oil.



32

TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.5; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.18 (m, 15H, CH Ar) 6.00-5.90 (m, 1H, CH Alloc), 5.43-5.26 (m, 2H, CH_2 Alloc), 5.11 (t, 1H, *J* = 6.9 Hz, H-7), 4.98 (t, 1H, *J* = 9.3 Hz, H-3), 4.74 (d, 1H, *J* = 7.2 Hz, H-1), 4.60-4.42 (m, 4H, CH_2 Bn, CH_2 Alloc), 4.27 (dd, 2H, *J* = 2.1 Hz, *J* = 11.7 Hz, H-6a), 4.07 (dd, 1H, *J* = 6.3 Hz, *J* = 12.0 Hz, H-6b), 3.56-3.34 (m, 3H, H-5, H-8a, H-4), 3.25 (dd, 1H, *J* = 7.2 Hz, *J* = 9.3 Hz, H-2), 3.14 (dd, 1H, *J* = 7.2 Hz, *J* = 12.9 Hz, H-8b), 1.99 (s, 3H, CH_3 Ac), 0.96 (s, 9H, *t*-Bu), 0.17 (s, 3H, CH_3), 0.16 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 154.2, 139.6, 137.1, 136.8, 131.3, 128.8-127.5, 125.5, 119.0, 98.0, 80.8, 80.0, 77.7, 76.1, 74.3, 72.3, 68.8, 40.8, 25.7, 20.5, 17.8, -4.4, -4.8; HR MALDI-TOF MS: m/z: calcd for $C_{39}H_{50}O_9SSi$ $[M+Na]^+$: 745.2843; found: 745.2819.

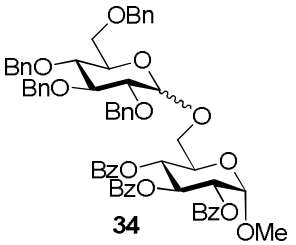
Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside



33

(33); Glycosyl donor **9** (50 mg, 0.07 mmol) and glycosyl acceptor **3** (40 mg, 0.9 mmol) were dissolved in CH_2Cl_2 (2 mL) and molecular sieves were added. The mixture was cooled (-15°C) and TMSOTf (1 µL, 0.01 mmol) was added. The mixture was stirred for 5 min before Et_3N (0.1 mL) was added and the mixture was concentrated *in vacuo*. Sephadex® LH20 size exlusion chromatography (CH_2Cl_2/MeOH, 1/1) of the residue afforded **33** (52 mg, 73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21-7.04 (m, 35H, CH Ar), 5.64 (d, 1H, *J* = 3.0 Hz, H-1'), 4.98 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.83-4.31 (m, 13H, CH*H*Ph, C*H*HPh, 5 x CH_2 Bn, H-1), 4.24 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.03-3.35 (m, 12H, H-2, H-3, H-4, H-5, H-6a/b, H-2', H-3', H-4', H-5', H-6a/b'), 3.32 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.7, 138.5, 138.4, 138.1, 137.9, 137.8, 128.4-126.7, 97.7, 96.6, 82.0, 80.2, 79.4, 77.6, 75.5, 75.1, 73.4, 73.3, 73.2, 73.1, 72.3, 70.9, 69.5, 69.0, 68.1, 55.1; HR MALDI-TOF MS: m/z: calcd for $C_{62}H_{66}O_{11}$ $[M+Na]^+$: 1009.4503; found: 1009.4530.

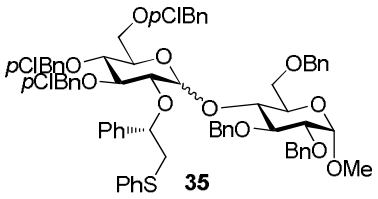
Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside



34

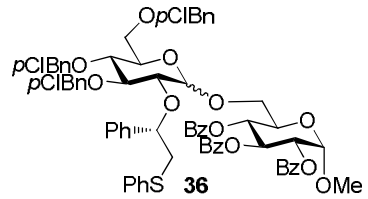
(34); Compound **34** was prepared following the same procedure as for the synthesis of **33** by using **4** as glycosyl acceptor. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.76 (m, 6H, CH Ar), 7.43-7.04 (m, 29H, CH Ar), 6.06 (t, 1H, *J* = 9.5 Hz, H-3), 5.46 (t, 1H, *J* =10.0 Hz, H-4), 5.20-5.12 (m, 3H, H-2, H-1, H-1'), 4.84 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.75-4.29 (m, 7H, CH*H*Ph, 3 x CH_2 Bn), 4.24 (m, 1H, H-5), 4.05-5.02 (m, 1H, H-2'), 3.88 (t, 1H, *J* = 9.0 Hz, H-5'), 3.79-3.71 (m, 2H, H-6a, H-3'), 3.56-3.45 (m, 3H, H-6b, H-6a/b'), 3.35 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 165.4, 165.2, 138.8, 138.5, 138.4, 138.3, 138.0, 137.7 133.3, 133.3, 133.0, 129.9-127.4, 97.2, 96.7, 81.7, 79.9, 77.5, 75.4, 74.9, 74.7, 73.3, 73.0, 72.2, 70.5, 70.0, 69.7, 68.9, 68.5, 68.2, 66.6, 55.5; HR MALDI-TOF MS: m/z: calcd for $C_{62}H_{60}O_{14}$ $[M+Na]^+$: 1051.3881; found: 1051.3892.

Methyl 3,4,6-tri-*O*-*p*-chlorobenzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (35); Compound **35**



was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-6.90 (), 5.83 (d, 1H, J = 3.0 Hz, H-1'), 5.20 (d, 1H, J = 12.0 Hz, C*H*HPh), 5.11 (t, 1H, *J* = 7.5 Hz, H-7'), 4.94 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.98-4.79 (m, 2H, CH_2 Bn), 4.73-4.36 (m, 9H, 4 x CH_2 Bn, H-1), 4.29-3.56 (m, 7H, H-2,H-3, H-4, H-5, H-3', H-4', H-5'), 3.47-3.3.1 (m, H, OMe, H-2', H-6a/b, H-6a/b', H-8a'), 3.21 (dd, 1H, *J* = 5.5 Hz, *J* = 13.5 Hz, H-8b'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 139.0, 137.9, 137.1, 136.8, 136.5, 133.4, 133.1, 132.9, 129.3-125.6, 98.4, 94.4, 84.2, 81.0, 78.8, 78.5, 77.0, 75.1, 73.8, 73.7, 73.6, 70.6, 70.5, 68.9, 68.7, 55.5, 41.2; HR MALDI-TOF MS: m/z: calcd for $C_{69}H_{69}Cl_3O_{11}S$ $[M+Na]^+$: 1233.3524; found: 1233.3510.

Methyl 3,4,6-tri-*O*-*p*-chlorobenzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (36); Compound **36**



was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, 2H, *J* = 7.5 Hz, CH Ar), 7.92 (d, 2H, *J* = 8.0 Hz, CH Ar), 7.87 (d, 2H, *J* = 8.0 Hz, CH Ar), 7.51-7.07 (m, 29 H, CH Ar), 6.94 (d, 2H, *J* = 8.5 Hz, CH Ar), 6.17 (t, 1H, *J* = 9.5 Hz, H-3), 5.65 (t, 1H, *J* = 9.5 Hz, H-4), 5.30 (dd, 1H, *J* = 10.5 Hz, *J* = 3.5 Hz, H-2), 5.20 (d, 1H, *J* = 3.5 Hz, H-1), 4.99 (d, 1H, *J* = 3.0 Hz, H-1'), 4.80 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.63-4.26 (m, 7H, 2 x CH_2 Bn, CH*H*Ph, H-5, H-7'), 3.92-3.74 (m, 4H, H-3', H-4', H-6a/b), 3.52-3.30 (m, 8H, OMe, H-2', H-5', H-6a/b'. H-8a), 3.17 (dd, 1H, *J* = 14.0 Hz, *J* = 5.0 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 165.2, 139.7, 137.4, 136.8, 136.2, 133.3, 133.2, 129.9-125.6, 96.8, 96.3, 80.8, 79.3, 77.9, 77.5, 74.5, 73.7, 72.2, 72.0, 70.6, 70.0, 69.7, 68.1, 55.8, 41.6; HR MALDI-TOF MS: m/z: calcd for $C_{69}H_{63}Cl_3O_{14}S$ $[M+Na]^+$: 1275.2902; found: 1275.2925.

Methyl 4,6-di-*O*-benzyl-3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (37*α*); Compound **37** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.03 (m, 35H, CH Ar), 5.75 (d, 1H, *J* = 3.5 Hz, H-1'), 5.14 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.97 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.72 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.71 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.64 (d, 1H, *J* = 3.5 Hz, H-1), 4.60 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.57 (t, 1H, *J* = 7.0 Hz, H-7'), 4.49-4.46 (m, 3H, C*H*HPh × 3), 4.34 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.27 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.20 (t, 1H, *J* = 9.5 Hz), 4.07 (t, 1H, *J* = 9.5 Hz), 3.85-3.81 (m, 2H), 3.67-3.61 (m, 3H), 3.50 (s, 3H, OMe), 3.41-3.31 (m, 6H), 3.38 (s, 3H, OCH_3), 3.30 (dd, 1H, *J* = 10.0, 3.5 Hz, H-2'), 3.01 (dd, 1H, *J* = 12.5, 7.0 Hz, H-8b'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.91, 139.13, 138.74, 138.17, 138.08, 137.97, 136.97, 128.74, 128.68, 128.43, 128.39, 128.29, 128.26, 128.20, 128.18, 128.15, 128.07, 128.04, 127.89, 127.77, 127.59, 127.47, 127.28, 127.20, 127.14, 126.73, 125.58, 97.81, 94.96, 83.10, 81.94, 80.26, 79.71, 77.22, 74.67, 74.16, 73.37, 73.21, 73.05, 71.44, 70.56, 69.67, 68.97, 68.13, 60.99, 55.22, 41.15; HR MALDI-TOF MS: m/z: calcd for $C_{63}H_{68}O_{11}S$ $[M+Na]^+$: 1055.4380; found: 1055.4387.

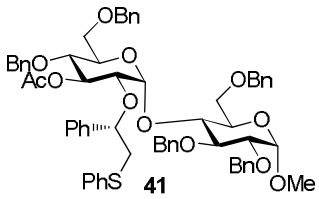
Methyl 4,6-di-*O*-benzyl-3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (37β); $[\alpha]^{20}_D$ = +22° (*c* = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.10 (m, 35H, CH Ar), 5.03 (t, 1H, *J* = 6.5 Hz, H-7'), 4.91 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.79 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.74 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.67 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.66 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.61 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.59 (d, 1H, *J* = 4.0 Hz, H-1), 4.48-4.44 (m, 3H, C*H*HPh × 3), 4.36 (d, 1H, *J* = 13.5 Hz, C*H*HPh), 4.33 (d, 1H, *J* = 8.0 Hz, H-1'), 4.07 (t, 1H, *J* = 9.5 Hz), 4.01 (dd, 1H, *J* = 11.0, 2.5 Hz), 3.84 (t, 1H, *J* = 9.5 Hz), 3.70-3.55 (m, 3H), 3.50 (s, 3H, OMe), 3.47-3.35 (m, 4H), 3.34 (s, 3H, OCH_3), 3.27 (t, 1H, *J* = 9.5 Hz), 3.19-3.05 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.07, 139.42, 138.67, 138.48, 138.46, 137.72, 137.22, 128.90, 128.54, 128.32, 128.21, 128.15, 128.04, 127.92, 127.83, 127.76, 127.72, 127.58, 127.52, 127.22, 127.09, 125.60, 101.76, 98.52, 86.29, 81.17, 80.74, 78.81, 78.15, 77.22, 75.54, 75.19, 74.88, 74.53, 73.63, 73.52, 73.34,

69.95, 68.84, 68.20, 61.27, 55.49, 40.77; HR MALDI-TOF MS: m/z: calcd for $C_{63}H_{68}O_{11}S$ $[M+Na]^+$: 1055.4380; found: 1055.4387.

Methyl 4,6-di-*O*-benzyl-3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (38*α*); Compound **38** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (m, 6H, CH Ar), 7.52-7.07 (m, 29H, CH Ar), 6.17 (t, 1H, *J* = 10.0 Hz, H-3), 5.57 (t, 1H, *J* = 10.0 Hz, H-4), 5.29 (dd, 1H, *J* = 10.0, 3.0 Hz, H-2), 5.20 (d, 1H, *J* = 3.0 Hz, H-1), 4.96 (d, 1H, *J* = 3.5 Hz, H-1'), 4.74 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.60 (dd, 1H, *J* = 7.5, 5.0 Hz, H-7'), 4.54 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.40-4.35 (m, 3H, H-5, C*H*HPh × 2), 3.90 (dd, 1H, *J* = 11.0, 7.0 Hz, H-6a), 3.82-3.80 (m, 1H, H-5), 3.76 (dd, 1H, *J* = 11.0, 2.0 Hz, H-6b), 3.62-3.32 (m, 5H, H-6a', H-6b', H-4', H-3', H-8a'), 3.47 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.21 (dd, 1H, *J* = 10.0, 3.5 Hz, H-2'), 3.15 (dd, 1H, *J* = 13.5, 5.0 Hz, H-8b'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5, 133.4, 130.2, 129.9, 128.6, 128.5, 127.9, 127.5, 127.2, 126.0, 97.0, 96.8, 83.3, 80.3, 78.5, 78.1, 75.1, 74.1, 72.7, 71.1, 70.5, 70.3, 69.3, 68.7, 67.5, 61.5, 56.5, 42.7; HR MALDI-TOF MS: m/z: calcd for $C_{63}H_{62}O_{14}S$ $[M+Na]^+$: 1097.3758; found: 1097.3753. **Methyl 4,6-di-*O*-benzyl-3-*O*-methyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (38β);** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.85 (m, 6H, CH Ar), 7.51-7.12 (m, 29H, CH Ar), 6.17 (t, 1H, *J* = 10.0 Hz, H-3), 5.48 (t, 1H, *J* = 10.0 Hz, H-4), 5.27-5.23 (m, 2H, H-2, H-7'), 5.19 (d, 1H, *J* = 3.0 Hz, H-1), 4.72 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.48 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.40-4.35 (m, 4H, H-5, H-1', C*H*HPh × 2), 4.03 (d, 1H, *J* = 10.0 Hz, H-6a), 3.84 (dd, 1H, *J* = 10.0, 8.0 Hz, H-6b), 3.66-3.45 (m, 6H, H-5', H-6a', H-6b', H-4', H-3', H-8a'), 3.50 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.26-3.20 (m, 2H, H-2', H-8b'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5, 133.3, 130.2, 130.1, 130.0, 129.9, 128.7, 128.5, 128.3, 128.0, 126.9, 104.1, 97.1, 86.4, 80.8, 78.3, 77.6, 75.0, 74.9, 73.7, 72.4, 70.8, 70.2,

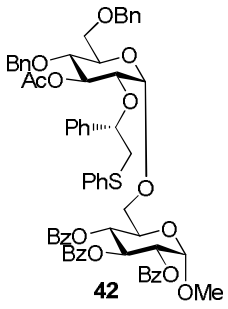
69.2, 68.8, 65.9, 61.5, 56.1, 41.3; HR MALDI-TOF MS: m/z: calcd for $C_{63}H_{62}O_{14}S$ $[M+Na]^+$: 1097.3758; found: 1097.3754.

Methyl 3-*O*-acetyl-4,6-di-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-



(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (41); Compound **41** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-6.95 (m, 35H, CH Ar), 5.75 (d, 1H, *J* = 3.5 Hz, H-1'), 5.40 (t, 1H, *J* = 9.5 Hz, H-3'), 5.11 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.96 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.73 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.62-4.58 (m, 2H, H-1, C*H*HPh), 4.50-4.26 (m, 7H, H-7', C*H*HPh × 6), 4.16 (t, 1H, *J* = 9.5 Hz, H-3), 4.07 (t, 1H, *J* = 9.5 Hz, H-4), 3.90 (dd, 1H, *J* = 11.0, 3.0 Hz, H-6a), 3.79-3.77 (m, 1H, H-5'), 3.72-3.70 (m, 1H, H-5), 3.62-3.59 (m, 2H, H-2, H-6b), 3.50 (t, 1H, *J* = 9.5 Hz, H-4'), 3.36 (s, 3H, OCH_3), 3.34-3.29 (m, 3H, H-6a', H-6b', H-8a'), 3.29 (dd, 1H, *J* = 9.5, 3.5 Hz, H-2'), 2.92 (dd, 1H, *J* = 13.0, 6.5 Hz, H-8b'), 1.76 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.83, 140.00, 139.32, 138.23, 138.16, 138.14, 137.86, 136.74, 128.94, 128.78, 128.58, 128.52, 128.43, 128.32, 128.29, 128.25, 128.16, 128.13, 128.11, 128.04, 128.00, 127.88, 127.68, 127.56, 127.35, 127.23, 127.15, 127.05, 126.93, 125.53, 97.85, 94.85, 81.71, 80.77, 80.30, 77.21, 76.02, 74.37, 74.21, 73.44, 73.28, 73.03, 72.06, 70.31, 69.58, 68.87, 67.95, 55.23, 40.63, 21.04; HR MALDI-TOF MS: m/z: calcd for $C_{64}H_{68}O_{12}S$ $[M+Na]^+$: 1083.4329; found: 1083.4340.

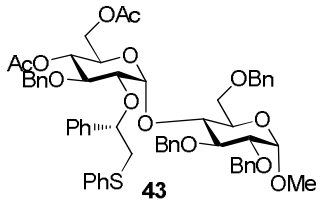
Methyl 3-*O*-acetyl-4,6-di-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-



(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (42); Compound **42** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.85 (m, 6H, CH Ar), 7.52-7.05 (m, 29H, CH Ar), 6.16 (t, 1H, *J* = 10.0 Hz, H-3), 5.48 (t, 1H, *J* = 9.5 Hz, H-3'), 5.41 (t, 1H, *J* = 10.0 Hz, H-4), 5.24 (dd, 1H, *J* = 10.0, 3.5 Hz, H-2), 5.16 (d, 1H, *J* = 3.5 Hz, H-1), 5.03 (d, 1H, *J* = 3.0 Hz, H-1'), 4.62 (d,

1H, *J* = 12.0 Hz, C*H*HPh), 4.44 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.40-4.32 (m, 4H, H-5, H-7', C*H*HPh × 2), 4.04-4.01 (m, 1H, H-5'), 3.93 (dd, 1H, *J* = 10.0, 9.0 Hz, H-6a), 3.75 (d, 1H, *J* = 10.0 Hz, H-6b), 3.70 (dd, 1H, *J* = 11.0, 2.5 Hz, H-6a'), 3.61 (dd, 1H, *J* = 11.0, 2.0 Hz, H-6b'), 3.56 (t, 1H, *J* = 9.5 Hz, H-4'), 3.49 (s, 3H, OMe), 3.38 (dd, 1H, *J* = 9.5, 3.0 Hz, H-2'), 3.25 (dd, 1H, *J* = 14.0, 8.5 Hz, H-8a'), 3.03 (dd, 1H, *J* = 14.0, 4.0 Hz, H-8b'), 1.64 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.83, 165.85, 165.74, 165.59, 140.75, 138.12, 137.78, 136.52, 133.41, 133.29.,133.01, 129.95, 129.93, 129.66, 129.31, 129.14, 128.92, 128.86, 128.61, 128.48, 128.44, 128.40, 128.27, 128.13, 127.78, 127.56, 126.76, 125.82, 96.54, 96.40, 81.63, 76.11, 74.02, 73.55, 72.90, 72.29, 70.59, 69.97, 69.87, 68.70, 68.03, 67.03, 55.67, 41.41, 20.96; HR MALDI-TOF MS: m/z: calcd for $C_{64}H_{62}O_{15}S$ $[M+Na]^+$: 1125.3707; found: 1125.3714.

Methyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (43); Compound **43** was prepared according to the general procedure. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-6.94 (m, 30H, CH Ar), 5.73 (d, 1H, *J* = 3.5 Hz, H-1'), 5.15 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.97 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.82 (t, 1H, *J* = 10.0 Hz, H-4'), 4.74 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.69 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.67(d, 1H, *J* = 3.5 Hz, H-1), 4.61 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.58 (t, 1H, *J* = 7.0 Hz, H-7'), 4.55 (s, 2H, C*H*HPh), 4.51 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.24 (t, 1H, *J* = 9.5 Hz, H-3), 4.04 (t, 1H, *J* = 9.5 Hz, H-4), 4.01 (dd, 1H, *J* = 12.0, 4.0 Hz, H-6a'), 3.91-3.84 (m, 3H, H-5', H-5, H-6a), 3.83 (dd, 1H, *J* = 12.0, 2.5 Hz, H-6b), 3.76 (t, 1H, *J* = 9.5 Hz, H-3'), 3.70 (d, 1H, *J* = 12.0 Hz, H-6b'), 3.63 (dd, 1H, *J* = 9.5, 3.5 Hz, H-2), 3.42 (s, 3H, OCH_3), 3.38 (dd, 1H, *J* = 10.0, 3.5 Hz, H-2'), 3.33 (dd, 1H, *J* = 13.0, 7.0 Hz, H-8a'), 3.02 (dd, 1H, *J* = 13.0, 7.0 Hz, H-8a'), 1.96 (s, 3H, CH_3), 1.86 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.70, 169.45, 139.25, 139.01, 138.58, 137.98, 137.91, 136.92, 128.82, 128.77, 128.46, 128.42, 128.38, 128.23, 128.14, 127.95, 127.65, 127.53, 127.39, 127.22, 127.16, 126.68, 125.71, 97.84, 94.87, 81.77, 80.09, 79.61, 77.97, 77.21, 74.85, 74.12,



43

73.45, 73.19, 72.22, 69.73, 69.64, 69.02, 68.16, 62.24, 55.33, 41.13, 20.77 20.77; HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{13}S$ $[M+Na]^+$: 1035.3965; found: 1035.3979.

Methyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (44*α*); Compound **44** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.87 (m, 6H, CH Ar), 7.54-7.09 (m, 24H, CH Ar), 6.20 (t, 1H, *J* = 10.0 Hz, H-3), 5.66 (t, 1H, *J* = 10.0 Hz, H-4), 5.33 (dd, 1H, *J* = 10.0, 4.0 Hz, H-2), 5.25 (d, 1H, *J* = 4.0 Hz, H-1), 5.01 (d, 1H, *J* = 3.0 Hz, H-1'), 4.83 (t, 1H, *J* = 10.0 Hz, H-4'), 4.74 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.65 (dd, 1H, *J* = 8.0, 5.0 Hz, H-7'), 4.56 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.40-4.37 (m, 1H, H-5), 4.04 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a'), 3.96-3.81 (m, 4H, H-3', H-4', H-5', H-6a), 3.79 (dd, 1H, *J* = 12.0, 1.0 Hz, H-6b'), 3.52-3.48 (m, 2H, H-2', H-6b), 3.51 (s, 3H, OCH_3), 3.39 (dd, 1H, *J* = 14.0, 8.0 Hz, H-8a'), 3.20 (dd, 1H, *J* = 14.0, 5.0 Hz, H-8b'), 2.00 (s, 3H, CH_3), 1.86 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.73, 169.61, 165.82, 165.33, 139.60, 138.64, 136.83, 133.52, 133.37, 133.10, 129.95, 129.87, 129.69, 129.26, 129.08, 128.95, 128.90, 128.58, 128.49, 128.42, 128.28, 128.19, 127.80, 127.39, 126.99, 125.88, 96.91, 96.28, 79.68, 77.93, 77.21, 75.03, 72.21, 70.60, 69.52, 68.74, 67.83, 66.70, 62.16, 55.60, 41.75, 20.75, 20.72; HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{58}O_{16}S$ $[M+Na]^+$: 1077.3343; found: 1077.3396. **Methyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (44β);** $[\alpha]^{20}_D$ = +53.4° (*c* = 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.87 (m, 6H, aromatic), 7.54-7.09 (m, 24H, aromatic), 6.18 (t, 1H, *J* = 10.0 Hz, H-3), 5.52 (t, 1H, *J* = 10.0 Hz, H-4), 5.28 (dd, 1H, *J* = 10.0, 4.0 Hz, H-2), 5.26 (d, 1H, *J* = 4.0 Hz, H-1), 5.04 (d, 1H, *J* = 7.2 Hz, H-1'), 4.89 (t, 1H, *J* = 10.0 Hz, H-4'), 4.68 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.56 (dd, 1H, *J* = 8.0, 5.0 Hz, H-7'), 4.56 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.29-4.26 (m, 1H, H-5), 4.00 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a'), 3.96-3.81 (m, 4H, H-3', H-4', H-5', H-6a), 3.82 (dd, 1H, *J* = 12.0, 1.0 Hz, H-6b'), 3.52 (s, 3H, OCH_3), 3.51-3.46 (m, 2H, H-2', H-6b), 3.46 (dd, 1H, *J* = 14.0, 8.0 Hz,

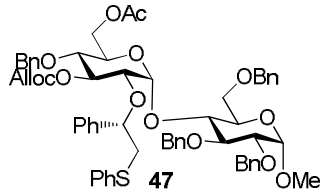
H-8a'), 3.13 (dd, 1H, *J* = 14.0, 5.0 Hz, H-8b'), 1.98 (s, 3H, $COCH_3$), 1.87 (s, 3H, $COCH_3$); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{58}O_{16}S$ $[M+Na]^+$: 1077.3343; found: 1077.3396.

Methyl 3-*O*-benzoyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (45); Compound **45** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 2H, *J* = 8.0 Hz, CH Ar), 7.78 (d, 2H, *J* = 7.5 Hz, CH Ar), 7.64-7.06 (m, 35H, CH Ar), 6.97 (t, 2H, *J* = 7.5 Hz, CH Ar), 6.81 (d, 2H, *J* = 8.0 Hz, CH Ar), 5.80 (dd, 1H, *J* = 9.0 Hz, H-3'), 5.76 (dd, 1H, *J* = 3.0 Hz, H-1'), 5.12 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 5.01 (d, 1H, *J* = 12.5 Hz, CH*H*Ph), 4.74-4.47 (m,8H, CH_2 Bn, CH_2 Bn, H-1, CH Fmoc, C*H*HPh), 4.40-4.33 (m, 4H,CH*H*Ph, CH_2 Fmoc, H-7'), 4.27-3.97 (m, 7H, H-3, H-3', H-4, H-5', H-6a/b', H-6b,), 3.72-3.56 (m, 4H, H-2, H-4', H-5, H-6a), 3.40-3.38 (m, 4H, OMe, H-2'), 3.32 (dd, 1H, *J* = 7.0 , *J* = 13.5 Hz, H-8a), 2.76 (dd, 1H, *J* = 7.0 , *J* = 13.5 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 155.0, 143.6, 143.5, 141.5, 139.7, 139.5,138.3, 138.2, 137.5, 137.0, 133.2, 130.3-125.4, 120.2, 98.1, 94.7, 82.0, 80.4, 80.3, 75.9, 75.3, 74.6, 73.6, 73.5, 73.4, 72.7, 70.1, 69.8, 69.0, 68.9, 66.4, 55.5, 46.9, 40.3; HR MALDI-TOF MS: m/z: calcd for $C_{77}H_{74}O_{14}S$ $[M+Na]^+$: 1277.4697; found: 1277.4686.

Methyl 3-*O*-benzoyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (46); Compound **46** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (t, 3H, *J* = 8.5 Hz, CH Ar), 7.87 (dd, 3H, *J* = 7.0 Hz, *J* = 5.0 Hz, CH Ar), 7.76 (d, 2H, *J* = 7.5 Hz, CH Ar), 7.65-6.94 (m, 35H, CH Ar),6.20 (t, 1H, *J* = 10.0 Hz, H-3), 5.87 (t, 1H, *J* = 9.5 Hz, H-3'), 5.47 (t, 1H, *J* = 10.0 Hz, H-4), 5.27-5.23 (m, 2H, H-1, H-2), 5.08 (d, 1H, *J* = 3.0 Hz, H-1'), 4.50-4.23 (m, 10H, H-5, H-5', H-6a/b, H-7', CH Fmoc, CH_2 Fmoc, CH_2 Bn), 3.97 (t, 1H, *J* = 8.5 Hz, H-6a'), 3.82 (t, 1H, *J* = 10.0

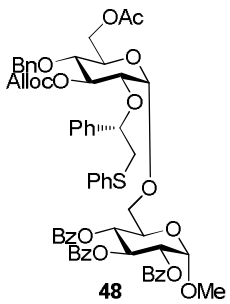
Hz, H-6b), 3.63 (t, 1H, *J* = 9.5 Hz, H-4'), 3.55 (s, 3H, OMe), 3.52 (dd, 1H, *J* = 3.0 Hz, *J* = 10.0 Hz, H-2'), 3.26 (dd, 1H, *J* = 8.5 Hz, *J* = 14.0 Hz, H-8a), 2.94 (dd, 1H, *J* = 4.5 Hz, *J* = 14.0 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 165.7, 165.5, 165.2, 154.9, 143.,4 143.4, 141.2, 139.9, 137.2, 136.5, 133.3, 133.2, 132.9, 132.8, 130.0-125.1, 119.9, 96.6, 95.9, 80.9, 76.3, 75.6, 74.1, 73.2, 72.2, 70.5, 69.9, 69.8, 68.6, 68.4, 67.1, 66.1, 55.7, 46.6, 41.1; HR MALDI-TOF MS: m/z: calcd for $C_{77}H_{68}O_{17}S$ $[M+Na]^+$: 1319.4075; found: 1319.4058.

Methyl 6-*O*-acetyl-3-*O*-allyloxycarbonyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (47);



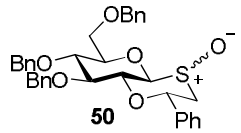
Compound **47** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-6.92 (m, 35H, CH Ar), 5.87-5.82 (m, 1H, CH Alloc), 5.58 (d, 1H, J = 3.0 Hz, H-1'), 5.32-5.18 (m, 3H, CH_2 Alloc, H-3'), 5.00 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.91 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.68-4.40 (m, 10H, 3 x CH_2 Bn, CH_2 Alloc, H-1, H-7'), 4.07 (t, 1H, *J* = 9.5 Hz, H-3), 3.98-3.79 (m, 5H, H-4, H-5', H-6a/b', H-6a), 3.63-3.50 (m, 3H, H-5, H-2, H-6b), 3.30 (m, 4H, OMe, H-4'), 3.25-3.19 (m, 2H, H-2', H-8a'), 2.79 (dd, 1H, *J* = 6.5 Hz, *J* = 13.5 Hz, H-8b), 1.87 (s, 3H Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 154.3, 139.6, 139.3, 138.0, 137.9, 137.5, 136.7, 131.5, 128.8-125.5, 119.1, 97.8, 94.8, 81.5, 81.4, 80.5, 80.0, 78.0, 75.8, 85.6, 74.5, 74.3, 73.2, 73.2, 72.9, 69.6, 68.7, 68.9, 68.5, 62.6, 55.2, 40.6, 20.8; HR MALDI-TOF MS: m/z: calcd for $C_{61}H_{66}O_{14}S$ $[M+Na]^+$: 1077.4071; found: 1077.4042.

Methyl 6-*O*-acetyl-3-*O*-allyloxycarbonyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (48);



Compound **48** was prepared according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.83 (m, 5H, CH Ar), 7.49-7.04 (m, 25H, CH Ar), 6.15 (t, 1H, *J* = 9.5 Hz, H-3), 5.87-5.81 (m, 1H, CH Alloc), 5.43 (t, 1H, *J* = 10.0 Hz, H-4), 5.33-

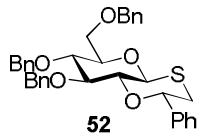
5.20 (m, 4H, H-2, H-3', CH_2 Alloc), 5.18 (d, 1H, *J* = 4.0 Hz, H-1), 4.99 (d, 1H, *J* = 3.0 Hz, H-1'), 4.56-4.39 (m, 5H, CH_2 Bn, CH_2 Alloc, H-7'), 4.34 (t, 1H, *J* = 9.0 Hz, H-5), 4.22-4.07 (m, 3H, H-5', H-6a/b'), 3.89 (dd, 1H, *J* = 8.0 Hz, *J* = 10.5 Hz, H-6a), 3.72 (d, 1H, *J* = 10.5 Hz, H-6b), 3.48 (s, 3H, OMe), 3.42-3.37 (m, 2H, H-2', H-4'), 3.27 (dd, 1H, *J* = 8.5 Hz, *J* = 14.0 Hz, H-8a'), 3.02 (dd, 1H, *J* = 4.5 Hz, *J* = 14.0 Hz, H-8a'), 1.99 (s, 3H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 165.7, 165.7, 165.4, 154.1, 140.2, 137.5, 136.5, 133.4, 133.2, 133.0, 131.5, 129.9-125.8, 118.9, 96.6, 96.1, 81.3, 77.9, 76.5, 75.9, 74.1, 72.2, 70.5, 69.7, 68.6, 68.4, 68.4, 67.0, 62.7, 55.6, 41.6, 20.8; HR MALDI-TOF MS: m/z: calcd for $C_{61}H_{60}O_{17}S$ $[M+Na]^+$: 1119.3449; found: 1119.3441.

2-(*S*)-Phenyl-(3,4,6-tri-*O*-benzyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (*R*,*S*)-S-oxide (50). 

50

m-CPBA (0.31 g, 1.4 mmol) was added to a cooled (-78°C) solution of **S17** (0.62 g, 1.1 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at -78°C for 30 min, diluted with CH_2Cl_2 (30 mL) and poured into sat. aq. $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 30% - EtOAc in PE) of the residue afforded **34** (0.48 g, 74 %). TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.04 (m, 20H, CH Ar), 5.33 (d, 1H, *J* = 11.0 Hz, H-7), 4.48-4.41 (m, 8H, 3 x CH_2 Bn, H-7, H-2), 4.16 (d, 1H, *J* = 10.0 Hz, H-1), 3.95 (d, 1H, *J* = 9.5 Hz, H-1), 3.77-3.45 (m, 12H, H-2, 2 x H-3, 2 x H-4, 2 x H-5, 2 x H-6a/b, H-8a), 3.08-2.96 (m, 2H, H-8b, H-8a), 2.66 (dd, 1H, *J* = 14.0 Hz, *J* = 11.5 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.0, 137.9, 137.8, 137.7, 137.6, 128.6-127.4, 125.6, 125.5, 94.9, 85.1, 83.6, 83.5, 80.5, 80.1, 78.3, 76.6, 76.2, 75.3, 75.1, 75.0, 73.5, 73.4, 72.1, 68.8, 68.3, 67.8, 56.9, 52.2; HR MALDI-TOF MS: m/z: calcd for $C_{35}H_{36}O_6S$ $[M+Na]^+$: 607.2130; found: 607.2111.

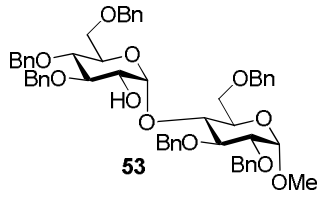
2-(*S*)-Phenyl-(3,4,6-tri-*O*-benzyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (52).



52

Benzylbromide (1.8 mL, 15.26 mmol) and 60% NaH in mineral oil (0.61 g, 15.26 mmol) were added to a cooled (0°C) solution of 2-(*S*)-Phenyl-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane[24] (1.3 g, 4.36 mmol) in DMF (20 mL). The resulting mixture was stirred for 3 h, diluted with MeOH (1 mL) and EtOAc (50 mL) and then poured into sat. aq. $NaHCO_3$ (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 10% - EtOAc in PE) of the residue afforded **52** (2.08 g, 84 %). TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.76; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.16 (m, 15H, CH Ar) 4.96-4.87(m, 2H, CH_2 Bn), 4.80-4.74 (m, 2H, C*H*HPh, H-7), 4.65-4.53 (m, 3H, CH*H*Ph, CH_2 Bn), 4.45 (d, 1H, *J* = 8.1 Hz, H-1), 3.83-3.7- (m, 5H, H-2. H-3. H-4, H-6a/b), 3.65-3.61 (m, 1H, H-5), 3.10 (dd, 1H, *J* = 10.8 Hz, *J* = 14.1 Hz, H-8a), 2.82 (dd, 1H, *J* = 1.8 Hz, *J* = 14.1 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 138.4, 138.0, 138.0, 128.4-127.5, 125.6, 84.7, 83.5, 80.3, 79.7, 77.4, 75.5, 75.3, 75.2, 73.4, 68.7, 35.3; HR MALDI-TOF MS: m/z: calcd for $C_{35}H_{36}O_5S$ $[M+Na]^+$: 591.2181; found: 591.2169.

Methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (53);

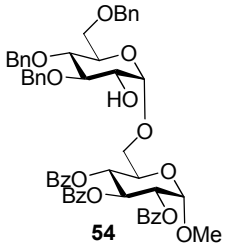


53

To a solution of glycosyl donor **49** (50 mg, 0.08 mmol) in DCE (1 mL), 1,3,5-trimethoxybenzene (35 mg, 0.2 mmol), DTBMP (50 mg, 0.25 mmol) and activated molecular sieves were added. After stirring the mixture at rt for 10 min, it was cooled (-30°C) and Tf_2O (15 μL, 0.09 mmol) was added. The mixture was allowed to warm to -10°C over a period of 10 min. A solution of **3** (67 mg, 0.12 mmol) in DCE (0.5 mL) was added and the mixture was heated (50°C) for 16 h. EtOAc (10 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1 mL) and $BF_3{\cdot}Et_2O$ (5 μL) and MeOH (10 μL) were added. The mixture was stirred for 10 min at rt, Et_3N (0.1 mL) was added and the mixture was concentrated *in vacuo*. Sephadex® LH20 size exlusion chromatography (CH_2Cl_2/MeOH, 1/1) of the residue afforded **53** (30 mg, 42%); ^{1}H NMR (600

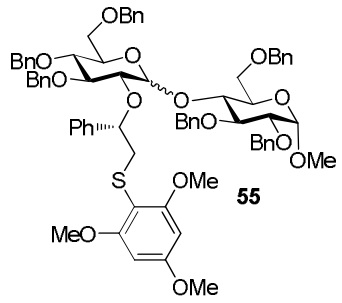
MHz, $CDCl_3$) δ 5.13-5.11 (m, 2H, H-1', C*H*HPh), 4.78 (d, 1H, *J* = 10.8 Hz, CH*H*Ph), 4.74 (d, 1H, *J* = 11.4 Hz, C*H*HPh), 4.65-4.37 (m, 9H, 4 x CH_2 Bn, CH*H*Ph), 3.92 (t, 1H, *J* = 9.0 Hz, H-3), 3.88 (dd, 1H, *J* = 4.2 Hz, *J* = 11.4 Hz, H-6a), 3.83-3.80 (m, 2H, H-4, H-5'), 3.65-3.55 (6H, H-2, H-2', H-4', H-5, H-6a', H-6b), 3.50-3.47 (m, 2H, H-3', H-6b'), 3.32 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.2, 138.0, 137.9, 137.8, 137.6, 128.5-127.4, 101.2, 97.7, 83.7, 80.6, 80.3, 77.6, 75.3, 75.1, 75.0, 74.0, 73.4, 73.3, 73.1, 71.6, 70.2, 68.8, 68.5, 55.3; HR MALDI-TOF MS: m/z: calcd for $C_{55}H_{60}O_{11}$ $[M+Na]^+$: 919.4033; found: 919.4043.

Methyl 3,4,6-tri-*O*-benzyl-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (54); Compound **54** was prepared following the same procedure as for the synthesis of **53** by using **4** as glycosyl acceptor. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, 1H, J = 7.5 Hz, CH Ar), 7.86 (d, 1H, J = 7.5 Hz, CH Ar), 7.79 (d, 1H, J = 7.5 Hz, CH Ar), 7.45-7.07 (m, 24H, CH Ar), 6.06 (t, 1H, *J* = 10.0 Hz, H-3), 5.56 (t, 1H, *J* = 10.0 Hz, H-4), 5.18 (dd, 1H, *J* = 10.0 Hz, *J* = 1.5 Hz, H-2), 5.13 (d, 1H, *J* = 3.5 Hz, H-1), 4.94 (s, 1H, H-1'), 4.88 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.75-4.72 (m, 2H, CH*H*Ph, C*H*HPh), 4.46 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.39 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.32 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.19-4.17 (m, 1H, H-5), 3.82 (dd, 1H, *J* = 11.5 Hz, *J* = 5.0 Hz, H-6a), 3.70-3.64 (m, 4H, H-3'. H-4', H-5', H-6b), 3.58-3.52 (m, 2H, H-2', H-6a'), 3.45 (d, 1H, *J* = 10.5 Hz, H-6b), 3.36 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 165.3, 138.7, 138.7, 137.9, 133.4, 133.3, 133.0, 129.9-127.5, 98.5, 97.0, 83.0, 77.2, 76.5, 75.2, 74.8, 73.4, 73.1, 72.1, 70.6, 70.5, 69.2, 68.5, 68.3, 65.5, 55.6; HR MALDI-TOF MS: m/z: calcd for $C_{55}H_{54}O_{14}$ $[M+Na]^+$: 961.3411; found: 961.3401.



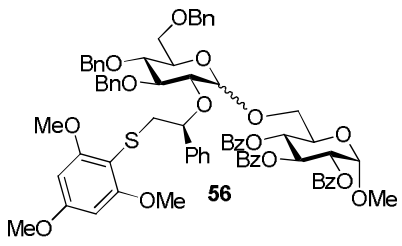
54

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-[2,3,5-trimethoxyphenylsulfanyl]-ethyl}-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (55);



55

To a solution of glycosyl donor **50** (50 mg, 0.09 mmol) in CH_2Cl_2 (1 mL), 1,3,5-trimethoxybenzene (35 mg, 0.2 mmol), DTBMP (50 mg, 0.25 mmol) and activated molecular sieves were added. After stirring the mixture at rt for 10 min, it was cooled (-30°C) and Tf_2O (15 μL, 0.09 mmol) was added. The mixture was allowed to warm to -10°C over a period of 10 min. The mixture was cooled (-78°C) and a solution of **3** (67 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added and the mixture allowed to warm to rt and was stirred for 16 h. EtOAc (10 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Sephadex® LH20 size exlusion chromatography (CH_2Cl_2/MeOH, 1/1) of the residue afforded **55** (70 mg, 68%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39-7.04 (m, 30H, CH Ar), 6.01 (s, 2H, CH Ar), 5.82 (d, 1H, *J* = 3.0 Hz, H-1'), 5.10 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.97 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.73-4.68 (m, 2H, CH_2 Bn), 4.65-4.57 (m, 3H, CH_2 Bn, H-1), 4.51-4.44 (m, 4H, CH_2 Bn, C*H*HPh, H-7'), 4.38-4.26 (m, 3H, CH_2 Bn, CH*H*Ph), 4.15 (t, 1H, *J* = 9.0 Hz, H-3), 4.07 (t, 1H, *J* = 9.0 Hz, H-4), 3.89-3.84 (m, 1H, H-5), 3.82-3.67 (m, 14H, 3 x OMe, H-3', H-4', H-5', H-6a/b), 3.63 (dd, 1H, *J* = 9.0 Hz, *J* = 3.6 Hz, H-2), 3.50-3.35 (m, 5H, H-2', H-6a/b', OMe), 3.19 (dd, 1H, *J* = 6.0 Hz, *J* = 13.2 Hz, H-8a'), 2.83 (dd, 1H, *J* = 13.2 Hz, *J* = 7.8 Hz, H-8b'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.4, 161.3, 140.6, 139.0, 138.6, 138.2, 138.1, 138.0, 128.4, 126.9, 97.7, 95.6, 90.8, 81.7, 81.4, 80.7, 80.3, 77.6, 75.2, 75.0, 73.4, 73.2, 73.1, 71.4, 70.8, 69.5, 69.9, 68.3, 67.0, 55.9, 55.7, 55.1, 41.1; HR MALDI-TOF MS: m/z: calcd for $C_{72}H_{78}O_{14}S$ $[M+Na]^+$: 1221.5010; found: 1221.5034.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-[2,3,5-trimethoxyphenylsulfanyl]-ethyl}-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (56); 

56

Compound **56** was prepared following the same procedure as for the synthesis of **55** by using **4** as glycosyl acceptor. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01-7.85 (m, 6H, CH Ar), 7.51-7.07 (m, 29H, CH Ar), 6.17 (t, 1H, *J* = 9.6 Hz, H-3), 6.01 (s, 2H, CH Ar), 5.51 (t, 1H, *J* = 9.6 Hz, H-4), 5.29 (dd, 1H, *J* = 10.2 Hz, *J* = 4.2 Hz, H-2), 5.21-5.20 (m, 2H, H-1, H-1'), 4.74 (m, 2H, C*H*HPh, C*H*HPh), 4.64 (d, 1H, *J* = 11.4 Hz, CH*H*Ph), 4.56 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.50-4.39 (m, 4H, H-5, H-7', CH*H*Ph, CH*H*Ph), 3.96-3.88 (m, 4H, H-3', H-5', H-6a/b), 3.79 (s, 3H, OMe), 3.72 (s, 6H, 2 x OMe), 3.68 (dd, 1H, *J* = 3.0 Hz, *J* = 10.2 Hz, H-6a'), 3.59-3.47 (m, 6H, H-2', H-4', H-6b', OMe), 3.15 (dd, 1H, *J* = 13.8 Hz, *J* = 7.2 Hz, H-8a'), 2.92 (dd, 1H, *J* = 13.2 Hz, *J* = 5.4 Hz, H-8b'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 165.7, 165.3, 161.4, 161.4, 140.9, 138.9, 138.5, 137.9, 133.2, 133.0, 132.9, 129.8-126.9, 102.2, 97.2, 96.5, 90.8, 81.7, 81.0, 78.4, 77.6, 75.0, 74.6, 73.3, 72.2, 70.6, 70.2, 69.8, 68.7, 68.3, 67.0, 55.9, 55.8, 55.4, 55.2, 42.5; HR MALDI-TOF MS: m/z: calcd for $C_{72}H_{72}O_{17}S$ $[M+Na]^+$: 1263.4388; found: 1263.4360.

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CHAPTER 3

CHIRAL-AUXILIARY MEDIATED 1,2-*CIS*-GLYCOSYLATIONS FOR THE SOLID-SUPPORTED SYNTHESIS OF A BIOLOGICALLY IMPORTANT BRANCHED α-GLUCAN[†]

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Abstract. Solid-phase oligosaccharide synthesis offers the promise of providing libraries of oligosaccharides for glycomics research. A major stumbling block to solid-phase oligosaccharide synthesis has been a lack of general methods for the stereoselective installation of 1,2-*cis*-glycosides, and intractable mixtures of compounds are obtained if several such glycosides need to be installed. We have prepared on-resin a biologically important glucoside containing multiple 1,2-*cis*-glycosidic linkages with complete anomeric control by using glycosyl donors having a participating (*S*)-(phenylthiomethyl)benzyl chiral auxiliary at C-2. A branching point could be installed by using 9-fluorenylmethyloxycarbonyl (Fmoc) and allyloxycarbonyl (Alloc) as a versatile set of orthogonal protecting groups. The synthetic strategy made it possible to achieve partial on-resin deprotection of the completed oligosaccharide, thereby increasing the overall efficiency of the synthesis. The combination of classical and auxiliary-mediated neighboring-group participation for controlling anomeric selectivity is bringing the promise of routine automated solid-supported oligosaccharide synthesis closer.

Introduction. As many as 50% of human proteins are *O*- or *N*-glycosylated, and the carbohydrate moieties of these glycoproteins have been implicated as essential mediators of cellular processes such as protein folding, regulation of cell signaling, fertilization, embryogenesis, neuronal development, and hormone activities[1]. However, carbohydrates are also important for pathogen recognition, modulation of innate immune responses, control of immune-cell homeostasis, inflammation, and the development of autoimmune diseases and cancer[2-4]. The ability of cells to generate information-rich glycans has created a new field of research termed 'glycomics', which seeks to identify and understand the processes involved in the formation of cell-type and developmental-stage specific oligosaccharide patterns[5-8]. In this respect, collections of well-defined oligosaccharides are needed for the development of algorithms for the assignment of oligosaccharide mass spectrometry (MS) spectra, for fabricating microarrays, for elucidating the biosynthetic pathways of glycoconjugate assembly, and as immunogens to produce monoclonal antibodies (MABs) for glycoprotein visualization and isolation by immunoprecipitation. In many cases, well-defined oligosaccharides can only be obtained by chemical or enzymatic approaches.

Although tremendous progress has been made, complex oligosaccharide synthesis is still very time consuming, and it is not uncommon that the preparation of a single well-defined derivative can take as long as a year[9-13]. Solid-phase oligosaccharide synthesis (SPOS) offers the promise of increasing the speed of oligosaccharide assembly, primarily by eliminating intermediate purification steps and by automation[14]. However, SPOS requires that each glycosidic linkage is introduced with absolute stereoselectivity; otherwise, an intractable mixture of compounds will be obtained after several reaction cycles. In this respect, 1,2-*trans*-glycosides can be reliably introduced by taking advantage of neighboring-group participation of a 2-*O*-acyl functionality (Figure 3.1A).

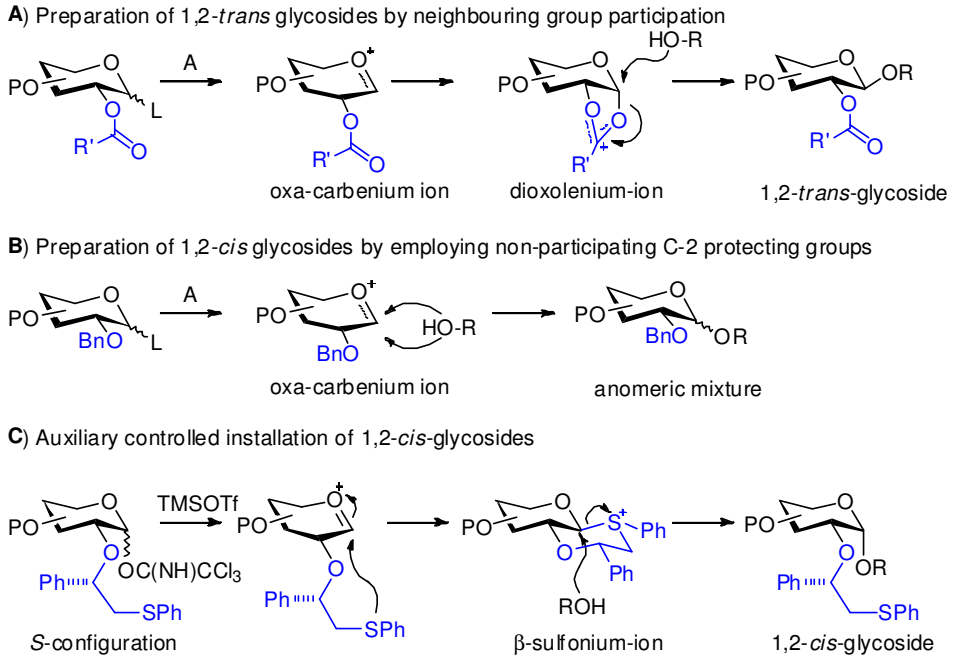


Figure 3.1: Stereoselective introduction of glycosidic linkages. A) Preparation of 1,2-*trans*-glycosides by neighboring group participation of a C-2 ester. B) The use of a non-participating protecting group at C-2 of a glycosyl donor generally results in the formation of mixture of anomers although the axial glycoside often predominates. C) Chiral auxiliary controlled installation of 1,2-*cis*-glycosides.

The Seeberger group used this type of anomeric control for the automated solid-phase synthesis of a phytoalexin elicitor β-glycan using a modified peptide synthesizer[15]. The introduction of 1,2-*cis*-glycosidic linkages, such as α-glucosides and α-galactosides, requires glycosyl donors having a non-assisting functionality at C-2, and in general these glycosylations give mixtures of anomers (Figure

3.1B)[16]. Not surprisingly, only a few examples of SPOS of oligosaccharides containing 1,2-*cis*-glycosides have been reported. These rely on tedious separation of the anomers by high-performance liquid chromatography (HPLC) or the preparation of a 1,2-*cis*-linked disaccharide in solution, which after purification to remove the unwanted 1,2-*trans*-anomer can be used in solid-phase synthesis[17-19]. Thus, a major stumbling block in SPOS is the inability to reliably introduce 1,2-*cis*-glycosides with complete stereoselectivity. Herein, we report the solid-phase synthesis of a well-defined biologically important branched 1,2-*cis*-linked pentaglucoside. Anomeric control was achieved by using neighbouring-group participation by an (*S*)-(phenylthiomethyl)benzyl chiral auxiliary at C-2 of the glucosyl donors[20-21]. In this approach, neighboring group participation by the C-2 auxiliary results in the formation of an anomeric sulfonium ion as a *trans*-decalin system, because the alternative *cis*-decalin system will place the phenyl-substituent in an axial position, inducing unfavourable steric interactions. Displacement of the equatorial anomeric sulfonium ion by a sugar alcohol will then lead to the formation of a 1,2-*cis* glycoside (Figure 3.1C). Furthermore, a branching unit could easily be installed by using 9-fluorenylmethyloxycarbonyl (Fmoc) and allyloxycarbonyl (Alloc) as a versatile set of orthogonal protecting groups[22-23]. The synthetic strategy also makes it possible for partial on-resin deprotection of the completed oligosaccharide, thereby increasing the overall efficiency of synthesis.

Results and discussion. α-Glucans (Figure 3.2) are structural elements of an immune-modulatory polysaccharide isolated from *Aconitum carmichaeli* that have the potential to be developed as an adjuvant[24]. The polysaccharide is composed of an α(1,6)-linked glucosyl backbone branched with α(1,3)-linked glucoside moieties. α-Glucans have also been isolated from various microbial sources such as *Pseudallescheria boydii*, producing a polysaccharide essential for conidial phagocytosis by macrophages and induction of innate immune responses in a TLR2-dependent manner[25]. Furthermore, it has been found that the *Streptococcus pneumoniae* α-glucan metabolizing machinery is an important virulence factor[26]. α-Glucans isolated from natural sources are heterogeneous in composition, and well-defined derivatives are required to identify biologically active fragments. It was envisioned that pentasaccharide **1** (which

represents a significant synthetic challenge owing to the presence of multiple α-glucosides at primary and secondary sugar alcohols and also because of its branched architecture) could be assembled from the strategically selected glycosyl donors **2**–**6** (Figure 3.2).

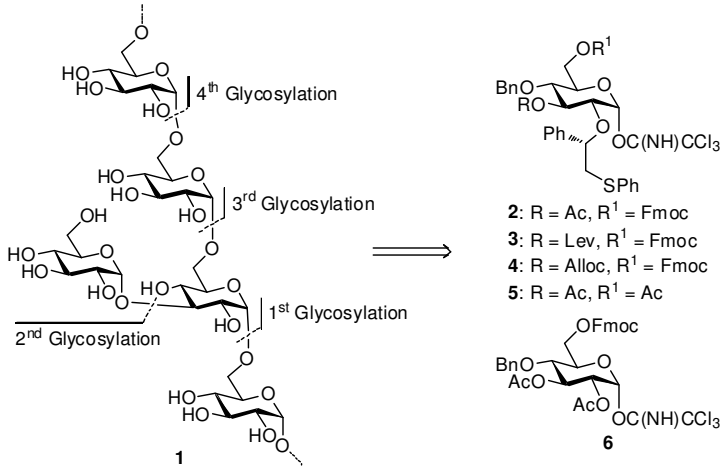
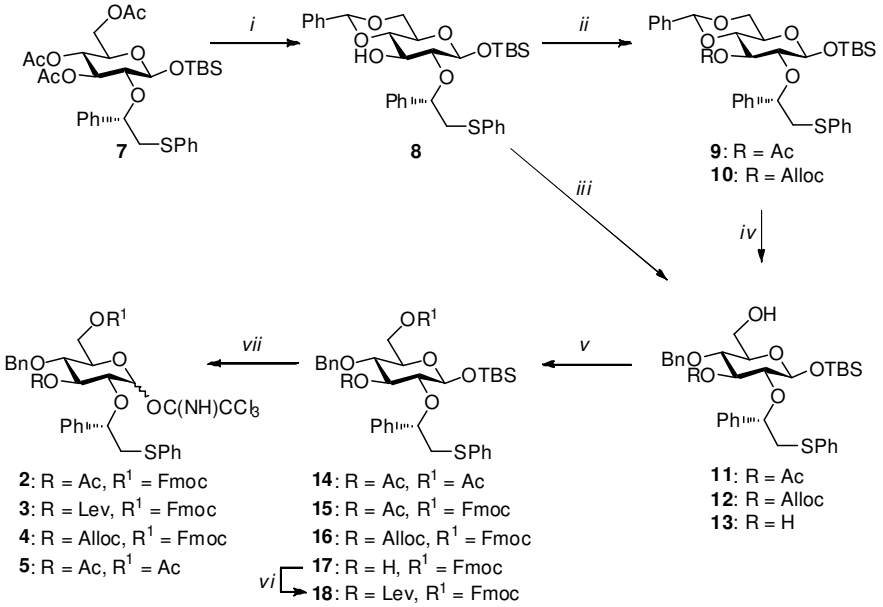


Figure 3.2. Structure of an α-Glucan pentasaccharide repeating unit found in *Aconitum carmichaeli*.

The temporary Fmoc carbonate of **2**-**4** can be cleaved under mild conditions using piperidine/*N*,*N*-dimethylformamide (DMF; 1/9, v/v) and the use of this protecting group will make it possible to form the α(1,6)-linked backbone. Furthermore, monosaccharide buildingblocks **3** and **4** have a temporary protecting group at C-3 which will allow for the introduction of the branching unit. Glycosyl donor **3** has a C-3 levulinyl ester which can be cleaved using hydrazinium acetate and glycosyl donor **4** carries an Alloc carbonate at C-3, which can be removed with $Pd(PPh_3)_4$ in a mixture of tetrahydrofuran (THF) and AcOH without affecting the Fmoc protecting group or the anomeric linker. Glycosyl donor **5** will be used as the branching unit. Furthermore, glycosyl donor **6**, which is modified with an acetyl ester at C-2, will be coupled with the benzyl alcohol linker-modified resin to give a resin-bound β-linked glucoside. After completion of the synthesis, the resulting oligosaccharide can be cleaved from the resin by transesterification, and the remaining anomeric 4-hydroxymethylbenzyl ether can be removed during the final hydrogenation step, providing the anomeric lactol. Thus, the anomeric identity of the glycosidic linkage will be lost and therefore it was installed as a straightforward β-glucoside.

Glycosyl donors **2**-**5** were prepared from common intermediate **7** by deacetylation under Zemplén conditions, followed by reaction of the resulting triol, with benzaldehyde dimethylacetal under acid catalysis to afford 4,6-*O*-benzylidene derivative **8**. At this stage the C-3 alcohol was converted into an acetyl ester using acetic anhydride and pyridine (**9**) or an Alloc carbonate using allyl chloroformate and TMEDA (**10**). The 4,6-*O*-benzylidene of **9** and **10** were regioselectively opened using dichlorophenyl borane and triethyl silane to afford the corresponding C-6 alcohols **11** and **12**. The preparation of the C-3 levulinyl derivative was achieved by the regioselective opening of **8** prior to installation of the levulinyl ester due to its sensitivity to reductive conditions. Next, the C-6 alcohols of **11**-**13** were (selectively) protected using either acetic anhydride and pyridine (**14**) or FmocCl and pyridine (**15**-**17**).

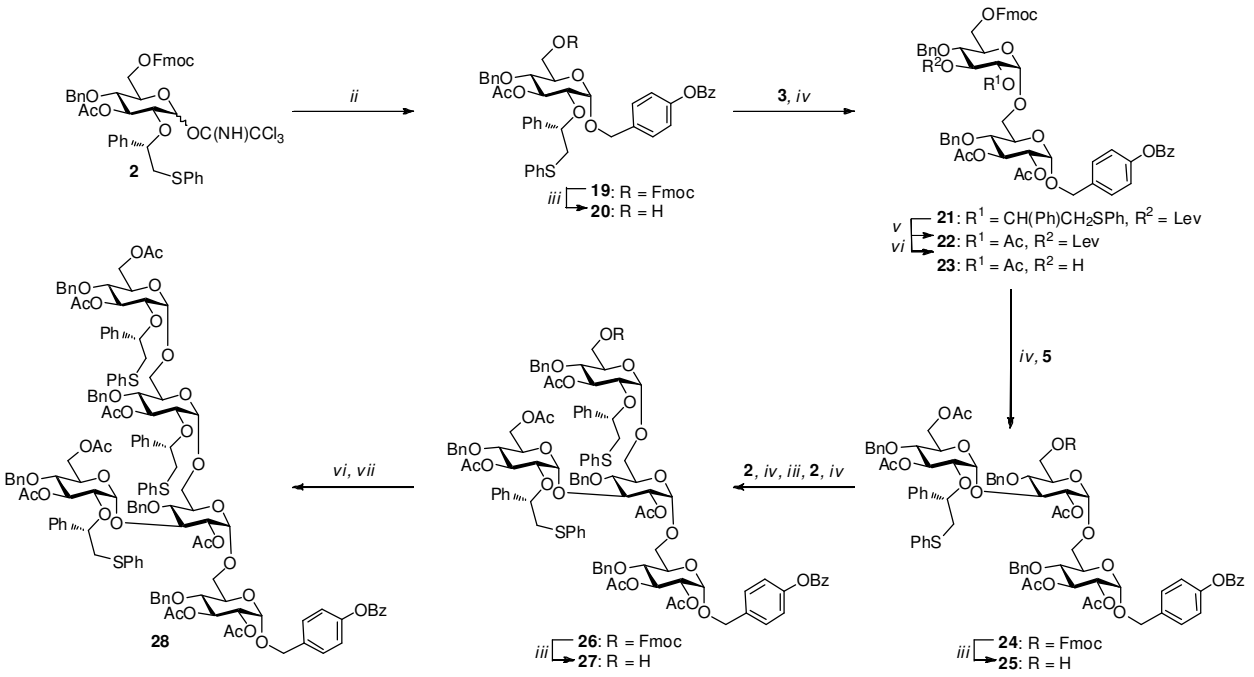


Scheme 3.1: Synthesis of glycosyl donor **2**-**5**. Reagents and conditions. *i)* 1. NaOMe, MeOH, 4 hrs, rt. 2. $PhCH(OMe)_2$, *p*-TsOH, DMF, 16 hrs, rt. *ii)* Ac_2O, pyridine, 4 hrs, rt for **9**, 90%. AllocCl, TEMED, CH_2Cl_2, 4 hrs, 0°C → rt for **10**, 81%. *iii)* Et_3SiH, Cl_2BPh, CH_2Cl_2, MS4Å, 45 min, -78°C. **11** (95%), **12** (86%), **13** (70%). *v)* Ac_2O, pyridine, 4 hrs, rt for **14**, (91%). FmocCl, pyridine, 3 hrs, rt. for **15** (93%), **16** (88%), **17** (76%). *vi)* Levulinic acid, DCC, DMAP, CH_2Cl_2, 3 hrs, rt. (80%) *vii)* 1. HF·pyridine, THF, 16 hrs, rt. 2. trichloroacetonitrile, NaH, CH_2Cl_2, 1 hr, 0°C, **2** (94%), **3** (80%), **4** (92%), **5** (80%).

At this stage, the levulinyl ester was installed using levulinic acid, dicylcohexyl carbodiimide (DCC), and 4-*N,N'*-dimethylamino pyridine (DMAP) to afford fully protected **18**. Finally, **14**-**16** and **18** were

converted into trichloroacetimidates **2**-**5** by a two step procedure. First, HF·pyridine was used to cleave the anomeric TBS ether and the resulting lactols were converted into trichloroacetimidates using trichloroacetonitrile and base. In case of Fmoc containing donors **2**-**4**, sodium hydride was used as the base to prevent Fmoc cleavage.[17]

Next, glycosyl donors **2**-**5** were used to synthesize the α-pentaglucoside found in *Aconitum carmichaeli*. Since monitoring of reactions on solid phase is very challenging, solution phase studies were first conducted to ensure absolute stereoselectivity was obtained at each step. *p*-Benzoyloxybenzyl alcohol was used to mimic the phenolic ester linker commonly used in solid phase synthesis.[27] Glycosyl donor **2** was activated at -40 ^{o}C using an equimolar amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf). After complete activation of the trichloroacetimidate (~15 min), *p*-benzoyloxybenzyl alcohol, and the non-nucleophilic base 2,5-di-*tert*-butyl-4-methyl-pyridine (DTBMP) were added. DTBMP is added since upon glycosylation an equimolar amount of acid is formed, which needs to be neutralized to prevent cleavage of the (*S*)-(phenylthiomethyl)benzyl chiral auxiliary. After gradual warming of the reaction mixture to rt, **19** was formed as one anomer. Removal of the Fmoc of **19** using triethyl amine (TEA), gave rise to glycosyl acceptor **20** in high yield. Next, glycosyl donor **3** was used to install the branching unit under aforementioned pre-activation conditions to afford **21**. It was found that removal of the lev ester of **21** followed by glycosylation with **5** did not afford the desired trisaccharide, and the disaccharide acceptor was recovered. Propably, the bulky (*S*)-(phenylthiomethyl)benzyl auxiliary on C-2 sterically blocks the C-3 alcohol. Hence, the (*S*)-(phenylthiomethyl)benzyl auxiliaries of **21** were removed under mild acetolysis conditions to afford the acetylated derivative **22**. The lev ester of **22** was removed using hydrazinium acetate in a mixture of MeOH and CH_2Cl_2 to smoothly afford acceptor **23**. Glycsylation with pre-activated **5** proceeded uneventfully and afforded trisaccharide **24** as a single anomer. With the branching unit in place, the α(1→6) backbone was further extended by two cycles of Fmoc deprotection and glycosylation using donor **2**, to afford protected α-pentaglucoside **28**. Each glycosylation proceeded in high yield and with absolute anomeric stereoselectivity.

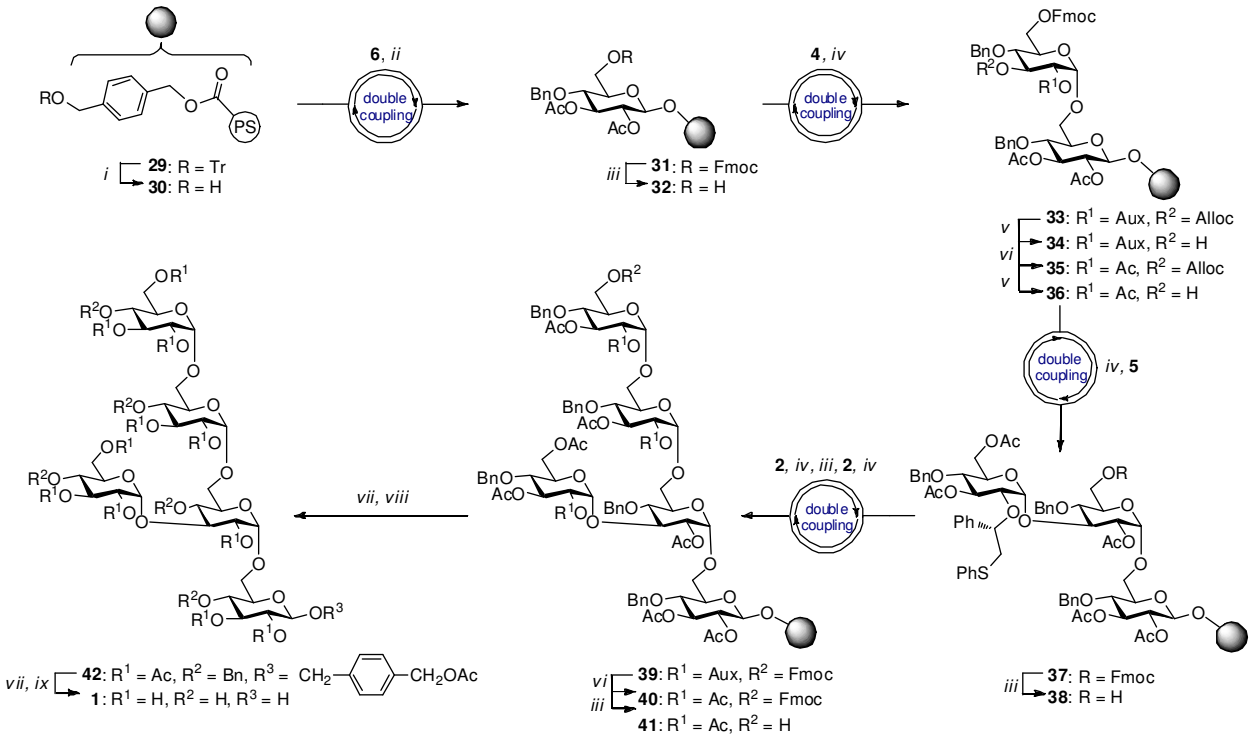


Scheme 3.2: Solution phase synthesis of branched pentaglucoside **28**. Reagents and conditions. *i)* 1). **2**, TMSOTf, CH_2Cl_2, MS4Å, 15 min, -40°C. 2). *p*-benzoyloxybenzyl alcohol, DTBMP, CH_2Cl_2, 16 hrs, -40°C → rt, 95% *ii)* TEA, CH_2Cl_2, 3 hrs, rt, **20** (92%), **25** (98%), **27** (93%) *iii)* 1). **3**, TMSOTf, CH_2Cl_2, MS4Å, -40°C. 2). **20**, DTBMP, CH_2Cl_2, 16 hrs, -40°C → rt, 88% *iv)* $BF_3{\cdot}Et_2O$, Ac_2O, 1 hr, 0°C, 94% *v)* $N_2H_4{\cdot}AcOH$, MeOH, CH_2Cl_2, 3 hrs, rt, 83% *vi)* 1). **5**, TMSOTf, CH_2Cl_2, MS4Å, -40°C. 2). **23**, DTBMP, CH_2Cl_2, 16 hrs, -40°C → rt, 89% *vii)* 1). **2**, TMSOTf, CH_2Cl_2, MS4Å, -40°C. 2). **25**, DTBMP, CH_2Cl_2, 16 hrs, -40°C → rt, 83% *viii)* 1). **5**, TMSOTf, CH_2Cl_2, MS4Å, -40°C. 2). **27**, DTBMP, CH_2Cl_2, 16 hrs, -40°C → rt, 72%.

Next, attention was focused on the preparation of the branched α-pentaglucoside on solid phase. The on-resin deprotection of temporary protecting groups typically requires a large excess of reagents to ensure complete conversion. Hence, glycosyl donor **3** was found to be unsuitable for solid phase synthesis since large amounts hydrazinium acetate might also cleave acetyl esters or the anomeric linker. Thus, donor **4** was used since its C-3 Alloc group is cleaved under very mild conditions. Also, instead of the phenolic ester linker, a more stable benzoic acid linker was used.

Thus, linker-modified resin **29** was prepared by ester formation between the carboxylic acids of carboxypolystyrene resin (Advanced ChemTech, 2.0 mmol g^{-1}) and (4-trityloxymethylphenyl)-methanol

using *N*,*N*′-diisopropylcarbodiimide (DIC) and *N*,*N*dimethyl-4-aminopyridine (DMAP). The remaining carboxylic acids were capped as methyl esters by subsequent addition of methanol (Scheme 3.3). The trityl ether was removed using trifluoroacetic acid (TFA) in CH_2Cl_2 (1/9, v/v) and triethylsilane as the scavenger to give **30** (loading 0.148 mmol g^{-1})[28]. It is important to note that different resin loadings could be achieved by using different molar quantities of (4-trityloxymethylphenyl)methanol.



Scheme 3.3: Solid phase synthesis of branched pentaglucoside **1**. Reagents and conditions: *i)* 10% v/v TFA in CH_2Cl_2, Et_3SiH, 10 min, rt. *ii)* **6**, TMSOTf, CH_2Cl_2, MS4Å, 30 min, -40°C, double coupling. *iii)* 10% v/v piperidine in DMF, 5 min, rt. *iv)* **2**, **4** or **5**, TMSOTf, CH_2Cl_2, MS4Å, 15 min, -40°C then added to **32**, **36** or **38**, DTBMP, CH_2Cl_2, MS4Å, 16 hrs -40°C → rt, double coupling. *v)* 40 mol% $Pd(PPh_3)_4$, THF/AcOH 10/1, 16 hrs, rt. *vi)* $BF_3{\cdot}Et_2O$, Ac_2O/CH_2Cl_2 1/2, 16 hrs, 0°C. *vii)* NaOMe, $MeOH/CH_2Cl_2$ 1/1, 9 hrs for **42**, 16 hrs for **1**, rt. *viii)* Ac_2O/Pyridine 1/3, 12 hrs, rt *ix)* 20 wt% $Pd(OH)_2/C$, H_2, $EtOH/H_2O$ 1/1, 16 hrs, rt, 87%. MS = molecular sieves, PS = polystyrene, rt = room temperature, Tr = Trityl.

However, it was found that a loading of 0.15 mmol g^{-1} resin gives optimal glycosylation results, and further increases in loading led to decreases in coupling efficiencies[28-29]. The hydroxyl of resin **30** was next coupled with glycosyl donor **6** (3.0 equiv.) in the presence of a catalytic amount of trimethylsilyl

trifluoromethanesulfonate (TMSOTf) in CH_2Cl_2 at -40 ^{0}C for 30 min to yield **31**. The glycosylation was repeated to ensure completion of the reaction. Next, the Fmoc protecting group of **31** was removed by treatment with piperidine/DMF (1/9, v/v) to give resin-bound acceptor **32**, which was coupled with auxiliary-containing glucosyl donor **4** to install the first 1,2-*cis* linkage. For this coupling, glucosyl donor **4** was pre-activated in a separate flask with a stoichiometric amount of TMSOTf at -40 ^{0}C to form an intermediate sulfonium ion. The solution containing the sulfonium ion was added via a cannula to a cooled (-40 ^{0}C) suspension of resin **32** and 2,6-di-tert-butyl-4-methylpyridine (DTBMP) in CH_2Cl_2. The reaction mixture was allowed to warm to room temperature over a period of 5 h and was shaken at ambient temperature for an additional 11 h. After this period of time, a small sample of resin (~5.0 mg) was analyzed for product formation and the possible presence of starting material by treatment with methanolic sodium methoxide to cleave the ester linkage of the linker, followed by analysis of the released product by thin layer chromatography (TLC) and matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI–TOF MS). This study showed that the disaccharide product had predominantly been formed, but also revealed the presence of a small amount of starting material (≤5%). Glycosylation was therefore repeated under identical conditions to ensure that a homogeneous product was formed at the end of the synthetic sequence. The Alloc function of **33** was easily removed by treatment with $Pd(PPh_3)_4$ in a mixture of THF and AcOH to give disaccharide acceptor **34**. Interestingly, attachment of **33** to the insoluble polymeric support did not appear to influence the outcome of the deprotection reaction. A number of attempts were made to couple the resulting glycosyl acceptor with glycosyl donor **5**. However, analysis of a small sample of resin indicated that no coupling had occurred. As mentioned earlier, the C3′ hydroxyl of **34** is sterically shielded owing to the neighbouring (*S*)-(phenylthiomethyl)benzyl ether. Thus, the auxiliary of **33** was converted into acetyl ester **35** by treatment with acetic anhydride in the presence of $BF_3{\cdot}OEt_2$. The Alloc of compound **35** could be removed under standard conditions to provide glycosyl acceptor **36**, which was coupled with pre-activated **5** to give smooth formation of resin-bound trisaccharide **37**. Thus, it was found that the auxiliary can be removed without affecting the Alloc and Fmoc protecting groups as well as the anomeric linker. The terminal

Fmoc of **37** was cleaved by treatment with piperidine/DMF (1/9, v/v), and the resulting alcohol was glycosylated with pre-activated **2** to give the corresponding tetrasaccharide. The reaction sequence of Fmoc removal and glycosylation was repeated to give the fully protected pentasaccharide **39**. Each glycosylation was performed twice with 2.0 equiv. of glycosyl donor to ensure complete conversion of the starting material. After each reaction step, a small sample of resin was treated with methanolic sodium methoxide, and the resulting released material was analysed by TLC and MALDI-TOF MS. These studies showed clearly that each reaction step proceeded to completion, with no or very little formation of side products. The pentaglucoside was also prepared in solution, and careful examination of the products of each glycosylation confirmed complete α-anomeric selectivity. We next explored whether pentasaccharide **39** could be partially deprotected when still attached to the resin. The auxiliaries of **39** were therefore converted in the acetyl ester by treatment with acetic anhydride and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 to give **40** Next, the Fmoc carbonate was removed with piperidine/DMF (1/9, v/v) to give **41**, which was released from the polymeric support with concomitant acetyl ester removal using methanolic sodium methoxide in CH_2Cl_2. The crude pentasaccharide was re-acetylated and then purified by size exclusion chromatography (LH-20). HPLC analysis of the resulting product revealed **42** to be the major product, with a small amount of mono-debenzylated material (~10%), which was probably formed during removal of the auxiliaries. Importantly, no anomeric isomers of **42** were detected. Further purification by preparative HPLC gave pure **42** in an overall yield of 25%, which corresponds to a yield per step of 90% (13 on-resin steps). The identity and purity of **42** were confirmed by 1H NMR (nuclear magnetic resonance) and coupled heteronuclear single quantum coherence (HSQC) experiments (Figure 3.3). The homonuclear anomeric coupling constants, as well as the heteronuclear one-bond C1–H1 coupling constants, unambiguously confirmed the presence of four 1,2-*cis* linkages and one 1,2-*trans* linkage. Correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY) and HSQC experiments were used for full spectral assignment (see appendix A). Furthermore, a heteronuclear multiple bond correlation (HMBC) experiment confirmed the appropriate connectivity between the individual monosaccharides. Finally, **42** was converted into target compound **1** by removal of the acetyl esters, using

standard conditions followed by hydrogenation of the benzyl ethers using $Pd(OH)_2/C$ (20 wt%) and H_2 gas.

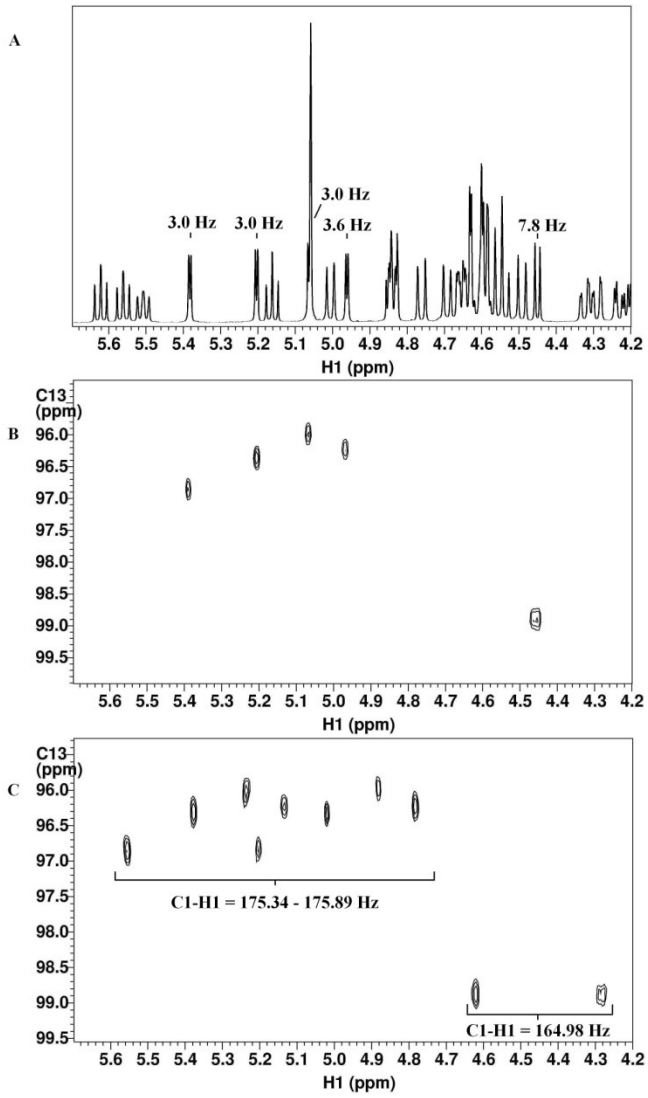
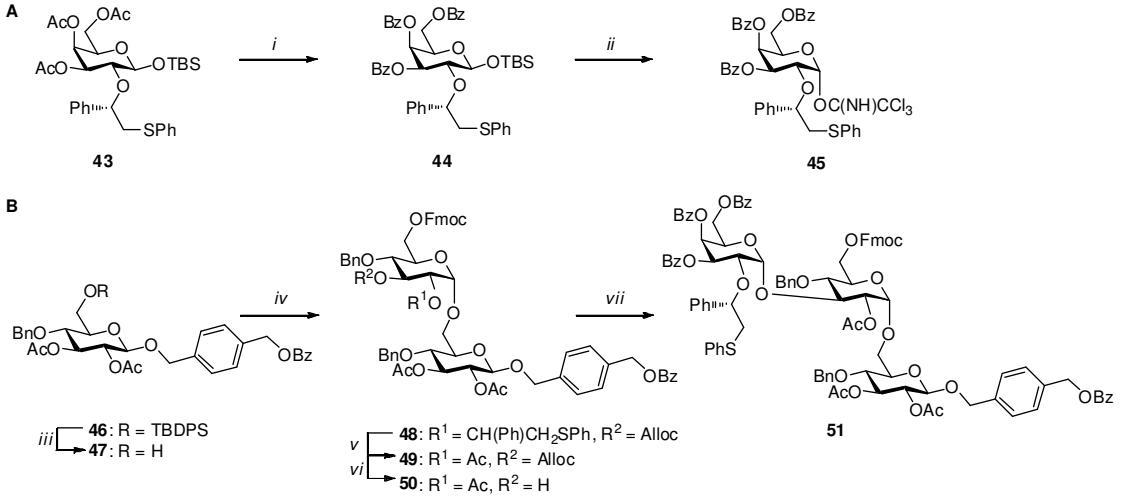


Figure 3.3: NMR data of **42**: A) ^1H NMR spectrum B) decoupled HSQC C) coupled HSQC. The homonuclear and heteronuclear coupling constants confirm the correct anomeric configuration.

Attention was then focused on the preparation of pentasaccharide **55** to demonstrate that the methodology can be extended to the stereoselective introduction of other types of monosaccharides and can be used for the preparation of complex structural analogues (Scheme 3.5). Compound **55** contains an α-galactoside at the C-3 branching position, which is challenging to introduce owing to the relatively low reactivity of the corresponding glycosyl acceptor. Furthermore, branching points of α-glucans are expected to be critical

for biological activity, so compounds such as **55** provide an opportunity to explore the influence of subtle structural changes on biological activity. To this end, galactosyl donor **45** was prepared, the sulfonium ion of which was found to glycosylate at ambient temperature (Scheme 3.4A).

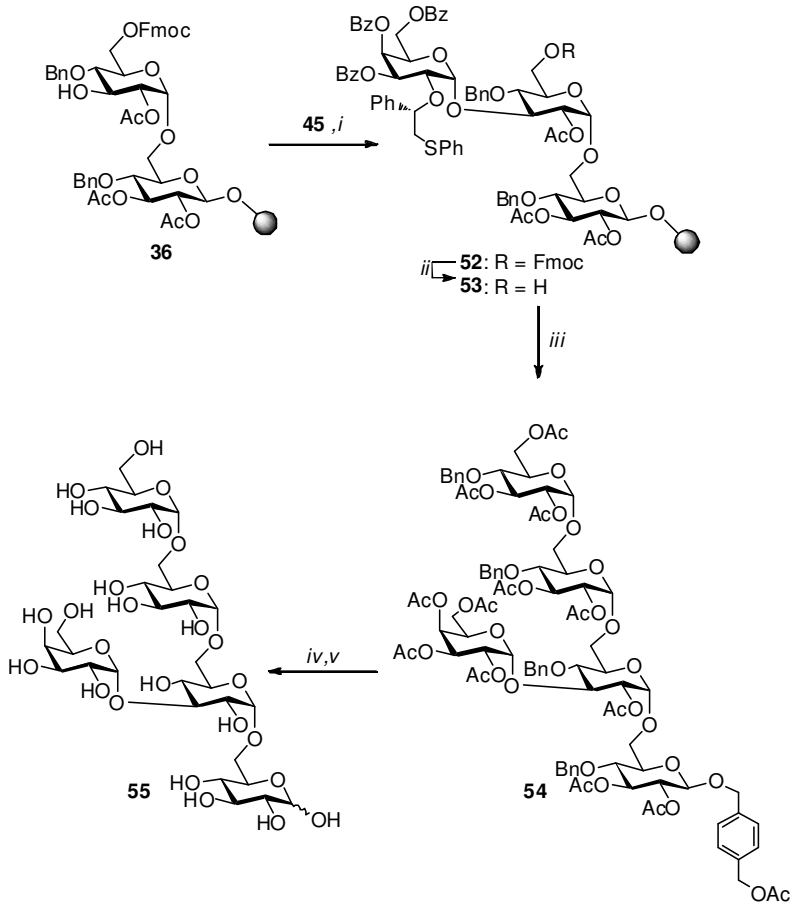


Scheme 3.4: Solution-phase α-galactosylation A). Synthesis of galactosyl donor **45** B) Solution-phase studies. Reagents and conditions. *i)* 1). NaOMe, MeOH, 4 hrs, rt. 2). BzCl, Pyridine, 16 hrs, rt, 80% *ii)* 1). HF·pyridine, THF, 16 hrs, rt. 2). trichloroacetonitrile, cat. DBU, CH_2Cl_2, 1 hr, 0°C, 68% *iii)* TBAF, AcOH, THF, 16 hrs, rt, 95% *iv)* 1). **4**, TMSOTf, DCM, MS4Å, -40°C. 2). **47**, DTBMP, DCM, 3 hrs, -40°C → 0°C, 72% *v)* $BF_3{\cdot}Et_2O$, Ac_2O, DCM, 1 hr, 0°C, 87% *vi)* $Pd(PPh_3)_4$, THF, AcOH, 1 hr, rt, 92% *vii)* 1). **45**, TfOH, DCM, MS4Å, -40°C. 2). **50**, DTBMP, DCM, 5 hrs, -40°C → 0°C, 61%.

Solution-phase studies were performed to ensure the α-galatosylation would proceed with absolute stereoselectivity (Scheme 3.4B). Removal of the TBDPS ether of **46** using buffered TBAF afforded glycosyl acceptor **47**. Glycosylation with pre-activated **4** afforded disaccharide **48** with absolute stereoselectivity. Next, the (*S*)-(phenylthiomethyl)benzyl auxiliary was removed under mild acetolysis conditions after which the Alloc was cleaved using $Pd(PPh_3)_4$ in a mixture of THF and AcOH. Finally, treatment of **50** with pre-activated **45** afforded trisaccharide **51** with absolute stereoselectivity.

Since, absolute stereoselectivity was obtained in solution, solid-phase synthesis of **55** was performed. Thus, galactosyl donor **45** was activated with a stochiometric amount of TfOH at -40 °C to form the intermediate sulfonium ion, which was added to a cooled (-40 °C) suspension of resin-bound **36** and

DTBMP in CH_2Cl_2 (Scheme 3.5). The reaction mixture was allowed to warm to room temperature over a period of 5 h, and was shaken at ambient temperature for an additional 11 h.



Scheme 3.5: Solid phase synthesis of α-Galactose containing pentasaccharide **55**. Reagents and conditions: *i)* **45**, TfOH, CH_2Cl_2, MS4Å, 15 min, -40°C then added to **36**, DTBMP, CH_2Cl_2, MS4Å, 16 hrs -40°C → rt, double coupling. *ii)* 10% v/v piperidine in DMF, 5 min, rt. *iii)* the same sequence and reagents as used for the conversion of **38** to **42**. *iv)* NaOMe, MeOH/CH_2Cl_2 1/1, 8 hrs, rt. *v)* 20 wt% $Pd(OH)_2$/C, H_2, EtOH/H_2O 1/1, 16 hrs, rt, 81%. MS = molecular sieves, rt = room temperature.

A repetition of the glycosylation led to clean formation of trisaccharide **52**, as determined by TLC and MS analysis of a small sample of oligosaccharide released from the resin by NaOMe treatment. Removal of the Fmoc protecting group of **52** followed by glucosylation with **2** and a repetition of the reaction sequence led to the formation of polymer-bound pentasaccharide, which was partially deprotected and released from the resin using standard procedures. Purification as before gave anomerically pure **54** in an

overall yield of 13%, which corresponds to a yield per step of 86% (13 on-resin steps). The same analytical procedures were used to confirm the purity and identity of **54** (see appendix A). Finally, **54** was deprotected under the same conditions used before to give **55**.

Conclusions. Glycosyl donors having an (*S*)-(phenylthiomethyl) benzyl chiral auxiliary at C-2 have been successfully used for the solid supported synthesis of complex branched oligosaccharides. To the best of our knowledge, this is the first example of a stereoselective solid-supported synthesis of an oligosaccharide having multiple 1,2-*cis*-glycosidic linkages. A particularly interesting feature was that a relatively small excess of glycosyl donor was required to drive the glycosylations to completion. It is likely that the intermediate sulfonium ion is sufficiently stable to diffuse into the polymer support for glycosylation of the resin-bound sugar hydroxyls. Furthermore, it has been found that Fmoc and Alloc form an attractive set of orthogonal protecting groups for solid supported synthesis, compatible with the auxiliary-based glycosylation methodology. Deprotection of the fully assembled oligosaccharide could partially be performed when still attached to the resin, thereby further reducing the number of purification steps. The convenient protection of monosaccharides by a one-pot multi-step approach[30], combined with classical and auxiliarymediated neighbouring group participation for controlling anomeric selectivity, is bringing the fulfilment of routine automated solid supported oligosaccharide synthesis closer. Such an approach could provide the libraries of well-defined oligosaccharides needed for glycomics research.

Experimental Section:

General procedures: ^{1}H and ^{13}C NMR spectra were recorded on Varian inova-300 (300/75 MHz), Varian inova-500 (500/125 MHz) and Varian inova-600 (600/150 MHz) spectrometers equipped with Sun workstations. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. NMR data are presented as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet and/or multiple resonances), coupling constant in

hertz (Hz), integration. All NMR signals were assigned on the basis of ^{1}H NMR, ^{13}C NMR, COSY and HSQC experiments. HPLC analysis was performed using an Agilent Technologies 1200 series HPLC systemwith UV detection at 250 nm. Optical rotations were measured using a Jasco P-1020 polarimeter. Mass spectra were recorded on an Applied Biosystems 4700 MALDI-TOF proteomics analyser. The matrix used was 2,5-dihydroxybenzoic acid (DHB) and Ultramark 1621 as the internal standard. Column chromatography was performed on silica gel G60 (Silicycle, 60–200 mm, 60 Å). TLC analysis was conducted on Silicagel 60 F254 (EMD Chemicals Inc.) with detection by UV absorption (254 nm) where applicable, and by spraying with 20% sulfuric acid in ethanol followed by charring at ~150 ^{0}C or by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (25 g l^{-1}) in 10% sulfuric acid in ethanol followed by charring at ~150 ^{0}C. CH_2Cl_2 was freshly distilled from calcium hydride under nitrogen before use. Molecular sieves (4 Å) were flame activated under vacuum before use. Solid-phase reactions were shaken using an IKA Labortechnik KS 125 shaker. All reactions were carried out under an argon atmosphere.

General procedure for on-resin glycosylation with glycosyl donor 6. Glycosyl donor (0.3 mmol) was added to a suspension of the resin-bound glycosyl acceptor (0.670 g, 0.1 mmol, 0.148 mmol g^{-1}) and activated 4 Å molecular sieves in CH_2Cl_2 (6 ml). The mixture was shaken for 15 min at room temperature before being cooled to -40 ^{0}C. TMSOTf (8.15 ml, 0.045 mmol) was added at this temperature and the mixture was shaken for 30 min. The resin was decanted into a filter to remove the molecular sieves, washed with CH_2Cl_2 (2 × 5 ml), MeOH (2 ×5 ml), CH_2Cl_2 (2 × 5 ml) and MeOH (2 × 5 ml) followed by drying under vacuum in a desiccator for 16 h. This procedure was repeated to complete one coupling cycle.

General procedure for on-resin glycosylation with (*S*)-(phenylthiomethyl)benzyl containing glycosyl donor 2, **3**, **4**, **5 or 45**. Glycosyl donor (0.2 mmol) was dissolved in CH_2Cl_2 (2 ml) and activated 4Å molecular sieves were added. The mixture was stirred for 15 min at room temperature before being cooled to -40 ^{0}C. TMSOTf (36.2 ml, 0.2 mmol for **2**, **3**, **4** and **5**) or TfOH (17.6 ml, 0.2 mmol for **45**) was

added at this temperature and the mixture was stirred at -40 ^{0}C for 15 min. The mixture containing the activated donor was transferred via a cannula to a cooled (-40 ^{0}C) flask containing the resin-bound glycosyl acceptor (0.670 g, 0.1 mmol, 0.148 mmol g^{-1}), DTBMP (82.4 mg, 0.4 mmol), activated 4 Å molecular sieves and CH_2Cl_2 (6 ml). The mixture was shaken and allowed to slowly warm to room temperature for 5 h, after which it was shaken for an additional 11 h at room temperature. The resin was decanted into a filter to remove the molecular sieves, washed with CH_2Cl_2 (2 × 5 ml), MeOH (2 ×5 ml), CH_2Cl_2 (2 × 5 ml) and MeOH (2 × 5 ml), followed by drying under vacuum in a desiccator for 16 h. This procedure was repeated to complete one coupling cycle.

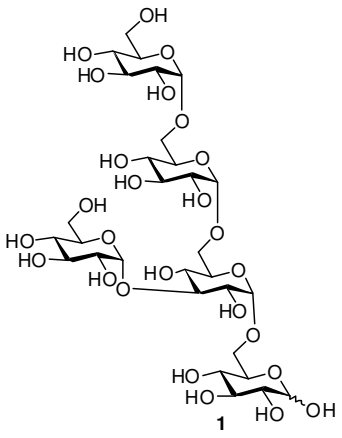
General procedure for Fmoc cleavage. The resin (0.670 g, 0.1 mmol, 0.148 mmol g^{-1}) was allowed to swell in DMF (6.3 ml) for 5 min. Piperidine (0.7 ml) was added and the mixture was shaken for 5 min at room temperature. The resin was filtered, washed with CH_2Cl_2 (2 × 5 ml), MeOH (2 ×5 ml), CH_2Cl_2 (2 × 5 ml) and MeOH (2 × 5 ml), followed by drying under vacuum in a desiccator for 16 h.

General procedure for (*S*)-(phenylthiomethyl)benzyl cleavage. The resin (0.670 g, 0.1 mmol, 0.148 mmol g^{-1}) was allowed to swell in CH_2Cl_2 (6 ml) for 5 min at room temperature. Acetic anhydride (3 ml) was added and the mixture was cooled to 0 ^{0}C. $BF_3{\cdot}Et_2O$ (50.0 ml 0.4 mmol) was added and the mixture was shaken at 0 ^{0}C for 16 h. The resin was filtered, washed with CH_2Cl_2 (2×5 ml), MeOH(2×5 ml), CH_2Cl_2 (2× 5 ml) and MeOH (2× 5 ml), followed by drying under vacuum in a desiccator for 16 h.

General procedure for Alloc cleavage. The resin (0.670 g, 0.1 mmol, 0.148 mmol g^{-1}) was allowed to swell in a mixture of THF (7 ml) and acetic acid (0.7 ml) for 5 min at room temperature. The solution was purged with argon gas for 2 min followed by the addition of $Pd(PPh_3)_4$ (46.2 mg, 0.04 mmol). The mixture was shaken for 16 h at room temperature. The resin was filtered, washed with THF (2 × 5 ml), MeOH (2 ×5 ml), THF (2 × 5 ml) and MeOH (2 ×5 ml), followed by drying under vacuum in a desiccator for 16 h.

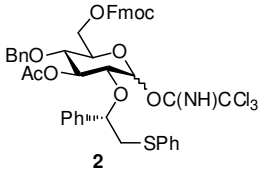
General procedure for product cleavage from the resin. The resin (0.670 g, 0.1 mmol, 0.148 mmol g21) was allowed to swell in CH_2Cl_2 (5 ml) for 5 min at room temperature. MeOH (5 ml) and NaOMe (27.0 mg, 0.5 mmol) were added and the mixture shaken for 3 h at room temperature. The resin was filtered and washed with a mixture of CH_2Cl_2/MeOH 1/1 (4 × 5 ml). This procedure was repeated three times to ensure complete product cleavage, and the combined filtrates were neutralized using Dowex 50W X8-200 H^+ resin. The resin was removed by filtration and the filtrate was concentrated under reduced pressure.

(*α*-D-glucopyranosyl)-(1→6)-(*α*-D-glucopyranosyl)-(1→6)-(3-*O*-[*α*-D-glucopyranosyl (1→3)]-α-D-glucopyranosyl)-(1→6)-*α*/*β*-D-glucopyranoside (1). Compound **41** (18.5 mg, 9.73 μmol) was dissolved in a mixture of CH_2Cl_2 (1 mL) and MeOH (1 mL) and a catalytic amount of sodium methoxide was added. The mixture was stirred for 16 h at rt and neutralized using Dowex® 50W X8-200 H^+ resin. The resin was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in a mixture of EtOH (1 mL) and H_2O (1 mL) and a catalytic amount of 20 wt% $Pd(OH)_2$/C was added. The reaction mixture was purged with H_2 gas for 2 min followed by stirring for 16 h under H_2 atmosphere. The reaction mixture was purged with Ar gas followed by filtration through a plug of Celite. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on Iatrobeads (CH_2Cl_2/MeOH/H_2O = 5/5/1) to afford **1** (7.0 mg, α/β = 1/2, 87% over two steps). TLC (CH_2Cl_2:MeOH:H_2O, 5:5:1 v/v/v): R_f = 0.40; $[\alpha]^{D}_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +37.0 (*c* = 0.01 in H_2O); ^1H NMR (500 MHz, D_2O/CD_3OD): **1β** δ 5.35 (d, *J* = 3.5 Hz, 1H, H-1), 5.00-4.96 (m, 3H, H-1, H-1, H-1), 4.70 (d, *J* = 7.5 Hz, 1H, H-1), 4.04-3.41 (m, 29H), 3.26 (t, *J* = 9.5 Hz, 1H, H-2) **1α** δ = 5.26 p.p.m. (d, *J* = 3.5 Hz, 1H, H-1), 4.96-5.00 (m, 4H, H-1, H-1, H-1, H-1), 4.04-3.41 (m, 30H); ^{13}C NMR (HSQC, 125 MHz, D_2O/CD_3OD) δ = 102.0, 100.6-100.4 (7), 99.0, 95.1, 83.4, 78.8, 76.9, 75.9, 74.9, 74.8, 74.3, 73.2,



73.0, 72.7, 72.6, 72.4, 68.4, 68.3, 63.2; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{30}H_{52}O_{26}$, 851.2645; found, 851.2678.

3-*O*-acetyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-[(*S*)-2-(phenylthiomethyl)benzyl]-



2

***α/β*-D-glucopyranosyl trichloroacetimidate (2).** Compound **15** (5.05 g, 5.87 mmol) was dissolved in THF (20 mL) in a Teflon reaction bottle. HF·pyridine (10 mL) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EtOAc (100 mL) and sat. aq. $NaHCO_3$ (100 mL) was slowly added. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 25% - EtOAc in PE). The purified lactol (4.25 g, 5.70 mmol) was dissolved in CH_2Cl_2 (15 mL) and trichloroacetonitrile (15 mL). The resulting mixture was cooled to 0°C and a catalytic amount of 60% sodium hydride in mineral oil suspension (23.0 mg, 0.57 mmol, 0.1 equiv) was added. The reaction mixture was stirred for 1 hr at 0°C. The solution was filtered to a short plug of silica gel which was rinsed with EtOAc. The filtrate was concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded **2** (4.91 g, 5.52 mmol, 94% yield over two steps) as a white foam (*α/β* = 1:1). TLC (EtOAc:PE, 30:70 v/v): R_f = 0.30; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +43.0 (*c* = 0.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.69 (s, 1H, C(N*H*)CCl_3 α), 8.60 (s, 1H, C(N*H*)CCl_3 β), 7.73 (d, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 6.0 Hz, 1H), 7.15-7.41 (m, 23H), 6.63 (d, $J_{1,2}$ = 3.0 Hz, 1H, α-H-1), 5.88 (d, $J_{1,2}$ = Hz, 1H, β-H-1), 5.57 (t, $J_{3,2}$ = 9.6 Hz, 1H, H-3), 5.23 (t, $J_{3,2}$ = 9.0 Hz, 1H, H-3), 4.94 (t, $J_{7,8a/b}$ = 6.9 Hz, 1H, H-7), 4.20-4.53 (m, 6H, CH_2 Fmoc, CH Fmoc, C*H*$_2$Ph, H-7), 4.10 (m, 1H, H-5), 3.75 (m, 1H, H-5), 3.58 (m, 4H, H-2, H-2, H-4, H-4), 3.38 (dd, $J_{8b,7}$ = 7.5 Hz, $J_{8b,8a}$ = 13.5 Hz, 1H, H-8b), 3.25 (dd, $J_{8b,7}$ = 6.9 Hz, $J_{8b,8a}$ = 14.1 Hz, 1H, □-H-8b), 3.12 (dd, $J_{8a,7}$ = 6.9 Hz, $J_{8a,8b}$ = 13.5 Hz, 1H, H-8a), 3.04 (dd, $J_{8a,7}$ = 6.3 Hz, $J_{8a,8b}$ = 13.8 Hz, 1H, H-8a), 1.82 (s, 3H, CH_3), 1.79 (s, 3H, CH_3); ^{13}C {^1H} NMR(APT) (75 MHz, $CDCl_3$): δ169.8, 169.8, 161.8, 161.8, 154.9, 154.6, 136.1-143.4, 120.0-129.2, 93.2, 92.0, 81.2, 80.9, 75.7, 75.7, 75.6, 75.4, 75.3, 74.7, 73.8, 73.8, 72.6, 71.4, 70.9, 70.0, 70.0, 68.7, 46.5, 46.5, 41.3, 40.7, 21.0, 20.9.

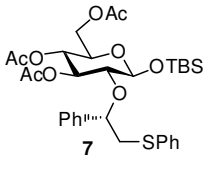
4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-3-*O*-levulinoyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl trichloroacetimidate (3). Hydrogen fluoride in pyridine (70%, 6 mL) and acetic acid (8 mL) were added to a solution of **18** (800 mg, 0.87 mmol) in THF (20 mL) at 0°C. After stirring overnight at rt, the reaction mixture was diluted with ethyl acetate (20 mL), and then quenched with saturated aqueous $NaHCO_3$ (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded the lactol (671 mg, 0.84 mmol, 96%) as a colorless syrup. Trichloroacetonitrile (10 mL) and sodium hydride (60% dispersion in mineral oil, 12 mg, 0.30 mmol, 0.35 equiv) were added to a solution of the lactol (671 mg, 0.84 mmol) in dichloromethane (10 mL) at 0°C. The reaction mixture was stirred at the same temperature for 1 h and then filtered, concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded **3** (636 mg, 0.62 mmol, 80%) as a white foam. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.34; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +53.2 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H, N*H*), 7.79-7.18 (m, 23H), 6.66 (d, 1H, *J* = 3.5 Hz, H-1), 5.62 (t, 1H, *J* = 9.5 Hz, H-3), 4.63 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.55 (t, 1H, *J* = 7.0 Hz, H-7), 4.51 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.41-4.24 (m, 5H, H-6a, H-6b, Fmoc), 4.15-4.12 (m, 1H, H-5), 3.62 (dd, 1H, *J* = 9.5 Hz, *J* = 3.5 Hz, H-2), 3.61 (t, 1H, *J* = 9.5 Hz, H-4), 3.29 (dd, 1H, *J* = 14.0 Hz, *J* = 7.0 Hz, H-8a), 3.12 (dd, 1H, *J* = 14.0 Hz, *J* = 7.0 Hz, H-8b), 2.68-2.19 (m, 4H, Lev), 2.19 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.47, 171.78, 161.22, 154.98, 143.59, 143.43, 141.51, 139.92, 137.50, 136.49, 129.56, 129.19, 128.81, 128.72, 128.45, 128.26, 128.13, 127.56, 127.41, 127.38, 126.31, 125.41, 125.36, 120.28, 93.33, 91.28, 80.93, 77.44, 75.55, 75.46, 74.94, 73.32, 71.23, 70.29, 65.90, 46.92, 41.44, 37.83, 30.15, 28.01.

3-*O*-allyloxycarbonyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-[(*S*)-2-phenylthiomethyl) benzyl]-*α*/*β*-D-glucopyranosyl trichloroacetimidate (4). Compound **16** (1.26 g, 1.40 mmol) was dissolved in THF (6 mL) in a Teflon reaction bottle. HF·pyridine (3 mL) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EtOAc (75 mL) and sat. aq. $NaHCO_3$ (75 mL) was slowly added. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 20% - EtOAc in PE). The purified lactol (1.07 g, 1.35 mmol) was dissolved in CH_2Cl_2 (5 mL) and trichloroacetonitrile (5 mL). The resulting mixture was cooled to 0°C and a catalytic amount of 60% sodium hydride in mineral oil suspension (5.6 mg, 0.14 mmol, 0.1 equiv) was added. The reaction mixture was stirred for 1 hr at 0°C. The solution was filtered to a short plug of silica gel which was rinsed with EtOAc. The filtrate was concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded **4** (1.20 g, 1.28 mmol, 92% over two steps) as a white foam (*α*/*β* = 2:1). TLC (EtOAc:PE, 30:70 v/v): R_f = 0.30; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +61.3 (*c* = 0.1 in $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.61 (s, 1H, C(N*H*)CCl_3), 7.77 (dd, *J* = 3.0 Hz, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 8.0 Hz, 2H), 7.19-7.43 (m, 19H), 6.66 (d, $J_{1,2}$ = 3.5 Hz, 1H, H-1), 5.93 (m, 1H, CH_2CH=CH_2), 5.38-5.43 (m, 2H, H-3, CH_2CH=CH_2), 5.29 (d, *J* = 10.5 Hz, 1H, CH_2CH=CH_2), 4.92 (d, *J* = 11.0 Hz, 1H, C*H*HPh), 4.63 (d, *J* = 11.0 Hz, 1H, CH*H*Ph), 4.53-4.62 (m, 3H, H-7, CH_2CH=CH_2), 4.31-4.42 (m, 4H,H-6a, H-6b, CH_2 Fmoc), 4.25(t, *J* = 7.5 Hz, 1H, CH Fmoc), 4.14 (m, 1H, H-5), 3.66 (dd, $J_{2,1}$ = 3.5 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 3.63 (t, $J_{4,3}$ = 9.5 Hz, 1H, H-4), 3.26 (dd, $J_{8a,7}$ = 6.5 Hz, $J_{8a,8b}$ = 14.0 Hz, 1H, H-8b), 3.08 (dd, $J_{8a,7}$ = 6.5 Hz, $J_{8a,8b}$ = 14.0 Hz, 1H, H-8a).

3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(*S*)-2-(phenylthiomethyl)benzyl]-*α*/*β*-D-glucopyranosyl trichloroacetimidate (5). Compound **14** (0.61 g, 0.89 mmol) was dissolved in THF (3 mL) in a Teflon reaction bottle. HF·pyridine (1.5 mL) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EtOAc (10 mL) and sat. aq. $NaHCO_3$ (10 mL) was slowly added. The organic layer was dried ($MgSO_4$), filtered,

and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 30% - EtOAc in PE). The purified lactol (0.50 g, 0.88 mmol) was dissolved in CH_2Cl_2 (3 mL) and trichloroacetonitrile (3 mL). The resulting mixture was cooled to 0°C and a catalytic amount of 60% sodium hydride in mineral oil suspension (3.6 mg, 0.09 mmol, 0.1 equiv) was added. The reaction mixture was stirred for 1 hr at 0°C. The solution was filtered through a short plug of silica gel which was rinsed with EtOAc. The filtrate was concentrated *in vacuo* and silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded **5** (0.51 g, 0.71 mmol, 80 % over two steps) as a white foam (α/β = 1:2). TLC (EtOAc:PE, 30:70 v/v): R_f = 0.30; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +51.1 (c = 0.1 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.75 (s, 1H, C(N*H*)CCl_3 α), 8.62 (s, 1H, C(N*H*)CCl_3 β), 7.13-7.38 (m, 15H), 6.63 (d, $J_{1/2}$ = 3.4 Hz, 1H, α-H-1), 5.88 (d, $J_{1/2}$ = 7.5 Hz, 1H, β-H-1), 5.58 (t, $J_{3/4}$ = 9.5 Hz, 1H, α-H-3), 5.25 (t, $J_{3,4}$ = 8.5 Hz, 1H, β-H-3), 4.96 (t, $J_{7,8a/b}$ = 7.0 Hz, 1H, □-H-7), 4.43-4.51 (m, 4H, CH_2Ph α, CH_2Ph β), 4.13-4.31 (m, 4H, α-H-6a,b,β-H-6a,b), 4.13 (m, 1H, α-H-5), 3.75 (m, 1H, β-H-5), 3.58 (m, 3H, β-H-4, β-H-2, α-H-2), 3.51 (t, $J_{4,3}$ = 9.5 Hz, 1H, α-H-4), 3.40 (dd, $J_{8b,7}$ = 7.0 Hz, $J_{8b,8a}$ = 13.0 Hz, 1H, β-H-8b), 3.27 (dd, $J_{8b,7}$ = 6.5 Hz, $J_{8b,8a}$ = 13.5 Hz, 1H, α-H-8b), 3.15 (dd, $J_{8a,7}$ = 7.0 Hz, $J_{8a,8b}$ = 13.0 Hz, 1H, β-H-8a), 3.07 (dd, $J_{8a,7}$ = 6.5 Hz, $J_{8a,8b}$ = 14.0 Hz, 1H, α-H-8a), 2.02 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.83 (s, 3H, CH_3); ^{13}C {^1H} NMR(APT) (75 MHz, $CDCl_3$): δ 170.4, 170.4, 169.5, 169.5, 161.0, 160.3, 139.7, 139.6, 137.0, 137.0, 136.5, 136.1, 125.8-129.3, 98.1 (C-1-β), 93.0 (C-1-α), 91.1, 90.7, 81.1 (C-7-β), 80.8 (C-7-α), 75.6 (C-2-β), 75.4 (C-4-α), 75.4 (C-2-α), 75.3 (C-4-β), 74.9 (C-3-β), 76.5, 74.1, 73.0 (C-5-β), 72.5 (C-3-α), 70.8 (C-5-α), 62.4 (C-6-β) 62.2 (C-6-α), 41.2 (C-8-β), 40.6 (C-8-α), 21.0, 20.9, 20.8, 20.7;

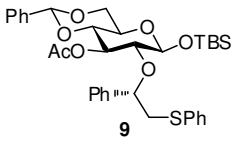
_t_-Butyldimethylsilyl 3,4,6-tri-_O_-acetyl-2-_O_-[(_S_)-2-(phenylthiomethyl)benzyl]-_β_-D-glucopyranose



7

(7). 3,4,6-tri-*O*-acetyl-2-*O*-[(*S*)-2-(phenylthiomethyl)benzyl]-*α*/*β*-D-glucopyranoside (7.57 g, 14.6 mmol) was dissolved in DMF (75 mL). Imidazol (2.98 g, 43.8 mmol, 3.0 equiv) and *tert*-butyldimethylsilylchloride (4.40 g, 29.2 mmol, 2.0 equiv) were added

and the resulting mixture was stirred for 16 h at rt.[21] The reaction mixture was diluted with EtOAc (200 mL) and sat. aq. NH_4Cl (100 mL) was added. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded **7** (8.22 g, 13.0 mmol, 89%) as a colorless oil. TLC (EtOAc:PE, 35:65 v/v): R_f = 0.40; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +43.7 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10-7.35 (m, 10H), 5.06 (t, 1H, $J_{3,2}$ = 9.3 Hz, H-3), 5.03 (t, $J_{7,8a/b}$ = 7.8 Hz, 1H, H-7), 4.76 (m, 1H, H-4), 4.73 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1), 4.06 (m, 2H, H-6), 3.62 (m, 1H, H-5), 3.42 (dd, $J_{8b,7}$ = 6.9 Hz, $J_{8b,8a}$ = 12.6 Hz, 1H, H-8b), 3.25 (dd, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 9.3 Hz, 1H, H-2), 3.13 (dd, $J_{8a,7}$ = 7.5 Hz, $J_{8a,8b}$ = 12.9 Hz, 1H, H-8a), 2.03 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 0.94 (s, 9H, 3 x CH_3), 0.16 (s, 6H, 2 x CH_3); ^{13}C {^{1}H} NMR(APT) (75 MHz, $CDCl_3$): δ 170.6, 170.0, 169.7, 139.8, 136.9, 125.8-129.1, 98.4 (C-1), 81.2 (C-7), 77.9 (C-2), 73.5 (C-3), 71.4 (C-5), 69.2 (C-4), 62.5 (C-6), 40.8 (C-8), 25.8, 20.8, 20.7, 20.6, 18.0, -4.3, -4.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{44}O_9SSi$, 655.2373; found, 655.2331.

***t*-Butyldimethylsilyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-[(*S*)-2-(phenylthiomethyl)benzyl]-*β*-D-glucopyranose (9).** 

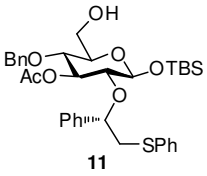
9

A catalytic amount of sodium methoxide was added to a stirred solution of **7** (4.86 g, 7.70 mmol) in methanol (50 mL) The reaction mixture was stirred for 4 h and neutralized upon addition of Dowex® 50W X8-200 H^+ resin. The resin was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in DMF (50 mL) followed by the addition of benzaldehydedimethyl acetal (1.39 mL, 9.24 mmol, 1.20 equiv) and a catalytic amount of *p*-TsOH·H_2O. The mixture was stirred for 16 h at rt. Triethylamine (2 mL) was added and the mixture was concentrated *in vacuo*. The residue was dissolved in pyridine (30 mL) and acetic anhydride (20 mL) was added. The reaction mixture was stirred for 4 h after which the volatiles were removed under reduced pressure. Silica gel purification (0% → 10% - EtOAc in PE) of the residue afforded **9** (4.40 g, 6.93 mmol, 90%) as a white solid. TLC (EtOAc:PE, 15:85 v/v): R_f = 0.40;

$[\alpha]^{D}_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +55.2 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11-7.39 (m, 15H), 5.36 (s, 1H), 5.17 (t, $J_{3,2}$ = 9.6 Hz, 1H, H-3), 5.03 (t, $J_{7,8a/b}$ = 7.2 Hz, 1H, H-7), 4.84 (d, $J_{1,2}$ = 7.0 Hz, 1H, H-1), 4.25 (dd, $J_{6a,5}$ = 4.5 Hz, $J_{6a,6b}$ = 12.6 Hz, 1H, H-6a), 3.66 (m, 1H, H-6b), 3.41 (m, 3H, H-4, H-5, H-8b), 3.27 (dd, $J_{2,1}$ = 7.2 Hz, $J_{2,3}$ = 9.0 Hz, 1H, H-2), 3.16 (dd, $J_{8a,7}$ = 7.5 Hz, $J_{8a,8b}$ = 12.9 Hz, 1H, H-8a), 1.88 (s, 3H, CH_3), 0.95 (s, 9H, 3 x CH_3), 0.16 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C {^{1}H} NMR(APT) (75 MHz, $CDCl_3$): δ 169.7, 139.8, 136.9, 136.8, 125.2-129.2, 101.2, 98.9 (C-1), 81.2 (C-7), 78.8 (C-4), 78.7 (C-2), 72.2 (C-3), 68.6 (C-6), 65.9 (C-5), 40.7 (C-8), 25.8, 21.0, 17.6, -4.2, -4.6; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{35}H_{44}O_7SSi$, 659.2475; found, 659.2411.

***t*-Butyldimethylsilyl 3-*O*-allyloxycarbonyl-4,6-*O*-benzylidene-2-*O*-[(*S*)-2-(phenylthiomethyl) benzyl]-*β*-D-glucopyranose (10).** A catalytic amount of sodium methoxide was added to a stirred solution of **7** (3.02 g, 4.78 mmol) in methanol (40 mL). The reaction mixture was stirred for 4 h at rt and neutralized upon addition of Dowex® 50W X8-200 H^+ resin. The resin was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in DMF (40 mL) followed by the addition of benzaldehydedimethyl acetal (0.62 mL, 5.73 mmol, 1.20 equiv) and a catalytic amount of *p*-TsOH. The mixture was stirred for 16 h at rt. Triethylamine (2 mL) was added and the mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (40 mL) and the mixture was cooled to 0°C, followed by the addition of AllocCl (0.61 mL, 5.73 mmol, 1.20 equiv) and TMEDA (1.10 mL. 7.17 mmol, 1.50 equiv). The reaction mixture was stirred for 4 h at rt. The mixture was diluted with CH_2Cl_2 (50 mL) and sat. aq. NaCl (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **10** (2.63 g, 3.87 mmol, 81%) as a white solid. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.50; $[\alpha]^{D}_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +60.4 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12-7.40 (m, 15H), 5.95 (m, 1H, CH_2CH=CH_2), 5.36 (m, 2H, C-7′, CH_2CH=CH_2), 5.27 (d, *J* = 10.0 Hz, 1H, CH_2CH=CH_2), 5.09 (t, $J_{7,8a/b}$ =

6.5 Hz, 1H, H-7), 4.99 (t, $J_{3,2}$ = 9.0 Hz, 1H, H-3), 4.85 (d, $J_{1,2}$ = 7.0 Hz, 1H, H-1), 4.59 (d, J = 5.5 Hz, 2H, CH_2CH=CH_2), 3.68 (dd, $J_{6b,6a}$ = 11.0 Hz, $J_{6b,5}$ = 5.0 Hz, 1H, H-6b), 3.68 (t, $J_{6b,6a}$ = 9.5 Hz, 1H, H-6b), 3.43-3.48 (m, 3H, H-4, H-5, H-8b), 3.31 (dd, $J_{2,1}$ = 7.5 Hz, $J_{2,3}$ = 9.0 Hz, 1H, H-2), 3.17 (dd, $J_{8a,7}$ = 7.0 Hz, $J_{8a,8b}$ = 12.5 Hz, 1H, H-8a), 0.96 (s, 9H, 3 x CH_3), 0.17 (s, 3H, CH_3), 0.16 (s, 3H, CH_3); ^{13}C {^{1}H} NMR(APT) (75 MHz, $CDCl_3$): δ 154.1, 139.4, 137.0, 136.9, 131.4, 125.7-129.1, 118.9, 101.3, 98.8 (C-1), 81.3 (C-7), 78.7 (C-2), 78.3 (C-4), 76.6 (C-3), 68.6 (C-6), 68.6, 65.8 (C-6), 40.9 (C-8), 25.8, 17.9, -4.2, -4.6. HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{37}H_{46}O_8SSi$, 701.2580; found, 701.2523.

***t*-Butyldimethylsilyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-[(*S*)-2-(phenylthiomethyl)benzyl]-*β*-D-glucopyranose (11).** 

11

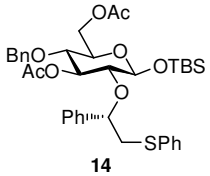
9 (3.94 g, 6.20 mmol) was dissolved in CH_2Cl_2 (60 mL) and activated MS4Å were added. The mixture was stirred for 5 min at rt before being cooled to -78°C. Triethylsilane (1.48 mL, 9.30 mmol, 1.50 equiv) was added followed by the addition of dichlorophenylborane (1.37 mL, 10.5 mmol, 1.70 equiv). The reaction mixture was stirred for 45 min at -78°C and quenched upon addition of MeOH (3 mL) and Et_3N (3 mL). The mixture was warmed to rt, diluted with EtOAc (150 mL) and sat. aq. NaCl (50 mL) was added. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **11** (3.80 g, 5.90 mmol, 95%) as a colorless oil. TLC (EtOAc:PE, 15:85 v/v): R_f = 0.20; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +44.3 (c = 0.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08-7.33 (m, 15H), 5.13 (t, $J_{3,2}$ = 9.3 Hz, 1H, H-3), 5.02 (dd, $J_{7,8a}$ = 6.3 Hz, $J_{7,8b}$ = 7.5 Hz, 1H, H-7), 4.76 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 4.43 (m, 2H, CH_2Ph), 3.76 (m, 1H, H-6a), 3.63 (m, 1H, H-6b), 3.37 (m, 3H, H-4, H-5, H-8b), 3.16 (m, 2H, H-2, H-8a), 1.81 (m, 1H, OH-6), 1.79 (s, 3H, CH_3), 0.95 (s, 9H, 3 x CH_3), 0.15 (s, 6H, 2 x CH_3); ^{13}C {^{1}H} NMR(APT) (75 MHz, $CDCl_3$): δ 169.7, 139.8, 137.5, 136.7, 125.6-129.0, 98.3 (C-1), 80.9 (C-7), 78.2 (C-2), 75.8 (C-4), 74.9 (C-5), 74.7 (C-3), 74.2, 61.5 (C-6), 40.6 (C-8), 25.7, 21.0, 17.8, -4.2, -4.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{35}H_{46}O_7SSi$, 661.2631; found, 661.2595.

***t*-Butyldimethylsilyl 3-*O*-allyloxycarbonyl-4-*O*-benzyl-2-*O*-[(*S*)-2-(phenylthiomethyl)benzyl]-*β*-D-glucopyranose (12). 10** (1.67 g, 2.46 mmol) was dissolved in CH_2Cl_2 (30 mL) and activated MS4Å were added. The mixture was stirred for 5 min at rt before being cooled to -78°C. Triethylsilane (0.59 mL, 3.69 mmol, 1.50 equiv) was added followed by the addition of dichlorophenylborane (0.54 mL, 4.18 mmol, 1.70 equiv). The reaction mixture was stirred for 45 min at -78 °C and quenched upon addition of MeOH (1 mL) and Et_3N (1 mL). The mixture was warmed to rt, diluted with EtOAc (70 mL) and sat. aq. NaCl (30 mL) was added. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **12** (1.42 g, 2.1 mmol, 86%) as a colorless oil. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.40; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +57.2 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10-7.32 (m, 15H), 5.93 (m, 1H, CH_2CH=CH_2), 5.36 (d, *J* = 17.4 Hz, 1H, CH_2CH=CH_2), 5.26 (d, *J* = 10.2 Hz, 1H, CH_2CH=CH_2), 5.06 (t, $J_{7,8a/b}$ = 7.2 Hz, 1H, H-7), 4.93 (t, $J_{3,2}$ = 9.3 Hz, 1H, H-3), 4.74 (d, $J_{1,2}$ = 7.2 Hz, 1H, H-1), 4.55 (m, 4H, CH_2Ph, CH_2CH=CH_2), 3.77 (m, 1H, H-6a), 3.60 (m, 1H, H-6b), 3.43 (m, 3H, H-4, H-5, H-8b), 3.20 (dd, $J_{2,1}$ = 7.5 Hz, $J_{2,3}$ = 9.6 Hz, 1H, H-2), 3.14 (dd, $J_{8a,7}$ = 7.2 Hz, $J_{8a,8b}$ = 12.9 Hz, 1H, H-8a), 1.78 (bt, $J_{OH\text{-}6,6a/b}$ = 5.7 Hz, 1H, OH-6), 0.94 (s, 9H, 3 x CH_3), 0.15 (s, 3H, CH_3), 0.14 (s, 3H, CH_3); ^{13}C {^{1}H} NMR(APT) (75 MHz, $CDCl_3$): δ 154.4, 139.6, 137.5, 136.9, 131.4, 125.6-129.3, 119.1, 98.1 (C-1), 81.0 (C-7), 80.0 (C-3), 77.8 (C-2), 76.5 (C-5), 75.7 (C-4), 74.5, 68.5, 61.7 (C-6), 40.9 (C-8), 25.8, 17.9, -4.3, -4.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{37}H_{48}O_8SSi$, 703.2737; found, 703.2765.

***t*-Butyldimethylsilyl 4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*β*-D-glucopyranoside (13).** Triethyl silane (927 µL, 5.79 mmol, 3.0 equiv) and dichlorophenyl borane (753 µL, 5.79 mmol, 3.0 equiv) were added to a solution of *t*-Butyldimethylsilyl 4,6-*O*-benzylidene-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*β*-D-glucose (See **9**) (1.15 g, 1.93 mmol) in dichloromethane (20 mL) at -78°C. After stirring at the same temperature for 20 min, the reaction mixture was quenched with methanol (2 mL) and triethylamine (2 mL) and then concentrated *in*

vacuo. Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **13** (807 mg, 1.35 mmol, 70%) as a colorless syrup. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.48; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +9.2 (*c* = 2.6 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.11 (m, 15H), 5.13 (t, 1H, *J* = 7.0 Hz, H-7), 4.84 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.69 (d, 1H, *J* = 7.5 Hz, H-1), 4.56 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 3.79-3.76 (m, 1H, H-6a), 3.66-3.60 (m, 2H, H-6b, H-3), 3.48 (dd, 1H, *J* = 12.5 Hz, *J* = 7.0 Hz, H-8a), 3.34-3.28 (m, 2H, H-5, H-4), 3.22 (dd, 1H, *J* = 12.5, 7.0 Hz, H-8b), 3.05 (dd, 1H, *J* = 9.5 Hz, *J* = 7.5 Hz, H-2), 0.95 (s, 9H, 3 x CH_3), 0.16 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.14, 138.25, 129.29, 128.90, 128.78, 128.74, 128.58, 128.43, 127.96, 127.80, 127.53, 125.94, 97.87, 80.88, 80.23, 77.32, 76.39, 74.83, 74.44, 62.37, 40.89, 25.87, 17.98, -4.07, -4.57; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{33}H_{44}O_6SSi$, 619.2526; found, 619.2543.

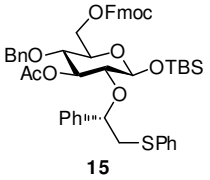
***t*-Butyldimethylsilyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(*S*)-2-(phenylthiomethyl)benzyl]-β-D-glucopyranose (14).** Compound **11** (1.05 g, 1.65 mmol) was dissolved in a mixture of pyridine (7 mL) and acetic anhydride (3 mL) and the resulting mixture was stirred for 2 h at rt. The volatiles were removed under reduced pressure and silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **14** (1.02 g, 1.50 mmol, 91 %) as a white foam. TLC (EtOAc:PE, 20:80 v/v): R_f = 0.30; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +57.4 (*c* = 0.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.09-7.35 (m, 15H), 5.15 (t, *J* = 9.3 Hz, 1H, H-3), 5.05 (dd, $J_{7,8a}$ = 6.0 Hz, $J_{7,8b}$ = 7.8 Hz, 1H, H-7), 4.72 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 4.60 (d, *J* = 11.1 Hz, 1H, C*H*HPh), 4.45 (d, *J* = 11.1 Hz, 1H, CH*H*Ph), 4.28 (dd, $J_{6b,6a}$ = 11.4 Hz, $J_{6b,5}$ = 2.1 Hz, 1H, H-6b), 4.07 (dd, $J_{6a,6b}$ = 11.7 Hz, $J_{6a,5}$ = 6.3 Hz, 1H, H-6a), 3.55 (m, 1H, H-5), 3.44 (dd, $J_{8b,8a}$ = 12.3 Hz, $J_{8b,7}$ = 6.3 Hz, 1H, H-8b), 3.33 (t, $J_{4,3}$ = 9.3 Hz, 1H, H-4), 3.12-3.21 (m, 2H, H-2, H-8a), 2.02 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 0.94 (s, 9H, 3 x CH_3), 0.15 (s, 3H, CH_3), 0.14 (s, 3H, CH_3); ^{13}C {^1H} NMR(APT) (75 MHz, $CDCl_3$): δ 170.6, 169.7, 140.0, 137.3, 136.8, 125.7-129.1, 98.4 (C-1), 81.0 (C-7), 78.3 (C-2), 76.2 (C-4), 75.4 (C-3), 74.8, 74.3 (C-



14

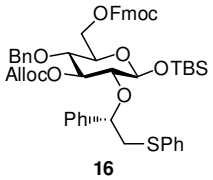
5), 63.0 (C-6), 40.7 (C-8), 25.8, 21.1, 20.7, 17.9, -4.3, -4.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{37}H_{48}O_8SSi$, 703.2737; found, 703.2689.

***t*-Butyldimethylsilyl 3-*O*-acetyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-[(*S*)-2-(phenylthiomethyl)benzyl]-*β*-D-glucopyranose (15). 11** (2.75 g, 4.32 mmol) was dissolved in pyridine (50 mL) and the resulting mixture was cooled to 0°C. FmocCl (2.23 gram, 8.64 mmol, 2.0 equiv) was added and stirred for 3 h at rt. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (2 x 50 mL), sat. aq. $CuSO_4$ (2 x 50 mL) and water (2 x 50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **15** (3.50 g, 4.02 mmol, 93%) as a white foam. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.50; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +43.0 (*c* = 0.1 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 6.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.10-7.33 (m, 17H), 5.16 (t, $J_{3,2}$ = 9.5 Hz, 1H, H-3), 5.05 (t, $J_{7,8a/b}$ = 7.0 Hz, 1H, H-7), 4.74 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 4.45 (dd, *J* = 11.5 Hz, 2H, CH_2Ph), 4.32-4.43 (m, 3H, H-6b, CH_2 Fmoc), 4.24 (t, *J* = 7.5 Hz, 1H, CH Fmoc), 4.16 (dd, $J_{6a,5}$ = 6.0 Hz, $J_{6a,6b}$ = 11.5 Hz, 1H, H-6a), 3.56 (m, 1H, H-5), 3.45 (dd, $J_{8b,7}$ = 6.5 Hz, $J_{8b,8a}$ = 12.5 Hz, 1H, H-8b), 3.40 (t, $J_{4,3}$ = 10.0 Hz, 1H, H-4), 3.27 (t, $J_{2,3}$ = 9.5 Hz, 1H, H-2), 3.16 (dd, $J_{8a,7}$ = 8.0 Hz, $J_{8a,8b}$ = 12.5 Hz, 1H, H-8a), 1.84 (s, 3H, CH_3), 0.94 (s, 9H, 3 x CH_3), 0.15 (s, 6H, 2 x CH_3); ^{13}C {^1H} NMR(APT) (75 MHz, $CDCl_3$): δ 169.8, 154.9, 143.4, 143.2, 141.3, 141.2, 140.0, 137.3, 136.9, 120.0-129.2, 98.4 (C-1), 80.9 (C-7), 78.2 (C-2), 76.4 (C-4), 75.0 (C-3), 74.3, 72.5 (C-5), 69.9, 66.4 (C-6), 46.6, 40.7 (C-8), 25.8, 21.1, 17.9, -4.2, -4.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{50}H_{56}O_9SSi$, 883.3312; found, 883.3387.



15

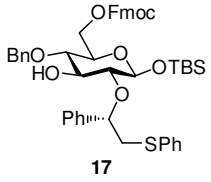
***t*-Butyldimethylsilyl 3-*O*-allyloxycarbonyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-[(*S*)-2-(phenylthiomethyl)benzyl]-*β*-D-glucopyranose (16). 12** (1.08 g, 1.59 mmol) was dissolved in pyridine (50 mL) and the resulting mixture was cooled to 0°C.



16

FmocCl (0.82 g, 3.18 mmol, 2.0 equiv) was added and stirred for 3 h at rt. The reaction mixture was diluted with EtOAc (100 mL), washed with water (2 x 50 mL), sat. aq. $CuSO_4$ (2 x 50 mL) and water (2 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Silica gel purification (0% → 15% - EtOAc in PE) of the residue afforded **16** (1.26 g, 1.4 mmol, 88%) as a white foam. TLC (EtOAc:PE, 20:80 v/v): R_f = 0.40; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +49.8 (*c* = 0.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.57 (dd, *J* = 7.2 Hz, *J* = 3.3 Hz, 2H), 7.09-7.41 (m, 19H), 5.93 (m, 1H, CH_2CH=CH_2), 5.38 (dd, *J* = 16.8 Hz, *J* = 1.2 Hz, 1H, CH_2CH=CH_2), 5.26 (d, *J* = 10.2 Hz, 1H, CH_2CH=CH_2), 5.06 (t, $J_{7,8a/b}$ = 6.6 Hz, 1H, H-7), 4.96 (t, $J_{3,2}$ = 9.6 Hz, 1H, H-3), 4.72 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 4.57 (m, 3H, CH_2CH=CH_2, CH*H*Ph), 4.35 (m, 4H, C*H*HPh, CH_2 Fmoc, H-6b), 3.55 (m, 1H, H-5), 3.44 (m, 2H, H-4, H-8b), 3.24 (dd, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 9.9 Hz, 1H, H-2), 3.19 (m, 2H, H-6a, CH Fmoc), 3.14 (dd, $J_{8a,7}$ = 7.5 Hz, $J_{8a,8b}$ = 12.9 Hz, 1H, H-8a), 0.93 (s, 9H, 3 x CH_3), 0.14 (s, 3H, CH_3), 0.13 (s, 3H, CH_3); ^{13}C {^1H} NMR(APT) (75 MHz, $CDCl_3$): δ 154.9, 154.4, 143.4, 143.2, 141.3, 141.2, 139.7, 137.2, 136.9, 131.4, 120.1-129.0, 119.3, 98.2 (C-1), 81.0 (C-7), 80.1 (C-3), 77.8 (C-2), 76.2 (C-4), 74.6, 72.4 (C-5), 69.9, 68.6, 66.4 (C-6), 46.6, 41.0 (C-8), 25.8, 17.9, -4.3, -4.8; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{52}H_{58}O_{10}SSi$, 925.3418; found, 925.3391.

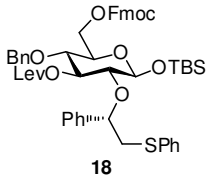
***t*-Butyldimethylsilyl 4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (17).** 9-Fluorenylmethyl chloroformate (680 mg, 2.62 mmol, 2.0 equiv) was added to a solution of **13** (784 mg, 1.31 mmol) in pyridine (20 mL) at rt. After stirring for 3 h at rt, the reaction mixture was concentrated *in vacuo*, and then diluted with dichloromethane (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo.* Silica gel purification (0% → 25% - EtOAc in PE) of the residue afforded **17** (620 mg, 0.99 mmol, 76%) as a colorless syrup. TLC (EtOAc:PE, 25:70 v/v): R_f = 0.34; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +18.1 (*c* = 1.9 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78-7.12 (m, 23H), 5.16 (t, 1H, *J* = 7.0 Hz, H-7), 4.87 (d,



17

1H, *J* = 11.0 Hz, C*H*HPh), 4.67 (d, 1H, *J* = 8.0 Hz, H-1), 4.53 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.40-4.04 (m, 5H, H-6a, H-6b, CH_2, CH Fmoc), 3.66 (ddd, 1H, *J* = 9.5 Hz, *J* = 8.0 Hz, *J* = 2.0 Hz, H-3), 3.54-3.52 (m, 1H, H-5), 3.49 (dd, 1H, *J* = 12.5 Hz, *J* = 7.0 Hz, H-8a), 3.26 (t, 1H, *J* = 9.5 Hz, H-4), 3.23 (dd, 1H, *J* = 12.5 Hz, *J* = 7.0 Hz, H-8b), 3.09 (dd, 1H, *J* = 9.5, *J* = 8.0 Hz, H-2), 0.94 (s, 9H, 3 x CH_3), 0.16 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.03, 143.44, 143.32, 141.29, 141.26, 140.19, 138.06, 136.84, 129.28, 128.93, 128.77, 128.42, 127.98, 127.87, 127.80, 127.60, 127.50, 127.14, 127.10, 125.93, 125.26, 125.18, 124.70, 120.08, 120.03, 97.88, 80.85, 80.16, 77.21, 74.35, 72.67, 69.89, 66.92, 65.20, 50.36, 46.69, 40.89, 25.89, 17.98, -4.15, -4.75; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{48}H_{54}O_8SSi$, 841.3206; found, 841.3213.

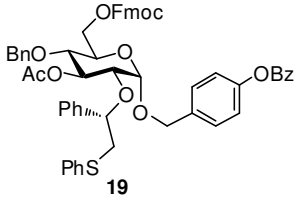
***t*-Butyldimethylsilyl 4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-3-*O*-levulinoyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-glucopyranoside (18).** Levulinic acid (885 mg, 7.63 mmol, 7.0 equiv), 1,3-dicyclohexylcarbodiimide (787 mg, 3.82 mmol, 3.5 equiv) and 4-(dimethylamino)-pyridine (6 mg, 0.05 mmol, 0.05 equiv) were added to a solution of **17** (890 mg, 1.09 mmol) in dichloromethane (20 mL) at 0°C. After stirring overnight at room temperature, the reaction mixture was filtered and concentrated *in vacuo.* Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded **18** (800 mg, 0.87 mmol, 80%) as a colorless syrup. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.32; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +40.0 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.07 (m, 23H), 5.16 (t, 1H, *J* = 9.6 Hz, H-3), 5.05 (t, 1H, *J* = 7.2 Hz, H-7), 4.61 (d, 1H, *J* = 7.2 Hz, H-1), 4.73 (d, 1H, *J* = 11.1 Hz, C*H*HPh), 4.44 (d, 1H, *J* = 11.1 Hz, C*H*HPh), 4.43-4.08 (m, 5H, H-6a, H-6b, Fmoc), 3.58-3.52 (m, 1H, H-5), 3.47 (dd, 1H, *J* = 12.9 Hz, *J* = 6.9 Hz, H-8a), 3.38 (t, 1H, *J* = 9.6 Hz, H-4), 3.22 (dd, 1H, *J* = 9.6 Hz, *J* = 7.2 Hz, H-2), 3.17 (dd, 1H, *J* = 12.9 Hz, *J* = 6.9 Hz, H-8b), 2.60-2.29 (m, 4H, Lev), 2.15 (s, 3H, CH_3), 0.92 (s, 9H, 3 x CH_3), 0.14 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.25, 171.60, 154.89, 143.39, 143.25, 141.28, 141.26, 140.04, 137.44, 136.99, 129.05, 128.69, 128.43, 128.34, 128.28, 127.95, 127.89, 127.14, 125.65, 125.21, 125.12, 120.05, 98.45,



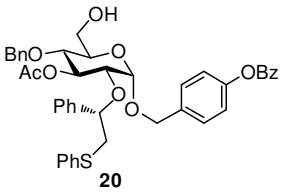
18

80.97, 78.11, 76.42, 75.43, 74.27, 72.52, 69.92, 66.43, 46.67, 40.65, 37.61, 29.92, 27.93, 25.86, 17.96, -4.26, -4.71; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{53}H_{60}O_{10}SSi$, 939.3574; found, 939.3571.

***p*-Benzoyloxybenzyl 3-*O*-acetyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranoside (19).** A mixture of glycosyl donor **2** (495 mg, 0.56 mmol) and activated molecular sieves (4Å) in dichloromethane (15 mL) was stirred for 10 min at rt under an atmosphere of argon. After cooling to -40°C, trimethylsilyl trifluoromethanesulfonate (102 µL, 0.56 mmol, 1.0 equiv) was added and the reaction mixture stirred for 15 min. *p*-benzoyloxybenzyl alcohol (192 mg, 0.84 mmol, 1.5 equiv) and 2,6-di-*tert*-butyl-4-methyl pyridine (344 mg, 1.68 mmol, 3.0 equiv) were added. The reaction mixture was allowed to warm slowly (5 h) to room temperature, and kept overnight at rt. After quenching with aqueous saturated $NaHCO_3$ (15 mL), the organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel purification (0% → 0.5% - acetone in DCM) of the residue afforded **19** (509 mg, 95%) as a colorless syrup. TLC (acetone:DCM, 1:99 v/v): R_f = 0.34; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +34.0 (*c* = 0.2 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.22-8.19 (m, 2H), 7.76-7.13 (m, 30H), 5.56 (t, 1H, *J* = 9.6 Hz, H-3), 5.16 (d, 1H, *J* = 3.6 Hz, H-1), 4.76 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.52-4.22 (m, 8H, H-7, H-6a, H-6b, C*H*HPh × 2, Fmoc), 3.96-3.91 (m, 1H, H-5), 3.47 (t, 1H, *J* = 9.6 Hz, H-4), 3.46 (dd, 1H, *J* = 9.6 Hz, *J* = 3.6 Hz, H-2), 3.31 (dd, 1H, *J* = 13.5 Hz, *J* = 7.8 Hz, H-8a), 3.12 (dd, 1H, *J* = 13.5 Hz, *J* = 5.4 Hz, H-8b), 1.72 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.73, 165.07, 154.97, 150.62, 143.40, 143.18, 141.27, 140.37, 137.34, 136.54, 134.64, 133.56, 130.19, 129.60, 129.55, 129.45, 128.99, 128.86, 128.81, 128.67, 128.57, 128.55, 128.49, 128.35, 128.02, 127.96, 127.89, 127.66, 127.15, 126.88, 125.97, 125.13, 125.07, 121.71, 120.07, 95.69, 81.44, 76.26, 74.40, 73.03, 69.98, 69.43, 68.57, 66.18, 46.71, 41.61, 20.92; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{58}H_{52}O_{11}S$, 979.3128; found, 979.3145.

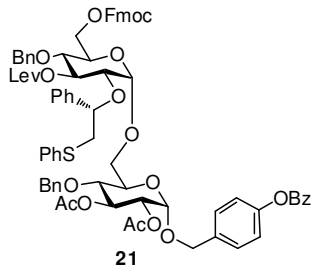


19

***p*-Benzoyloxybenzyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranoside (20).** 

20

Triethylamine (4 mL) was added to a solution of **19** (509 mg, 0.53 mmol) in dichloromethane (16 mL) at 0°C. The reaction mixture was stirred for 3 h at rt, and then concentrated *in vacuo*. Silica gel purification (0% → 0.5% - acetone in DCM) of the residue afforded **20** (358 mg, 0.49 mmol, 92%) as a white solid. TLC (acetone:DCM, 1:99 v/v): R_f = 0.15; $[\alpha]^{D}_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +37.1 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22-8.20 (m, 2H), 7.65-7.13 (m, 22H), 5.54 (t, 1H, *J* = 10.0 Hz, H-3), 5.14 (d, 1H, *J* = 4.0 Hz, H-1), 4.74 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.51 (s, 2H, C*H*HPh × 2), 4.40 (dd, 1H, *J* = 8.0Hz, *J* = 5.5 Hz, H-7), 3.74-3.67 (m, 3H, H-5, H-6a, H-6b), 3.47 (t, 1H, *J* = 10.0 Hz, H-4), 3.40 (dd, 1H, *J* = 10.0 Hz, *J* = 4.0 Hz, H-2), 3.30 (dd, 1H, *J* = 13.5 Hz, *J* = 8.0 Hz, H-8a), 3.12 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, H-8b), 1.68 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.81, 150.58, 140.41, 137.71, 134.88, 133.59, 130.21, 129.55, 129.37, 128.99, 128.88, 128.55, 128.57, 128.47, 128.31, 127.97, 127.90, 126.86, 125.96, 121.68, 95.92, 81.49, 76.00, 74.40, 73.06, 70.74, 69.50, 61.40, 41.69, 29.71, 20.91; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{43}H_{42}O_9S$, 757.2447; found, 757.2449.

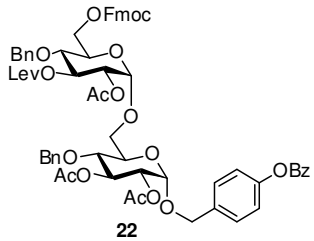
***p*-Benzoyloxybenzyl 4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-3-*O*-levulinoyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranoside (21).** 

21

A mixture of glycosyl donor **3** (464 mg, 0.49 mmol) and activated molecular sieves (4Å) in dichloromethane (10 mL) was stirred for 10 min under an atmosphere of argon at rt. After cooling to -40°C, trimethylsilyl trifluoromethanesulfonate (89 µL, 0.49 mmol, 1.0 equiv) was stirred for 15 min. Glycosyl acceptor **20** (358 mg, 0.49 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methyl pyridine (301 mg, 1.47 mmol, 3.0 equiv) were added. The reaction mixture was allowed to warm slowly (5 h) to rt, and kept overnight at rt. After quenching with aqueous saturated

$NaHCO_3$ (15 mL), the organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel purification (0% → 1% - acetone in DCM) of the residue afforded **21** (582 mg, 88%) as a white solid. TLC (acetone:DCM, 2:98 v/v): R_f = 0.36; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +12.9 (*c* = 0.6 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, 2H, *J* = 7.5 Hz), 7.75-7.06 (m, 45H), 5.59 (t, 1H, *J* = 9.5 Hz, H-3'), 5.54 (t, 1H, *J* = 9.5 Hz, H-3), 5.18 (d, 1H, *J* = 3.5 Hz, H-1'), 5.10 (d, 1H, *J* = 3.5 Hz, H-1), 4.80 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.63 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.59 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.54 (s, 2H, C*H*HPh × 2), 4.51 (t, 1H, *J* = 6.5 Hz, H-7), 4.47 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.39-4.21 (m, 6H, H-7', H-6a', H-6b', Fmoc), 3.95-3.92 (m, 1H, H-5), 3.89-3.87 (m, 1H, H-5'), 3.81 (dd, 1H, *J* = 12.0 Hz, *J* = 4.5 Hz, H-6a), 3.74 (d, 1H, *J* = 12.0 Hz, H-6b), 3.63 (t, 1H, *J* = 9.5 Hz, H-4), 3.52 (dd, 1H, *J* = 9.5 Hz, *J* = 3.5 Hz, H-2), 3.49 (t, 1H, *J* = 9.5 Hz, H-4'), 3.44 (dd, 1H, *J* = 9.5 Hz, *J* = 3.5 Hz, H-2'), 3.26 (dd, 1H, *J* = 13.5 Hz, *J* = 7.5 Hz, H-8a'), 3.18 (dd, 1H, *J* = 13.5 Hz, *J* = 6.5 Hz, H-8a), 3.06 (dd, 1H, *J* = 13.5 Hz, *J* = 6.0 Hz, H-8b'), 3.00 (dd, 1H, *J* = 13.5 Hz, *J* = 6.5 Hz, H-8b), 2.60-2.48 (m, 2H, Lev), 2.2.37-2.20 (m, 2H, Lev), 2.12 (s, 3H, Lev), 1.59 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.56, 169.87, 165.06, 154.94, 150.47, 143.38, 143.20, 141.29, 141.27, 140.41, 140.11, 137.89, 137.58, 136.74, 136.60, 134.86, 133.51, 130.19, 129.67, 129.42, 128.91, 128.76, 128.69, 128.54, 128.42, 128.32, 128.21, 128.08, 127.99, 127.92, 127.86, 127.65, 127.16, 126.98, 126.78, 125.80, 125.16, 125.09, 121.61, 120.07, 96.66, 95.23, 81.44, 80.40, 77.61, 77.22, 76.45, 76.37, 75.99, 74.53, 74.22, 73.55, 73.27, 70.28, 70.00, 68.78, 68.56, 66.13, 65.64, 46.71, 41.76, 41.32, 37.69, 29.91, 27.87, 20.88; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{90}H_{86}O_{18}S$, 1541.5153; found, 1541.5187.

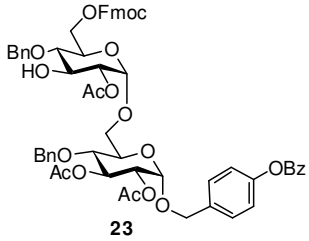
***p*-Benzoyloxybenzyl 2-*O*-acetyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-3-*O*-levulinoyl-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranoside (22).** To a solution of the disaccharide **21** (582 mg, 0.43 mmol) in acetic anhydride (20 mL) was added boron trifluoride diethyl etherate (109 μL, 0.86 mmol, 2.0 equiv) at 0°C. The reaction mixture was stirred for 1 h at the



22

same temperature and then quenched with aqueous saturated $NaHCO_3$ (30 mL). After dilution with dichloromethane (10 mL), the organic layer was separated. The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel purification (0% → 30% - EtOAc in PE) of the residue afforded **22** (477 mg, 94%) as a white solid. TLC (EtOAc:PE, 50:50 v/v): R_f = 0.24; $[\alpha]^{D}_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +48.8 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20-8.18 (m, 2H), 7.77-7.13 (m, 25H), 5.69 (dd, 1H, *J* = 10.5 Hz, *J* = 9.5 Hz, H-3'), 5.57 (t, 1H, *J* = 9.5 Hz, H-3), 5.21 (d, 1H, *J* = 3.5 Hz, H-1'), 4.97 (d, 1H, *J* = 3.5 Hz, H-1), 4.93 (dd, 1H, *J* = 10.5 Hz, *J* = 3.5 Hz, H-2'), 4.74-4.64 (m, 5H, H-2, C*H*HPh × 4), 4.61 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.53 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.47-4.26 (m, 5H, H-6a', H-6b', Fmoc), 4.01-3.98 (m, 1H, H-5'), 3.92-3.89 (m, 1H, H-5), 3.85 (dd, 1H, *J* = 12.5 Hz, *J* = 4.5 Hz, H-6a), 3.76-3.71 (m, 3H, H-6b, H-4', H-4), 2.78-2.17 (m, 4H, Lev), 2.17 (s, 3H, Lev), 2.14 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.90 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.66, 170.53, 170.23, 169.85, 165.05, 154.96, 150.57, 143.40, 143.23, 141.29, 137.60, 137.44, 134.57, 133.58, 130.16, 129.51, 128.93, 128.56, 128.51, 128.18, 128.14, 128.01, 127.93, 127.19, 125.21, 125.13, 121.67, 120.09, 96.38, 94.66, 75.78, 74.81, 74.59, 72.32, 71.98, 71.24, 70.94, 70.75, 70.04, 68.74, 65.92, 65.23, 46.71, 37.64, 29.78, 27.97, 20.87, 20.75, 20.67; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{66}H_{66}O_{20}$, 1201.4045; found, 1201.4186.

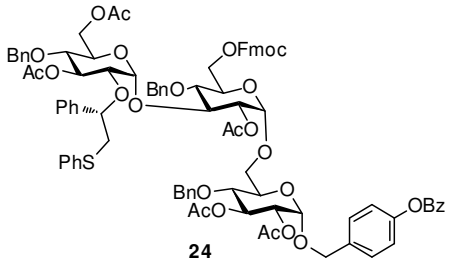
***p*-Benzoyloxybenzyl 2-*O*-acetyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranoside (23).** A solution of hydrazinium acetate (74 mg, 0.80 mmol, 2.0 equiv) in methanol (2 mL) was added to a solution of **22** (477 mg, 0.40 mmol) in dichloromethane (10 mL) at 0°C. After stirring for 3 h at rt, the reaction mixture was concentrated *in vacuo*. Silica gel purification (0% → 30% - EtOAc in PE) of the residue afforded **23** (359 mg, 83%) as a white solid. TLC (Acetone:DCM, 4:96 v/v): R_f = 0.48; $[\alpha]^{D}_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +29.6 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20-8.18 (m, 2H), 7.77-7.13 (m, 25H), 5.59 (t, 1H, *J* = 9.5 Hz, H-



23

3), 5.19 (d, 1H, *J* = 3.5 Hz, H-1), 4.98 (d, 1H, *J* = 3.5 Hz, H-1'), 4.89 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.76-4.70 (m, 4H, H-2, H-2', C*H*HPh × 2), 4.61 (s, 2H, C*H*HPh × 2), 4.53 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.46-4.25 (m, 5H, H-6a', H-6b', Fmoc), 4.15 (t, 1H, *J* = 9.5 Hz, H-3'), 3.95-3.91 (m, 2H, H-5', H-5), 3.86 (dd, 1H, *J* = 11.5 Hz, *J* = 4.5 Hz, H-6a), 3.71-3.66 (m, 2H, H-6b, H-4), 3.57 (t, 1H, *J* = 9.5 Hz, H-4'), 2.16 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.94 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.86, 170.32, 169.81, 165.13, 155.05, 150.55, 143.41, 143.28, 141.31, 137.88, 137.53, 134.55, 133.64, 130.19, 129.46, 128.92, 128.62, 128.59, 128.56, 128.22, 128.10, 128.02, 127.92, 127.86, 127.19, 125.22, 125.17, 121.73, 120.07, 96.25, 94.77, 77.61, 76.19, 75.07, 74.73, 73.52, 72.26, 72.15, 71.24, 70.61, 70.03, 68.85, 68.68, 66.27, 65.60, 46.74, 20.94, 20.89, 20.69; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{61}H_{60}O_{18}$, 1103.3677; found, 1103.3685.

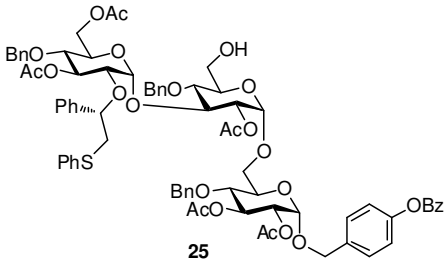
***p*-Benzoyloxybenzyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→3)-2-*O*-acetyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranoside (24).** A mixture of glycosyl donor **5** (469 mg, 0.66 mmol, 2.0 equiv) and activated molecular sieves (4Å) in dichloromethane (15 mL) was stirred for 10 min at rt under an atmosphere of argon. After cooling to -40°C, trimethylsilyl trifluoromethanesulfonate (120 µL, 0.66 mmol, 2.0 equiv) was added and the reaction mixture stirred for 15 min. Glycosyl acceptor **22** (359 mg, 0.33 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (410 mg, 2.0 mmol, 6.0 equiv) were added. The reaction mixture was allowed to warm slowly (5 h) to rt, and kept overnight at rt. After quenching with aqueous saturated $NaHCO_3$ (20 mL), the organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded **23** (478 mg, 0.29 mmol, 89%) as a white solid. TLC (Acetone:DCM, 2:98 v/v): R_f = 0.35; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +55.3 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20-8.18 (m, 2H), 7.75-6.98 (m, 40H), 5.61 (t, 1H, *J* = 10.0



24

Hz, H-3''), 5.57 (t, 1H, *J* = 9.5 Hz, H-3), 5.55 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 5.43 (d, 1H, *J* = 3.5 Hz, H-1''), 5.17 (d, 1H, *J* = 3.5 Hz, H-1'), 4.97 (d, 1H, *J* = 3.5 Hz, H-1), 4.92 (dd, 1H, *J* = 9.5 Hz, *J* = 3.5 Hz, H-2'), 4.78 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.74 (dd, 1H, *J* = 9.5 Hz, *J* = 3.5 Hz, H-2), 4.68 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.64 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.60 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.50-4.38 (m, 5H, H-6a'', H-6b'', C*H*HPh × 3), 4.28-4.21 (m, 4H, H-7'', Fmoc), 4.08-4.05 (m, 2H, H-5', H-5''), 3.94-3.91 (m, 2H, H-6a, H-6a'), 3.78-3.68 (m, 4H, H-6b', H-4', H-3', H-5), 3.42-3.32 (m, 3H, H-4, H-4'', H-6b), 3.32 (dd, 1H, *J* = 10.0 Hz, *J* = 3.5 Hz, H-2''), 2.95 (dd, 1H, *J* = 14.0 Hz, *J* = 7.5 Hz, H-8a''), 2.83 (dd, 1H, *J* = 14.0 Hz, *J* = 5.0 Hz, H-8b''), 2.16 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 1.54 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.14, 170.60, 170.46, 170.23, 169.77, 169.69, 155.06, 150.60, 143.43, 143.39, 141.27, 140.78, 139.09, 137.63, 137.36, 135.78, 134.55, 133.59, 130.18, 129.51, 129.40, 129.36, 129.12, 129.06, 128.98, 128.73, 128.69, 128.57, 128.50, 128.48, 128.46, 128.20, 128.15, 127.99, 127.96, 127.92, 127.90, 127.86, 127.66, 127.27, 127.21, 126.73, 126.65, 126.12, 125.28, 121.72, 119.99, 97.87, 96.51 94.80, 82.56, 81.05, 79.13, 76.32, 76.20, 75.05, 74.86, 74.57, 74.30, 73.26, 72.55, 72.14, 71.23, 70.33, 70.07, 69.76, 68.87, 68.76, 68.44, 66.31, 65.84, 62.52, 46.70, 40.71, 21.04, 20.97, 20.84, 20.81, 20.75, 20.68; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{92}H_{92}O_{25}$, 1651.5546; found, 1651.5576.

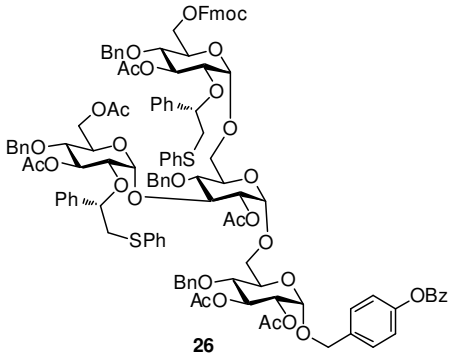
***p*-Benzoyloxybenzyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→3)-2-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranoside (25).** Compound **25** was synthesized from compound **24** (478 mg, 0.29 mmol) according to the procedure described for the synthesis of compound **20**. **25** (405 mg, .028 mmol, 98%). TLC (EtOAc:PE, 60:40 v/v): R_f = 0.50; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +46.0 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21-8.19 (m, 2H), 7.66-6.98 (m, 32H), 5.58 (t, 1H, *J* = 9.5 Hz, H-3''), 5.56 (t, 1H, *J* = 9.5 Hz, H-3), 5.48 (d, 1H, *J*



25

= 12.0 Hz, C*H*HPh), 5.43 (d, 1H, *J* = 3.5 Hz, H-1''), 5.12 (d, 1H, *J* = 3.5 Hz, H-1'), 4.98 (d, 1H, *J* = 3.5 Hz, H-1), 4.84 (dd, 1H, *J* = 10.0 Hz, *J* = 3.5 Hz, H-2'), 4.79 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.75-4.72 (m, 2H, H-2, H-6a), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.64 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.59 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.56 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.49 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.43 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.25-4.22 (m, 3H, H-6a'', H-6b'', H-7''), 4.11-4.08 (m, 1H, H-5''), 3.89-3.83 (m, 4H, H-3', H-5, H-5', H-6a'), 3.76-3.70 (m, 3H, H-6b, H-4', H-4), 3.60 (d, 1H, *J* = 10.5 Hz, H-6b'), 3.37 (t, 1H, *J* = 9.5 Hz, H-4''), 3.31 (dd, 1H, *J* = 9.5 Hz, *J* = 3.5 Hz, H-2''), 2.99 (dd, 1H, *J* = 14.0 Hz, *J* = 8.0 Hz, H-8a''), 2.84 (dd, 1H, *J* = 14.0 Hz, *J* = 5.0 Hz, H-8b''), 2.14 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.55 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.61, 170.51, 170.29, 169.79, 169.66, 165.16, 150.62, 140.72, 139.21, 137.63, 137.39, 135.86, 134.73, 133.64, 130.20, 129.47, 129.18, 129.09, 128.95, 128.59, 128.49, 128.48, 128.43, 128.21, 128.13, 127.96, 127.88, 127.74, 127.28, 127.20, 126.76, 126.07, 121.73, 97.70, 96.52, 95.19, 82.35, 80.69, 78.90, 77.23, 76.72, 76.24, 76.14, 74.93, 74.84, 74.48, 73.45, 72.57, 72.13, 71.27, 70.61, 70.31, 69.64, 69.38, 65.64, 62.53, 62.01, 40.75, 20.98, 20.84, 20.71; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{77}H_{82}O_{23}S$, 1429.4865; found, 1429.4895.

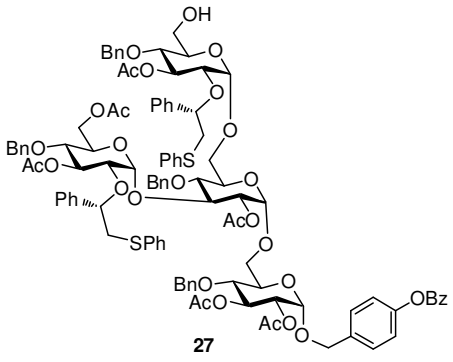
***p*-Benzoyloxybenzyl 3-*O*-acetyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→6)-2-*O*-acetyl-3-*O*-[3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→3)]-4-*O*-benzyl-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranoside (26).** A mixture of glycosyl donor **2** (500 mg, 0.56 mmol, 2.0 equiv) and activated molecular sieves (4Å) in dichloromethane (15 mL) was stirred for 10 min at rt under an atmosphere of argon. After cooling to -40°C, trimethylsilyl trifluoromethanesulfonate (101 μL, 0.56 mmol, 2.0 equiv) was added and the



26

reaction mixture was stirred for 15 min. Glycosyl acceptor **25** (390 mg, 0.28 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (344 mg, 1.68 mmol, 6.0 equiv) were added. The reaction mixture was allowed to slowly warm (5 h) to room temperature, and was stirred overnight at rt. After quenching with aqueous saturated $NaHCO_3$ (15 mL), the organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel purification (0% → 2% - acetone in DCM) of the residue afforded **26** (496 mg, 0.23 mmol, 83%) as a white solid. TLC (acetone:DCM, 2:98 v/v): R_f = 0.18; $[\alpha]^{D}_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +65.7 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20-8.18 (m, 2H), 7.75-6.93 (m, 55H), 5.59-5.54 (m, 4H, H-3, H-3'', H-3''', C*H*HPh), 5.41 (d, 1H, *J* = 3.5 Hz, H-1''), 5.23 (d, 1H, *J* = 3.5 Hz, H-1'''), 5.19 (d, 1H, *J* = 4.0 Hz, H-1'), 4.94-4.92 (m, 2H, H-1, H-2'), 4.78-4.75 (m, 3H, H-2, C*H*HPh × 2), 4.72 (d, 1H, *J* = 10.0 Hz, C*H*HPh), 4.68 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.64 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.57 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.48-4.32 (m, 9H, H-7''', Fmoc, H-6a''', H-6b''', C*H*HPh × 3), 4.26-3.74 (m, 14H, H-7'', H-5', H-5'', H-6a, H-6a', H-6b', H-4', H-4'', H-6b, H-6a'', H-6b'', H-4''', H-5''', H-3'), 3.48-3.45 (m, 2H, H-2'', H-5), 3.35 (t, 1H, *J* = 9.5 Hz, H-4), 3.30 (dd, 1H, *J* = 10.0 Hz, *J* = 3.5 Hz, H-2'''), 3.28 (dd, 1H, *J* = 14.0 Hz, *J* = 8.0 Hz, H-8a'''), 3.09 (dd, 1H, *J* = 14.0 Hz, *J* = 5.0 Hz, H-8b'''), 2.99 (dd, 1H, *J* = 14.0 Hz, *J* = 7.5 Hz, H-8a''), 2.78 (dd, 1H, *J* = 14.0 Hz, *J* = 5.5 Hz, H-8b''), 2.12 (s, 3H, CH_3), 2.00 (s, 6H, 2 x CH_3), 1.79 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.51 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.62, 170.35, 170.21, 169.84, 169.49, 165.04, 154.95, 150.47, 143.45, 143.26, 141.28, 140.79, 140.75, 139.34, 137.91, 137.56, 136.56, 135.89, 134.74, 133.55, 130.18, 129.58, 129.09, 128.98, 128.93, 128.56, 128.51, 128.45, 128.43, 128.40, 128.35, 128.18, 128.10, 128.02, 127.93, 127.88, 127.84, 127.76, 127.17, 127.14, 127.00, 126.78, 126.65, 126.02, 125.87, 125.21, 125.14, 121.58, 120.07, 98.00, 96.65, 96.25, 94.66, 82.45, 81.85, 81.41, 79.06, 77.91, 77.22, 76.30, 76.22, 74.95, 74.79, 74.36, 74.04, 73.54, 72.95, 72.60, 72.28, 71.25, 70.63, 69.96, 69.60, 68.48, 68.33, 66.42, 66.16, 65.67, 62.56, 46.73, 41.94, 40.66, 29.70, 20.96, 20.81, 20.76, 20.72; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{121}H_{122}O_{31}S_2$, 2157.7309; found, 2157.7334

***p*-Benzoyloxybenzyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→6)-2-*O*-acetyl-3-*O*-[3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→3)]-4-*O*-benzyl-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranoside (27).**



27

Compound **27** was synthesized from compound **26** (470 mg, 0.22 mmol) according to the procedure described for the synthesis of compound **20**. **27** (391 mg, 93%): TLC (EtOAC:PE, 50:50 v/v): R_f = 0.27; $[\alpha]^{D}_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +17.0 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20-8.18 (m, 2H), 7.65-6.93 (m, 47H), 5.59-5.51 (m, 4H, H-3, H-3'', H-3''', C*H*HPh), 5.42 (d, 1H, *J* = 3.0 Hz, H-1''), 5.21 (d, 1H, *J* = 3.0 Hz, H-1'''), 5.18 (d, 1H, *J* = 4.0 Hz, H-1'), 4.95 (dd, 1H, *J* = 9.5 Hz, *J* = 4.0 Hz, H-2'), 4.94 (d, 1H, *J* = 3.5 Hz, H-1), 4.81-4.72 (m, 3H, H-2, C*H*HPh × 2), 4.68 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.65 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.58 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.48-4.38 (m, 5H, H-7''', C*H*HPh × 4), 4.22-3.77 (m, 14H, H-7'', H-5', H-5'', H-6a, H-6a', H-6b', H-4', H-4'', H-6b, H-6a'', H-6b'', H-6a''', H-6b''', H-3'), 3.71-3.69 (m, 1H, H-5), 3.63-3.60 (m, 1H, H-5'''), 3.47-3.41 (m, 2H, H-4''', H-2''), 3.35 (t, 1H, *J* = 9.5 Hz, H-4), 3.30-3.26 (m, 2H, H-8a''', H-2'''), 3.09 (dd, 1H, *J* = 14.0 Hz, *J* = 4.5 Hz, H-8b'''), 2.97 (dd, 1H, *J* = 14.0 Hz, *J* = 7.0 Hz, H-8a''), 2.78 (dd, 1H, *J* = 14.0 Hz, *J* = 5.5 Hz, H-8b''), 2.13 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.51 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.62, 170.40, 170.23, 169.84, 169.57, 169.51, 165.05, 150.50, 140.80, 140.76, 139.39, 137.89, 137.54, 136.58, 135.88, 134.73, 133.57, 130.18, 129.58, 129.11, 129.08, 128.98, 128.96, 128.92, 128.57, 128.49, 128.46, 128.40, 128.37, 128.17, 128.06, 127.90, 127.84, 127.83, 127.77, 127.06, 127.01, 126.78, 126.60, 126.04, 125.89, 121.60, 97.93, 96.81, 96.28, 94.69, 82.43, 81.90, 81.35, 79.06, 78.23, 77.23, 76.34, 76.22, 75.96, 74.92, 74.81, 74.35, 74.07, 73.55, 73.04, 72.61, 72.26, 71.27, 70.56, 69.92, 69.62, 68.56 66.51, 65.75, 62.55, 61.41, 42.04, 40.67, 20.97, 20.82, 20.77, 20.73; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{106}H_{112}O_{29}S_2$, 1935.6628; found, 1935.6683.

***p*-Benzoyloxybenzyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→6)-2-*O*-acetyl-3-*O*-[3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→3)]-4-*O*-benzyl-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranoside (28).** A mixture of glycosyl donor **5** (171 mg, 0.24 mmol, 2.0 equiv) and activated molecular sieves (4Å) in dichloromethane (10 mL) was stirred for 10 min of argon at rt under an atmosphere. After cooling to -40°C, trimethylsilyl trifluoromethanesulfonate (44 μL, 0.24 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 15 min. Glycosyl acceptor **27** (230 mg, 0.12 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (148 mg, 0.72 mmol, 6.0 equiv) were added. The reaction mixture was allowed to warm slowly (5 h) to rt, and kept overnight at rt. After quenching with aqueous saturated $NaHCO_3$ (15 mL), the organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel purification (0% → 2% - acetone in DCM) of the residue afforded **28** (212 mg, 0.08 mmol, 72%) as a white solid. TLC (acetone:DCM, 7:93 v/v): R_f = 0.57; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +95.8 (*c* = 1.3 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.20-8.19 (m, 2H), 7.65-6.92 (m, 62H), 5.60-5.51 (m, 5H, H-3, H-3’’’, H-3’’, H-3’’’’, C*H*HPh), 5.41 (d, 1H, *J* = 2.5 Hz, H-1’’’’), 5.28 (d, 1H, *J* = 3.5 Hz, H-1’’), 5.21 (d, 1H, *J* = 3.5 Hz, H-1’), 5.20 (d, 1H, *J* = 2.5 Hz, H-1’’’), 5.01 (dd, 1H, *J* = 10.0 Hz, *J* = 3.5 Hz, H-2’), 4.93 (d, 1H, *J* = 4.0 Hz, H-1), 4.83 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.77 (dd, 1H, *J* = 10.0 Hz, *J* = 4.0 Hz, H-2), 4.73 (t, 1H, *J* = 10.0 Hz, H-3’), 4.71 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.69 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.64-4.35 (m, 11H, H-7’’’’, H-7’’’, H-6a’’’’, C*H*HPh × 8), 4.21-3.72 (m, 15H, H-7’’, H-5’’’’, H-5’’, H-6a, H-6a’, H-6b’, H-6b, H-6a’’, H-6b’’, H-6a’’’, H-6b’’’, H-5, H-5’, H-5’’’, H-4’’’), 3.39-3.32 (m, 4H, H-4’’’, H-2’’’, H-4’’, H-4), 3.30 (dd, 1H, *J* = 9.5 Hz, *J* = 2.5 Hz, H-2’’’’), 3.24-3.15 (m, 3H, H-4’, H-8a’’’, H-8a’’’’), 2.99-2.93 (m, 3H, H-8b’’’’, H-8b’’’, H-8a’’), 2.76 (dd, 1H, *J* = 14.0 Hz, *J* = 5.5 Hz, H-8b’’),

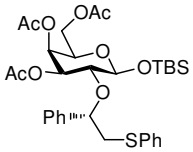
2.12 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.78 (s, 6H, 2 x CH_3), 1.50 (s, 3H, CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.62, 170.37, 169.85, 169.71, 169.61, 169.44, 165.04, 150.40, 140.95, 140.77, 139.99, 139.53, 138.08, 137.97, 137.57, 137.42, 136.78, 136.68, 135.91, 134.76, 133.55, 130.18, 129.61, 129.38, 129.22, 129.06, 128.91, 128.87, 128.74, 128.60, 128.56, 128.46, 128.43, 128.38, 128.37, 128.15, 128.04, 128.00, 127.95, 127.85, 127.78, 127.72, 127.53, 127.03, 126.81, 126.65, 126.41, 126.00, 125.69, 125.61, 121.57, 97.95, 96.73, 96.60, 96.27, 94.65, 82.40, 81.56, 79.82, 79.10, 78.84, 77.22, 76.35, 76.25, 76.02, 75.93, 74.85, 74.36, 74.27, 74.07, 73.62, 73.18, 72.64, 72.28, 71.31, 70.64, 70.54, 70.01, 69.56, 68.43, 65.6,. 64.98, 62.53, 42.17, 41.07, 40.60, 29.71, 20.98, 20.93, 20.86, 20.81, 20.76, 20.67; HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{137}H_{114}O_{36}S_3$, 2483.8497; found, 2483.8530.

Linker Loaded resin (29). Carboxylpolystyrene resin (0.670 g, 1.34 mmol, Advanced ChemTech™, 2.0 mmol g^{-1}, 1% DVB cross-linked) was allowed to swell in CH_2Cl_2 (10 mL) for 30 min. (4-Trityloxymethyl-phenyl)-methanol (38.0 mg, 0.1 mmol) was added followed by DMAP (12.0 mg, 0.1 mmol, 1.0 equiv) and DIC (0.463 mL, 3.0 mmol, 30.0 equiv).[31] The mixture was shaken of 16 h at rt, MeOH (0.30 mL) was added, and the mixture was shaken for an additional 8 h. The resin was filtered, washed with CH_2Cl_2 (2 x 5 mL), MeOH (2 x 5 mL), CH_2Cl_2 (2 x 5 mL) and MeOH (2 x 5 mL) followed by drying *in vacuo* in a desiccator for 2 h. The resin was allowed to swell in CH_2Cl_2 (10 mL) for 30 min. TFA (1.0 mL) and Et_3SiH (47.8 μL, 0.30 mmol, 3.0 equiv) were added and the mixture was shaken for 10 min at rt. The loading was found to be 0.148 mmol g^{-1}.[28] The resin was filtered, washed with CH_2Cl_2 (2 x 5 mL), MeOH (2 x 5 mL), CH_2Cl_2 (2 x 5 mL), and MeOH (2 x 5 mL) followed by drying *in vacuo* in a desiccator for 12 h.

4-(Acetoxymethyl) benzyl *O*-(2,3,6-tri-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranosyl)-(1→6)-(2,3-di-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranosyl)-(1→6)-(2-*O*-acetyl-3-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranosyl (1→3)]-4-*O*-benzyl-*α*-D-glucopyranosyl)-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*β*-D-glucopyranoside (42). Glycosyl donor **6** was coupled to resin **30** (0.1 mmol scale) according to the general. The Fmoc was removed according to the general procedure. Glycosyl donor **4** was coupled according to the general procedure. The chiral auxiliary was removed according to general the procedure. The Alloc was removed according to the general procedure**.** Glycosyl donor **5** was coupled according to the general procedure. The Fmoc was removed according to the general procedure. Glycosyl donor **1** was coupled according to the general procedure. The Fmoc was removed according to the general procedure. Glycosyl donor **2** was coupled according to the general procedure. The chiral auxiliaries were removed according to the general procedure. The Fmoc was removed according to the general procedure. The product was cleaved from the resin according to the general procedure. The residue was dissolved in pyridine (3 mL) and acetic anhydride (1 mL) was added and the resulting mixture was stirred for 12 h at rt. The solvents were removed under reduced pressure. The residue was purified by Sephadex LH-20 size exclusion chromatography (DCM:MeOH, 50/50 v/v) and the appropriate fractions were further purified by preparative HPLC to afforded **42** (47 mg, 25% overall yield, 90% per step: 13 on-resin steps) as a white solid. TLC (EtOAc:PE, 60:40 v/v): R_f = 0.30; $[\alpha]^D_{22}$ (deg cm^3 g^{-1} dm^{-1}) = +51.2 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36-7.18 (m, 29H), 5.63 (t, $J_{3,2}$ = 9.6 Hz, 1H, H-3-D), 5.57 (dd, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 10.6 Hz, 1H, H-3-E), 5.52 (dd, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 8.4 Hz, 1H, H-3-C), 5.39 (d, $J_{1,2}$ = 3.0 Hz, 1H, H-1-E), 5.22 (d, $J_{1,2}$ = 3.0 Hz, 1H, H-1-D), 5.17 (t, $J_{3,2}$ = 9.6 Hz, 1H, H-3-A), 5.07 (m, 3H, CH_2Ph Linker, H-1-C), 5.01 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.97 (d, $J_{1,2}$ = 3.6 Hz, 1H, H-1-B), 4.84-4.86 (m, 3H, H-2-A, H-2-E, H-2-D), 4.76 (d, *J* = 12.6 Hz, 1H, CH*H*Ph Linker), 4.71 (d, *J* = 11.4 Hz, 1H, C*H*HPh), 4.67 (dd, $J_{2,1}$ = 3.6 Hz, $J_{2,3}$ = 12.0 Hz, 1H, H-2-C), 4.66 (dd, $J_{2,1}$ = 3.6 Hz, $J_{2,3}$ = 9.6 Hz, 1H, H-2-B), 4.54-

4.64 (m, 8H, CH_2Ph), 4.50 (d, J = 12.0 Hz, 1H, CHHPh Linker), 4.45 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1-A), 4.34 (dd, $J_{6b,5}$ = 1.8 Hz, $J_{6b,6a}$ = 12.0 Hz, 1H, H-6b-E), 4.29 (dd, $J_{6b,5}$ = 2.4 Hz, $J_{6b,6a}$ = 12.0 Hz, 1H, H-6b-D), 4.23 (dd, $J_{6a,5}$ = 3.6 Hz, $J_{6a,6b}$ = 12.0 Hz, 1H, H-6a-E), 4.21 (dd, $J_{6a,5}$ = 4.2 Hz, $J_{6a,6b}$ = 12.0 Hz, 1H, H-6a-D), 4.15 (dt, $J_{5,4}$ = 2.4 Hz, $J_{5,6a/b}$ = 10.2 Hz, 1H, H-5-E), 4.11 (t, $J_{3,4}$ = 10.2 Hz, 1H, H-3-B), 3.88-3.91 (m, H-5-D), 3.80-3.83 (m, 2H, H-5-B, H-6a-C), 3.75-3.78 (m, 3H, H-4-C, H-5-C, H-6a-B), 3.71-3.74 (m, 4H, H-4-A, H-4-B, H-6a-A, H-6b-C), 3.68-3.71 (m, 2H, H-6b-A, H-6b-B), 3.63-3.67 (m, 1H, H-4-E), 3.62 (d, J = 3.6 Hz, 1H, H-4-D), 3.44 (m, 1H, H-5-A), 2.11 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 1.71 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.8, 170.6, 170.5, 170.5, 170.4, 170.3, 170.3, 170.2, 169.8, 169.7, 169.6, 169.6, 138.2, 137.7, 137.5, 137.3, 137.2, 136.9, 135.5, 127.1-128.5, 98.9 (C-1-A), 96.9 (C-1-E), 96.4 (C-1-D), 96.2 (C-1-B), 95.9 (C-1-C), 78.7 (C-3-B), 77.6 (C-4-B), 75.9 (C-4-D), 75.7 (C-4-C), 75.4 (C-4-E), 75.4 (C-5-C), 74.9, 74.9 (C-3-A), 74.8, 74.7, 74.6, 74.5, 74.4 (C-5-A), 72.5 (C-2-B), 72.1 (C-3-D), 72.0 (C-3-E), 71.9 (C-2-D), 71.7 (C-3-C), 71.2 (C-2-C), 71.2 (C-2-E), 71.2 (C-2-A), 70.8 (C-4-A), 70.3 (C-5-B), 69.9, 69.4 (C-5-E), 68.6 (C-5-D), 66.0, 65.7 (C-6-B), 65.0 (C-6-C), 64.8 (C-6-A), 62.5 (C-6-D), 62.3 (C-6-E), 21.0, 20.9, 20.9, 20.9, 20.8, 20.8, 20.8, 20.8, 20.7, 20.7, 20.7, 20.4; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{97}H_{114}O_{39}$, 1925.6835; found, 1925.6857.

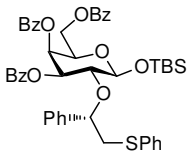
***t*-Butyldimethylsilyl 3,4,6-tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-galactopyranoside (43).** 3,4,6-tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-galactose[3] (2.0 g, 3.86 mmol) was dissolved in DMF (20 mL) and imdazol (0.52 g, 7.72 mmol, 2.0 equiv) and TBSCl (1.08 g, 7.72 mmol, 2.0 equiv) were added at 0°C. The resulting mixture was stirred for 16 h at rt. Water (20 mL) and EtOAc (100 mL) were added and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 20% - EtOAc in PE) of the residue afforded **43** (1.95 g, 3.08 mmol, 80%) as a colorless oil. TLC (EtOAc:PE,



43

30:70 v/v): R_f = 0.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13-6.94 (m, 10H), 5.06 (d, 1H, *J* = 2.5 Hz, H-4), 4.80 (t, 1H, *J* = 7.0 Hz, H-7), 4.64 (dd, 1H, *J* = 4.0 Hz, *J* = 10.5 Hz, H-3), 4.52 (d, 1H, *J* = 8.0 Hz, H-1), 3.92-3.81 (m, 2H, H-6a,b), 3.63 (t, 1H , *J* = 6.5 Hz, H-5), 3.29-3.24 (m, 2H, H-2, H-8a), 2.95 (dd, 1H, *J* = 13.0 Hz, *J* = 7.5 Hz, H-8b), 1.83 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 0.78 (s, 9H, 3 x CH_3), 0.00 (s, 6H, 2 x CH_3); HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{32}H_{44}O_9SSi$, 655.2373; found, 655.2338.

***t*-Butyldimethylsilyl 3,4,6-tri-*O*-benzoyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-β-D-galactopyranoside (44).** A catalytic amount of sodium methoxide was added to a stirred solution of **43** (1.95 g, 3.08 mmol) in methanol (20 mL). The reaction mixture was stirred for 4 h at rt and neutralized upon addition of Dowex® 50W X8-200 H^+ resin. The resin was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in pyridine (40 mL) followed by the addition of Benzoyl chloride (2.14 mL, 18.48 mmol, 6.0 equiv) at 0^{o}C. The mixture was stirred for 16 h at rt. MeOH (2 mL), Water (20 mL) and EtOAc (100 mL) were added and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (100% Toluene) of the residue afforded **44** (1.81 g, 2.22 mmol, 72%) as a colorless oil. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01-7.98 (m, 2H), 7.79-7.76 (m, 2H), 7.65-7.04 (m, 21H), 5.70 (d, 1H, *J* = 2.4 Hz, H-4), 5.35 (dd, 1H, *J* = 3.6 Hz, *J* = 10.2 Hz, H-3), 5.14 (t, 1H , *J* = 6.6 Hz, H-7), 4.90 (d, 1H, *J* = 7.5 Hz, H-1), 4.51-4.13 (m, 2H, H-6a,b), 4.15 (t, 1H , *J* = 6.6 Hz, H-5), 3.41 (dd, 1H, *J* = 7.5 Hz, *J* = 9.9 Hz, H-2), 3.39 (dd, 1H, *J* = 12.9 Hz, *J* = 6.6 Hz, H-8a), 3.06 (dd, 1H, *J* = 7.2 Hz, *J* = 12.9 Hz, H-8b), 0.97 (s, 9H, 3 x CH_3), 0.19 (s, 3H, CH_3), 0.19(s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 165.6, 165.2, 139.5, 136.8, 133.2, 133.1, 133.0, 129.8,-125.7, 98.8, 80.9, 75.0, 72.2, 71.0, 68.8, 62.6, 40.6, 25.9, 18.0, -4.1, -4.6. HR-MALDI-TOF/MS (*m/z*): calcd for $[M+Na]^+$ calcd for $C_{47}H_{50}O_9SSi$, 841.2842; found, 841.2834.



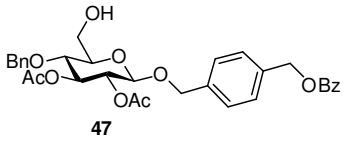
44

3,4,6-tri-*O*-benzoyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-galactopyranosyl trichloroacetimidate (45). Compound **44** (1.81 g, 2.22 mmol) was dissolved in THF (10 mL) in a Teflon reaction bottle. HF·pyridine (4.0 mL) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EtOAc (30 mL) and sat. aq. $NaHCO_3$ (30 mL) was slowly added. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0% → 30% - EtOAc in PE). The purified lactol (1.24 g, 1.77 mmol) was dissolved in CH_2Cl_2 (15 mL) and trichloroacetonitrile (5 mL). The resulting mixture was cooled to 0°C and a catalytic amount of DBU (0.1 equiv) was added. The reaction mixture was stirred for 1 hr at 0°C. The solution was concentrated *in vacuo* and silica gel purification (0% → 30% - EtOAc in PE) of the residue afforded **45** (1.80 g, 1.52 mmol, 68 % over two steps) as a white foam. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H, N*H*), 7.96-7.95 (m, 2H), 7.75-7.73 (m, 2H), 7.63-7.11 (m, 21H), 6.88 (d, 1H, *J* = 3.5 Hz, H-1), 5.94 (d, 1H, *J* = 2.5 Hz, H-4), 5.81 (dd, 1H, *J* = 3.5 Hz, *J* = 10.5 Hz, H-3), 4.76 (t, 1H , *J* = 6.5 Hz, H-5), 4.69 (t, 1H , *J* = 6.5 Hz, H-7), 4.50 (dd, 1H, *J* = 7.0 Hz, *J* = 11.5 Hz, H-6a), 4.31-4.26 (m, 2H, H-6b, H-2), 3.26 (dd, 1H, *J* = 7.0 Hz, *J* = 13.5 Hz, H-8a), 3.05 (dd, 1H, *J* = 6.5 Hz, *J* = 14.0 Hz, H-8b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 165.6, 165.2, 161.0, 139.2, 133.3, 133.1, 133.0, 129.7-126.0, 104.7, 93.5, 80.3, 71.4, 69.5, 69.3, 68.8, 62.2, 56.3, 41.2.

4-(Benzoyloxymethyl) benzyl 2,3-di-*O*-acetyl-4-*O*-benzyl-6-*O*-[*tert*-butyldiphenylsilyl]-*β*-D-glucopyranoside (46). A mixture of ethyl 2,3-di-*O*-acetyl-4-*O*-benzyl-6-[(*tert*-butyl) diphenylsilyl]-1-thio-β-D-glucose (1.3 g, 2.0 mmol), 4-(hydroxylmethyl)benzyl benzoate (1.0 g, 4.1 mmol, 2.0 equiv) and activated molecular sieves (4Å) in DCM (20 mL) was stirred for 10 min at rt and then cooled to 0°C. NIS (0.5 g, 2.0 mmol, 1.0 equiv) and TMSOTf (0.15 mL, 0.8 mmol, 0.4 equiv) were added and the mixture was stirred for 1hr at 0°C. The reaction mixture was diluted with DCM (30 mL) and quenched by the addition of 1M aq. $Na_2S_2O_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in*

vacuo. Silica gel purification (0% → 25% - EtOAc in PE) of the residue afforded **46** (1.03 g, 1.26 mmol, 63%) as a colorless oil. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.45; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01-7.99 (m, 2H), 7.70-7.63 (m, 4H), 7.48-7.11 (m, 18H), 5.29 (s, 2H, CH_2 Linker), 5.18 (t, 1H, *J* = 9.5 Hz, H-3), 4.95 (t, 1H, *J* = 10.0 Hz, H-2), 4.84 (d, 1H, *J* = 10.0 Hz, C*H*HPh Linker), 4.63-4.54 (m, 3H, CH*H*Ph Linker, CH_2 OBn), 4.46 (d, 1H, *J* = 8.0 Hz, H-1), 3.89 (s, 2H, H-6a,b), 3.85 (t, 1H, *J* = 9.5 Hz, H-5), 3.35-3.32 (m, 1H, H-4),1.96 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 1.04 (s, 9H, 3 x CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.8, 166.3, 137.7, 137.2, 135.8, 135.6, 135.5, 133.4, 133.0, 132.7, 130.0-127.5, 98.9, 95.0, 75.7, 75.7, 74.9, 74.8, 72.1, 69.6, 66.3, 62.3, 26.8, 20.7, 20.7, 19.3; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{48}H_{52}O_{10}Si$, 839.3227; found, 839.3256.

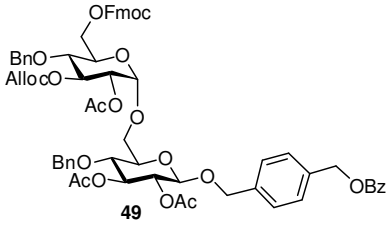
4-(Benzoyloxymethyl) benzyl 2,3-di-*O*-acetyl-4-*O*-benzyl-*β*-D-glucopyranoside (47). Compound **46** (0.45 g, 0.55 mmol) was dissolved in THF (5 mL) and 1M TBAF in THF (0.83 mL, 0.83 mmol, 1.5 equiv) was added. The reaction mixture was stirred for 16 h at rt. The reaction mixture was diluted with EtOAc (30 mL) and water (15 mL) was added. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 40% - EtOAc in PE) of the residue afforded **47** (0.30 g, 0.52 mmol, 95%) as a colorless oil. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.20; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00-9.78 (m, 2H), 7.50-7.17 (m, 12H), 5.27 (s, 2H, CH_2 Linker), 5.14 (t, 1H, *J* = 9.5 Hz, H-3), 4.87 (dd, 1H, *J* = 10.0 Hz, *J* = 8.0 Hz, H-2), 4.80 (d, 1H, *J* = 12.5 Hz, C*H*HPh Linker), 4.58-4.50 (m, 4H, H-1, CH*H*Ph Linker, CH_2 OBn), 3.84 (dd, 1H, *J* = 13.0 Hz, *J* = 2.5 Hz, H-6a), 3.69-3.65 (m, 2H, H-4, H-6b), 3.37-3.33 (m, 1H, H-5), 1.92 (s, 3H, CH_3), 1.86 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 169.6, 166.4, 137.4, 136.9, 135.8, 133.0, 130.0, 129.6-127.7, 99.6, 75.3, 75.2, 74.7, 74.4, 71.9, 70.7, 66.3, 61.4, 20.7, 20.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{34}O_{10}$, 601.2049; found, 601.2034.



47

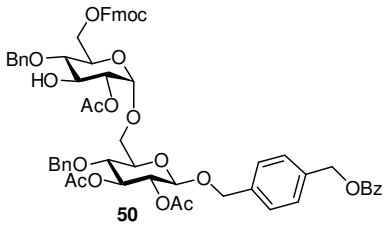
4-(Benzyloxymethyl) benzyl 3-*O*-allyoxycarbonyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*β*-D-glucopyranoside (48). A mixture of glycosyl donor **4** (200 mg, 0.22 mmol, 1.5 equiv) and activated molecular sieves (4Å) in DCM (5 mL) was cooled to -40°C. TMSOTf (40 μL, 0.22 mmol, 1.5 equiv) was added and the mixture was stirred at -40°C for 15 min. Glycosyl acceptor **47** (110 mg, 0.15 mmol) and DTBMP (90 mg, 0.44 mmol, 2.0 equiv) in DCM (2 mL) were added. The reaction was allowed to warm to 0°C over a period of 3 h. DCM (10 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 30% - EtOAc in PE) of the residue afforded **48** (210 mg, 0.16 mmol, 72%) as a white solid. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.36; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (m, 2H), 7.68 (m, 2H), 7.50-7.44 (m, 3H), 7.33-7.07 (m, 30H), 5.85-5.77 (m, 1H, CH_2CH=CH_2), 5.35 (t, 1H, *J* = 9.5 Hz, H-3'), 5.29-5,16 (m, 4H, CH_2CH=CH_2, CH_2 Linker), 5.14-5.10 (m, 2H, H-1', H-3), 4.96 (dd, 1H, *J* = 8.0 Hz, *J* = 9.5 Hz, H-2), 4.76 (d, 1H, *J* = 12.0 Hz, CHHPh Linker), 4.60 (dd, 1H, *J* = 4.5 Hz, *J* = 7.5 Hz, H-3), 4.54-4.37 (m, 9H, H-1, CHHPh Linker, 2 x CH_2 OBn, H-7, CH_2CH=CH_2), 4.33-4.26 (m, 3H, CH_2 Fmoc, H-6a'), 4.20 (dd, 1H, *J* = 4.0 Hz, *J* = 12.0 Hz, H-6b'), 4.15 (t, 1H, *J* = 7.0 Hz, CH Fmoc), 3.93.90 (m, 1H, H-5'), 3.80 (dd, 1H, *J* = 1.5 Hz, *J* = 11.5 Hz, H-5), 3.76-3.71 (m, 2H, H-4, H-6a), 3.47-3.42 (m, 3H, H-2', H-4', H-6b), 3.23 (dd, 1H, *J* = 8.0 Hz, *J* = 13.5 Hz, H-8a), 3.11 (dd, 1H, *J* = 4.5 Hz, *J* = 13.5 Hz, H-8b), 1.91 (s, 3H, CH_3), 1.77 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 169.5, 166.4, 154.9, 154.3, 143.3, 143.2, 141.2, 141.2, 139.7, 137.5, 137.4, 137.1, 136.9, 135.4, 133.0, 131.6, 130.1, 129.6-125.0, 120.0, 119.0, 99.2, 96.3, 80.7, 78.2, 76.0, 76.0, 75.8, 74.8, 74.7, 74.6, 72.1, 70.2, 70.0, 68.5, 68.5, 66.5, 66.0, 65.2, 46.6, 41.8, 20.7, 20.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{78}H_{76}O_{19}S$, 1371.4599; found, 1371.4512.

4-(Benzyloxymethyl) benzyl 2-*O*-acetyl-3-*O*-allyoxycarbonyl-4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*β*-D-glucopyranoside (49). Disaccharide **48** (200 mg, 0.15 mmol) was dissolved in a mixture of DCM (2 mL) and Ac_2O (3 mL) at 0°C. $BF_3{\cdot}Et_2O$ (37 µL, 0.30 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 1hr at 0°C. DCM (10 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 30% - EtOAc in PE) of the residue afforded **49** (175 mg, 0.13 mmol, 87%) as a white solid. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.30; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (m, 2H), 7.69 (m, 2H), 7.55-7.45 (m, 3H), 7.34-7.14 (m, 20H), 5.87-5.81 (m, 1H, $CH_2CH{=}CH_2$), 5.37 (t, 1H, *J* = 10.0 Hz, H-3'), 5.30-5,17 (m, 4H, $CH_2CH{=}CH_2$, CH_2 Linker), 5.12-5.08 (m, 2H, H-1', H-3), 4.81-4.75 (m, 2H, H-2', H-2), 4.72 (d, 1H, *J* = 12.5 Hz, CHHPh Linker), 4.62-4.48 (m, 7H, CHHPh Linker, 2 x CH_2 OBn, $CH_2CH{=}CH_2$), 4.42 (d, 1H, *J* = 8.0 Hz, H-1), 4.37-4.28 (m, 3H, CH_2 Fmoc, H-6a'), 4.23-4.17 (m, 2H, H-6b', CH Fmoc), 3.90 (m, 1H, H-5'), 3.77 (dd, *J* = 4.5 Hz, *J* = 12.0 Hz, H-6a), 3.68-3.63 (m, 3H, H-4, H-4', H-6b), 3.37 (m, 1H, H-5), 2.04 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 1.82 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 170.1, 169.6, 166.4, 154.9, 154.4, 143.4, 143.2, 141.3, 141.3, 137.4, 137.2, 137.0, 135.5, 133.0, 131.4, 130.1, 129.7-127.2, 125.2, 125.1, 120.0, 119.1, 99.0, 96.6, 76.6, 75.7, 75.5, 75.0, 74.7, 74.7, 74.6, 71.9, 71.0, 70.1, 70.1, 68.7, 68.7, 66.4, 65.8, 65.7, 46.7, 20.8, 20.8, 20.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{66}H_{66}O_{20}$, 1201.4045; found, 1201.4079.



49

4-(Benzyloxymethyl) benzyl 2-*O*-acetyl--4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*β*-D-glucopyranoside (50). To a solution of disaccharide **49** (55 mg, 0.04 mmol) in THF (2 mL) and AcOH (0.2 mL) was added $Pd(PPh_3)_4$ (24 mg, 0.016 mmol, 0.4 equiv) and the resulting mixture was stirred for



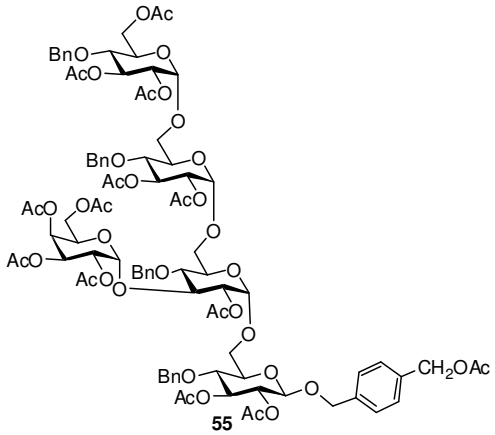
50

1hr at rt. The mixture was concentrated *in vacuo* and silica gel purification (0% → 30% - EtOAc in PE) of the residue afforded **50** (46 mg, 0.036 mmol, 92%) as a white solid. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.25; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (m, 2H), 7.70 (d, 2H, *J* = 7.5 Hz), 7.56-7.15 (m, 23H), 5.26 (s, CH_2 Linker), 5.08 (t, 1H, *J* = 9.9 Hz, H-3), 5.07 (d, 1H, *J* = 3.6 Hz, H-1'), 4.83-4.71 (m, 2H, H-2, H-2'), 4.68-4.62 (m, 2H, C*H*HPh, C*H*HPh), 4.53-4.50 (m, 3H, CH2 OBn, CH*H*Ph), 4.46-4.38 (m, 2H, H-1, CH*H*Ph), 4.35-4.28 (m, 3H, CH_2 Fmoc, H-6b'), 4.27-4.05 (m, 3H, CH Fmoc, H-6a', H-3'), 3.86-3.79 (m, 2H, H-5', H-6a), 3.71-3.68 (m, 2H, H-4, H-4'), 3.52 (t, 1H, *J* = 9.0 Hz, H-6b), 3.38 (m, 1H, H-5), 2.26 (bs, 1H, 3'-OH), 2.10 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 1.84 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 170.0, 169.7, 166.4, 155.0, 143.4, 143.2, 141.2, 138.7-125.1, 120.0, 99.1, 96.7, 77.5, 75.7, 75.0, 74.8, 74.8, 74.7, 74.5, 73.4, 71.9, 71.5, 70.1, 70.0, 68.7, 66.4, 66.4, 46.7, 20.9, 20.8, 20.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{62}H_{62}O_{18}$, 1117.3833; found, 1117.3878.

4-(Benzyloxymethyl) benzyl 3,4,6-*O*-benzoyl-2-*O*-{(1*S*)-phenyl-2-phenylsulfanyl-ethyl}-*α*-D-glucopyranosyl-(1→3)-2-*O*-acetyl--4-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-*α*-D-glucopyranosyl-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*β*-D-glucopyranoside (51). A mixture of glycosyl donor **45** (77 mg, 0.09 mmol, 2.0 equiv) and activated molecular sieves (4Å) in DCM (2 mL) was cooled to -40°C. TfOH (8.0 µL, 0.09 mmol, 2.0 equiv) was added and the mixture was stirred at -40°C for 15 min. Glycosyl acceptor **50** (50 mg, 0.04 mmol) and DTBMP (74 mg, 0.36 mmol, 4.0 equiv) in CH_2Cl_2 (2 mL) were added. The reaction mixture was stirred at -40°C for 1 hr and was then allowed to warm to 0°C over a period of 3 h. DCM (10 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel purification (0% → 30% - EtOAc in PE) of the residue afforded **51** (44 mg, 61%) as a white solid. TLC (EtOAc:PE, 30:70 v/v): R_f = 0.30; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (m, 2H), 7.87 (m, 2H), 7.68 (m, 4H), 7.56 (dd, 2H, *J* = 4.0 Hz, *J* = 7.5 Hz), 7.49-7.05 (m, 37H), 6.87-6.74 (m, 5H), 5.81

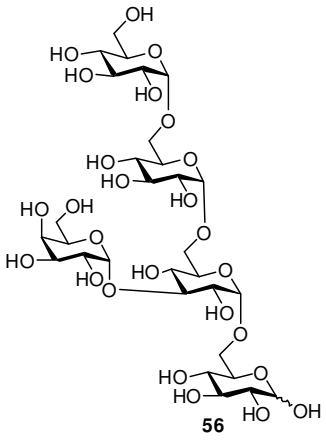
(dd, 1H, *J* = 3.0 Hz, *J* = 10.5 Hz, H-3''), 5.76 (dd, 1H, *J* = 1.5 Hz, *J* = 3.5 Hz, H-4''), 5.56 (d, 1H, *J* = 3.0 Hz, H-1''), 5.39 (dd, 1H, *J* = 11.5 Hz, C*H*HPh Linker), 5.24 (s, 2H, CH_2 Linker), 5.11 (t, 1H, *J* = 9.5 Hz, H-3), 5.07 (d, 1H, *J* = 3.5 Hz, H-1'), 4.95 (dd, 1H, *J* = 3.5 Hz, *J* = 9.5 Hz, H-2'), 483 (dd, 1H, *J* = 7.5 Hz, *J* = 9.5 Hz, H-2), 4.75-4.68 (m, 4H, CH*H*Ph Linker, C*H*HPh, H-3', H-5''), 4.52 (s, 2H, CH_2 OBn), 4.45-4.27 (m, 8H, CHHPh, H-6a', H-6a'', H-6b'', H-7'', H-1, CH_2 Fmoc), 4.22-4.15 (m, 2H, CH Fmoc, H-6b'), 4.03 (m, 1H, H-5'), 3.96 (dd, 1H, *J* = 3.5 Hz, *J* = 10.5 Hz, H-2''), 3.83 (dd, 1H, *J* = 4.5 Hz, *J* = 11.5 Hz, H-6a), 3.78 (m, 1H, H-4'), 3.70 (m, 1H, H-6b), 3.64 (t, 1H, *J* = 9.5 Hz, H-4), 3.43 (m, 1H, H-5), 2.93 (dd, 1H, *J* = 7.5 Hz, *J* = 14.5 Hz, H-8a), 2.68 (dd, 1H, *J* = 7.5 Hz, *J* = 14.5 Hz, H-8b), 2.11 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 1.77 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.0, 169.6, 166.4, 165.8, 165.4, 165.1, 155.0, 143.4, 143.4, 141.3, 139.7, 138.6, 137.4, 137.1, 135.9, 135.6, 133.1, 133.0, 133.0, 132.8, 130.0-125.2, 120.0, 120.0, 99.3, 98.2, 96.6, 81.4, 80.0, 76.1, 75.0, 75.0, 74.9, 74.6, 74.3, 72.9, 72.0, 70.3, 70.1, 69.4, 68.5, 67.5, 66.4, 66.4, 66.2, 61.4, 46.7, 40.4, 21.1, 20.7, 20.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{103}H_{96}O_{26}S$, 1803.5808; found, 1803.5827.

4-(Acetoxymethyl) benzyl *O*-(2,3,6-tri-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranosyl)-(1→6)-(2,3-di-*O*-acetyl-4-*O*-benzyl-*α*-D-glucopyranosyl)-(1→6)-(2-*O*-acetyl-3-*O*-[2,3,4,6-tetra-*O*-acetyl-*α*-D-galactopyranosyl (1→3)]-4-*O*-benzyl-*α*-D-glucopyranosyl)-(1→6)-2,3-di-*O*-acetyl-4-*O*-benzyl-*β*-D-glucopyranoside (55). Glycosyl donor **6** was coupled to resin **30** (0.075 mmol scale) according to the general. The Fmoc was removed according to the general procedure. Glycosyl donor **4** was coupled according to the general procedure. The chiral auxiliary was removed according to general the procedure. The Alloc was removed according to the general procedure**.** Glycosyl donor **45** was coupled according to the general procedure. The Fmoc was removed according to the general procedure. Glycosyl donor **2** was coupled according to the general procedure. The Fmoc was removed according to the general procedure. Glycosyl



donor **2** was coupled according to the general procedure. The chiral auxiliaries were removed according to the general procedure. The Fmoc was removed according to the general procedure. The product was cleaved from the resin according to the general procedure. The residue was dissolved in pyridine (3 mL) and acetic anhydride (1 mL) was added and the resulting mixture was stirred for 12 h at rt. The solvents were removed under reduced pressure. The residue was purified as described for **41** to afford **55** (18 mg, 13% overall yield, 86% per step: 13 on-resin steps) as a white solid. TLC (EtOAc:PE, 60:40 v/v): R_f = 0.25; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.15 (m, 24H), 5.56 (t, 1H, *J* = 10.0 Hz, H-3-D), 5.46-5.43 (m, 2H, H-1-E, H-3-C), 5.40-5.35 (m, 2H, H-4-E, H-3-E), 5.14-5.09 (m, 3H, H-1-D, H-3-A, H-2-E), 5.01 (s, 2H, CH_2 Linker), 4.97 (d, 1H, *J* = 3.5 Hz, H-1-C), 4.91 (d, 1H, *J* = 4.0 Hz, H-1-B), 4.86 (d, 1H, *J* = 11.5 Hz, C*H*HPh Linker), 4.80-4.76 (m, 2H, H-2-A, H-2-D), 4.70 (d, 1H, *J* = 12.5Hz, C*H*HPh), 4.61-4.53 (m, 8H, CH*H*Ph Linker, C*H*HPh, H-2-B, H-2-C, 2 x CH_2 OBn), 4.49 (d, 1H, *J* = 11.0 Hz, CH*H*Ph), 4.44-4.40 (m, 2H, CH*H*Ph, H-5-E), 4.38 (d, 1H, *J* = 8.0 Hz, H-1-A), 4.23 (dd, 1H, *J* = 2.0 Hz, *J* = 12.0 Hz, H-6a-D), 4.15-4.11 (m, 2H, H-6b-D, H-6a-E), 4.04 (t, 1H, *J* = 10.0 Hz, H-3-B), 3.90 (dd, 1H, *J* = 6.0 Hz, *J* = 11.0 Hz, H-6b-E), 3.81 (m, 1H, H-5-D), 3.78-3.54 (m, 12H, H-6ab-A, H-6ab-B, H-6ab-C, H-4-A, H-4-B, H-4-C, H-4-D, H-5-B, H-5-C), 3.38-3.36 (m, 1H, H-5-A), 2.07 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.64 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ170.8, 170.5, 170.4, 170.3, 170.3, 170.3, 170.3, 170.1, 170.1, 169.7, 169.7, 169.7, 169.5, 137.9, 137.6, 137.5, 137.1, 136.9, 135.5,128.5-127.2, 98.9, 97.2, 96.3, 96.3, 96.1, 78.8, 77.4, 75.8, 75.7, 75.3, 75.0, 74.8, 74.8, 74.6, 74.5, 74.3, 72.6, 72.0, 71.8, 71.7, 71.2, 71.1, 70.7, 70.2, 69.9, 68.6, 68.2, 67.8, 67.1, 67.0, 65.9, 65.7, 65.1, 64.7, 62.1, 60.9, 20.9, 20.9, 20.8, 20.8, 20.8, 20.7, 20.7, 20.7, 20.6, 20.6, 20.5, 20.5, 20.3. HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{92}H_{110}O_{40}$, 1877.6471; found, 1877.6412.

(*α*-D-glucopyranosyl)-(1→6)-(*α*-D-glucopyranosyl)-(1→6)-(3-*O*-[*α*-D-galactopyranosyl (1→3)]-*α*-D-glucopyranosyl)-(1→6)-*α*/*β*-D-glucopyranoside (56). Compound **55** (9.6 mg, 5.22 μmol) was dissolved in a mixture of CH_2Cl_2 (1 mL) and MeOH (1 mL) and a catalytic amount of sodium methoxide was added. The mixture was stirred for 16 h at rt and neutralized using Dowex® 50W X8-200 H^+ resin. The resin was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in a mixture of EtOH (1 mL) and H_2O (1 mL) and a catalytic amount of 20 wt% $Pd(OH)_2/C$ was added. The reaction mixture was purged with H_2 gas for 2 min followed by stirring for 16 h under H_2 atmosphere. The reaction mixture was purged with Ar gas followed by filtration through a plug of Celite. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on Iatrobeads (CH_2Cl_2/MeOH/H_2O = 5/5/1) to afford **56** (3.5 mg, 81% over two steps). TLC (CH_2Cl_2:MeOH:H_2O, 5:5:1 v/v/v): R_f = 0.41; ^{1}H NMR (600 MHz, D_2O): δ 5.38 (d, J = 3.6 Hz, 1H, H-1), 5.00-4.96 (m, 3H, H-1, H-1, H-1), 4.68 (d, J = 7.8 Hz, 1H, H-1), 4.25 (t, 1H, J = 6.0 Hz), 4.04-3.52 (m, 28H), 3.26 (t, J = 9.0 Hz, 1H, H-2); HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ calcd for $C_{30}H_{52}O_{26}$, 851.2645; found, 851.2592.



56

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CHAPTER 4

VERSATILE SET OF ORTHOGONAL PROTECTING GROUPS FOR THE PREPARATION OF HIGHLY BRANCHED OLIGOSACCHARIDES[†]

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Abstract. A new set of orthogonal protecting groups has been developed based on the use of a diethylisopropylsilyl (DEIPS), methylnaphthyl (Nap), allyl ether and levulinoyl (Lev) ester. The protecting groups are ideally suited for the preparation of highly branched oligosaccharides and their usefulness has been demonstrated by the chemical synthesis of a β-D-Man-(1→4)-D-Man disaccharide, which is appropriately protected for making a range of sub-structures of the unusual core region of the lipopolysaccharide of *Francisella tularensis*.

Introduction. *F. tularensis* is a gram-negative bacterium that can cause tularemia (rabbit fever) in animals and humans[1] and has been classified by the CDC as a top-priority (Class A) bio-terrorism agent.[2] Common to all class-A agents, tularemia transmits easily, has the capacity to inflict substantial morbidity and mortality on a large number of people, and can induce widespread panic. To prevent tularemia, an attenuated live vaccine strain (LVS) was developed in the 1950's, but was not licensed for use as a human vaccine because the nature of its attenuation was not known and might not be stable. Diagnoses are based on time consuming culture, serology, or sophisticated molecular techniques. Therefore improved vaccine candidates and rapid diagnostic tests are needed for this pathogen. The structure of the lipopolysaccharide (LPS) of *F. tularensis* has been determined (Figure 4.1 A)[3] and it was established that it has an unusual core structure. The core is linked to the lipid A region by only one 3-deoxy-D-manno-2-octulosonic acid (KDO) moiety instead of the usual two KDO residues. It does not contain heptosyl residues but contains two mannosyl moieties. One of the mannosides is β-linked to another mannoside, and this disaccharide fragment is further substituted at C-2, C-2′ and C-3′ by a β-glucoside, an α-galactosamine and a α-glucoside, respectively. It has been proposed that the lipopolysaccharide of *F. tularensis* is an attractive candidate for vaccine and diagnostic test development.[4]

However, isolation of saccharides from a Class A bio-terrorism agent is highly undesirable. Furthermore, it is difficult to conjugate short oligosaccharides to carrier proteins without destroying vital immunological domains. Synthetic chemistry can address these issues since it makes it possible to

incorporate an artificial linker for controlled conjugation to proteins. In addition, substructures can be prepared to determine the minimal epitope required to elicit protective immune responses.

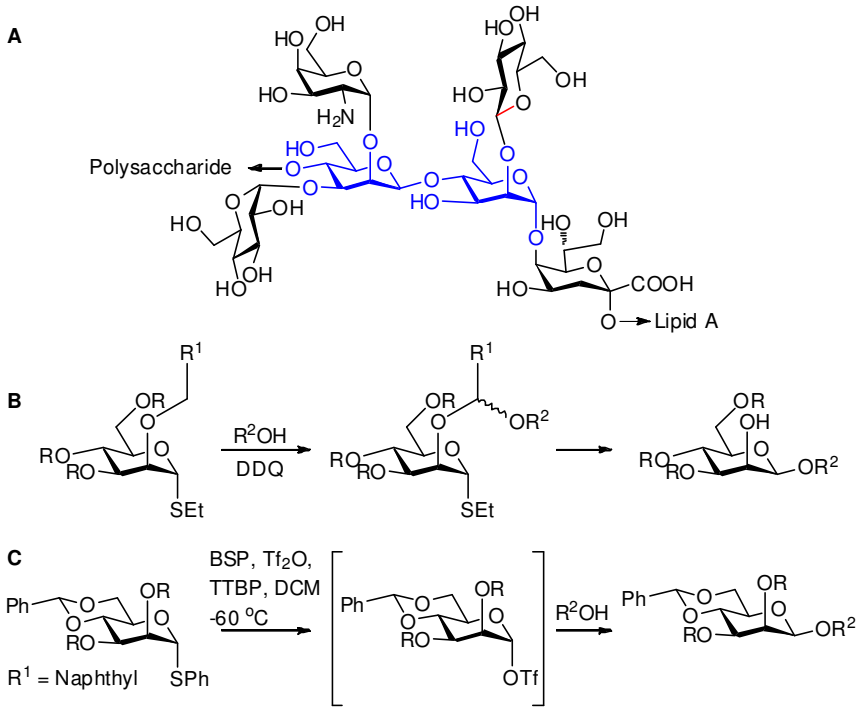
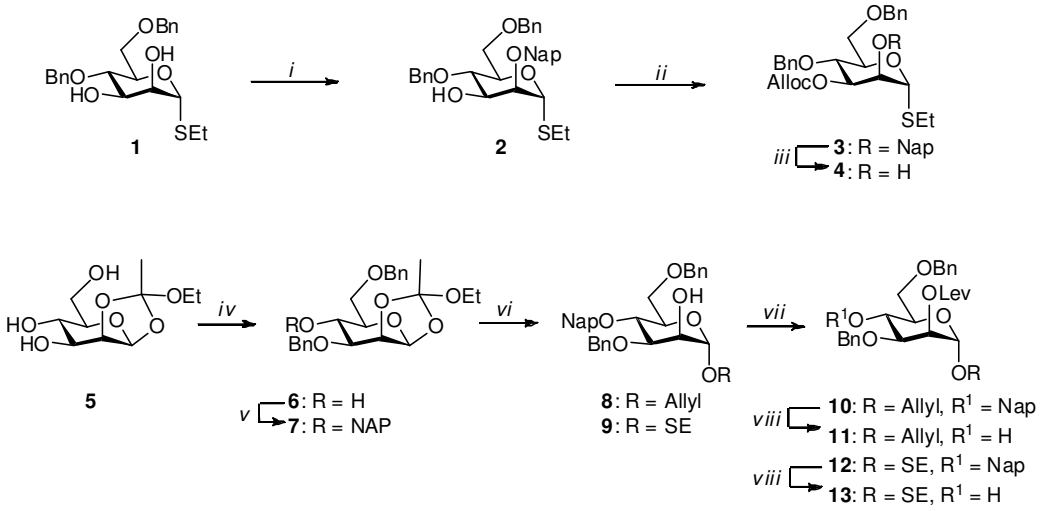


Figure 4.1. Target molecule and synthetic strategy. A) A highly branched hexasaccharide fragment isolated from *F. tularensis* LVS lipopolysaccharide, target β-D-Man-(1→4)-α-D-Man disaccharide highlighted in blue. B) Intramolecular aglycon delivery through acetal tethering. C) 4,6-benzylidene mediated α-triflate formation followed by S_N2-like displacement.

Herein we report the chemical synthesis of a β-D-Man-(1→4)-α-D-Man disaccharide that is functionalized with a set of orthogonal protecting groups at C-1, C-2, C-2′ and C-3′. The orthogonal protecting groups make it possible to selectively introduce glycosides for the synthesis of a library of *F. tularensis* oligosaccharides.[5-8] To this end, two β-mannosylation strategies were explored as well as a variety of orthogonal protecting group combinations. β-Mannosides, which are an important class of 1,2-*cis* glycosides, are difficult to introduce due to the axial C-2 substituent, which sterically blocks incoming nucleophiles from the β-face and the Δ-anomeric effect, which provides additional stabilization of the α-anomer.[9-10] An elegant method for the construction of β-mannosidic linkages is based on intramolecular

aglycon delivery (IAD), which usually gives absolute β-anomeric selectivity (Figure 4.1 B). In this two step protocol, the glycosyl donor and acceptor are tethered through a mixed acetal by for example oxidative coupling of a 4-methoxybenzyl- or methylnaphthyl (Nap) ether using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[11-15] The ether can be present on the glycosyl donor or acceptor, the latter being referred to as reverse tethering. In the second step, the glycosyl donor is activated and the glycosyl acceptor is forced to attack from the same face as the C-2′ tether leading to the introduction of a 1,2-*cis*-glycoside with concomitant loss of the C-2′ protecting group.

Results and Discussion. Monosaccharide building blocks **3**,**4**,**12** and **13** were prepared to explore the utility of IAD for the synthesis of an orthogonal protected β-D-Man-(1→4)-α-D-Man disaccharide (Scheme 4.2). It was envisaged that compound **3**, which is equipped with a methylnapthyl ether, would provide a useful starting material to make tethered derivative **14**, which upon IAD should provide disaccharide **15**. The resulting free hydroxyl at C-2′ of **15** can then immediately be used for the introduction of the GalN of the core region of *F. Tularensis*. It was expected that the allyloxycarbonyl (Alloc), levulinoyl ester (Lev)[16] and the 2-(trimethylsilyl)ethyl ether (SE)[17] would provide an attractive set of orthogonal protecting groups for further glycosylations. Two tethering approaches were tested: normal and inverse. To this end, two types of glycosyl donor and acceptor building blocks were prepared (Scheme 4.1). The monosaccharide glycosyl donor and acceptors **3**,**4** and **12**,**13** were prepared from known intermediate **1**[18] and **5**[19], respectively. Regioselective reaction of precursor **1** with 2-bormomethylnaphthalene and sodium hydroxide in a biphasic mixture of CH_2Cl_2/water afforded the C-2 Nap derivative **2**. Reaction of **2** with allylchloroformate and TMEDA in CH_2Cl_2 smoothly afforded glycosyl donor **3**. Glycosyl donor **4** for inverse tethering was prepared by oxidative removal of the Nap ether using DDQ in wet CH_2Cl_2. The synthesis of the mannosyl acceptors **12** and **13** was achieved starting from orthoester **5**. Deacetylation using ammonia in methanol afforded the triol which was selectively benzylated at C-3 and C-6 using bis(tri-*n*-butyltin)oxide and benzyl bromide.

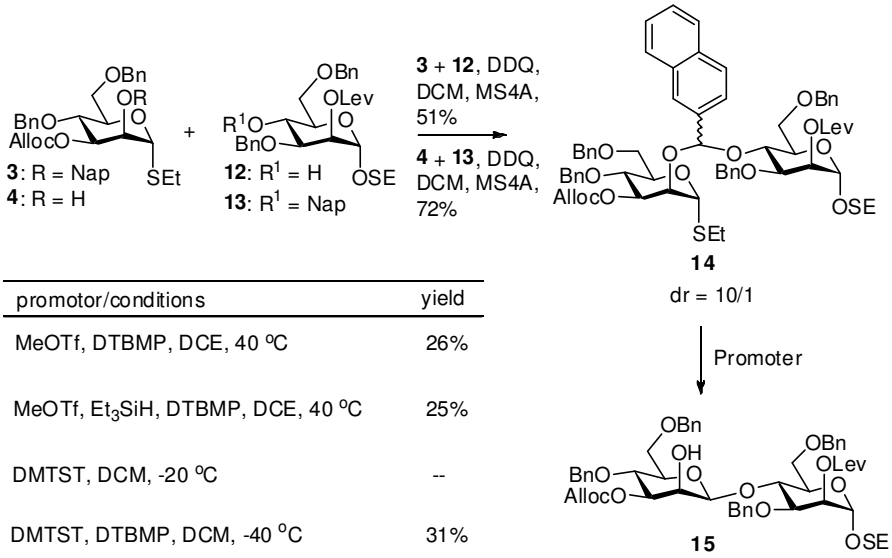


Scheme 4.1. Synthesis of the mannosyl building blocks **3,4** and **12,13**. Reagents and conditions: (*i*) NapBr, Bu_4NHSO_4, DCM/H_2O, reflux, 16 hrs, 77%. (*ii*) AllocCl, TMEDA, CH_2Cl_2, rt, 16 hrs, 95%. (*iii*) DDQ, CH_2Cl_2/H_2O, rt, 3 hrs, 88%. (*iv*) 1). $(Bu_3Sn)_2O$, Tol, reflux, 5 hrs. 2). BnBr, Bu_4NBr, Tol, reflux, 16 hrs, 43%. (*v*) NapBr, NaH, DMF, rt, 1 hr, 76%. (*vi*) for **10**: 1). AllOH, TMSOTf, CH_2Cl_2, 0°C, 10 min. 2). NaOMe, MeOH, rt ,16 hrs, 62%. for **12**: 1). AcOH/H_2O, rt, 3 hrs. 2). TCA, DBU, CH_2Cl_2, 0°C, 30 min. 3). 2-trimethylsilylethanol, TMSOTf, CH_2Cl_2, 0°C, 5 min. 4). NaOMe, MeOH, rt ,16 hrs, 54% (*vii*) Levulinic acid, DCC, DMAP, CH_2Cl_2, rt, 1.5 hrs, 96%. (*vii*) DDQ, CH_2Cl_2/H_2O, rt, 1.5 hrs, 90% for **11**, 81% for **13**.

The remaining C-4 alcohol was protected with a Nap ether using 2-bromo-methylnaphthalene and sodium hydride in DMF. At this point, two different anomeric protecting groups were incorporated, the allyl ether and the 2-trimethylsilylethyl ether. Allyl derivative **8** was prepared by direct opening of the orthoester using allyl alcohol followed by deacetylation. Installation of the 2-trimethylsilyl ethyl ether was achieved by hydrolysis of the the orthoester to afford the intermediate lactol. The lactol was converted into the trichloroacetimidate and glycosylated with 2-trimethylsilylethanol. Deacetylation using NaOMe in methanol afforded **9**. Both **8** and **9** were reacted with levulinic acid, DCC and DMAP to afford **10** and **12**, respectively. Finally the Nap ether was removed using DDQ in wet CH_2Cl_2 to afford **11** and **13**.

Next, building block **3**,**4**,**12** and **13** were used to investigate the IAD approach to the target β-mannoside disaccharide. A mixture of **3** and **12** in CH_2Cl_2 in the presence of molecular sieves was treated with DDQ to afford mixed acetal **5** in a moderate yield of 51% as a 10/1 mixture of diastereoisomers

(Scheme 4.2). The yield was significantly improved when reverse tethering was employed using **4** and **13** to give **14** in 72% yield.



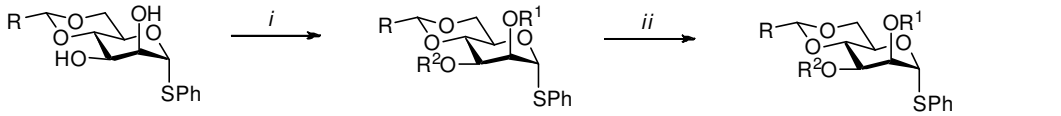
promotor/conditions	yield
MeOTf, DTBMP, DCE, 40 °C	26%
MeOTf, Et_3SiH, DTBMP, DCE, 40 °C	25%
DMTST, DCM, -20 °C	--
DMTST, DTBMP, DCM, -40 °C	31%

Scheme 4.2. Intramolecular aglycon delivery using acetal tethering.

Presumably, a higher yield is obtained due to the higher nucleophilicity of the C-2′ alcohol. Next, mixed acetal **14** was activated with methyl triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in 1,2-dichloroethane (DCE) at 40 °C. Despite the relatively high reaction temperature, the glycosylation was rather sluggish, and after a reaction time of 16 h, disaccharide **15** was isolated in a disappointing yield of 26%. The low yield was due to the formation of several byproducts including C-2′ methylated disaccharide. To address the problem of methylation, the methyl triflate promoted glycosylation was performed in the presence of triethyl silane. Under these conditions, the intermediate naphthylic cation is trapped providing a C-2′ Nap ether instead of a hydroxyl. Unfortunately, these modified reaction conditions did not improve the yield of β-mannoside **15**. Dimethyl(thiomethyl)sulfonium triflate (DMTST)[20] is also commonly employed as a thiophilic promoter for IAD.[21] However, the use of this promoter in the absence of a base did not lead to product formation. Nevertheless, the application of DMTST in combination with the base DTBMP gave **15** in a somewhat improved yield of 31%. Other promoter systems such as *N*-iodosuccinimide (NIS) could not be employed

because of incompatibility with the Alloc function. Although other orthogonal protecting group pairs could be examined, attention was focussed on an alternative approach for β-mannoside synthesis.

Crich and co-workers have pioneered an attractive approach for the introduction of β-mannosides by *in-situ* formation of an α-anomeric triflate because of a strong endo-anomeric effect (Figure 4.1 C).[22-23] An S_N2 like-displacement of the α-triflate by a sugar hydroxyl then results in the formation of a β-mannoside. A prerequisite of β-mannoside formation is that the donor is protected by a 4,6-*O*-benzylidene acetal. It has been proposed that this protecting group opposes oxacarbenium formation (S_N1 glycosylation) due to the torsional strain engendered by the half chair or boat conformation of this intermediate and a destabilizing electronic effect caused by placing the O-6 dipole antiparallel to the oxacarbenium ion.[24]



16: R = Ph
17: R = Ph

18: R = Ph, R^1 = Nap, R^2 = H
19: R = Ph, R^1 = H, R^2 = Nap
20: R = Ph, R^1 = H, R^2 = TOM
21: R = PMP, R^1 = H, R^2 = TOM
22: R = PMP, R^1 = H, R^2 = Nap

23: R = Ph, R^1 = Nap, R^2 = TBS
24: R = Ph, R^1 = TBS, R^2 = Nap
25: R = Ph, R^1 = Nap, R^2 = TOM
26: R = PMP, R^1 = Nap, R^2 = TOM
27: R = Ph, R^1 = DEIPS, R^2 = Nap
28: R = PMP, R^1 = DEIPS, R^2 = Nap

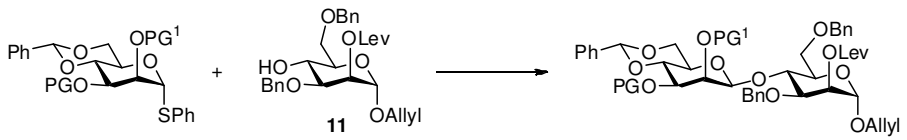
Scheme 4.3. Synthesis of the mannosyl building blocks **23**-**28**. (*i*) NapBr, Bu_4NHSO_4, CH_2Cl_2/H_2O, reflux, 16 grs, 87%. for **18**. 1). Bu_2SnO, MeOH, reflux, 4 hrs. 2). NapBr, CsF, DMF, rt 16 hrs for **19** (85%) and **22** (82%). 1). Bu_2SnO, MeOH, reflux, 3 hrs. 2). TOMCl, DIPEA, DCE, 80°C, 15 min for **20** (78%) and **21** (68%). (*ii*) TBSCl, imidazole, DMF, rt, 16 hrs, 96% for **23**. TBSOTf, Et_3N, CH_2Cl_2, rt 3 hrs, 99% for **24**. NapBr, NaH, DMF, rt 1 hr, **25** (95%) and **26** (73%). DEIPSCl, imidazole, DMF, rt, 3 hrs. for **27** (76%) and **28** (86%).

Glycosyl donors **23**-**28** were therefore prepared (Scheme 4.3) and examined in glycosylations with glycosyl acceptor **11** using trifluoromethanesulfonic anhydride (Tf_2O), 1-benzenesulfinylpiperidine (BSP) as the promoter system (Table 4.1).[25] The 4,6-diol of the glycosyl donors is protected as a benzylidene- or *p*-methoxybenzylidene acetal and the C-2 and C-3 hydroxyls by different sets of orthogonal protecting groups. The latter was deemed important because previous studies have indicated that steric and electronic features of the C-2 and C-3 protecting groups can influence the β-anomeric selectivity of

mannosylations.[25] It was anticipated that the Nap[26], TBS, Lev and allyl would provide an attractive set of orthogonal protecting groups. Intermediate **18** was obtained by regioselective reaction of precursor **16**[27] with 2-bormomethylnaphthalene and sodium hydroxide in a biphasic mixture of CH_2Cl_2/water (Scheme 4.3). The C-3 of **16**[27] and **17**[27] was selectively protected using a two step procedure.

First, the tin acetal was formed using dibutyltin oxide in methanol. Subsequent reaction with either 2-bromo-metyhlnaphthalene or TOMCl afforded intermediates **19**-**22** in good yield. The remaining alcohol of **18**-**22** was protected with a TBS-, 2-methylnaphthyl- or diethylisopropyl silyl ether to afford glycosyl donors **23**-**28**.

Glycosyl donor **23** has a similar structure as **24**, however, the bulky TBS group is used for the protection of the C-2 hydroxyl and the Nap ether for the C-3 position. Low temperature (-78 ^{o}C) activation of glycosyl donor **23** was achieved with BSP/Tf_2O in the presence of DTBMP in CH_2Cl_2.[25] Addition of the acceptor and slow warming to -35 ^{o}C afforded the mannoside in a disappointing yield of 31% as a 1/1.5 mixture of β/α anomers (Table 4.1). It has been observed that a bulky TBS groups at C-3 gives poor β/α ratios due to a so-called buttressing effect.[28] Indeed, when donor **24** was used, the stereoselectivity improved dramatically to β/α>20/1, however, the yield was still moderate (40%). Attempts to remove the TBS ether using TBAF led to partial Lev cleavage and buffering with AcOH made the desilylation impractically slow. Hence, glycosyl donors carrying more labile silyl protecting groups were evaluated. The triisopropylsiloxymethyl (TOM) ether was selected since it is less sterically demanding than the TBS ether and can thus be used as a C-3 protecting group and is also readily cleaved using TBAF buffered with AcOH.[29] Glycosyl donor **25** and its *p*-methoxybenzylidene derivative **26** showed good β-selectivity and moderate yields (53% and 34%, respectively). In each case, the activation of the donor was exceptionally clean but when the glycosyl acceptor was added some byproduct formation was observed. Sulfoxide promoter systems such as BSP/Tf_2O are known to generate electrophilic byproducts and since glycosyl acceptor **11** is relatively unreactive, it was assumed that it partly reacted with these electrophilic byproducts thus lowering the overall yield.[30] This assumption was supported by the fact that all the glycosyl acceptor was consumed even though it was used in excess.



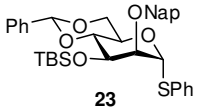
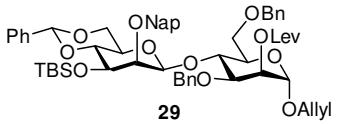
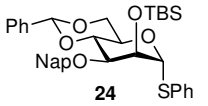
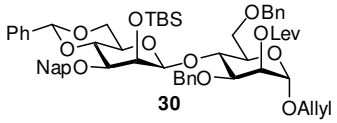
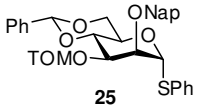
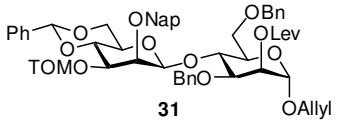
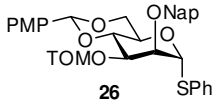
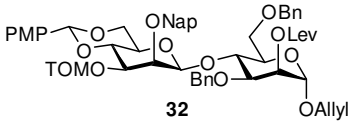
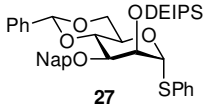
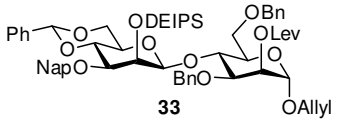
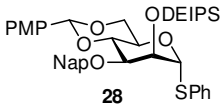
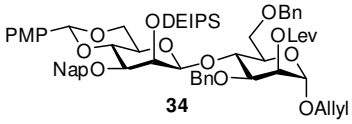
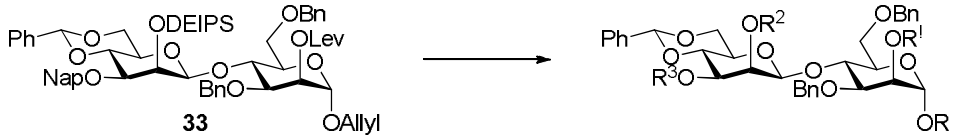
Glycosyl Donor	Product	yield[a]	ratio β/α[d]
 **23**	 **29**	31%[b]	1/1.5
 **24**	 **30**	40%[b]	>20/1
 **25**	 **31**	53%[b]	6/1
 **26**	 **32**	34%[b] 63%[c]	6/1[e]
 **27**	 **33**	41%[b] 73%[c]	>20/1[e]
 **28**	 **34**	40%[b] 73%[c]	>20/1[e]

Table 4.1. Stereoselective β-mannosylations. (a) Isolated yields of the pure β anomer. (b) BSP/Tf_2O promotor system (c) *p*-NO_2-C_6H_4SCl/AgOTf promotor system. (d) The β/α ratio was determined by intergration of key signals in the ^1H NMR of the reaction mixture purified by size exclusion chromotography. The β-anomeric configuration was confirmed by the C_1'-H_1' heteronuclear coupling constant (158-162Hz) and the chemical shift of H-5′ (~3 ppm) (e) β/α ratio was the same regardless of the promotor system used.

Benzenesulfenyl triflate (generated *in situ* from benzenesulfenyl chloride and silver trifluoromethane sulfonate) is known to be a powerful activator of thioglycosides that leads only to an inert disulfide as by-product when succesful. Thus, commercially available *p*-$NO_2C_6H_4SCl$ was used in combination with AgOTf in the presence of DTBMP for activation of **26**.[31] Indeed, when **26** was activated with these reagents, and reacted with **11**, disaccharide **32** was obtained in a much-improved yield of 63%. Although removability of the TOM was not an issue the stereoselectivity was moderate. Hence, the diethylisopropylsilyl ether (DEIPS) was evaluated as an orthogonal protecting group since it has a similar structure to the TBS ether but can more easily be removed.[32-33] Glycosyl donor **27** and it *p*-methoxybenzylidene derivative **28** showed excellent stereoselectivity (β/α>20/1). The yields with BSP/Tf_2O were moderate (41% and 40%, respectively) but could be improved to 73% using *p*-$NO_2C_6H_4SCl$/AgOTf. Disaccharide **33** was expected to be an excellent candidate for the preparation of the core region of *F. tularensis.*



33

entry	product	condition	yield
1	**35**: R = H, R^1 = Lev, R^2 = DEIPS, R^3 = Nap	$PdCl_2$, NaOAc, AcOH, H_2O	72%
2	**36**: R = Allyl, R^1 = H, R^2 = DEIPS, R^3 = Nap	NH_2NH_2·AcOH, Tol/EtOH	99%
3	**37**: R = Allyl, R^1 = Lev, R^2 = H, R^3 = Nap	TBAF, AcOH, THF	98%
4	**38**: R = Allyl, R^1 = Lev, R^2 = DEIPS, R^3 = H	DDQ, CH_2Cl_2, H_2O	93%

Table 4.2. Selective removal of the orthogonal protecting groups.

Having established conditions for a high yielding and stereoselective β-mannosylation, attention was focused on the selective removal of the temporary protecting groups (Table 4.2). The anomeric allyl ether of **33** could be removed using $PdCl_2$ in high yield without affecting the other protecting groups. It is to be

expected that lactol **35** can easily be converted into a trichloroacetimidate and used as a glycosyl donor in an ensuing glycosylation. The Lev ester was removed in near quantitative yield using hydrazinium acetate in a mixture of toluene and ethanol to afford **36**. DEIPS removal was performed under buffered conditions (TBAF/AcOH) to prevent the aforementioned Lev cleavage and gave **37** in 98% yield. Finally, the Nap ether was cleaved by DDQ oxidation in wet CH_2Cl_2 to provide compound **38** in high yield (93%).

Conclusion: The disaccharide β-D-Man-(1→4)-D-Man, modified with four orthogonal protecting groups, was prepared in high yield with excellent anomeric selectivity. It was found that the protecting group pattern was critical for achieving high β-anomeric selectivity and the best results were achieved with a mannosyl donor having a C-2 DEIPS, and a C-3 Nap ether and an acceptor modified with an anomeric allyl ether and a C-2 Lev ester. High yields of disaccharide were obtained when *p*-$NO_2C_6H_4SCl$/AgOTf was used as the promoter system for activating an anomeric thioglycoside. Each temporary protecting group could be removed in high yield without affecting the other protecting groups. The new set of orthogonal protecting groups is expected to be suited for the preparation of a library of *F. tularensis* inner-core oligosaccharides and will facilitate the preparation of other highly branched oligosaccharides.

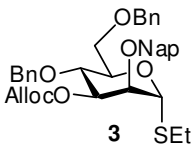
Experimental Section:

General procedures: ^1H and ^{13}C NMR spectra were recorded on a 300 MHz, 500 MHz or a 600 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. NMR data is presented as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration. All NMR signals were assigned on the basis of ^1H NMR, ^{13}C NMR, COSY and HSQC experiments. Mass spectra were recorded on an MALDI-TOF mass spectrometer. The matrix used was 2,5-dihydroxy-benzoicacid (DHB) and Ultamark 1621 as the internal standard. Column chromatography was performed on silica gel G60 (Silicycle, 60-200 μm, 60 Å). TLC-analysis was

conducted on Silicagel 60 F_{254} (EMD Chemicals inc.) with detection by UV-absorption (254nm) were applicable, and by spraying with 20% sulfuric acid in ethanol followed by charring at ~150°C or by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (25 g/L) in 10% sulfuric acid in ethanol followed by charring at ~150°C. CH_2Cl_2 was freshly distilled from calcium hydride under nitrogen prior to use. Molecular sieves (4Å) were flame activated under vacuum prior to use. All reactions were carried out under an argon atmosphere.

Ethyl 4,6-di-*O*-benzyl-2-*O*-(2-methylnaphthyl)-1-thio-α-D-mannopyranoside (2). Ethyl 4,6-di-*O*-benzyl-1-thio-α-D-mannopyranose (3.0 g, 7.4 mmol)[18] was dissolved in CH_2Cl_2 (40 mL) and a 5% w/w aqueous solution of NaOH (10 mL) was added. Bu_4NHSO_4 (0.47 g, 1.4 mmol) was added followed by 2-(bromomethyl)naphthalene (2.87 g, 13.0 mmol) and the resulting emulsion was refluxed for 16 hrs. The emulsion was diluted with CH_2Cl_2 (100 mL) and washed with water (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 30% - EtOAc in PE) of the residue afforded **2** (3.1 g, 77 %) as a white solid. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.3; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77-7.13 (m, 17H, CH Ar), 5.45 (s, 1H, H-1), 4.86 (d, 1H, *J* = 12.0 Hz, C*H*HNap), 4.77 (d, 1H, *J* = 11.4 Hz, C*H*HPh), 4.61 (d, 2H, *J* = 12.0 Hz, CH*H*Nap, C*H*HPh), 4.46 (d, 1H, *J* = 12.0 Hz, *J* = 11.4 Hz, CH*H*Ph, CH*H*Ph), 4.10-4.00 (m, 1H, H-5), 3.95-3.85 (m, 1H, H-3), 3.82 (dd, 1H, *J* = 1.5 Hz, *J* = 3.9 Hz, H-2), 3.81-3.62 (m, 3H, H-4, H6a, H6b), 2.61-2.50 (m, 2H, CH_2 SEt), 2.34 (d, 1H, *J* = 9.3 Hz, 3-OH), 1.17 (t, 3H, *J* = 7.2 Hz, CH_3 SEt); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 138.3, 134.9, 133.2, 133.1, 128.5-125.8, 80.9, 79.8, 76.8, 74.8, 73.3, 72.3, 72.3, 71.2, 69.0, 25.0, 14.8; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{33}H_{36}O_5S$, 567.2181; found, 567.2175.

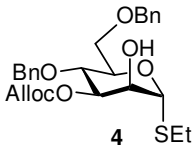
Ethyl 3-*O*-allyloxycarbonyl-4,6-di-*O*-benzyl-2-*O*-(2-methylnaphthyl)-1-thio-α-D-mannopyranoside



3

(3). To a cooled (0°C) solution of **2** (3.0 g, 5.5 mmol) in CH_2Cl_2 (20 mL) was added *N*,*N*-*N*′,*N*′-tetramethylethylenediamine (1.64 mL, 11.0 mmol) and allylchloroformate (0.88 mL, 8.3 mmol). The resulting solution was stirred for 16 hrs at rt. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 30% - EtOAc in PE) of the residue afforded **3** (3.27 g, 95 %) as a white solid. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.55; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89-7.24 (m, 17H, CH Ar), 5.99-5.90 (m, 1H, CH Alloc), 5.53 (d, 1H, *J* = 1.2 Hz, H-1), 5.40-5.26 (m, 2H, CH_2 Alloc), 5.13 (dd, 1H, *J* = 3.3 Hz, *J* = 8.7 Hz, H-3), 4.95 (d, 1H, *J* = 12.3 Hz, C*H*HPh), 4.81-4.73 (m, 2H, C*H*HNap, CH*H*Ph), 4.60-4.43 (m, 3H, CH*H*Nap, CH_2 OBn), 4.31-4.16 (m, 5H, H-2, H-5, CH_2, Alloc, H-4), 3.90 (dd, 1H, *J* = 3.6 Hz, *J* = 10.8 Hz, H6a), 3.78 (dd, 1H, *J* = 9.3 Hz, H6b), 2.75-2.60 (m, 2H, CH_2 SEt), 1.31 (t, *J* = 7.5 Hz, 3H, CH_3 SEt); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 138.0, 137.9, 135.0, 133.0, 132.9, 131.6, 128.1-125.7, 118.6, 81.5, 78.1, 76.8, 74.7, 73.4, 73.3, 72.2, 71.6, 68.7, 68.3, 25.0, 14.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{37}H_{40}O_7S$, 651.2392; found, 651.2389.

Ethyl 3-*O*-allyloxycarbonyl-4,6-di-*O*-benzyl-1-thio-α-D-mannopyranoside (4). To a well stirred

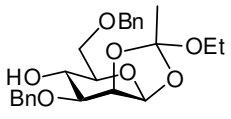


4

emulsion of **3** (1.0 g, 1.6 mmol) in CH_2Cl_2 (9 mL) and water (1 mL) was added DDQ (0.54 g, 2.4 mmol). The resulting solution was stirred for 3 hrs at rt in the dark. The mixture was diluted with CH_2Cl_2 (50 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*. Silica gel column chromatography (0% → 30% - EtOAc in PE) of the residue afforded **4** (0.69 g, 88 %) as a white solid. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.3; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.17 (m, 10H, CH Ar), 5.92-5.82 (m, 1H, CH Alloc), 5.38-5.23 (m, 3H, CH_2 All, H-1), 5.05 (dd, 1H, *J* = 3.0 Hz, *J* = 9.6 Hz, H-3), 4.69-4.48 (m, 6H, 2 x CH_2 OBn, CH_2 Alloc),

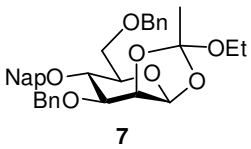
4.24-4.18 (m, 2H, H-2, H-5), 4.07 (t, 1H, *J* = 9.6 Hz, H-4), 3.81 (dd, 1H, *J* = 3.9 Hz, *J* = 6.9 Hz, H6a), 3.67 (dd, 1H, *J* = 1.5 Hz, *J* = 10.8 Hz, H6b), 2.88 (d, 1H, *J* = 6.0 Hz, 2-OH), 2.70-2.54 (m, 2H, CH_2 SEt), 1.29 (t, *J* = 7.5 Hz, 3H, CH_3 SEt); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 137.9, 137.8, 131.3, 128.3-127.6, 119.1, 84.0, 78.8, 74.8, 73.4, 73.1, 71.4, 70.7, 68.5, 24.9, 14.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{26}H_{32}O_7S$, 511.1766; found, 511.1762.

3,6-di-*O*-benzyl-β-D-mannopyranose 1,2-(ethyl orthoacetate) (6).[19,34] β-D-mannopyranose 1,2-(ethyl orthoacetate) (14.3 g, 57.4 mmol) was dissolved in toluene (500 mL) and bis(tri-*n*-butyltin)oxide (88 mL, 172.2 mmol) was added. A dean-stark apparatus was installed and water was removed by reflux during 5 hrs. The mixture was cooled to rt and concentrated *in vacuo* to ~150 mL. Benzyl bromide (20.4 mL, 172.2 mmol) and tetra-*n*-butylammonium bromide (9.2 g, 28.7 mmol) were added. The resulting mixture was refluxed for 16 hrs. After cooling to rt, water (200 mL) and EtOAc (500 mL) were added. The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The remaining oil was loaded on a silica gel column and flushed with hexanes (2.0 L) thereafter gradient column chromatography (0% → 40% - EtOAc in PE) afforded **6** (10.6 g, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.16 (m, 10H, CH Ar), 5.24 (d, 1H, *J* = 2.4 Hz, H-1), 4.72 (d, 1H, *J* = 12.3 Hz, C*H*HPh),4.60 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.55 (s, 2H, CH_2Ph), 4.28 (dd, 1H, *J* = 2.7 Hz, *J* = 4.2 Hz, H-2), 3.84 (t, 1H, *J* = 9.3 Hz, H-4), 3.65 (d, 2H, *J* = 4.5 Hz, H6a, H6b), 3.50-3.38 (m, 3H, H-3, CH_2 OEt), 3.32-3.26 (m, 1H, H-5), 1.11 (t, 1H, *J* = 6.9 Hz, CH_3, OEt): ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 137.6, 128.4-126.8, 123.7, 97.5, 78.6, 76.1, 73.5, 73.5, 72.0, 69.9, 67.2, 57.8, 24.7, 15.0; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{24}H_{30}O_7$, 453.1889; found, 453.1882.



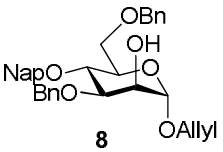
6

3,6-di-*O*-benzyl-4-*O*-(2-methylnaphthyl)-β-D-mannopyranose 1,2-(ethyl orthoacetate) (7). To a cooled (0°C) solution of **6** (10.0 g, 23.3 mmol) and 2-(bromomethyl)naphthalene (6.2 g, 28.0 mmol) in DMF (100 mL) was added sodium hydride (60% wt in mineral oil, 1.0 g, 25.6 mmol). The mixture was stirred for 1 hr at rt before MeOH (3 mL) was added. The mixture was diluted with EtOAc (400 mL) and washed with water (3 x 100 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in PE) of the residue afforded **7** (10.1 g, 76 %) as a yellow solid. TLC: (EtOAc/PE, 50/50 v/v): R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.15 (m, 17H, CH Ar), 5.24 (d, 1H, *J* = 2.1 Hz, H-1), 4.94 (d, 1H, *J* = 11.1 Hz, C*H*HNap), 4.70-4.67 (m, 3H, CH*H* Nap), 4.53 (d, 1H, *J* = 12.3 Hz, C*H*HPh), 4.42 (d, 1H, *J* = 12.6 Hz, CH*H*Ph), 4.31 (dd, 1H, *J* = 2.7 Hz, *J* = 4.2 Hz, H-2), 3.89 (t, 1H, *J* = 9.3 Hz, H-4), 3.69-3.64 (m, 3H, H6a, H6b, H-3), 3.50-3.48 (m, 1H, CH_2 OEt), 3.38-3.36 (m, 1H, H-5), 1.13 (t, 1H, *J* = 6.9 Hz, CH_3, OEt): ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 137.8, 135.7, 133.2, 132.9, 128.4-125.8, 123.7, 97.4, 79.0, 76.8, 75.2, 74.2, 74.1, 73.3, 72.3, 69.0, 57.9, 24.7, 15.2; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{35}H_{38}O_7$, 593.2515; found, 593.2519.



7

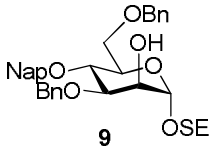
Allyl 3,6-di-*O*-benzyl-4-*O*-(2-methylnaphthyl)-α-D-mannopyranoside (8). To a cooled (0°C) solution of **7** (1.1 g, 1.9 mmol) in allylalcohol (4 mL) and CH_2Cl_2 (1 mL) was added TMSOTf (35 µL, 0.19 mmol). The mixture was stirred for 10 min at 0°C before Et_3N (1 mL) was added. The mixture was concentrated *in vacuo* and the residue was dissolved in a mixture of CH_2Cl_2 (1 mL) and MeOH (9 mL). A catalytic amount of NaOMe was added and the reaction mixture was stirred for 16 hrs at rt. Dowex® 50W X8-200 H^+ resin was added and the mixture was stirred for 5 min, filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 30% - EtOAc in PE) of the residue afforded **8** (0.63 g, 62 %) as a white solid. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.25; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82-7.23 (m, 17H, CH Ar), 5.90 (m, 1H, CH Alloc), 5.30-5.17 (m, 2H, CH_2 All), 5.00-4.97 (m, 2H, H-1, C*H*HNap), 4.76-4.48 (m, 5H, 2 x



8

CH_2 OBn, CH*H*Nap), 4.22-3.90 (m, 5H, H-2, H-5, H-3, CH_2 All), 3.84-3.71 (m, 3H, H-4, H6a, H6b), 2.52 (bs, 1H, 2-OH);); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 137.9, 133.6, 133.2, 132.9, 128.5-125.7, 117.4, 98.4, 80.2, 75.1, 74.3, 73.4, 71.9, 71.1, 68.8, 68.3, 67.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{34}H_{36}O_6$, 563.2410; found, 563.2419.

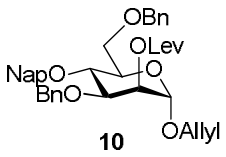
2-Trimethylsilylethyl 3,6-di-*O*-benzyl-4-*O*-(2-methylnaphthyl)-α-D-mannopyranoside (9). **7** (2.5 g, 4.38 mmol) was dissolved in a mixture of AcOH (16 mL) and H_2O (4 mL) and the resulting mixture was stirred for 3hrs at rt. The mixture was concentrated *in vacuo* and the residue was azeotropically dried with toluene (3 x 10 mL). The residue was dissolved in a mixture of CH_2Cl_2 (20 mL) and trichloroacetonitrile (2 mL) and cooled to 0°C. DBU (66 μL, 0.44 mmol) was added and the mixture was stirred for 30 min at 0°C. The mixture was concentrated *in vacuo* the residue was purified using silica gel column chromatography (0% → 30% - EtOAc in PE). The pure trichloroacetimidate was dissolved in a mixture of CH_2Cl_2 (10 mL) and 2-Trimethylsilylethanol (2 mL). Activated molecular sieves (4Å) were added and mixture was stirred for 5 min at 0°C. TMSOTf (80 μL, 0.44 mmol) was added and the mixture was stirred for 10 min at 0°C. Et_3N (0.5 mL) was added and the mixture was concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL), a catalytic amount of NaOMe was added and the mixture was stirred for 16 hrs at rt. Dowex® 50W X8-200 H^+ resin was added and the suspension was stirred for 10 min. The resin was removed by filtration and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 30% - EtOAc in PE) of the residue afforded **S10** (1.42 g, 54%) as a colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.3; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82-7.24 (m, 17H, CH Ar), 4.99 (d, 1H, *J* = 10.8 Hz, C*H*H Nap), 4.92 (d, 1H, *J* = 1.5 Hz, H-1), 4.71-4.44 (m, 5H, CH*H* Nap, 2 x CH_2 Bn), 4.02 (s, 1H, H-2), 3.91-3.70 (m, 6H, H-3, H-4, H-5, H6a, H6b, C*H*HSE), 3.52-3.46 (m, 1H, CH*H*SE), 1.01-0.86 (m, 2H, CH_2 SE), 0.05 (s, 9H, 3 x CH_3 TMS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 137.9, 135.8, 133.2, 132.9, 128.5-125.8, 98.7, 80.3, 75.1, 74.4, 73.4,



9

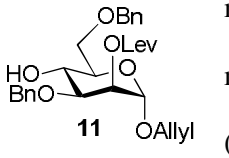
71.9, 70.9, 69.0, 68.5, 64.8, 17.8, 1.02; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{36}H_{44}O_6Si$, 623.2805; found, 623.2811.

Allyl 3,6-di-*O*-benzyl-2-*O*-levulinoyl-4-*O*-(2-methylnaphthyl)-α-D-mannopyranoside (10). To a solution of **8** (0.63 g, 1.18 mmol) in CH_2Cl_2 (10 mL) was added DMAP (15 mg, 0.12 mmol), levulinic acid (0.2 mL, 2.0 mmol) and DCC (0.36 g, 1.8 mmol). The mixture was stirred for 90 min at rt. The mixture was filtered and the filtrate was concentrated *in vacuo.* Silica gel column chromatography (0% → 30% - EtOAc in PE) of the residue afforded **8** (0.70 g, 96 %) as a white solid. TLC: (EtOAc/PE, 40/60 v/v): R_f = 0.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.17 (m, 17H, CH Ar), 5.89-5.80 (m, 1H, CH Alloc), 5.32 (dd, 1H, *J* = 1.8 Hz, *J* = 5.1 Hz, H-2), 5.21-5.08 (m, 2H, CH_2 All), 4.91 (d, 1H, *J* = 10.8 Hz, CH*H* Nap), 4.81 (d, 1H, *J* = 2.1 Hz, H-1), 4.65-4.40 (m, 5H, 2 x CH_2 OBn, CH*H* Nap), 4.12-4.05 (m, 1H, C*H*HAll), 3.98-3.73 (m, 5H, CH*H*All, H-3, H-4, H-5, H6a), 3.63 (m, 1H, H6b), 2.63 (m, 4H, 2 x CH_2 Lev), 2.05 (s, 3H, CH_3 Lev); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.3, 172.0, 138.2, 138.0, 135.8, 133.4, 133.2, 132.9, 117.7, 96.8, 78.1, 75.1, 74.3, 73.4, 71.6, 71.4, 68.8, 68.8, 68.1, 37.9, 29.7, 28.2; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{39}H_{42}O_8$, 661.2777; found, 661.2780.



10

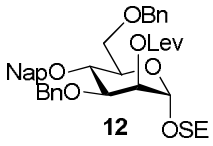
Allyl 3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (11). To a solution of **10** (0.70 g, 1.10 mmol) in CH_2Cl_2 (9 mL) and water (1 mL) was added DDQ (0.37 g, 1.65 mmol). The mixture was stirred for 90 min at rt in the dark. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with an 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*. Silica gel column chromatography (0% → 30% - EtOAc in PE) of the residue afforded **11** (0.48 g, 90 %) as a white solid. TLC: (EtOAc/PE, 40/60 v/v): R_f = 0.30; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.17 (m, 10H, CH Ar), 5.85-5.82 (m, 1H, CH All), 5.30-5.28 (m, 1H, H-2), 5.22-5.10 (m, 2H, CH_2 All),



11

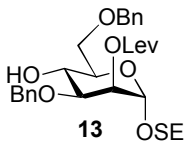
4.79 (d, 1H, *J* = 1.5 Hz, H-1), 4.79-4.35 (m, 4H, 2 x CH_2 OBn), 4.09 (dd, 1H, *J* = 5.1 Hz, *J* = 12.9 Hz, C*H*H All), 3.94-3.81 (m, 2H, CH*H* All, H-4), 3.74-3.68 (m, 4H, H-3, H-5, H6a, H6b), 2.63-2.54 (m, 4H, 2 x CH_2 Lev), 2.48 (bs, 1H, 4-OH), 2.04 (s, 3H, CH_3 Lev); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2, 171.9, 138.1, 137.6, 133.4, 128.4-127.5, 117.7, 96.9, 77.5, 73.5, 71.4, 71.2, 69.7, 68.1, 68.0, 67.2, 37.8, 29.7, 28.0; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{28}H_{34}O_8$, 521.2151; found, 521.2158.

2-Trimethylsilylethyl 3,6-di-*O*-benzyl-2-*O*-levulinoyl-4-*O*-(2-methylnaphthyl)-α-D-mannopyranoside



(12). The same procedure to prepare **10** was followed using **9** (1.42 g, 2.36 mmol) as the starting material. Silica gel column chromatography (0% → 20% - EtOAc in PE) afforded **12** (1.58 g, 96 %) as colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84-7.23 (m, 17H, CH Ar), 5.48-5.41 (m, H-2), 5.06 (d, *J* = 10.8 Hz, C*H*H Nap), 4.91 (s, 1H, H-1), 4.77-4.68 (m, 3H, CH*H* Nap, 2 x C*H*HPh), 4.55 (t, *J* = 12.0 Hz, 2 x CH*H*Ph), 4.06 (dd, 1H, *J* = 3.0 Hz, *J* = 9.0 Hz, H-3), 3.99-3.75 (m, 5H, H-4, H-5, H6a, H6b, C*H*H SE), 3.95-3.50 (m, 1H, CH*H* SE), 2.72 (s, 4H, 2 x CH_2 Lev), 2.12 (s, 3H, CH_3 Lev), 1.00-0.92 (m, 2H, CH_2 SE), 0.05 (9H, 3 x CH_3 SE); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 171.9, 138.1, 137.9, 135.7, 133.1, 132.7, 128.1-125.6, 97.0, 78.1, 74.9, 74.2, 73.2, 71.3, 71.1, 68.9, 68.8, 65.0, 37.7, 29.5, 28.0, 17.7, -1.5; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{41}H_{50}O_8Si$, 721.3173; found, 721.3179.

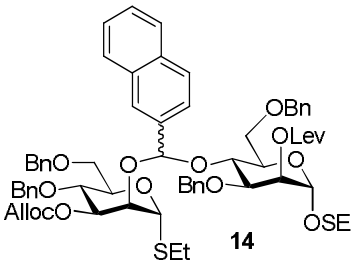
2-Trimethylsilylethyl 3,6-di-*O*-benzyl-3-*O*-levulinoyl-α-D-mannopyranoside (13). The same



procedure to prepare **11** was followed using **12** (0.5 g, 0.71 mmol) as the starting material. Silica gel column chromatography (0% → 20% - EtOAc in PE) afforded **13** (0.32 g, 81 %) as colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.20; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.28 (m, 10H, CH Ar), 5.35 (dd, 1H, *J* = 1.5 Hz, *J* = 2.7 Hz, H-2), 4.86 (d, 1H, *J* = 1.5 Hz, H-1), 4.75-4.45 (m, 4H, 2 x CH_2 OBn), 3.88 (dd, 1H, *J* = 9.3 Hz, *J* = 15.3 Hz, H-4), 3.86-3.80 (m, 5H, H-3, H-5, H6a, H6b, C*H*H SE), 3.59-3.50 (m, 1H, CH*H* SE), 2.75-2.64 (m, 4H, 2 x CH_2 Lev), 2.57

(bs, 1H, 4-OH), 2.16 (s, 3H, CH_3 Lev), 1.00-0.92 (m, 2H, CH_2, SE), 0.05 (9H, 3 x CH_3 SE); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2, 171.9, 138.2, 137.6, 128.4-127.5, 97.3, 77.5, 73.4, 71.4, 71.1, 69.8, 68.3, 67.3, 65.3, 37.8, 29.7, 28.0, 17.7, -1.4; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{30}H_{42}O_8Si$, 581.2547; found, 581.2541.

Mixed naphthyl acetal (14). Compound **3** (0.85 g, 1.35 mmol) and **12** (0.62 g, 1.12 mmol) or **4** (0.47 g, 0.96 mmol) and **13** (0.60 g, 1.16 mmol) were dissolved in CH_2Cl_2 (5 mL) and activate molecular sieves (4Å) were added. DDQ (1.2 equiv) was added and the resulting mixture was stirred for 2 hrs at rt. 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*. Silica gel column chromatography (0% → 25% - EtOAc in PE) of the residue afforded **5** (51% for **3**+**12**, 72% for **4**+**13**) as a white foam. TLC: (EtOAc/PE, 30/60 v/v): R_f = 0.40; ^1H NMR (500 MHz, $CDCl_3$): δ 7.83-7.17 (m, 27H, CH Ar), 5.89-5.82 (m, 2H, CH All, H-7'), 5.37-5.19 (m, 3H, CH_2 All, H-2), 5.04 (dd, 1H, *J* = 3.0 Hz, *J* = 6.0 Hz, H-3'), 4.88 (s, 1H, H-1), 4.76 (s, 1H, H-1'), 4.64-4.49 (m, 8H, 3 x CH_2 OBn, C*H*H All, C*H*HPh), 4.45 (dd, 1H, *J* = 5.5 Hz, *J* = 13.0 Hz, CH*H* All), 4.39 (d, 1H, *J* = 12.0 Hz, H-6a), 4.28 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.13-4.09 (m, 4H, H-2', H-4', H-4, H-5'), 4.05-3.98 (m, 3H, H-5, H-3, H-6b), 3.93-3.85 (m, 1H, C*H*H SE), 3.73 (dd, 1H, *J* = 3.5 Hz, *J* = 10.0 Hz, H-6a'), 3.61 (d, 1H, *J* = 10.0 Hz, H-6b'), 3.56-3.51 (m, 1H, CH*H* SE), 2.71-2.61 (m, 4H, 2 x CH_2 Lev), 2.33-2.19 (m, 2H, CH_2 SEt), 2.12 (s, 3H, CH_3 Lev), 1.01-0.87 (m, 5H, CH_2 SE, CH_3 Lev) 0.07 (m, 3H, CH_3 TMS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.1, 172.6, 154.4, 138.8, 138.1, 137.8, 137.8, 136.2, 133.7, 132.7, 131.7, 128.4-124.1, 118.7, 105.3, 97.0, 82.3, 78.4, 78.2, 74.9, 74.9, 73.6, 73.2, 73.0, 72.6, 71.8, 71.4, 71.3, 70.5, 68.8, 68.6, 68.5, 65.1, 37.8, 29.7, 29.9, 24.8, 17.8, 14.4, -1.4; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{67}H_{80}O_{15}SSi$, 1207.4885; found, 1207.4889.



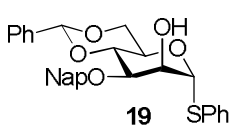
14

2-Trimethylsilyl ethyl 3-*O*-allyloxycarbonyl-4,6-di-*O*-benzyl-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (15). To a mixture of **14** (0.25 g, 0.21 mmol) in DCE (2 mL) was added DTBMP (86 mg, 0.42 mmol) and activated molecular sieves (4Å). After the mixture was stirred for 10 min, MeOTf (35 μL, 0.31 mmol) was added and the resulting mixture was stirred for 16 hrs at 40°C. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (2 x 5 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in PE) of the residue afforded **15** (54 mg, 26%) as a colorless oil. TLC: (EtOAc/PE, 30/60 v/v): R_f = 0.23; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.17 (m, 20H, CH Ar), 5.94-5.89 (m, 1H, CH All), 5.38-5.25 (m, 2H, CH_2 All), 5.30 (dd, 1H, *J* = 2.0 Hz, *J* = 3.5 Hz, H-2), 4.80 (d, 1H, *J* = 1.5 Hz, H-1), 4.75 (s, 1H, H-1'), 4.69-4.45 (m, 11H, 4 x CH_2 OBn, H-3', CH_2 All), 4.15 (t, 1H, *J* = 9.5 Hz, H-4), 4.05 (bs, 1H, H-2'), 4.01-3.96 (m, 2H, H-3, H-4'), 3.83-3.70 (m, 4H, H-5, C*H*H SE, H-6a,b), 3.67 (dd, 1H, *J* = 4.0 Hz, *J* = 11.0 Hz, H-6a), 3.59 (dd, 1H, *J* = 1.5 Hz, *J* = 12.5 Hz, H-6b), 3.51-3.45 (m, 1H, CH*H* SE), 3.29-3.26 (m, 1H, H-5'), 2.82 (bs, 1H, OH-2'), 2.70-2.57 (m, 4H, CH_2 Lev), 2.10 (s, 3H, CH_3 Lev), 0.96-0.82 (m, 2H, CH_2 SE), -0.20 (s, 3H, CH_3 TMS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.3, 172.0, 154.3, 138.1, 138.1, 137.9, 137.9, 131.4, 131.4, 129.5-127.8, 127.7, 122.7, 118.8, 99.0, 97.0, 79.5, 77.5, 76.7, 75.3, 74.9, 73.4, 72.4, 72.2, 71.5, 70.6, 69.2, 68.9, 68.7, 68.6, 68.6, 68.3, 65.3, 37.9, 29.6, 28.1, 17.8, -1.3; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{54}H_{68}O_{15}Si$, 1007.4225; found, 1007.4219.

Phenyl 4,6-*O*-benzylidene-2-*O*-(2-methylnaphthyl)-1-thio-α-D-mannopyranoside (18). To a solution of 4,6-*O*-benzylidene-1-thio-α-D-mannopyranose[27] (5.0 g, 13.8 mmol) in CH_2Cl_2 (50 mL) and 5% aq NaOH (15 mL) was added Bu_4NHSO_4 (0.91 g, 2.7 mmol) and 2-bromomethylnaphthalene (4.6 g, 20.7 mmol). The resulting mixture was refluxed for 16 hrs. The mixture was diluted with CH_2Cl_2 (150 mL) and washed with water (2 x 50 mL). The organic layer was

dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized form DCM/PE to afford **18** (6.0 g, 87 %) as a white solid. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.4; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84-7.23 (m, 17H, CH Ar), 5.59 (s, 1H, H-7), 5.55 (s, 1H, H-1), 4.90 (d, 1H, *J* = 11.7 Hz, C*H*HNap), 4.84 (d, 1H, *J* = 11.7 Hz, CH*H*Nap), 4.31-4.20 (m, 2H, H-5, H6a), 4.16-3.99 (m, 3H, H-2, H-3, H-4), 3.85 (t, 1H, *J* = 10.2 Hz, H6b), 2.44 (bd, 1H, *J* = 7.8 Hz, 3-OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 134.6, 133.5, 133.2, 131.8, 129.1-125.8, 102.2, 86.5, 79.9, 79.6, 73.4, 69.0, 68.5, 64.7, 60.4; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{30}H_{28}O_5S$, 523.1555; found, 523.1546.

Phenyl 4,6-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-1-thio-α-D-mannopyranoside (19). Bu_2SnO (1.24 g, 5.0 mmol, 1.0 eq) was added to a stirred solution of phenyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside[27] (1.8 g, 5.0 mmol) in toluene (50 mL). The reaction mixture was refluxed for 4 h, allowed to cool and concentrated *in vacuo*. The residue was dissolved in DMF (25 mL) and CsF (1.52 g, 10 mmol) and 2-bromomethylnaphthalene (1.66 g, 7.5 mmol) were added. The reaction mixture was stirred for 16 hrs at rt. The white precipitate was removed by filtration, the filtrate was diluted with CH_2Cl_2 (100 mL) and washed with water (2 x 40 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in PE) of the residue afforded **19** (2.13 g, 85 %) as a white solid. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72-7.10 (m, 17H, CH Ar), 5.50 (s, 1H, H-7), 5.48 (s, 1H, H-1), 4.86 (d, 1H, *J* = 12.0 Hz, C*H*HNap), 4.79 (d, 1H, *J* = 11.7 Hz, CH*H*Nap), 4.27-4.40 (m, 4H, H-5, H6a, H-2, H-4), 3.90 (dd, 1H, *J* = 3.3 Hz, *J* = 9.6 Hz, H-3), 3.73 (t, 1H, *J* = 10.2 Hz, H6b), 3.01 (bs, 1H, 2-OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 137.4, 135.0, 133.2, 133.3, 131.6-125.0, 101.6, 87.8, 78.8, 75.7, 73.0, 71.2, 68.4, 65.2, 64.6; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{30}H_{28}O_5S$, 523.1555; found, 523.1551.

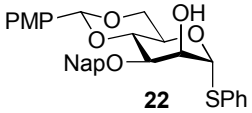


Phenyl 4,6-benzylidene-3-*O*-(triisopropylsilyloxymethyl)-1-thio-α-D-mannopyranoside (20). Bu_2SnO (1.24 g, 5.0 mmol) was added to a stirred solution of phenyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranose[27] (1.8 g, 5.0 mmol) in MeOH (25 mL). The reaction mixture was refluxed for 3 hrs, allowed to cool and concentrated *in vacuo*. The residue was coevaporated with DCE (2 x 30 mL) and dissolved in DCE (25 mL). DIPEA (1.04 mL, 6.0 mmol) was added and the mixture was heated to 80°C. At this temperature TOMCl (1.33 g, 6.0 mmol) was added and the mixture was stirred for 15 min at 80°C. The mixture was cooled to rt, diluted with CH_2Cl_2 (50 mL) and washed with water (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 10% - EtOAc in PE) of the residue afforded **20** (2.12 g, 78 %) as a colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.7; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.27 (m, 10H, CH Ar), 5.64 (s, 1H, H-1), 5.58 (s, 1H, H-7), 5.19 (d, 1H, *J* = 4.8 Hz, C*H*H TOM), 5.08 (d, 1H, *J* = 4.8 Hz, CH*H* TOM), 4.42-4.35 (m, 1H, H-2), 4.23-4.09 (m, 4H, H-3, H-4, H-5, H6a), 3.85 (t, 1H, *J* = 10.2 Hz, H6b), 3.01 (d, 1H, *J* = 1.2 Hz, 2-OH), 1.11-1.08 (m, 21H, CH CH_3 TOM); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 133.4, 131.7, 129.1-126.2, 101.9, 90.3, 87.6, 78.0, 75.0, 72.4, 68.5, 64.6, 17.8, 11.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{29}H_{42}O_6SSi$, 569.2369; found, 569.2361.

Phenyl 4,6-*O*-*p*-methoxybenzylidene-3-*O*-(triisopropylsilyloxymethyl)-1-thio-α-D-mannopyranoside (21). The same procedure to prepare **20** was followed using phenyl 4,6-*O*-*p*-methoxybenzylidene-1-thio-α-D-mannopyranoside[27] (1.15 g, 2.94 mmol) as the starting material. Silica gel column chromatography (0% → 10% - EtOAc in PE) afforded **21** (1.14 g, 68 %) as a white solid. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.7; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.17 (m, 7H, CH Ar), 6.81 (m, 2H, CH Ar), 5.56 (s, 1H, H-1), 5.46 (s, 1H, H-7), 5.01 (d, 1H, *J* = 4.8 Hz, C*H*H TOM) 4.99 (d, 1H, *J* = 4.8 Hz, CH*H* TOM), 4.33 (m, 1H, H-2), 4.28 (m, 1H, H-5), 4.12-3.99 (m, 3H, H-3, H-4, H6a), 3.78 (m, 1H, H6b), 3.73 (s, 3H, OMe), 2.93 (d, 1H, *J* = 1.8 Hz, 2-OH), 1.00 (s, 21H, 3 x isoprop TOM); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 133.4, 131.7, 129.9, 129.1, 127.6, 127.6, 113.5,

101.9, 90.3, 87.6, 77.9, 75.1, 72.3, 68.5, 64.6, 55.2, 17.8, 11.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{30}H_{44}O_7SSi$, 599.2475; found, 599.2469.

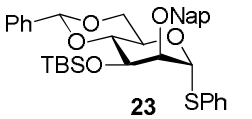
Phenyl 4,6-*O*-*p*-methoxybenzylidene-3-*O*-(2-methylnaphthyl)-1-thio-α-D-mannopyranoside (22).



22

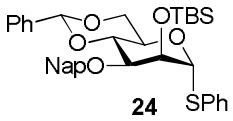
The same procedure to prepare **19** was followed using phenyl 4,6-*O*-*p*-methoxybenzylidene-1-thio-α-D-mannopyranoside[27] (3.04 g, 7.8 mmol) as the starting material. Silica gel column chromatography (0% → 30% - EtOAc in PE) afforded **22** (3.39 g, 82 %) as a white solid. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.35; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85-7.25 (m, 14H, CH Ar), 6.99-6.89 (m, 2H, CH Ar), 5.59 (s, 2H, H-7, H-1), 4.99 (d, 1H, *J* = 12.3 Hz, C*H*H Nap), 4.90 (d, 1H, *J* = 12.3 Hz, CH*H* Nap), 4.32-4.28 (m, 2H, H-2, H-5), 4.22-4.16 (m, 2H, H-4, H6a), 3.99 (dd, 1H, *J* = 3.3 Hz, *J* = 9.3 Hz, H-3), 3.87-3.81 (m, 4H, H6b, CH_3 OMe), 2.88 (d, 1H, *J* = 1.2 Hz, 2-OH); ^{13}C NMR (75 MHz, $CDCl_3$); δ 160.0, 135.1, 133.2, 133.1, 131.7, 129.9, 129.1-125.6, 133.6, 104.7, 101.7, 87.8, 78.8, 75.7, 73.0, 71.4, 68.5, 64.6, 55.3; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{31}H_{30}O_6S$, 553.1661; found, 553.1670.

Phenyl 4,6-benzylidene-3-*O*-(*t*-butyldimethylsilyl)-2-*O*-(2-methylnaphthyl)-1-thio-α-D-mannopyranoside (23). To a solution of **18** (1.5 g, 3.0 mmol) in DMF (10 mL) was added imidazole (0.6 g, 9.0 mmol) and TBDMSCl (0.9 g, 6.0 mmol). The mixture was stirred for 16 hrs at rt before CH_2Cl_2 (50 mL) was added. The mixture was washed with water (2 x 20 mL) and the organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 10% - EtOAc in PE) afforded **23** (1.76 g, 96 %) as a colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83-7.2 (m, 17H, CH Ar), 5.61 (s, 1H, H-7), 5.5 (s, 1H, H-1), 5.03 (d, 1H, *J* = 12.0 Hz, C*H*H Nap), 4.86 (d, 1H, *J* = 12.3 Hz, CH*H* Nap), 4.29-4.11 (m, 4H, H-3, H-4, H-5, H6a), 4.03-4.02 (m, 1H, H-2), 3.88 (t, 1H, *J* = 9.6 Hz, H6b), 0.94 (s, 9H, 3 x CH_3 TBS), 0.15 (s, 3H, CH_3 TBS), 0.10 (s, 3H, CH_3 TBS); ^{13}C NMR (75 MHz,



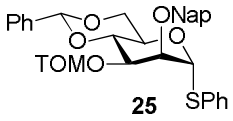
23

$CDCl_3$): δ 137.6, 135.5, 133.8, 133.2, 133.1, 131.5, 129.0-125.9, 101.9, 87.9, 81.1, 79.2, 74.1, 70.8, 68.5, 65.6, 25.9, 18.4, -4.4, -4.4; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{36}H_{42}O_5SSi$, 637.2420; found, 637.2429.

Phenyl 4,6-benzylidene-2-*O*-(*t*-butyldimethylsilyl)-3-*O*-(2-methylnaphthyl)-1-thio-α-D-mannopyranoside (24). 

24

To a cooled (-20°C) solution of **19** (0.61 g, 1.2 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (1.0 mL, 7.2 mmol) and TBDMSOTf (0.99 mL, 4.3 mmol). The mixture was allowed to warm to rt and stirred for 3 hrs. CH_2Cl_2 (20 mL) and water (10 mL) was added. The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 5% - EtOAc in PE) afforded **24** (0.76 g, 99 %) as a colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.85; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77-7.16 (m, 17H, CH Ar), 5.59 (s, 1H, H-7), 5.27 (d, 1H, *J* = 1.5 Hz, H-1), 4.90 (d, 1H, *J* = 12.3 Hz, C*H*H Nap), 4.83 (d, 1H, *J* = 12.6 Hz, CH*H* Nap), 4.27 (dd, 1H, *J* = 1.8 Hz, *J* = 3.0 Hz, H-2), 4.26-4.12 (m, 3H, H-4, H-5, H6a), 3.89 (dd, 1H, *J* = 3.0 Hz, *J* = 9.0 Hz, H-3), 3.79 (t, 1H, *J* = 9.6 Hz, H6b), 0.85 (s, 9H, 3 x CH_3 TBS), 0.06 (s, 3H, CH_3 TBS), 0.05 (s, 3H, CH_3 TBS); ^{13}C NMR (75MHz, $CDCl_3$): δ 137.7, 135.9, 133.7, 133.2, 132.9, 129.1-124.3, 101.6, 90.2, 79.2, 76.0, 2.8, 72.7, 68.6, 65.5, 65.1, 25.8, 18.1, -4.4, -4.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{36}H_{42}O_5SSi$, 637.2420; found, 637.2430.

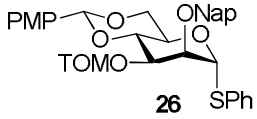
Phenyl 4,6-*O*-benzylidene-2-*O*-(2-methylnaphthyl)-3-*O*-(triisopropylsilyloxymethyl)-1-thio-α-D-mannopyranoside (25). 

25

To a cooled (0°C) solution of **18** (1.9 g, 3.8 mmol) and 2-(bromomethyl)naphthalene (0.92 g, 4.2 mmol) in DMF (20 mL) was added sodium hydride (60% wt in mineral oil, 0.22 g, 5.4 mmol). The mixture was stirred for 1 hr at rt before MeOH (3 mL) was added. The mixture was diluted with EtOAc (100 mL) and washed with water (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 5% - EtOAc in PE) of the residue afforded **25** (2.41 g, 95 %) as a colorless oil.

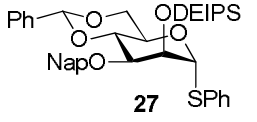
TLC: (EtOAc/PE, 20/80 v/v): R_f = 0.6; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85-7.20 (m, 17H, CH Ar), 5.63 (s, 1H, H-7), 5.51 (s, 1H, H-1), 5.13 (s, 2H, CH_2 TOM), 4.98 (d, 1H, *J* = 12.0 Hz, C*H*H Nap), 4.90 (d, 1H, *J* = 12.6 Hz, CH*H* Nap), 4.36-4.22 (m, 5H, H-2, H-3, H-4, H-5, H6a), 3.91 (t, 1H, *J* = 9.3 Hz, H6b), 1.10-1.08 (m, 21H, CH CH_3 TOM); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 135.3, 133.8, 133.2, 133.0, 131.7, 128.9-125.9, 101.7, 90.0, 87.5, 79.7, 78.7, 73.5, 73.1, 68.5, 65.5, 17.9, 11.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{40}H_{50}O_6SSi$, 709.2995; found, 709.2986.

Phenyl 4,6-*O*-*p*-methoxybenzylidene-2-*O*-(2-methylnaphthyl)-3-*O*-(triisopropylsilyloxymethyl)-1-thio-α-D-mannopyranoside (26). To a cooled (0°C) solution of **21** (1.13 g, 1.9 mmol) and 2-(bromomethyl)naphthalene (0.48 g, 2.2 mmol) in DMF (10 mL) was added sodium hydride (60% wt in mineral oil, 71 mg, 2.96 mmol). The mixture was stirred for 1 hr at rt before MeOH (3 mL) was added. The mixture was diluted with EtOAc (50 mL) and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 10% - EtOAc in PE) of the residue afforded **26** (1.02 g, 73 %) as a colorless oil. TLC: (EtOAc/PE, 20/80 v/v): R_f = 0.6; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.10 (m, 14H, CH Ar), 6.81-6.77 (m, 2H, CH Ar), 5.47 (s, 1H, H-7), 5.40 (s, 1H, H-1), 5.02 (s, 2H, CH_2 TOM), 4.91 (d, 1H, *J* = 12.0 Hz, C*H*H Nap), 4.79 (d, 1H, *J* = 12.6 Hz, CH*H* Nap), 4.23-4.10 (m, 5H, H-2, H-3, H-4, H-5, H6a), 3.78-3.73 (m, 1H, H6b), 3.71 (s, 3H, CH_3 OMe), 1.01-0.99 (m, 21H, CH CH_3 TOM); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 135.6, 133.8, 133.0, 133.0, 131.9, 130.1, 128.9-125.5, 113.4, 101.7, 90.0, 87.7, 79.8, 78.6, 73.5, 73.2, 68.5, 65.5, 55.2, 17.9, 11.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{41}H_{52}O_7SSi$, 739.3101; found, 739.3110.



26

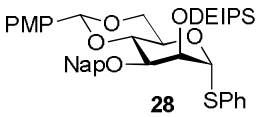
Phenyl 4,6-benzylidene-2-*O*-(diethylisopropylsilyl)-3-*O*-(2-methylnaphthyl)-1-thio-α-D-mannopyranoside (27). To a solution of **19** (0.50 g, 1.0 mmol) in DMF (10 mL) was added imidazole (0.2 g, 3.0 mmol) and DEIPSCl (0.33 mL, 2.0 mmol). The



27

mixture was stirred for 3 hrs at rt before CH_2Cl_2 (40 mL) and water (10 mL) were added. The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 5% - EtOAc in PE) afforded **27** (0.48 g, 76 %) as a colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85-7.23 (m, 17H, CH Ar), 5.66 (s, 1H, H-7), 5.36 (d, 1H, *J* = 1.5 Hz, H-1), 4.99 (d, 1H, *J* = 12.3 Hz, C*H*H Nap), 4.92 (d, 1H, *J* = 12.6 Hz, CH*H* Nap), 4.39 (dd, 1H, *J* = 1.5 Hz, *J* = 2.7 Hz, H-2), 4.31-4.20 (m, 3H, H-4, H-5, H6a), 3.96-3.84 (m, 2H, H-3, H6b), 1.03-0.94 (m, 12H, 4 x CH_3 DEIPS), 0.71-0.59 (m, 5H, CH CH_2 DEIPS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 135.9, 133.7, 133.2, 132.9, 131.9, 129.1-125.7, 101.6, 90.4, 79.2, 76.0, 72.9, 72.8, 68.6, 65.6, 17.3, 13.0, 7.1, 3.8, 3.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{37}H_{44}O_5SSi$, 651.2576; found, 651.2569.

Phenyl 4,6-*p*-methoxybenzylidene-2-*O*-(diethylisopropylsilyl)-3-*O*-(2-methylnaphthyl)-1-thio-α-D-mannopyranoside (28). The same procedure to prepare **27** was followed using **22** (1.8 g, 3.4 mmol) as the starting material. Silica gel column chromatography (0% → 5% - EtOAc in PE) afforded **28** (1.9 g, 86 %) as colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86-7.27 (m, 14H, CH Ar), 6.92-6.89 (m, 2H, CH Ar), 5.63 (s, 1H, H-7), 5.37 (d, 1H, *J* = 1.2 Hz, H-1), 4.99 (d, 1H, *J* = 12.3 Hz, C*H*H Nap), 4.96 (d, 1H, *J* = 12.6 Hz, CH*H* Nap), 4.39 (dd, 1H, *J* = 1.5 Hz, *J* = 2.7 Hz, H-2), 4.30-4.18 (m, 3H, H-4, H-5, H6a), 3.96-3.86 (m, 2H, H-3, H6b), 3.84 (s, 3H, CH_3 OMe), 1.03-0.95 (m, 12H, 4 x CH_3 DEIPS), 0.72-0.63 (m, 5H, CH CH_2 DEIPS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 136.0, 133.8, 133.3, 132.9, 131.9, 130.2, 129.1-125.7, 113.5, 101.6, 90.4, 79.1, 76.1, 72.9, 72.8, 68.6, 65.6, 55.3, 17.3, 13.0, 7.0, 3.8, 3.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{38}H_{46}O_6SSi$, 681.2682; found, 681.2675.



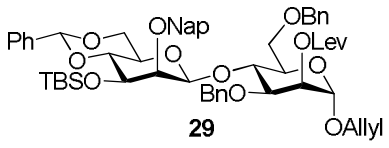
28

General procedure for β-mannosylation using BSP. Glycosyl donor (1.0 mmol), BSP (1.2 mmol) and DTBMP (3.0 mmol) were dissolved in CH_2Cl_2 (10 mL). Flame activated MS4Å were added and the

mixture was stirred for 15 min at rt. The reaction mixture was cooled to -78°C and Tf_2O (1.15 mmol) was added. The mixture was stirred for 10 min at -78°C before the glycosyl acceptor (1.25 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred for 1 hr at -78°C and then slowly (3 hrs) warmed to -35°C. Sat aq. $NaHCO_3$ was added (2.0 mL) and the organic layer is dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography was the used to obtain the pure β-mannoside.

General procedure for β-mannosylation using *p*-$NO_2C_6H_4SCl$/AgOTf. Glycosyl donor (1.0 mmol), AgOTf (2.0 mmol) and DTBMP (3.0 mmol) were dissolved in CH_2Cl_2 (10 mL). Flame activated MS4Å were added and the mixture was stirred for 15 min at rt in the dark. The reaction mixture was cooled to -78°C and *p*-$NO_2C_6H_4SCl$ (1.1 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise. The mixture was stirred for 10 min at -78°C before the glycosyl acceptor (1.25 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred for 1 hr at -78°C and then slowly (3 hrs) warmed to -35°C. Sat aq. $NaHCO_3$ was added (2.0 mL) and the organic layer is dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography was the used to obtain the pure β-mannoside.

Allyl 4,6-di-*O*-benzylidene-3-*O*-(*t*-butyldimethylsilyl)-2-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (29).

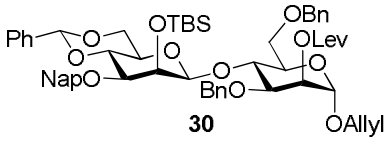


29

According to the BSP general procedure. Silica gel column chromatography (0% → 15% - EtOAc in toluene) afforded **29** (87 mg, 31 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79-7.73 (m, 4H, CH Ar), 7.52 (dd, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz, CH Ar), 7.44-7.24 (m, 17H, CH Ar), 5.91-5.85 (m, 1H, CH All), 5.46 (s, 1H, H-7'), 5.32 (dd, 1H, *J* = 3.5 Hz, *J* = 2.0 Hz, H-2), 5.29-5.19 (m, 2H, CH_2 All), 5.03 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.87-4.83 (m, 2H, H-1', CH*H*Ph), 4.65-4.63 (m, 2H, CH_2 OBn), 4.56 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.36 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.15-4.11 (m, 2H, H-4, C*H*H All), 4.01-3.99 (m, 2H, H-4', H-3), 3.96-3.93 (m, 1H, CH*H* All), 3.90 (t, 1H, *J* = 9.5 Hz, H-6a'), 3.74-3.65 (m, 4H, H-2', H-3', H-5, H-6b'), 3.55 (dd,

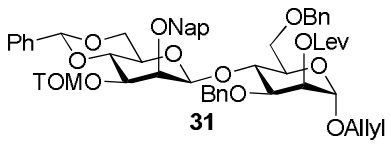
1H, *J* = 4.0 Hz, *J* = 11.0 Hz, H-6a), 3.47 (dd, 1H, *J* = 2.0 Hz, *J* = 9.0 Hz, H-6b), 3.08-3.06 (m, 1H, H-5'), 2.66-2.62 (m, 4H, 2 x CH_2 Lev), 2.08 (s, 3H, CH_3 Lev), 0.86 (m, 9H, *t*-Bu TBS) 0.05 (s, 3H, CH_3 TBS), -0.01 (s, 3H, CH_3 TBS); ^{13}C NMR (150 MHz, $CDCl_3$): □ 206.3, 171.9, 138.3, 138.2, 137.5, 136.5, 133.4, 133.2, 132.9, 128.8-125.6, 117.7, 101.8, 101.2, 96.7, 80.3, 78.7, 75.6, 75.5, 74.7, 73.4, 71.7, 69.1, 68.7, 68.6, 68.1, 67.3, 37.9, 29.7, 28.1, 25.8, 18.3, -4.3, -4.8; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{58}H_{70}O_{13}Si$, 1025.4483; found, 1025.4486.

Allyl 4,6-di-*O*-benzylidene-2-*O*-(*t*-butyldimethylsilyl)-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (30).



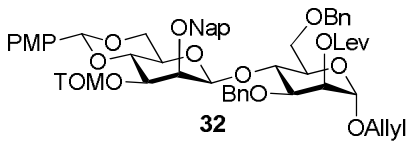
30

According to the BSP general procedure. Silica gel column chromatography (0% → 20% - EtOAc in toluene) afforded **30** (104 mg, 40 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.59 (m, 4H, CH Ar), 7.43-7.08 (m, 18H, CH Ar), 5.83-5.77 (m, 1H, CH All), 5.48 (s, 1H, H-7'), 5.24-5.11 (m, 3H, H-2', CH_2 All), 4.82-4.73 (m, 3H, CH_2 Nap, H-1), 4.64 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.57 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.50 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.31 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.21 (s, 1H, H-1'), 4.10 (dd, 1H, *J* = 13.0 Hz, *J* = 3.0 Hz, C*H*H All), 4.05-3.90 (m, 4H, CH*H* All, H-4', H-6a', H-4), 3.81 (m, 2H, H-2', H-3), 3.71 (m, 1H, H-5), 3.59 (m, 2H, H-6a,b), 3.53 (t, 1H, *J* = 10.0 Hz, H-6b'), 3.25 (dd, 1H, *J* = 2.0 Hz, *J* = 9.5 Hz, H-3'), 3.00 (m, 1H, H-5'), 2.56-2.57 (m, 4H, 2 x CH_2 Lev), 1.99 (s, 3H, CH_3 Lev), 0.84 (m, 9H, *t*-Bu TBS) 0.01 (s, 3H, CH_3 TBS), -0.01 (s, 3H, CH_3 TBS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.3, 171.9, 138.7, 137.9, 137.7, 136.0, 133.4, 133.2, 132.8, 128.8-125.7, 117.4, 101.5, 101.1, 96.6, 78.9, 78.0, 75.7, 75.0, 73.4, 72.3, 72.2, 71.8, 71.1, 69.7, 68.8, 68.0, 67.2, 38.0, 29.6, 28.2, 25.9, 18.5, -4.0, -4.4; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{58}H_{70}O_{13}Si$, 1025.4483; found, 1025.4490.

Allyl 4,6-di-*O*-benzylidene-3-*O*-(triisopropylsilyloxymethyl)-2-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (31). 

31

According to the BSP general procedure. Silica gel column chromatography (0% → 20% - EtOAc in toluene) afforded **31** (286 mg, 53 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71-7.44 (m, 4H, CH Ar), 7.36-7.15 (m, 17H), 5.84-5.77 (m, 1H, CH All), 5.39 (s, 1H, H-7'), 5.24-5.13 (m, 3H, CH_2 All, H-2), 4.92-4.83 (m, 4H, CH_2 Nap, CH_2 TOM), 4.76 (d, 1H, *J* = 2.0 Hz, H-1), 4.61-4.48 (m, 4H, C*H*HPh, H-1', CH*2* OBn), 4.31 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.08-4.04 (m, 2H, H-4, C*H*H All), 3.97-3.86 (m, 4H, CH*H* All, H-3, H-4', H-6a'), 3.81 (d, 1H, *J* = 3.0 Hz, H-2'), 3.69-3.65 (m, 1H, H-5), 3.59 (t, 1H, *J* = 10.2 Hz, H6b'), 3.50 (dd, 1H, *J* = 11.0 Hz, *J* = 4.0 Hz, H-6a), 3.45 (dd, 1H, *J* = 9.5 Hz, *J* = 2.0 Hz, H-6b), 3.02-2.99 (m, 1H, H-5'), 2.58-2.57 (m, 4H, 2 x CH_2 Lev), 2.01 (s, 3H, CH_3 Lev), 0.97-0.93 (m, 21H, 3 x CH, 6 x CH_3 TOM); ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.3, 171.9, 138.3, 138.1, 137.5, 136.2, 133.4, 133.1, 132.9, 128.8-125.6, 117.6, 101.6, 101.3, 96.7, 89.6, 78.4, 78.2, 75.6, 75.2, 75.1, 74.9, 73.4, 71.7, 70.9, 69.3, 68.7, 68.6, 68.2, 67.3, 37.9, 29.7, 28.1, 17.8, 11.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{62}H_{78}O_{14}Si$, 1097.5059; found, 1097.5053.

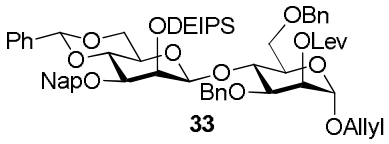
Allyl 4,6-di-*O*-*p*-methoxybenzylidene-3-*O*-(triisopropylsilyloxymethyl)-2-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (32). 

32

According to the BSP general procedure. Silica gel column chromatography (0% → 20% - EtOAc in toluene) afforded **32** (141 mg, 34 %) as a colorless oil. According to the *p*-$NO_2C_6H_4SCl$/AgOTf general procedure afforded **32** (57 mg, 63 %) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72-7.67 (m, 4H, CH Ar), 7.40 (dd, 1H, *J* = 1.2 Hz, *J* = 8.4 Hz, CH Ar), 7.37-7.17 (m, 12H, CH Ar), 6.87-6.80 (m, 2H, CH Ar), 5.85-5.78 (m, 1H, CH All), 5.36 (s, 1H, H-7'), 5.25 (dd, 1H, *J* = 3.6 Hz, *J* = 1.8 Hz, H-2), 5.23-5.13 (m, 2H, CH_2 All), 4.93-4.85 (m, 4H, CH_2 Nap, CH_2 TOM), 4.77 (d, 1H, *J* = 1.8 Hz, H-1), 4.61-4.58 (m, 3H,

CH_2 OBn, H-1'), 4.51 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.32 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.08-4.05 (m, 2H, C*H*H All, H-4), 3.96-3.88 (m, 4H, CH*H* All, H-4', H-3, H6a), 3.81 (d, 1H, *J* = 3.0 Hz, H-2'), 3.80-3.69 (m, 4H, CH_3 OMe, H-3'), 3.67 (dt, 1H, *J* = 1.8 Hz, *J* = 7.8 Hz, H-5), 3.58 (t, 1H, *J* = 10.2 Hz, H6b'), 3.51 (dd, 1H, *J* = 11.4 Hz, *J* = 3.6 Hz, H-6a), 3.46 (dd, 1H, *J* = 11.4 Hz, *J* = 1.8 Hz, H-6b), 3.03-2.99 (m, 1H, H-5'), 2.60-2.57 (m, 4H, 2 x CH_2 Lev), 2.02 (s, 3H, CH_3 Lev), 1.02-0.91 (m, 21H, 3 x CH, 6 x CH_3 TOM); ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.3, 171.9, 159.9, 138.3, 138.1, 133.4, 133.1, 132.8, 130.1, 128.3-126.4, 125.8, 125.5, 117.6, 113.4, 101.5, 101.2, 96.6, 89.6, 78.4, 78.1, 75.7, 75.2, 75.1, 74.9, 73.3, 71.7, 70.9, 69.3, 68.6, 68.5, 68.1, 67.3, 55.2, 37.9, 29.7, 29.6, 28.1, 17.8, 11.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{63}H_{80}O_{15}Si$, 1127.5164; found, 1127.5169.

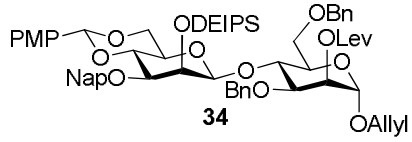
Allyl 4,6-di-*O*-benzylidene-2-*O*-(diethylisopropylsilyl)-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (33).



33

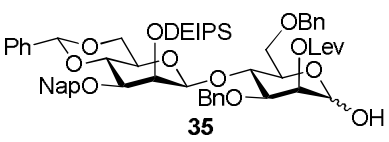
According to the BSP general procedure. Silica gel column chromatography (0% → 20% - EtOAc in toluene) afforded **33** (119 mg, 41 %) as a colorless oil. According to the *p*-$NO_2C_6H_4SCl$/AgOTf general procedure afforded **33** (2.21 g, 73 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86-7.30 (m, 4H, CH Ar), 7.55-7.21 (m, 18H, CH Ar), 5.96-5.89 (m, 1H, CH All), 5.59 (s, 1H, H-7'), 5.36-5.23 (m, 3H, CH_2 All, H-2), 4.97-4.87 (m, 3H, H-1, CH_2 Nap), 4.76-4.60 (m, 3H, CH_2 OBn, C*H*HPh), 4.34 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.34 (s, 1H, H-1'), 4.20 (dd, 1H, *J* = 5.0 Hz, *J* = 13.0 Hz, C*H*H All), 4.17-4.02 (m, 4H, CH*H* All, H-4', H-6a', H-4), 3.99 (d, 1H, *J* = 2.5 Hz, H-2'), 3.93 (dd, 1H, *J* = 9.5 Hz, *J* = 2.5 Hz, H-3), 3.88-3.84 (m, 1H, H-5), 3.75-3.64 (m, 3H, H-6b', H6a,b), 3.36 (dd, 1H, *J* = 2.5 Hz, *J* = 9.5 Hz, H-3'), 3.14-3.11 (m, 1H, H-5'), 2.69-2.67 (m, 4H, 2 x CH_2 Lev), 2.10 (s, 3H, CH_3 Lev), 1.08-1.00 (m, 15H, 5 x CH_3 DEIPS), 0.73-0.69 (m, 5H, 2 x CH, CH_2 DEIPS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2, 171.9, 138.6, 137.8, 137.7, 136.0, 133.3, 133.2, 132.8, 128.7-125.6, 117.3, 101.4, 101.1, 96.5, 78.9, 77.9, 75.7, 75.0, 73.3, 72.4, 72.1,

72.0, 71.0,, 69.6, 68.7, 67.9, 67.1, 37.9, 29.6, 28.2, 17.4, 13.2, 7.1, 4.0, 3.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{59}H_{72}O_{13}Si$, 1039.4640; found, 1039.4647.

Allyl 4,6-di-*O*-*p*-methoxybenzylidene-2-*O*-(diethylisopropylsilyl)-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (34). 

34

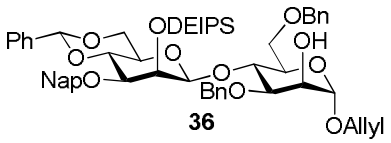
According to the BSP general procedure. Silica gel column chromatography (0% → 20% - EtOAc in toluene) afforded **34** (156 mg, 40 %) as a colorless oil. According to the *p*-$NO_2C_6H_4SCl$/AgOTf general procedure afforded **34** (2.83 g, 73 %) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.75-7.61 (m, 3H, CH Ar), 7.39-7.08 (m, 16H, CH Ar), 6.80 (d, 2H, *J* = 9.0 Hz, CH Ar), 5.85-5.77 (m, 1H, CH All), 5.43 (s, 1H, H-7'), 5.24-5.11 (m, 3H, CH_2 All, H-2), 4.84-4.74 (m, 3H, H-1, CH_2 Nap), 4.63-4.47 (m, 3H, CH_2 OBn, C*H*HPh), 4.28 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.21 (s, 1H, H-1'), 4.08 (dd, 1H, *J* = 5.0 Hz, *J* = 13.0 Hz, C*H*H All), 4.00-3.93 (m, 4H, CH*H* All, H-4. H-4', H6a'), 3.87 (d, 1H, *J* = 2.5 Hz, H-2'), 3.83 (dd, 1H, *J* = 9.0 Hz, *J* = 2.0 Hz, H-3), 3.74 (s, 3H, CH_3 OMe), 3.73-3.69 (m, 1H, H-5), 3.62-3.57 (m, 2H, H-6a,b), 3.52 (t, 1H, *J* = 10.0 Hz, H-6b'), 3.22 (dd, 1H, *J* = 2.5 Hz, *J* = 9.5 Hz, H-3'), 3.04-2.99 (m, 1H, H-5'), 2.59-2.52 (m, 4H, 2 x CH_2 Lev), 1.98 (s, 3H, CH_3 Lev), 0.93-0.88 (m, 15H, 5 x CH_3 DEIPS), 0.61-0.53 (m, 5H, 2 x CH, CH_2 DEIPS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2, 171.9, 159.9, 138.7, 137.9, 136.1, 133.4, 133.2, 132.8, 130.0-125.7, 117.4, 133.5, 101.4, 101.2, 96.6, 78.8, 78.1, 75.8, 75.1, 73.4, 72.5, 72.1, 72.1, 71.1, 69.9, 68.8, 68.7, 68.7, 67.9, 67.1, 55.2, 38.0, 29.6, 28.2, 17.4, 13.3, 7.2, 4.1, 4.0; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{60}H_{74}O_{14}Si$, 1069.4746; found, 1069.4750.

4,6-di-*O*-benzylidene-2-*O*-(diethylisopropylsilyl)-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (35). 

35

33 (51 mg, 0.05 mmol) was dissolved in a mixture of AcOH (1.8 mL) and H_2O (0.2 mL). $PdCl_2$ (19 mg, 0.1 mmol) and NaOAc (17 mg, 0.2

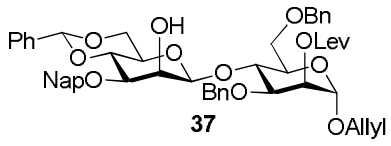
mmol) were added and the resulting mixture was stirred for 16 hrs at rt. CH_2Cl_2 (10 mL) was added and the organic layer was washed with water (2 x 5 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 40% - EtOAc in PE) afforded **35** (35 mg, 72 %) as colorless oil. TLC: (EtOAc/PE, 50/50 v/v): R_f = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79-7.16 (m, 22H, CH Ar), 5.53 (s, 2H, H-7'-α/β), 5.34 (m, 1H, H-2-β), 5.30-5.27 (m, 1H, H-2-α), 5.16 (s, 1H, H-1-α), 4.91-4.81 (m, 2H, CH_2 Nap), 4.81 (s, 1H, H-1-β), 4.71-4.54 (m, 3H, CH_2 OBn, C*H*HPh), 4.38-4.33 (m, 1H, CH*H*Ph), 4.27 (s, 1H, H-1'), 4.17-3.87 (m, H-3, H-3', H-4, H-4', H-6a'), 3.82-3.78 (m, 1H, H-5), 3.66-3.57 (m, 3H, H-6b', H-6a/b), 3.33-3.31 (m, 1H, H-3'), 3.14 (d, 1H, 1-OH-α), 3.11-3.07 (m, 1H, H-5'), 2.63-2.58 (4H, 2 x CH_2 Lev), 2.21 (s, 3H, CH_3 Lev-β), 2.04 (s, 3H, CH_3 Lev-α), 0.99-0.94 (m, 15H, 5 x CH_3 DEIPS), 0.66-0.61 (m, 5H, 2 x CH, CH_2 DEIPS); ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.4, 206.3, 172.2, 172.0, 138.6, 138.6, 137.7, 137.7, 137.7, 137.7, 137.7, 136.0, 133.2, 132.8, 128.8, 128.4-125.7, 101.5, 101.2, 97.6, 92.1, 78.9, 78.9, 78.0, 77.9, 77.9, 76.0, 75.6, 75.0, 74.6, 73.4, 73.4, 72.5, 72.5, 72.4, 72.3, 72.3, 72.1, 72.0, 72.0, 71.6, 71.0, 70.2, 69.5, 69.0, 68.7, 68.7, 68.6, 67.2, 38.0, 37.9, 29.6, 29.6, 28.2, 28.1, 26.4, 17.4, 17.4, 13.2, 7.2, 7.2, 4.1, 4.1; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{56}H_{68}O_{13}Si$, 999.4327; found, 999.4320.

Allyl 4,6-di-*O*-benzylidene-2-*O*-(diethylisopropylsilyl)-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-α-D-mannopyranoside (36). 

36 **33** (51 mg, 0.05 mmol) was dissolved in a mixture of toluene (2 mL) and EtOH (1 mL). Hydrazinium acetate (5 mg, 0.06 mmol) was added and the resulting mixture was stirred for 3 hrs at rt. Acetone (0.1 mL) was added followed by the addition of water (2 mL) and EtOAc (10 mL). The organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 30% - EtOAc in PE) afforded **36** (45 mg, 99 %) as colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.30; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73-7.61 (m, 4H), 7.42-7.07 (m, 18H, CH Ar), 5.86-5.78 (m, 1H, CH All), 5.47 (s, 1H, H-7'),

5.22-5.10 (m, 2H, CH_2 All), 4.89-4.74 (m, 4H, CH_2 Nap, C*H*HPh, H-1), 4.55-4.48 (m, 2H, CH*H*Ph, C*H*HPh), 4.30-4.26 (m, CH*H*Ph, H-1'), 4.11 (dd, 1H, *J* = 3.5 Hz, *J* = 9.0 Hz, C*H*H All), 4.08-3.89 (m, 6H, H-2', H-2, H-4, H-4', H-6a', CH*H* All), 3.71 (dd, 1H, *J* = 3.5 Hz, *J* = 9.0 Hz, H-3), 3.70-3.67 (m, 1H, H-5), 3.24 (dd, 1H, *J* = 9.0 Hz, *J* = 2.5 Hz, H-3'), 3.10-3.05 (m, 1H, H-5') 0.92-0.84 (m, 15H, 5 x CH_3 DEIPS), 0.63-0.54 (m, 5H, 2 x CH, CH_2 DEIPS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 137.7, 137.7, 136.1, 133.6, 133.2, 132.8, 128.8-125.6, 117.2, 101.5, 101.4, 98.2, 78.9, 78.0, 77.6, 75.8, 73.4, 73.1, 72.5, 72.0, 70.8, 69.4, 68.8, 68.7, 67.7, 67.1, 29.6, 17.4, 13.2, 7.2, 4.1, 3.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{54}H_{66}O_{11}Si$, 941.4272; found, 941.4270.

Allyl 4,6-di-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (37). 33 (51 mg, 0.05 mmol) was dissolved in THF (1 mL). AcOH (12 μL, 0.2 mmol) and TBAF (1M in THF, 0.4 mL, 0.4 mmol) was added. The resulting mixture was stirred for 16 hrs at rt. Water (2 mL) and EtOAc (10 mL) were added and the organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 40% - EtOAc in PE) afforded **37** (41 mg, 98 %) as colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.15; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84-7.71 (m, 4H, CH Ar), 7.52-7.22 (m, 18H, CH Ar), 5.92-.5.86 (m, 1H, CH All), 5.57 (s, 1H, H-7'), 5.38-5.21 (m, 3H, CH_2 All, H-2), 4.88-4.85 (m, 3H, H-1, CH_2 Nap), 4.73-4.67 (m, 3H, H-1', CH_2 OBn), 4.56-4.50 (m, 2H, CH_2 OBn), 4.18-4.12 (m, 3H, C*H*H All, H6a', H-4), 4.10 (t, 1H, *J* = 9.5 Hz, H-4'), 4.05-3.97 (m, 3H, CH*H* All, H-2', H-4), 3.89-3.86 (m, 2H, H6a, H-5), 3.75 (t, 1H, *J* = 10.5 Hz, H-6b'), 3.74-3.71 (m, 1H, H-6b), 3.51 (dd, 1H, *J* = 9.5 Hz, *J* = 3.0 Hz, H-3'), 3.15-3.11 (m, 1H, H-5'), 2.75-2.65 (m, 4H, 2 x CH_2 Lev), 2.11 (s, 3H, CH_3 Lev); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.1, 171.8, 137.9, 137.8, 137.4, 135.4, 133.1, 133.1, 132.9, 128.8-125.5, 117.6, 101.4, 100.3, 96.7, 78.0, 76.4, 73.4, 73.1, 72.0, 71.6, 70.6, 69.1, 68.8, 68.7, 68.5, 68.1, 66.8, 37.8, 29.6, 28.0; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{52}H_{56}O_{13}$, 911.3619; found, 911.3620.



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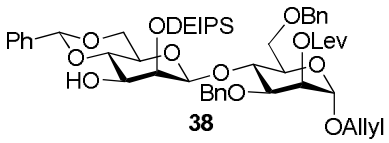
Allyl 4,6-di-*O*-benzylidene-2-*O*-(diethylisopropyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (38). 

33 (51 mg, 0.05 mmol) was dissolved in a mixture of DCM (1 mL) and water (0.1 mL). DDQ (23 mg, 0.1 mmol) was added and the resulting mixture was stirred for 4 hrs at rt in the dark. The mixture was diluted with CH_2Cl_2 (5 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*. Silica gel column chromatography (0% → 20% - EtOAc in PE) afforded **38** (41 mg, 93 %) as colorless oil. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.35; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.27 (m, 15H, CH Ar), 5.95-5.87 (m, 1H, CH All), 5.48 (s, 1H, H-7'), 55.37 (dd, 1H, *J* = 2.0 Hz, *J* = 3.5 Hz, H-2), 5.33-5.22 (m, 2H, CH_2 All), 4.90 (d, 1H, *J* = 1.5 Hz, H-1), 4.79 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 2.63 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.49 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.38 (s, 1H, H-1'), 4.21 (dd, 1H, *J* = 13.0 Hz, *J* = 5.0 Hz, C*H*H All), 4.13-4.08 (m, 2H, H-4, H-6a'), 4.03 (dd, 1H, *J* = 13.0 Hz, *J* = 7.0 Hz, CH*H* All), 3.90 (dd, 1H, *J* = 9.5 Hz, *J* = 3.5 Hz, H-3), 3.85-3.81 (m, 2H, H-2', H-5), 3.75 (dd, 1H, *J* = 4.0 Hz, *J* = 11.0 Hz, H-6a), 3.76-3.70 (m, 2H, H-4', H-6b), 3.58 (t, 1H, *J* = 10.0 Hz, H-6b'), 3.50-3.47 (m, 1H, H-3'), 3.17-1.12 (m, 1H, H-5'), 2.71-2.64 (m, 4H, 2 x CH_2 Lev), 2.23 (bd, 1H, *J* = 5.0 Hz, 3'-OH), 2.10 (s, 3H, CH_3 Lev), 1.03-0.98 (m, 15H, 5 x CH_3 DEIPS), 0.71-0.65 (m, 5H, 2 x CH, CH_2 DEIPS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.,2 171.9, 138.6, 137.7, 137.3, 133.3, 129.0-126.3, 117.4, 101.9, 101.1, 96.6, 79.1, 76.1, 75.1, 73.5, 72.9, 71.8, 71.3, 71.0, 69.3, 68.7, 68.5, 67.9, 66.7, 37.9, 29.6, 28.1, 17.3, 17.3, 13.2, 7.1, 7.1, 4.1, 3.8; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{48}H_{64}O_{13}Si$, 899.4014; found, 899.4010.

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CHAPTER 5

SYNTHESIS OF THE LIPOPOLYSACCHARIDE CORE HEXASACCHARIDE DOMAIN OF POTENTIAL BIOTERRORISM AGEN *FRANCISELLA TULARENSIS*[†]

[†] Thomas J. Boltje, Wei Zhong, Jin Park and Geert-Jan Boons*

To be submitted to J. Am. Chem. Soc.

Abstract. *Francisella tularensis* has been classified by centers for disease control and prevention (CDC) as a Class A bio-terrorism agent. *F. tularensis* is highly virulent, requiring as few as 10-50 cells to cause human infection, and speading of *F. tularensis* by aerosolization over an urban area would result in thousands of deaths. A vaccine and diagnostic test are needed to combat such an event. The lipopolysaccharide of *F. tularensis* is an attractive candidate for vaccine and diagnostic test development and herein, the synthesis of the inner core hexasaccharide domain of *F. tularensis* is described. A central orthogonally protected β-D-Man-(1→4)-D-Man disaccharide was used for the preparation of a collection of oligosaccharides and protein conjugates thereof.

Introduction. *F. tularensis* is the etiologic agent of tularemia (rabbit fever) in humans and animals.[1] It is a gram-negative facultative intracellular pathogen that can survive and propagate within phagocytic cells. In nature, a disease cycle is maintained between wild animals such as rabbits, beavers, squirrels, and water rats and biting vectors such as flies, ticks, mosquitoes, and mites and the contaminated environment.[2] *F. tularensis* is highly virulent, requiring as few as 10-50 cells to cause human infection. It can survive for long periods of time under harsh environmental conditions. Tularemia may occur in different forms but the pneumonic form is associated with the highest mortality (30% without antibiotic treatment). *F. tularensis* has been classified by the CDC as a top-priority (Class A) bio-terrorism agent. Common to all class-A agents, tularemia transmits easily, has the capacity to inflict substantial morbidity and mortality on a large number of people and can induce widespread panic.[3] Aerosol dispersal is considered the most hazardous mode of transmission, as it would affect the most people. The World Health Organization estimated that 50 Kg of *F. tularensis* spread by aerosolization over an urban area would result in thousands of deaths. In order to prevent *F. tularensis,* an attenuated life vaccine strain (LVS) was developed in the 1950's, but was not licensed for use as a human vaccine because the nature of its attenuation was not known and may not be stable. Diagnoses are based on time consuming culture, serology or sophisticated molecular techniques. Therefore improved vaccine candidates and rapid diagnostic tests are needed for this pathogen. Recently, the structure of the lipopolysaccharide (LPS) of *F.*

tularensis was determined (Figure 5.1)[4] and it was established that it has an unusual core structure. The core is linked to the lipid A region by only one 3-deoxy-D-manno-2-octulosonic acid (KDO) moiety instead of the usual two KDO residues. It does not contain heptosyl residues but contains two mannosyl moieties. One of the mannosides is β-linked to another mannoside, and this disaccharide fragment is further substituted at C-2, C-2' and C-3' by a β-glucoside, an α-galactosamine and a α-glucoside, respectively. The *O*-chain polysaccharide is composed of tetrasaccharide repeating units, which consist of two *N*-acetyl galactosamine uronamides and a *N*-acetyl quinovosamine and *N*-formyl-4-amino-quinovose moieties. It has been proposed that the lipopolysaccharide of *F. tularensis* is an attractive candidate for vaccine and diagnostic test development.[5]

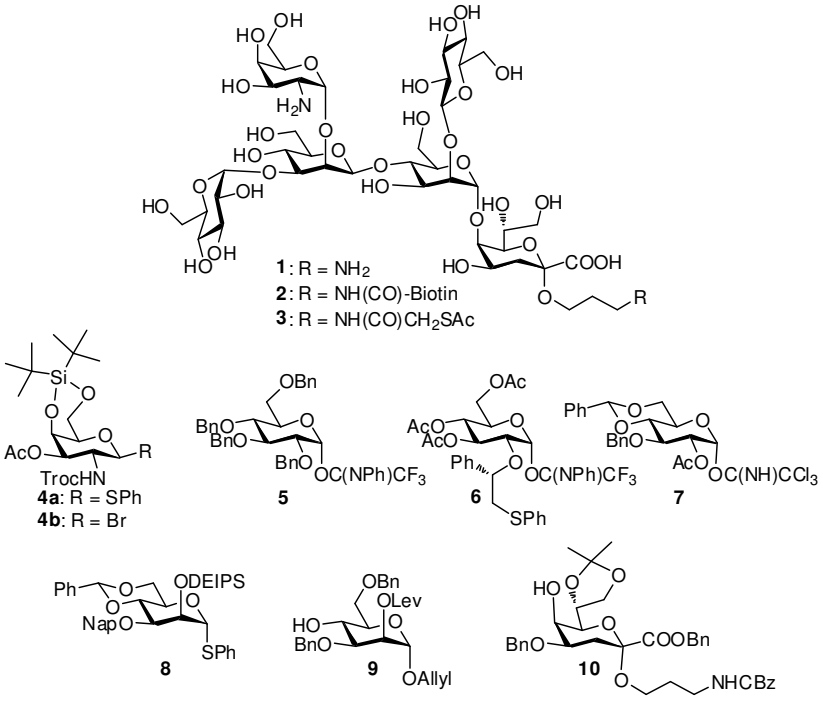


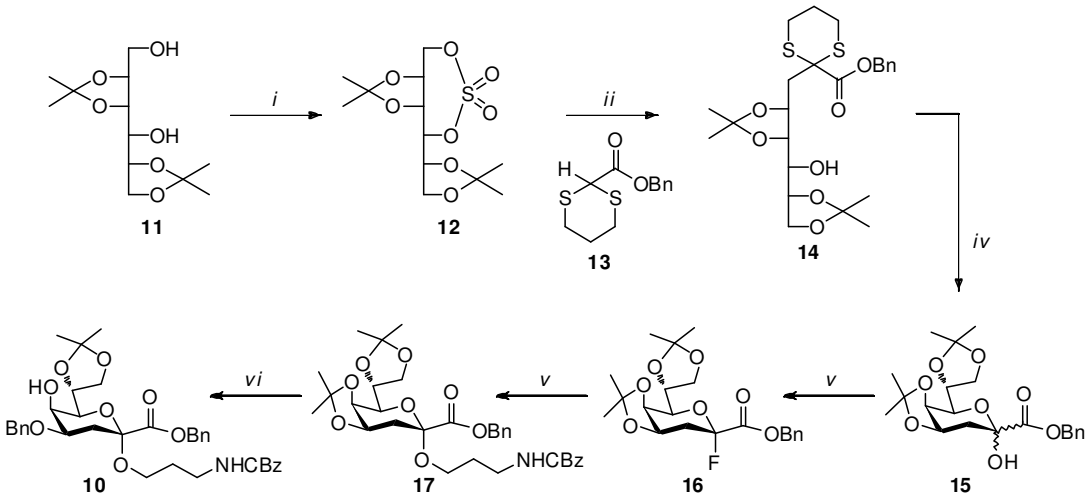
Figure 5.1: Target hexasaccharide **1** and the monosaccharide building block required for its assembly.

Chemically synthesized oligosaccharides offer the most attractive materials for vaccine and diagnostic development for *F. tularensis*.[6] Obviously, isolation of saccharides from a Class A bio-terrorism agent is highly undesirable. Furthermore, it is also difficult to conjugate short oligosaccharides to carrier proteins without destroying vital immunological domains. In the case of the LPS of *F. tularensis*, it will be

difficult to release the core oligosaccharide from LPS. Synthetic chemistry can address these issues since it makes it possible to incorporate an artificial linker for controlled conjugation to proteins. Furthermore, sub-structures can be prepared and employed to determine the minimal epitope requirement to elicit protective immune responses.

Herein we report the synthesis of the complete hexasaccharide domain of *Francisella Tularensis* LPS and the preparation of biotin and protein conjugates thereof. A modular strategy was employed that relied on the use of orthogonal protecting groups to rapidly synthesize sub-structures. As discussed in chapter 4, a central β-D-Man-(1→4)-α-D-Man disaccharide was prepared which served as a scaffold for further modifications by sequential deprotection of an orthogonal protecting group and glycosylation of the resulting alcohol. This approach rapidly gave access to all possible sub-structures as well as the fully assembled hexasaccharide **1**. The chemical synthesis of hexasaccharide **1** is challenging due to the multiple 1,2-cis-linkages such as the α-glucoside, α-galactosamine, and β-mannoside residues. The α-glucoside was installed using glycosyl donor **6** which carries a chiral auxiliary at C-2. The 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether of **6** provides α-glycosides by formation of an intermediate β-sulfonium ion thereby preventing attack from the β-face.[7-9] In addition, glycosyl donor **5** was be used to prepare the α-glucoside linkage by relying on solvent effects to ensure α-selectivity. For the introduction of the α-galactosamine linkage, building block **4a/b** was used. The DBTS group in **4a/b** ensures α-selectivity even though the participating Troc group is present.[10] The introduction of the β-mannoside can be achieved by employing 4,6-*O*-benzylidene protected mannosyl donor **8**.[11] The β-selectivity of mannosyl donor **8** arises from the *in-situ* formation of an α-anomeric triflate because of a strong endo-anomeric effect.[12-13] An S_N2 like-displacement of the α-triflate by a sugar hydroxyl then results in the formation of a β-mannoside. The α-mannoside and β-glucoside moieties of **1** were installed by employing neighboring group particitation (NPG) by the levulinyl (Lev) and acetyl ester of **9** and **8**, respectively. The completed hexasaccharide **1** was conjugated to biotin and KLH by selective modification of the aminopropyl spacer on the KDO residue.

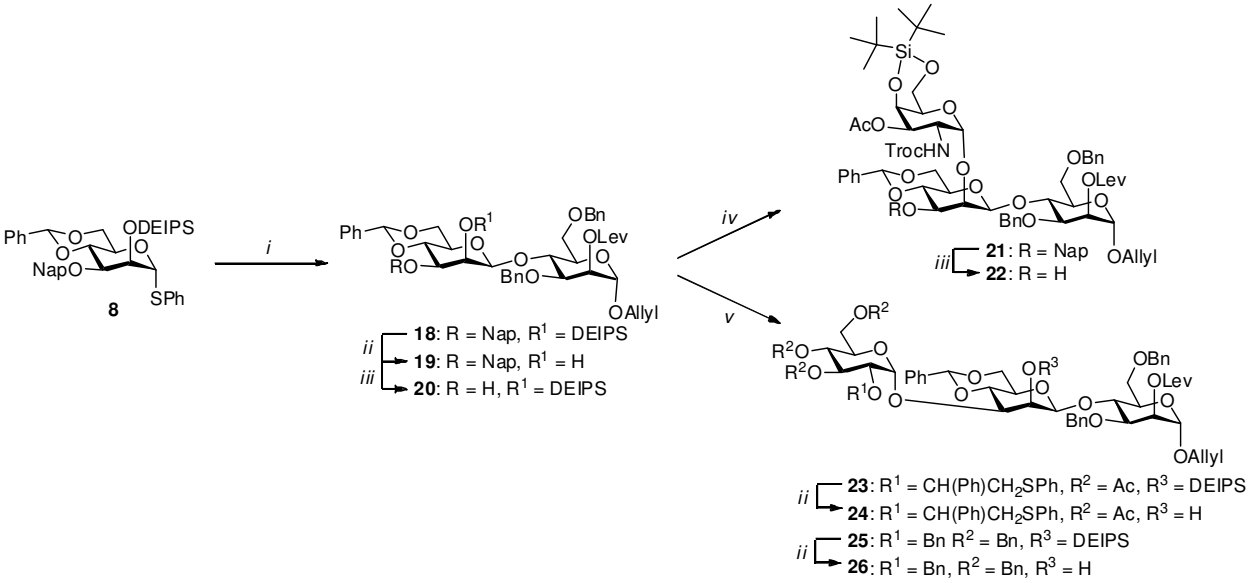
Results and Discussion. The synthesis of building block **4-9** was achieved by following reported procedures.[10-11,14] The KDO building block **10** was prepared from di-acetonide protected mannitol **11** (Scheme 5.1) using a modified reported procedure.[15] Reaction of **11** with thionylchloride and triethyl amine afforded the cyclic sulfite which was oxidized to the cyclic sulfate **12** using $RuCl_3$ and $NaIO_4$. Thioacetal **13** was treated with lithium hexamethyldisilazane (LHMDS) and the resulting anion was reacted with cyclic sulfate **12**.



Scheme 5.1: Synthesis of KDO building block **10**. Reagents and Conditions: *i)* 1). $SOCl_2$, Et_3N, CH_2Cl_2, 10 min, -20°C. 2). $RuCl_3$, $NaIO_4$, CH_2Cl_2, ACN, H_2O, 10 min, rt, 84%. *ii)* 1).**13**, LHMDS, THF, HMPA, -45°C, 1 hr, then **14**, 16 hrs, rt. 2). Pyridine, dioxane, reflux, 1 hr, 58%. *iii)* NBS, acetone, H_2O, 3 min, 0°C, 86%. *iv)* DAST, CH_2Cl_2, -50°C, 1 hr, 50%. *v)* $BF_3{\cdot}Et_2O$, *N*-benzyloxycarbonyl-aminopropanol, 0°C, 1 hr, 55%. *vi)* 1). AcOH, H_2O, reflux, 1hr, 96%. 2). 2-methoxy-propene, *p*-TsOH, DMF, 6 hrs, rt 85% 3). Bu_2SnO, MeOH, reflux 3 hrs, then CsF, BnBr, DMF, 16 hrs, rt, 84%.

The resulting C-6 sulfate was cleaved by refluxing in a mixture of pyridine and dioxane to afford **14**. Hydrolysis of thioacetal **14** using *N*-bromosuccinimide (NBS) and wet acetone smoothly afforded ketol **15**. The reaction of hemiketal **15** with diehtylaminosulfur trifluoride (DAST) afforded glycosyl fluoride **16** in a moderate yield. The major by-product of this transformation was an 2,3-unsaturated derivative. Glycosylation of benzyloxycarbonyl protected aminopropanol with **16** using $BF_3{\cdot}Et_2O$ afforded **17** as mainly the α-anomer (α/β = 6/1). Removal of the acetonides using AcOH and water afforded the tetraol

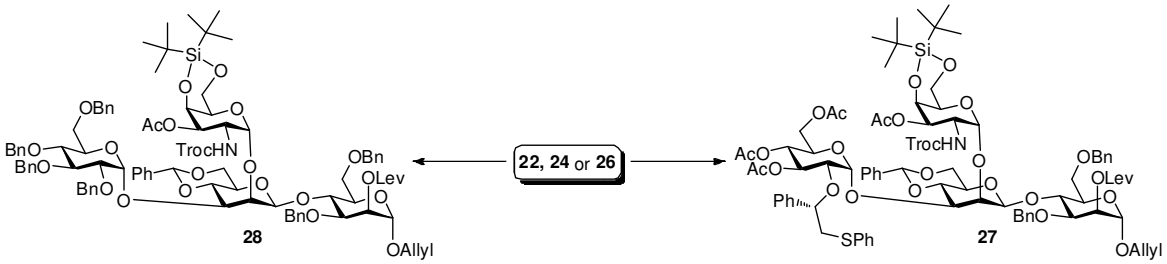
in 96% yield. The tetraol was selectively protected with an isopropylidene and subsequent selective benzylation afforded **10**.



Scheme 5.2: Synthesis of the β-D-Man-(1→4)-D-Man disaccharide core. Reagents and conditions: *i)* 1). *p*-$NO_2C_6H_4SCl$, AgOTf, DTBMP, 5 min, -78°C 2). **9**, 3 hrs, -78°C→35°C, 73 %. *ii)* TBAF, AcOH, THF, 16 hrs, rt, (98%, **19**), (81%, **24**), (85%, **26**) *iii)* DDQ, CH_2Cl_2, H_2O, 3 hrs, rt, 93%. *iv)* **4a**, NIS, TfOH, CH_2Cl_2, 10 min, 0°C, 77%. *v)* 1). **6**, TfOH, CH_2Cl_2, 30 min, -35°C→0°C 2). **20**, DTBMP, 16 hrs, -35°C→rt, 73%. for **23**. **6**, TfOH, Et_2O, 10 min, -35°C, 72% for **25**.

Next, the core β-D-Man-(1→4)-D-Man disaccharide was prepared. Low-temperature activation of **8** with *p*-nitrobenzenesulfenyl chloride and silver trifluoromethanesulfonate (AgOTf) was complete within several minutes and addition of glycosyl acceptor **9**, afforded β-mannoside **18** in good yield and excellent stereoselectivity, α/β = >1/20 (Scheme 5.2). To investigate the installation of the α-glucoside at C-3' and the α-galactoside at C-2', the 2-methylnaphthyl and diethylisopropylsilyl ether were selectively removed using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or buffered tetrabutylammonium fluoride (TBAF) to afford **19** and **20**, respectively. In case of diethylisopropylsilyl (DEIPS) removal, buffering of the TBAF using AcOH was essential to prevent cleavage of the Lev ester. Reaction of **19** with **4a** in the presence of NIS and triflic acid (TfOH) smoothly afforded trisaccharide **21** as only the α-anomer. The 2-

methylnaphthyl ether was removed by oxidation with DDQ in wet CH_2Cl_2 to afford trisaccharide acceptor **22**. Introduction of the α-glycoside was achieved by glycosylation of **20** with pre-activated glycosyl donor **6** to afford trisaccharide **23** as only the α-anomer. Removal of the DEIPS ether using buffered TBAF afforded trisaccharide acceptor **24**. The installation of the additional glycosides onto trisaccharide acceptors **22** and **24** proved to be challenging. Low temperature activation of glycosyl donor **6** with TfOH was complete within minutes however, addition of trisaccharide acceptor **22** did not yield a significant amount of the expected tetrasaccharide **27**.



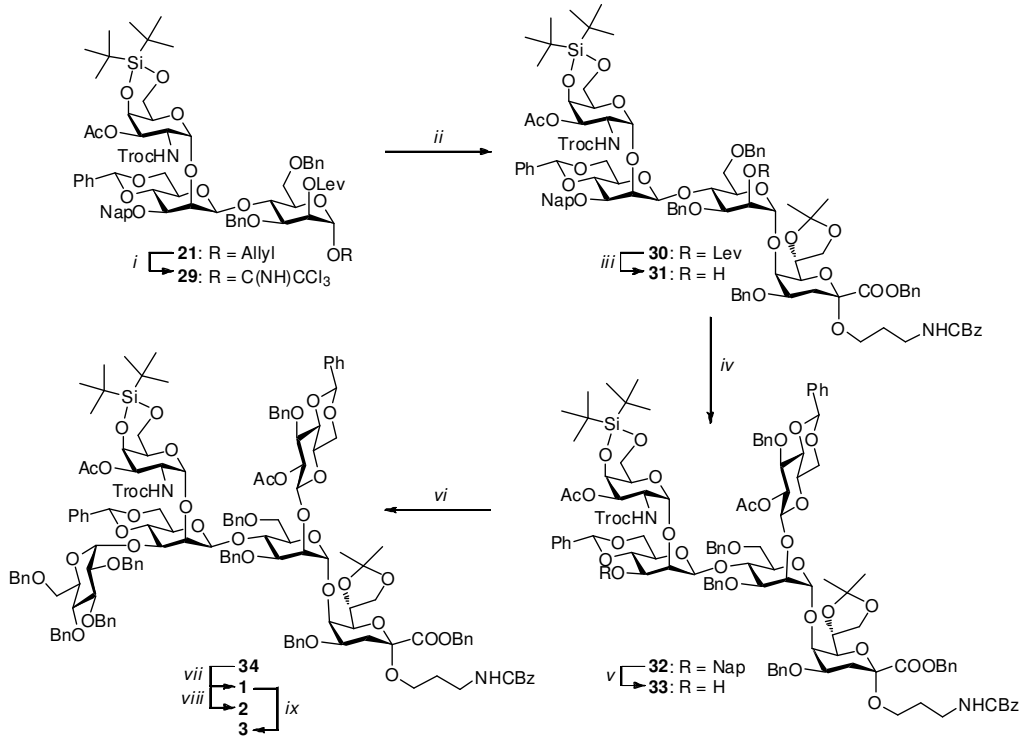
entry	Glycosyl acceptor	Glycosyl donor	Product	Yield
1	**22**	**6**	**27**	~10%
2	**24**	**4a**	**27**	~10%
3	**24**	**4b**	**27**	~10%
4	**26**	**4a**	**28**	~10%
4	**24**	**5**	**28**	74%

Scheme 5.3: Investigations toward the synthesis of the triglycosylated β-mannoside **28**.

Only a small amount of **27** (~10% as judged by TLC and MS analysis) was formed and **22** could be recovered (Scheme 5.3, entry 1). This result was unexpected since the glycosylation of **20** with **6** proceeded smoothly and hence it was concluded that the bulky galactoseamine was responsible for the poor yield. Therefore, installation of the galatosamine at a later stage was expected to give rise to **27**. When trisaccharide acceptor **24** was reacted with galactosamine **4a** using aforementioned conditions a complex mixture of products was obtained and some of **24** could be recovered (Scheme 5.3, entry 2). MS analysis showed cleavage of the 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether of **24** which probably arose from

reaction with the thiophilic iodonium ion formed under these reaction conditions. Glycosyl bromide **4b** was prepared since it can be activated under milder conditions that were expected to be compatible with the presence of the 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether. However, reaction of **4b** with AgOTf, DTBMP and trisaccharide acceptor **24** only afforded a small amount of tetrasaccharide **27** (~10% as judges by TLC and MS analysis) even though the reaction was cleaner this time and the acceptor could be recovered (Scheme 5.3, entry 3). In earlier research, we have observed that the bulky nature of the 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether can interfere with glycosylations (see chapter 3).[9] To evaluate this possibility, trisaccharide **25** was prepared in good yield and α-selectivitly (>20/1, α/β) by reaction of disaccharide **20** with glucosyl donor **5** and TfOH in ethereal solvent (Scheme 5.2). Removal of the DEIPS ether under aforementioned conditions afforded trisaccharide **26**. Reaction of trisaccharide **26** with galactosyl donor **4a**, in the presence of NIS and TfOH again did not produce significant amounts of the expected tetrasaccharide **27** (Scheme 5.3, entry 4). Instead again only the hydrolyzed donor and unreacted acceptor were recovered. These results suggest that the bulky nature of the 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether is not responsible for the detrimental effect on the glycosylation of **24**. The β-mannoside in **27** is glycosylated and C-1, C-2 and C-3 which are all oriented in a 1,2,3-*cis* relative configuration. This 1,2,3-*cis*-configuration may render the bisecting C-2 alcohol to be inaccessible when C-1 and C-3 are glycosylated such as in **24** and **26**. In addition, the C-3 alcohol also seems to be less unreactive when C-2 and C-1 are glycosylated such as in the reaction of **22** with **6** (Scheme 5.3, entry 1). However, the failed glycosylation of **22** and **6** can also be due to the bulky nature of the intermediate sulfonium ion. A severely sterically hindered alcohol such as in **24** is not able to attack the sulfonium ion whereas the less hindered alcohol in **20** does react. To test this hypothesis, trisaccharide **24** was reacted with glycosyl donor **5** using TfOH in diethylether and as expected afforded tetrasaccharide **28** in 74% yield as mainly the α-anomer (α/β = >20/1). These results suggest that indeed the nature of the reactive intermediate, in addition to the order of glycosylations, plays a key role in the successful assembly of the tetrasaccharide. Glycosyl donor **5** is expected to react through a solvent stabilized oxa-carbenium ion which is more accessible and reactive that the corresponding β-sulfonium ion of **6**. Having established the

best order of introduction of the α-glucoside and α-galactosamine attention was focused on the introduction of the KDO moiety.



Scheme 5.4: Synthesis of *F. Tularensis* LPS fragment **1**. Reagents and conditions: *i)* 1). $Pd(PPh_3)_3$, AcOH, CH_2Cl_2, 3 hrs, rt 2). TCA, DBU, CH_2Cl_2, 1 hr, rt, 75%. *ii)* **10**, TfOH, CH_2Cl_2, 10 min, 0°C, 61%. *iii)* N_2H_4·AcOH, EtOH, Toluene, 30 min, rt, 78%. *iv)* **7**, TfOH, CH_2Cl_2, 10 min, 0°C, 82%. *v)* DDQ, CH_2Cl_2, H_2O, 3 hrs, rt, 76%. *vi)* **6**, TfOH, Et_2O, 10 min, -35°C, 73%. *vii)* 1). TFA, CH_2Cl_2, H_2O, 1 hr, rt 2). HF·Pyridine, THF, 30 min, rt 3). Zn, AcOH, CH_2Cl_2, 3 hrs, rt, 89% 4) NaOMe, MeOH, H_2O, THF, 1 hr, rt, 55% 5) $Pd(OH)_2$, H_2, *t*-BuOH, H_2O, 16 hrs, rt, 85%. *viii)* PBS pH 7.4, BiotinOSu, 16 hrs, rt, 62%. *ix)* SAMAOpfp, DIPEA, DMF, 3 hrs, rt, 53%.

The anomeric allyl ether of **21** was removed using $Pd(PPh_3)_4$ in a mixture of CH_2Cl_2 and AcOH and the resulting trisaccharide lactol was converted into the corresponding trichloroacetimidate **29** using trichloroacetonitrile and 1,8-diazazdicycloundec-7-ene (DBU). The trisaccharide donor **29** was used to glycosylate KDO acceptor **10** using TfOH in CH_2Cl_2 to afford tetrasacchraide **30** in a yield of 61%. The levulinyl ester could be selectively removed using hydrazinium acetate in a mixture of toluene and

ethanol to afford tetrasacchride **31**. Attempts to glycosylate this tetrasaccharide with a 2-*O*-acetyl-3,4,6-tri-*O*-benzyl protected glucosyl donor afforded the corresponding pentasaccharide in moderate yields. However, the use of 4,6-*O*-benzylidene protected donor **7**[14] afforded pentasaccharide **32** in a good yield. Oxidative cleavage of the 2-methylnaphthyl ether was performed using DDQ in a mixture of CH_2Cl_2 and water to afford **33**. Finally, the α-glycoside was installed using glycosyl donor **5** under aforementioned conditions to afford the fully assembled hexasaccharide **34**. The deprotection of **34** started with the removal of the acetals using TFA in a mixture of CH_2Cl_2 and water. It was expected that the DTBS group would also be cleaved under these conditions but instead proved to be remarkably stable. Hence, HF·pyridine was used next to remove the DBS group which was complete in only 30 minutes. Removal of the Troc carbamate proceeded uneventfully using Zn powder in a mixture of CH_2Cl_2 and AcOH. Next the acetyl and benzyl esters were removed using NaOMe in a mixture of MeOH/THF/H_2O. Finally, hydrogenation using H_2 and $Pd(OH)_2$ in mixture of *t*-BuOH and water afforded the LPS hexasaccharide fragment **1**.

The ^{1}H NMR spectrum of compound **1** is nearly identical to the reported ^{1}H NMR spectrum of the isolated LPS fragment (see Figure 5.2A). In addition, the anomeric signals of **1** displayed the appropriate chemical shifts and homonuclear as well heteronuclear coupling constants consistent with the desired product. Together these findings unequivocally confirm that the reported structural assignment of the isolated LPS fragment is correct and that the synthetic analogue **1** is of the right composition.

To perform immunological experiments the aminopropanol linker of **1** needs to be derivatized using a biotin moiety (**2**). Reaction of **1** with biotinOSu in PBS buffer (pH 7.4) afforded a monobiotinylated product as the major reaction component by MALDI-TOF and TLC analysis. The major product was purified by reverse phase C-18 chromatography and separated from starting material **1** and a dibiotinylated product. ^{1}H NMR analysis of **2** revealed that the signals adjacent to the amine had moved downfield compared to **1**, consistent with amide formation at this site. Furthermore, the heteronuclear multiple bond coherence (HMBC) spectrum (Figure 5.2) showed coupling between the amide carbonyl and the CH_2 protons on the linker confirming that reaction indeed occurred at the desired site.

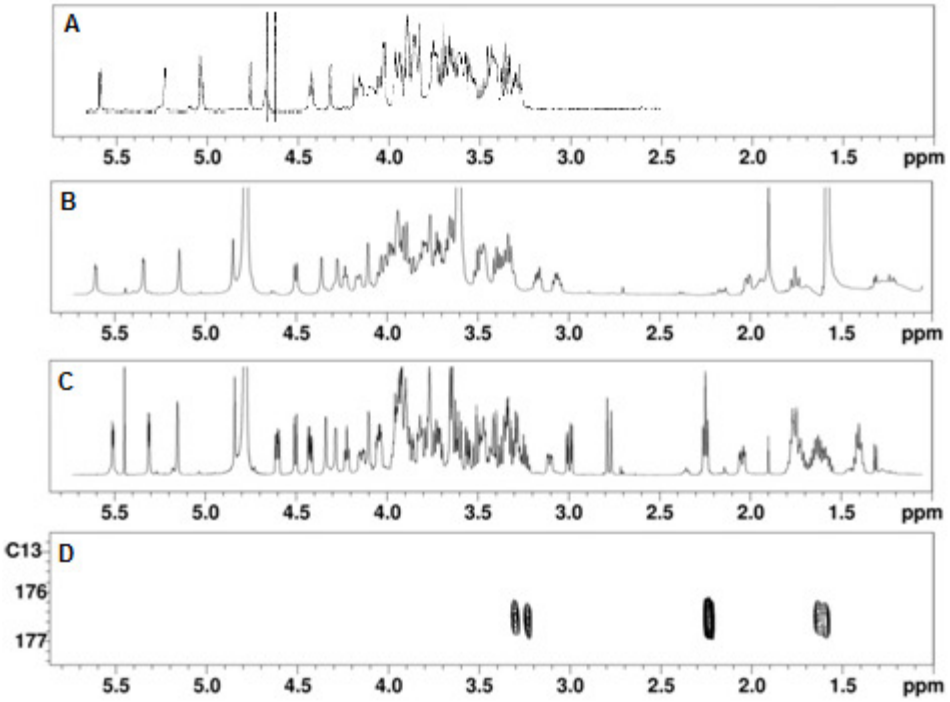


Figure 5.2: NMR data of hexasaccharide **1**. A) Reported ^{1}H NMR spectrum of the isolated hexasaccharide fragment.[4] B) ^{1}H NMR spectrum of the synthetic hexasaccharide fragment **1**. C) ^{1}H NMR spectrum of the synthetic biotin conjugate **2**. D) HMBC spectrum of **2**. The correlation between the amide carbonyl at 176.6 ppm and the CH_2 signals of the linker (3.21-3.35 ppm) and biotin (2.25 ppm and 1.62 ppm) moiety shows that biotinylation occurred at the desired site.

In addition to the biotin derivative **2**, a Keyhole Limpet Hemocyanin (KLH) conjugate was prepared to perform immunizations. The conjugation of **1** to KLH entailed a two step procedure. First, hexasaccharide **1** was reacted with perfluorophenyl 2-(acetylthio)acetate and DIPEA in DMF to afford **3**. The regioselectivity was again confirmed by the heteronuclear multiple bond coherence coupling between the amide carbonyl and the CH_2 protons on the linker. Next, the thioacetyl was cleaved using ammonia in methanol under an inert atmosphere to prevent disulfide formation. The resulting thiol was reacted with maleimide activated KLH to afford the corresponding KLH-conjugate. Analysis of the KLH-conjugate using high-pH anion-exchange chromatography (HPAEC) showed that 339 glycans were present per protein molecule. Immunological experiments are underway to generate antibodies against

hexasaccharide **1** and to investigate the ability of these antibodies to detect and protect against infection by *F. tularensis.*

Conclusion. The inner core LPS hexasaccharide of *Francisella Tularensis* was prepared using a flexible strategy that can easily enable the synthesis of truncated derivatives. Key to this approach was a β-D-Man-(1→4)-D-Man disaccharide, modified with four orthogonal protecting groups, the DEIPS, 2-methynaphthyl, and allyl ether and a levulinyl ester. The order of introduction and nature of the glycosyl donors was found to be critical in glycosylation of the β-mannoside. Further, sequential deprotection and glycosylation followed by global deprotection afforded the native hexasaccharide. Comparison of the ^{1}H NMR spectra of isolated material and the synthetic derivative confirmed that the reported structural assignment of the isolated LPS fragment is correct and that the synthetic analogue is of the right composition. A selective modification of the aminopropyl linker with biotin or KLH-protein was achieved.

Experimental Section.

General procedures: ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz, 500 MHz or a 600 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. NMR data is presented as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration. All NMR signals were assigned on the basis of ^{1}H NMR, ^{13}C NMR, COSY and HSQC experiments. Mass spectra were recorded on an MALDI-TOF mass spectrometer. The matrix used was 2,5-dihydroxy-benzoicacid (DHB) and Ultamark 1621 as the internal standard. Column chromatography was performed on silica gel G60 (Silicycle, 60-200 μm, 60 Å). TLC-analysis was conducted on Silicagel 60 F_{254} (EMD Chemicals inc.) with detection by UV-absorption (254nm) were applicable, and by spraying with 20% sulfuric acid in ethanol followed by charring at ~150^{o}C or by

spraying with a solution of $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (25 g/L) in 10% sulfuric acid in ethanol followed by charring at ~150°C. CH_2Cl_2 was freshly distilled from calcium hydride under nitrogen prior to use. Molecular sieves (4Å) were flame activated under vacuum prior to use. All reactions were carried out under an argon atmosphere.

2-deoxy-2-amino-α-D-galactosamine-(1→2)-3-*O*-[α-D-glucopyranosyl-(1→3)]-β-D-mannopyranosyl-(1→4)-2-*O*-[β-D-glucopyranosyl-(1→2)]-α-D-mannopyranosyl-(1→5)-3-amino-propyl-3-deoxy-α-D-manno-octulopyranosidonate (1). **34** (70 mg, 26 μmol) was dissolved in a mixture of CH_2Cl_2 (4 mL), H_2O (0.2 mL) and TFA (0.4 mL), and the resulting mixture was stirred for 2 hrs at rt. Toluene (4 mL) was added and the mixture was concentrated *in vacuo*. The residue was dissolved in THF (4 mL) and HF·Pyridine (0.7 mL) was added and the resulting mixture was stirred for 2 hrs at rt. EtOAc (10 mL) and sat. aq. $NaHCO_3$ (4 mL) was added drop wise and the organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by LH-20 size exclusion column chromatography (CH_2Cl_2/MeOH, 1/1) and the appropriate fractions were concentrated *in vacuo*. The residue was dissolved in a mixture of AcOH (2 mL) and CH_2Cl_2 (1 mL) and Zn powerder (30 mg) was added. The resulting suspension was stirred for 2 hrs at rt after which the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by LH-20 size exclusion column chromatography (CH_2Cl_2/MeOH, 1/1) and the appropriate fractions were concentrated *in vacuo*. The residue (50 mg, 89 % for three steps) was dissolved in mixture of MeOH (1 mL), THF (1 mL) and water (0.3 mL), and 30% NaOMe in MeOH (0.05 mL) was added. The resulting mixture was stirred for 2 hrs at rt and AcOH (0.1 mL) was added. The mixure was concentrated *in vacuo* and the residue was purified by reverse-phase C-18 column chromatography (0 – 90% MeOH/H_2O). The appropriate fractions were collected and concentrated *in vacuo*. The residue (25 mg, 55%) was dissolved

in a mixture of water (1 mL) and *t*-BuOH (1 mL) and $Pd(OH)_2$ (20 mg) was added. A hydrogen atmosphere was created and the mixture was stirred for 36 hrs at rt. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford **1** (12 mg, 85 %); ^{1}H NMR (600 MHz, D_2O): δ 5.61 (d, 1H, *J* = 3.0 Hz ,H-1-D), 5.34 (d, 1H, *J* = 3.0 Hz ,H-1-F), 5.14 (s, 1H, H-1-B), 4.85 (d, 1H, *J* = 7.8 Hz ,H-1-C), 4.51 (d, 1H, *J* = 7.8 Hz ,H-1-E), 4.37-4,35 (m, 1H, H-2-C), 4.29-4.26 (m, 1H, H-2-B), 4.23 (t, 1H, *J* = 9.0 Hz, H-5-D), 4.17-4.13 (m, 1H, H-4-A), 4.10-3.61 (m, H, H-6a,b-B,C,D,E,F, H-3D, H-4-D, H-2-F, H-3-F, H-4-F, H-5-F, H-3-B, H-4-B, H-3-C, H-4-C, H-5-C, H-3-E, H-4-E, H-5-E,), 3.52-3.33 (m, 6H, CH_2 Linker, H-2-E, H-2-D, H-3-E, H-5-B), 3.20-3.19 (m, 1H, C*H*H Linker), 3.08-3.04 (m, 1H, CH*H* Linker), 2.01 (dd, 1H, *J* = 4.2 Hz, *J* = 12.6 Hz, H-3a-A), 1.94-1.91 (m, 2H, CH_2 Linker), 1.75 (t, 1H, *J* = 12.0 Hz, H-3b-A); ^{13}C NMR (125 MHz, D_2O) δ 175.4, 101.6, 100.2, 99.4, 99.4, 99.3, 85.2, 78.5, 76.9, 76.4, 76.0, 76.0, 76.0, 75.8 ,75.8, 75.1, 72.9, 72.6, 72.5, 72.5, 71.5, 71.0, 70.9, 70.9, 69.5, 69.4, 69.0, 68.3, 67.9, 66.9, 65.4, 62.6, 61.7, 60.7, 60.6, 60.5, 50.2, 59.6, 50.7, 38.3, 35.0, 26.0, 23.1; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{41}H_{72}N_2O_{32}$, 1127.3965; found, 1127.3918.

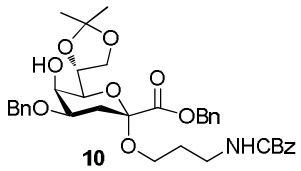
2-deoxy-2-amino-α-D-galactosamine-(1→2)-3-*O*-[α-D-glucopyranosyl-(1→3)]-β-D-mannopyranosyl-(1→4)-2-*O*-[β-D-glucopyranosyl-(1→2)]-α-D-mannopyranosyl-(1→5)-*N*-biotinyl-3-amino-propyl-3-deoxy-α-D-manno-octulopyranosidonate (2). **1** (5.0 mg, 4.5 μmol) was dissolved in PBS buffer pH 7.4 (0.5 mL) and BiotinOSu (1.8 mg, 4.5 μmol) in PBS buffer pH 7.4 (0.2 mL) was added. The resulting mixture was stirred for 3 hrs at rt. The mixture was directly transferred to a reverse phase C-18 column and purified by eluting with 0 -10% MeOH/H_2O. The appropriate fractions were collected and concentrated *in vacuo* to afford **2** (3.7 mg, 62%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.51 (d,

1H, *J* = 3.6 Hz ,H-1-D), 5.31 (d, 1H, *J* = 3.6 Hz, H-1-F), 5.15 (s, 1H, H-1-B), 4.84 (s, 1H, H-1-C), 4.61 (dd, 1H, *J* = 4.5 Hz, *J* = 7.8 Hz, CH Biotin), 4.49 (d, 1H, *J* = 7.8 Hz, H-1-E), 4.61 (dd, 1H, *J* = 4.2 Hz, *J* = 8.4 Hz, CH Biotin), 4.33 (m, 1H, H-2-C), 4.28 (m, 1H, H-2-B), 4.22-4.04 (m, 3H, H-4-A, H-3-B, H-3-C), 3.95-3.22 (m, 29H, H-6a,b-B,C,D,E,F, H-2-E, H-3-E, H-4-E, H-5-E, H-2-F, H-3-F, H-4-F, H-5-F, H-3-D, H-4-D, H-5-D, H-4-C, H-5-C, H-4-B, H-5-B, H-5-A, H-6-A, H-7-A, H-8-A), 3.11 (dd, 1H, *J* = 10.8 Hz, *J* = 4.2 Hz, H-2-D), 3.00 (dd, 1H, *J* = 12.6 Hz, *J* = 4.8 Hz, C*H*H Biotin), 2.78 (d, 1H, *J* = 13.2 Hz, CH*H* Biotin), 2.24 (t, 1H, *J* = 7.2 Hz, CH_2 Biotin), 2.05 (dd, 1H, *J* = 12.6 Hz, *J* = 4.2 Hz, H-3a-A), 1.79-1.56 (m, 8H, CH_2 Linker, 2 x CH_2 Biotin, H-3b-A), 1.42-1.38 (m, 2H, CH_2 Biotin); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 175.0, 165.2, 101.5, 100.1, 99.8, 88.7, 99.2, 97.2, 79.0, 76.7, 76.5, 76.5, 76.2, 75.9, 75.8, 75.1, 72.9, 72.7, 72.6, 72.5, 71.4, 71.2, 71.0, 70.8, 69.6, 69.4, 69.3, 68.3, 68.1, 66.9, 65.5, 63.0, 61.8, 60.9, 60.7, 60.6, 60.4, 60.1, 59.5, 55.1, 53.7, 50.6, 39.5, 36.5, 35.4, 35.0, 28.1, 27.7, 27.5, 25.0; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{51}H_{86}N_4O_{34}S$, 1353.4741; found, 1353.4726.

2-deoxy-2-amino-α-D-galactosamine-(1→2)-3-*O*-[α-D-glucopyranosyl-(1→3)]-β-D-mannopyranosyl-(1→4)-2-*O*-[β-D-glucopyranosyl-(1→2)]-α-D-mannopyranosyl-(1→5)-*N*-thioacetylacetyl-3-amino-propyl-3-deoxy-α-D-manno-octulopyranosidonate (3). **1** (5.0 mg, 4.5 μmol) was dissolved in DMF (0.5 mL) and SAMAOpfp (1.4 mg, 4.5 μmol) in DMF (0.2 mL) and DIPEA (0.2 uL, 9.0 μmol) were added. The resulting mixture was stirred for 3 hrs at rt. The mixture was directly transferred to a reverse phase C-18 column and purified by eluting with 0 -10% MeOH/H_2O. The appropriate fractions were collected and concentrated *in vacuo* to afford **3** (2.9 mg, 53%) as a white solid. ^{1}H NMR (600 MHz, D_2O): δ 5.34 (s, 1H, H-1-D), 5.09 (d, 1H, *J* = 3.6 Hz ,H-1-F), 4.90 (s, 1H, H-1-B), 4.60 (s, 1H, H-1-C), 4.27 (d, 1H, *J* = 7.8 Hz ,H-1-E), 4.12-4.14 (m, 1H, H-2-C), 4.05-4.00 (m, 1H, H-2-

B), 3.97 (t, 1H, *J* = 9.0 Hz, H-5-D), 3.88-3.86 (m, 1H, H-4-A), 4.10-3.00 (m, H, H-6a,b-B,C,D,E,F, H-3D, H-4-D, H-2-F, H-3-F, H-4-F, H-5-F, H-3-B, H-4-B, H-3-C, H-4-C, H-5-C, H-3-E, H-4-E, H-5-E, CH_2 Linker, H-2-E, H-2-D, H-3-E, H-5-B, CH_2 Linker), 1.92-1.87 (m, 1H, H-3a-A), 1.56-1.46 (m, 3H, CH_2 Linker, H-3b-A). HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{45}H_{76}N_2O_{34}S$, 1243.3897; found, 1243.3847.

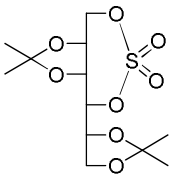
Benzyl [N-benzyloxycarbonyl-3-amino-propyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-manno-octulopyranosid] onate (10). AcOH (120 mL) and water (80 mL) were added to **17** (6.0 g, 10.0 mmol) and the resulting mixture was refluxed for 1hr. The mixture was cooled to rt and concentrated *in vacuo*. Silica gel column chromatography (0% → 10% - MeOH in DCM) of the residue afforded Benzyl [N-benzyloxycarbonyl-3-amino-propyl 3-deoxy-α-D-manno-octulopyranosid] onate (5.0 g, 96%). DMF (60 mL) and 1,4-Dioxane (30 mL), 2-methoxy-propene (1.1 mL, 11.5 mmol) and *p*-TsOH (0.44 g, 2.3 mmol) were added and the resulting mixture was stirred for 16 hrs at rt. Et_3N (2 mL) was added and the mixture was concentrated *in vacuo*. Silica gel column chromatography (0% → 3% - MeOH in DCM) of the residue afforded Benzyl [N-benzyloxycarbonyl-3-amino-propyl 3-deoxy-7,8-isopropylidene-α-D-manno-octulopyranosid] onate (4.6 g, 85%). MeOH (100 mL) and Bu_2SnO (2.11 g, 8.2 mmol) were added and the resulting suspension was refluxed for 3 hrs, cooled (rt) and concentrated *in vacuo*. The residue was dissolved in DMF (50 mL) and benzylbromide (1.26 mL, 10.6 mmol) and CsF (1.6 g, 10.6 mmol) were added. The resulting mixture was stirred for 16 hrs at rt. EtOAc (300 mL) and water (100 mL) were added and the organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 40% - EtOAc in PE) of the residue afforded **10** (4.5 g, 84%). TLC: (EtOAc/PE, 50/50 v/v): R_f = 0.65; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.29 (m, 15H, CH Ar), 5.41 (t, 1H, *J* = 3.0 Hz, N*H*), 5.25-5.19 (m, 2H, CH_2 Bn), 5.11 (s, 2H, CH_2 CBz), 4.55 (dd, 1H, *J* = 13.2 Hz, *J* = 3.6 Hz, CH_2 Bn), 4.43 (dd, 1H, *J* = 3.6 Hz, *J* = 7.5 Hz, H-7), 4.15-4.06 (m, 3H, H-5, H-8a,b), 3.92-3.90 (m, 1H, H-4), 3.57-3.52 (m, 2H, H-6, C*H*H), 3.34-3.27 (m, 2H, C*H*H, CH*H*), 3.23-3.19 (m, 1H, CH*H*), 2.46 (bs, 1H, 5-OH),



10

2.24 (dd, 1H, *J* = 3.0 Hz, *J* = 7.6 Hz, H-3a), 2.02 (t, 1H, *J* = 7.2 Hz, H-3b), 1.73 (t, 2H, *J* = 3.6 Hz, CH_2), 1.42 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{36}H_{43}O_{10}$, 672.2784; found, 672.2715.

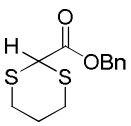
2,3-5,6-di-*O*-isopropylidene-1,4-*O*-sulfate-D-mannitol (12). 2,3-5,6-di-*O*-isopropylidene-D-mannitol[15]



12

(10 g, 38.0 mmol), was dissolved in DCM (200 mL), Et_3N (13.2 mL, 95 mmol) was added and the resulting mixture was cooled (-20°C). Thionyl chloride (3.4 mL, 45.6 mmol) was slowly added at this temperature and stirring was continued for 10 min. DCM (200 mL) and water (100 mL) were added and the organic layer was extracted with water (2 x 100 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dissolved in DCM (75 mL), acetonitrile (75 mL) and water (120 mL). Sodium periodate (16.1 g, 76 mmol) and $RuCl_3$ (0.45 g) were added and the mixture was stirred for 10 min at rt. Water (50 mL) and DCM (400 mL) were added and the organic layer was extracted with water (2 x 100 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dissolved in a 1/1 mixture of EtOAc and PE (200 mL) and filtered through a short silica column. The filter was washed with EtOAc/PE, 1/1 (300 mL) and the filtrate was concentrated *in vacuo* to afford 10.31 g **12** (31.8 mmol, 84%). ^1H NMR (300 MHz, $CDCl_3$): δ 4.57 (d, 2H, *J* = 6.9 Hz, H-2, H-4), 4.48-4.32 (m, 4H, H-1a,b, H-3, H-5), 4.16 (dd, 1H, *J* = 6.3 Hz, *J* = 9.3 Hz, H-6a), 4.06 (dd, 1H, *J* = 4.5 Hz, *J* = 9.3 Hz, H-6b), 1.52 (s, 3H, CH_3), 144 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.05, 110.1, 79.4, 73.9, 73.3, 73.2, 72.9, 68.1, 66.6, 27.3, 26.8, 25.1, 24.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{12}H_{20}O_8S$, 347.0776; found, 347.0729.

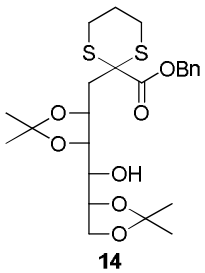
Benzyl 1,3-dithiane-2-carboxylate (13). Glycoxylic acid (50 g, 67 mmol) was dissolved in toluene (300 mL). 1,3-propanedithiol (5.8 mL, 80 mmol) and *p*-toluenesulfonic acid monohydrate (1.3 g, 6.7 mmol) were added and the resulting mixture was refluxed using a dean-stark apparatus



13

for 16 hrs. Benzyl alcohol (10.3 mL, 100 mmol) was added and refluxing was continued for 6 hrs. The reaction mixture was cooled to rt and Et_3N (10 mL) was added and the mixture was concentrated *in vacuo*. Silica gel column chromatography (0% → 50% - DCM in PE) of the residue afforded **13** (1.42 g, 54%) as a white solid.^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.25 (m, 5H, CH Ar) 5.21 (s, 2H, CH_2 Bn), 4.21 (s, 1H, CH), 3.45-3.35 (m, 2H, CH_2), 2.62-2.54 (m, 2H, CH_2), 2.16-1.99 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 135.3, 128.6, 128.4, 128.1, 67.2, 39.7, 25.8, 24.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{12}H_{14}O_2S_2$, 277.0332; found, 277.0376.

Benzyl [2-1,3-dithiane-3-deoxy-4,5-7,8-di-*O*-isopropylidene-α-D-manno-octulopyranosid] onate

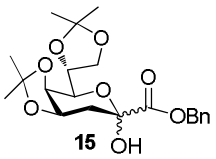


14

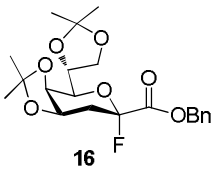
(14). 13 (10.5 g, 41.3 mmol) was dissolved in freshly distilled THF (70 mL) and hexamethyl phosphoramide (25 mL). The mixture was cooled (-45^{o}C), 1M LHMDS in THF (45.4 mL, 45.4 mmol) was added and the mixture was stirred for 30 min at -45^{o}C. A solution of **12** (10.3 g, 31.7 mmmol) in THF (20 mL) was added and the mixture was allowed to warm to rt over a period of 1 hr. EtOAc (500 mL) and water (75 mL) were added and the organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in pyridine (200 mL) and 1,3-dioxane (200 mL) and refluxed for 1 hr. The mixture was cooled to rt and concentrated *in vacuo*. Silica gel column chromatography (0% → 25% - DCM in PE) of the residue afforded **14** (9.1 g, 58%). TLC: (EtOAc/PE, 25/75 v/v): R_f = 0.34; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.14 (m, 5H, CH Ar), 5.20 (d, 1H *J* = 12.0 Hz, C*H*HPh), 5.15 (d, 1H, *J* = 12.6 Hz, CH*H*Ph), 4.58-4.52 (m, 1H, H-4), 4.27 (d, 1H, *J* = 7.2 Hz, H-3), 4.11-3.95 (m, 3H, H-7, H-8a,b), 3.56 (t, 1H, *J* = 7.5 Hz, H-6), 3.53-3.25 (m, 1H, C*H*H), 3.16-3.06 (m, 1H, CH*H*), 2.70-2.59 (m, 3H, CH_2, H-3a), 2.46 (dd, 1H, *J* = 3.6 Hz, *J* = 15.0 Hz, H-3b), 2.13-2.05 (m, 2H, 6-OH, C*H*H), 1.89-1.80 (m, 1H, CH*H*), 1.39 (s, 6H, 2 x CH_3), 1.33 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 135.5, 128.4-127.9, 109.2, 107.7, 76.2, 76.0, 73.3, 73.2, 70.6, 67.3, 66.9, 51.7, 39.0, 27.7, 27.6, 27.1,

26.5, 25.2, 25.0, 24.0; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{24}H_{34}O_7S_2$ 521.1643; found, 521.1648.

Benzyl [3-deoxy-4,5-7,8-di-*O*-isopropylidene-α-D-manno-octulopyranosid] onate (15). **14** (30.0 g, 60.0 mmol) was dissolved in mixture of acetone (485 mL) and water (15 mL). The resulting mixture was cooled (0°C) and recrystallized NBS (53.4 g, 300 mmol) was added. The mixture was stirred for 3 min before 1M aq. $Na_2S_2O_4$ (200 mL) and DCM (1 L) were added. The aqueous layer was extracted with DCM (2 x 300 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 30% - DCM in PE) of the residue afforded **15** (21.0 g, 86%). TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.25; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.23 (m, 5H, CH Ar), 5.18 (d, 1H, *J* = 12.3 Hz, C*H*HPh), 5.13 (d, 1H, *J* = 12.3 Hz, CH*H*Ph), 4.44 (ddd, 1H, *J* = 4.8 Hz, *J* = 6.3 Hz, *J* = 11.1 Hz, H-4), 4.30-4.23 (m, 1H, H-7), 4.15 (dd, 1H , *J* = 2.1 Hz, *J* = 6.6 Hz, H-5), 4.00 (dd, 1H, *J* = 6.0 Hz, *J* = 8.7 Hz, H-8a), 3.92 (dd, 1H, *J* = 4.8 Hz, *J* = 8.7 Hz, H-8b), 2.48 (dd, 1H, *J* = 6.6 Hz, *J* = 14.4 Hz, H-3a), 1.84 (dd, 1H, *J* = 4.8 Hz, *J* = 14.4 Hz, H-3b), 1.33 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 135.0, 128.6-128.1, 109.3, 109.2, 94.5, 73.9, 71.3, 70.6, 69.8, 67.6, 66.7, 32.1, 26.9, 26.9, 25.6, 25.3; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{21}H_{28}O_8$, 431.1681; found, 431.1637.

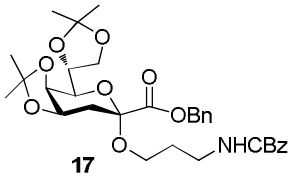


Benzyl [Fluoro 3-deoxy-4,5-7,8-di-*O*-isopropylidene-α-D-manno-octulopyranosid] onate (16). **15** (1.0 g, 2.4 mmol) was dissolved in DCM (40 mL) and activated MS4Å were added. The resulting suspension was cooled (-50°C), DAST (0.32 mL, 3.36 mmol) was added and stirring was continued for 15 min. MeOH (0.2 mL) and sat. aq. $NaHCO_3$ (10 mL) were added and the organic layer was separated, dried ($Na_2S_2O_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 10% - EtOAc in PE) of the residue afforded **16** (0.5 g, 50%). TLC: (EtOAc/PE, 20/80 v/v): R_f = 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H, CH Ar), 5.23



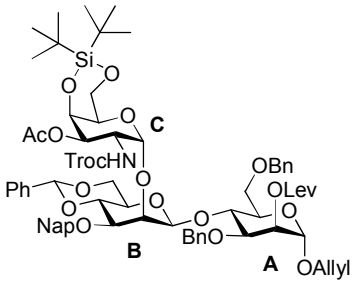
(s, 2H, CH_2 Bn), 4.56-4.53 (m, 1H, H-4), 4.40-4.34 (m, 2H, H-5, H-7), 4.15-4.04 (m, 2H, H-8a,b), 3.65 (td, 1H, *J* = 2.4 Hz, *J* = 8.1 Hz, H-6), 3.65 (td, 1H, *J* = 3.6 Hz, *J* = 15.6 Hz, H-3a), 2.03-1.91 (m, 1H, H-3b), 1.42 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 164.9, 134.9, 128.5-128.2, 109.6, 109.5, 108.8, 105.8, 73.3, 73.0, 71.4, 69.3, 69.2, 67.5, 66.8, 30.8, 30.4, 26.8, 26.8, 25.3, 25.0, 24.6; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{21}H_{27}O_7$, 433.1638; found, 433.1638.

Benzyl [N-benzyloxycarbonyl-3-amino-propyl 3-deoxy-4,5-7,8-di-*O*-isopropylidene-α-D-manno-octulopyranosid] onate (17). *N*-benzyloxycarbonyl-3-amino-propanol (0.51 g, 2.44 mmol) and **16** (0.5 g, 1.21 mmol) were dissolved in DCM (12 mL) and MS4Å were added. The resulting suspension was cooled (0°C) and $BF_3{\cdot}Et_2O$ (0.15 mL, mmol) was added. The mixture was stirred for 1hr at 0°C before Et_3N (0.3 mL) was added and the mixture was concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in PE) of the residue afforded **17** (0.4 g, 55%). TLC: (EtOAc/PE, 40/60 v/v): R_f = 0.30; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.26 (m, 10H, CH Ar), 5.19 (dd, 2H, *J* = 12.0 Hz, *J* = 3.9 Hz, CH_2 Bn), 5.07 (s, 2H, CH_2 CBz), 4.46 (dd, 1H = *J* = 7.2 Hz, *J* = 3.3 Hz, H-4), 4.34 (dd, 1H, *J* = 5.7 Hz, *J* = 12.0 Hz, H-7), 4.22 (d, 1H, *J* = 7.5 Hz, H-5), 4.11 (dd, 1H, *J* = 3.6 Hz, *J* = 6.0 Hz, H-8a), 4.01 (dd, 1H, *J* = 5.7 Hz, *J* = 8.7 Hz, H-8b), 3.73-3.61 (m, 2H, H-6, C*H*H), 3.23-3.06 (m, 3H, CH*H*, CH_2), 2.82 (dd, 1H, *J* = 3.6 Hz, *J* = 15.3 Hz, H-3a), 1.81 (dd, 1H, *J* = 3.0 Hz, *J* = 15.6 Hz, H-3b), 1.40 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 156.3, 136.6, 135.5, 128.5-128.0, 109.5, 108.9, 97.3, 74.3, 71.9, 71.0, 70.0, 67.1, 66.5, 60.5, 38.2, 32.7, 29.3, 26.6, 25.4, 24.8; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{32}H_{41}O_{10}$, 622.2628; found, 622.2619.



17

Allyl 3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-α-D-galactosamine-(1→2)-4,6-di-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (21): To a cooled (0°C) suspension of allyl 4,6-di-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (0.33 g, 0.37 mmol), phenyl 3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-1-thio-β-D-galactosamine (0.35 g, 1.5 equiv), *N*-iodosuccinimide (0.125 g, 1.5 equiv) and molecular sieves in CH_2Cl_2 (5 mL) was added TfOH (6.5 μL, 0.2 equiv). The mixture was stirred for 10 min at 0°C before 1M aq. $Na_2S_20_3$ (10 mL) and CH_2Cl_2 (10 mL) were added. The organic layer separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - Toluene in PE) of the residue afforded **21** (0.40 g, 77%) as a white foam. TLC: (EtOAc/PE, 30/70 v/v): R_f = 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.60 (m, 4H, CH Ar), 7.42-7.32 (m, 8H, CH Ar), 7.22-7.06 (m, 10H, CH Ar), 6.27 (d, 1H, *J* = 9.5 Hz, N*H*), 5.83-5.77 (m, 1H, CH Allyl), 5.51 (s, 1H, H-7-B), 5.21-5.12 (m, 3H, CH_2 Allyl, H-2-A), 4.91-4.80 (m, 3H, CH_2 Troc, H-3-C), 4.83 (s, 1H, H-1-C), 4.76 (s, 1H, H-1-A), 4.64-4.42 (m, 5H, CH_2 Bn, C*H*HPh, C*H*HPh, H-4-C), 4.40-4.37 (m, 1H, H-2-C), 4.30-4.21 (m, 3H, CH*H*Ph, CH*H*Ph, H-1-B), 4.07 (dd, 1H, *J* = 13.0 Hz, *J* = 5.5 Hz, C*H*H Allyl), 3.97-3.87 (m, 6H, CH*H* Allyl, H-5-C, H-6a-B, H-4-A, H-6-a,b-C), 3.83 (t, 1H, *J* = 9.5 Hz, H-4-B), 3.69-3.66 (m, 2H, H-3-A, H-6a-A), 3.61-3.58 (m, 3H, H-2-B, H-6b-B, H-5-A), 3.51 (d, 1H, J = 1.05 Hz, H-6b-A), 3.36 (d, 1H, *J* = 9.5 Hz, H-3-B), 2.92-2.87 (m, 1H, H-5-B), 2.58-2.55 (m, 4H, 2 x CH_2 Lev), 2.00 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.02 (s, 9H, $C(CH_3)_3$), 0.92 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 171.6, 170.9, 154.3, 137.8, 137.6, 137.2, 134.8, 133.0, 132.9, 132.7, 128.8-125.3, 117.8, 101.3, 100.7, 100.3, 96.4, 95.3, 79.1, 78.7, 76.3, 75.6, 75.0, 74.1, 73.1, 72.3, 71.7, 70.9, 79.4, 70.0, 68.4, 68.1, 67.3, 66.7, 66.6, 60.0, 49.7, 37.6, 29.4, 27.8, 27.3, 27.1, 23.0, 20.7, 20.5, 13.9; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{71}H_{86}Cl_3NO_{20}Si$, 1428.4475; found, 1428.4423.



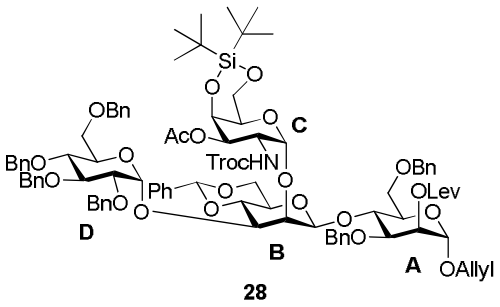
21

Allyl 3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-α-D-galactosamine-(1→2)-4,6-di-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (22): DDQ (0.2 g, 0.58 mmol) was added to a vigorously stirred emulsion of **21** (0.40 g, 0.29 mmol) in DCM (3 mL) and water (0.3 mL). The resulting emulsion was stirred for 3 hrs before the mixture was diluted with CH_2Cl_2 (5 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*. Silica gel column chromatography (0% → 20% - EtOAc in Toluene) afforded **22** (0.26 g, 72 %) as colorless oil. TLC: (EtOAc/Tol, 30/70 v/v): R_f = 0.20; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-71.9 (m, 15H, CH Ar), 5.96 (d, 1H, *J* = 10.0 Hz, N*H*), 5.85-5.79 (m, 1H, CH Allyl), 5.42 (s, 1H, H-7-B), 5.24-5.12 (m, 3H, CH_2 Allyl, H-2-A), 4.89 (d, 1H, J = 11.0 Hz, H-3-C), 4.79-4.78 (m, 2H, H-1-A, H-1-C), 4.73-4.33 (m, 6H, CH_2 Bn, CH*H*Ph, CH_2 Troc, H-4-C), 4.37-4.33 (m, 3H, H-1-B, H-2-C, CH*H*Ph), 4.01 (dd, 1H, *J* = 5.0 Hz, *J* = 12.5 Hz, C*H*H Allyl), 4.01 (t, 1H, *J* = 9.5 Hz, H-4-A), 3.97-3.89 (m, 6H, CH*H* Allyl, H-5-C, H-6a,b-B, H6a,b-C), 3.79 (d, 1H, *J* = 11.0 Hz, H-6a-A), 3.68 (d, 1H, *J* = 9.0 Hz, H-3-A), 3.58-3.46 (m, 5H, H-6b-A, H-5-A, H-4-B, H-3-B, H-2-B), 3.01-2.95 (m, 1H, H-5-B), 2.68-2.53 (m, 4H, 2 x CH_2 Lev), 2.05 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.76 (bs, 1H, 3-OH), 0.99 (s, 9H, $C(CH_3)_3$), 0.92 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 171.9, 171.2, 154.5, 138.2, 137.8, 136.9, 133.1, 129.3-126.2, 117.9, 102.0, 100.9, 100.7, 96.7, 95.7, 78.7, 78.2, 76.3, 75.3, 74.4, 73.5, 71.6, 71.5, 71.4, 70.7, 70.1, 68.9, 68.4, 68.3, 68.3, 68.1, 67.3, 66.9, 66.6, 50.1, 49.7, 37.9, 29.7, 29.6, 28.0, 27.4, 27.2, 23.1, 20.9, 20.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{60}H_{78}Cl_3NO_{20}Si$, 1288.3849; found, 1288.3837.

Allyl 3,4,6-tri-*O*-acetyl-2-*O*-[(*S*)-2-phenylthiomethyl) benzyl]-α-D-glucopyranosyl-(1→3)-4,6-di-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (24). **6** (0.16 g, 0.23 mmol) was dissolved in DCM (2 mL) and activated MS4Å were added. The resulting suspension was cooled (-30°C) and TfOH (20 µL, 0.23 mmol) was added and the mixture was allowed to slowly (~30 min) warm to 0°C. The mixture was cooled (-30°C) and a solution of **20** (0.135 g, 0.15 mmol) and DTBMP (0.14 g, 0.69 mmol) in DCM (2 mL) was slowly added. The mixture was allowed to warm to rt and was stirred for 16 hrs at rt. Silica gel column chromatography (0% → 15% - EtOAc in Toluene) afforded Allyl 3,4,6-tri-*O*-acetyl-2-*O*-[(*S*)-2-phenylthiomethyl) benzyl]-α-D-glucopyranosyl-(1→3)-4,6-di-*O*-benzylidene-2-*O*-diethylisopropylsilyl-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (0.155 g, 73 %) as white foam. Allyl 3,4,6-tri-*O*-acetyl-2-*O*-[(*S*)-2-phenylthiomethyl) benzyl]-α-D-glucopyranosyl-(1→3)-4,6-di-*O*-benzylidene-2-*O*-diethylisopropylsilyl-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (0.155 g, 0.12 mmol) was dissolved in THF (2 mL). AcOH (36 µL, 0.6 mmol) and TBAF (1M in THF, 1.2 mL, 1.2 mmol) was added. The resulting mixture was stirred for 16 hrs at rt. Water (4 mL) and EtOAc (20 mL) were added and the organic layer was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (0% → 30% - EtOAc in PE) afforded **24** (121 mg, 81 %; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.04 (m, 23H, CH Ar), 6.60 (d, 2H, *J* = 7.0 Hz, CH Ar), 5.82-5.78 (m, 1H, CH Allyl), 5.35 (s, 1H, H-1-C), 5.33-5.31 (m, 3H, H-2-A, H-3-B, H-7-B), 5.21 (d, 1H, *J* = 17.0 Hz, C*H*H Allyl), 5.13 (d, 1H, *J* = 10.5 Hz, CH*H* Allyl), 4.79 (s, 1H, H-1-A), 4.74 (s, 1H, H-1-B), 4.73-4.49 (m, 5H, 2 x CH_2 Bn, H-4-C), 4.37 (t, 1H, *J* = 4.5 Hz, H-7-C), 4.24 (t, 1H, *J* = 9.5 Hz, H-4-B), 4.13-3.81 (m, 10H, H-3-A, H-5-C, CH_2 Allyl, H-6a-B, H-6a,b-C, H6a-A, H-4-A, H-5-A), 3.75-3.68 (m, 2H, H-3-B, H-6b-A), 3.61 (t, 1H, *J* = 10.5 Hz, H-6b-B), 3.27 (bd, 1H, *J* = 10.0 Hz, H-2-C), 3.15-3.11 (m, 1H, H-5-B), 3.04 (dd, 1H, *J* = 9.0 Hz, *J* = 13.5 Hz, H-8a-C), 2.82 (dd, 1H, *J* = 3.0 Hz, *J* = 13.5 Hz, H-8b-C), 2.64-2.58 (m, 4H, 2 x CH_2 Lev), 2.03 (s, 3H, CH_3), 1.91 (s,

3H, CH_3), 1.89 (s, 3H, CH_3), 1.85 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 171.9, 170.5, 170.0, 169.7, 139.2, 138.2, 137.9, 137.4, 137.1, 133.2, 129.4-125.2, 117.8, 102.2, 100.5, 96.7, 96.0, 78.7, 77.9, 76.7, 74.8, 73.6, 73.5, 73.5, 71.7, 71.4, 70.8, 70.4, 68.9, 68.9, 68.7, 68.4, 68.1, 67.1, 66.7, 61.7, 41.2, 37.9, 29.7, 29.6, 28.1, 20.6, 20.6, 20.6, 20.6; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{67}H_{76}O_{21}S$, 1271.4497; found, 1271.4426.

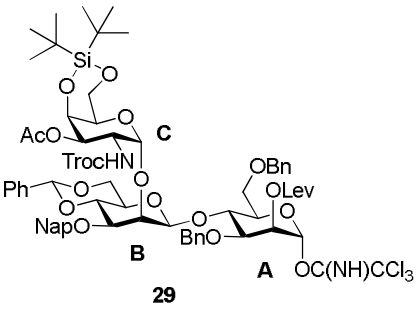
Allyl 3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-α-D-galactosamine-(1→2)-4,6-di-*O*-benzylidene-3-*O*-[2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranosyl]-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranoside (28): To a cooled (-30°C) solution of glycosyl donor **5** (0.4 g, 0.55 mmol) and glycosyl acceptor **21** (0.37 g, 0.29 mmol) in Et_2O (5 mL) was added activated MS4Å and the resulting solution was stirred for 30 min. TfOH (19.4 uL, 0.22 mmol) was added and the resulting mixture was stirred for 10 min at -30°C. DTBMP (0.14 g, 0.66 mmol) was added and the mixture was concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in Toluene) of the residue afforded **28** (0.37 g, 72%) as a white foam. TLC: (EtOAc/Tol, 30/70 v/v): R_f = 0.35; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-6.98 (m, 33H, CH Ar), 6.73 (d, 2H, *J* = 5.5 Hz, CH Ar), 5.83-5.80 (m, 1H, CH Allyl), 5.49 (s, 1H, H-1-C), 5.41 (s, 1H, H-7-B), 5.27-5.12 (m, 4H, H-2-A, H-1-D, CH_2 Allyl), 4.86-4.79 (m, 2H, H-3-C, H-1-A), 4.77-4.33 (17 m, H-4-C, H-2-C, H-1-B, 6 x CH_2 Bn, CH_2 Troc), 4.16-3.73 (m, 19, H-4-A, H-5-A, H-5-D, H-5-C, H-3-A, CH_2 Allyl, H-6a,b-B), 3.67-3.50 (m, 7H, H-6a,b-C, H-6a,b-A, H-3-D, H-4-B, H-4-D), 3.41 (t, 1H, *J* = 8.0 Hz, H-3-B), 3.33-3.31 (m, 1H, H-2-D), 2.90-2.85 (m, 1H, H-5-B), 2.70-2.59 (m, 4H, 2 x CH_2 Lev), 2.03 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 0.90-0.88 (m, 18H, 2 x $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 171.9, 171.0, 162.5, 154.2, 139.1, 138.4, 138.1, 138.1, 138.0, 137.8, 137.1, 133.3, 133.2, 129.4, 129.0, 128.5-126.3, 117.7, 102.5, 99.3, 98.0, 97.4, 96.7, 96.7, 95.8, 95.0, 95.0, 81.6, 79.2, 78.3, 77.3, 76.4, 75.6,



28

75.6, 74.8, 74.6, 74.3, 74.0, 73.9, 73.8, 73.4, 73.3, 71.6, 61.6, 71.4, 70.4, 70.3, 70.2, 69.2, 69.0, 68.7, 68.6, 68.5, 68.4, 68.3, 67.3, 67.2, 67.0, 66.8, 48.8, 37.9, 36.4, 31.4, 30.1, 29.7, 29.6, 28.2, 28.1, 27.5, 27.1, 23.2, 20.9, 20.6; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{94}H_{112}Cl_3NO_{25}Si$, 1810.6256; found, 1810.6220.

3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-α-D-galactosamine-(1→2)-4,6-di-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranosyl trichloroacetimidate (29): To a degassed solution of **21** (0.8 g, 0.57 mmol) in CH_2Cl_2 (5 mL) and AcOH (0.5 mL), $Pd(PPh_3)_4$ (0.26 g, 0.4 equiv) was added and the resulting solution was stirred for 2 hrs at rt. The mixture was concentrated *in vacuo* and silica gel column chromatography (0% → 30% - EtOAc in Toluene) of the residue afforded the pure lactol (0.62 g, 80%) as a white foam. To a cooled (0°C) solution of the lactol (0.62 g, 0.45 mmol) in CH_2Cl_2 (5 mL) and trichloroacetonitrile (2 mL), DBU (14 μL, 0.2 equiv) was added. The mixture was stirred at 0°C for 30 min and concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in Toluene) of the residue afforded **29** (0.64 g, 75% yield over two steps) as a white foam. TLC: (EtOAc/Tol, 30/70 v/v): R_f = 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (s, 1H, N*H*), 7.74-7.60 (m, 4H, CH Ar), 7.43-7.07 (m, 18H, CH Ar), 6.26 (d, 1H, *J* = 9.3 Hz, N*H*), 6.16 (d, 1H, *J* = 2.1 Hz, H-1-A), 5.53 (s, 1H, H-7-B), 5.32 (t, 1H, *J* = 2.7 Hz, H-2-A), 4.92-4.79 (m, 4H, CH_2 Bn, H-3-C, H-1-C), 4.64-4.46 (m, 5H, 2 x CH_2 Bn, H-4-C), 4.40 (dd, 1H, *J* = 3.3 Hz, *J* = 10.5 Hz, H-2-C), 4.35-4.21 (m, 3H, CH_2 Bn, H-1-B), 4.08 (t, 1H, *J* = 9.3 Hz, H-5-A), 3.97-3.60 (m, 8H, H-5-C, H-6a,b-B, H-6a,b-C, H-4-B, H-2-B, H-6a-A), 3.54 (d, 1H, J = 10.8 Hz, H-6b-A), 3.36 (dd, 1H, *J* = 3.0 Hz, *J* = 9.6 Hz, H-3-B), 2.95-2.89 (m, 1H, H-5-B), 2.59-2.56 (m, 4H, 2 x CH_2 Lev), 2.01(s, 3H, CH_3), 1.99 (s, 3H, CH_3), 0.99 (s, 9H, $C(CH_3)_3$), 0.92 (s, 9H, $C(CH_3)_3$); 8 (d, 1H, *J* = 6.0 Hz, 2-OH), 2.70-2.54 (m, 2H, CH_2 SEt), 1.29 (t, *J* = 7.5 Hz, 3H, CH_3, SEt); 13C NMR (75 MHz,



29

$CDCl_3$) d 205.9, 171.5, 171.2, 159.9, 154.4, 137.7, 137.6, 137.3, 134.9, 133.1, 132.9, 128.9-125.2, 101.5, 101.0, 100.9, 95.0, 90.0, 79.2, 78.8, 76.4, 75.5, 74.6, 74.3, 73.4, 72.6, 72.0, 71.5, 70.1, 68.3, 68.1, 67.7, 67.4, 66.9, 49.9, 37.7, 29.6, 27.3, 23.1, 20.9, 20.6.

3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-α-D-galactosamine-(1→2)-4,6-di-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranosyl-(1→5)-Benzyl [*N*-benzyloxycarbonyl-3-amino-propyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-manno-octulopyranosid] onate (30). To a cooled (0°C) solution of glycosyl donor **29** (0.5 g, 0.33 mmol) and glycosyl acceptor **10** (0.32 g, 0.5 mmol) in CH_2Cl_2 (5 mL) was added activated MS4Å and the resulting solution was stirred for 30 min. TfOH (5.8 uL, 0.07 mmol) was added and the resulting mixture was stirred for 10 min at 0°C. DTBMP (0.14 g, 0.66 mmol) was added and the mixture was concentrated *in vacuo*. Silica gel column chromatography (0% → 10% - Acetone in Toluene) of the residue afforded **30** (0.40 g, 61%) as a white foam. TLC: (Acetone/Toluene, 20/80 v/v): R_f = 0.45; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80-7.02 (m, 38H, CH Ar), 6.28 (d, 1H, *J* = 9.0 Hz, N*H*), 5.56 (s, 1H, H-7), 5.36-5.34 (m, 1H, H-2-B), 5.26-5.04 (m, 7H, H-1-A, 2 x CH_2 Bn, CH_2 Troc), 4.93 (t, 1H, *J* = 12.6 Hz, H-3-D), 4.86-4.83 (m, 2H, CH_2 Bn), 4.71-4.41 (m, 8H, 3 x CH_2 Bn, H-4-D, H-2-D), 4.24-3.73 (m, H-1-C, H-3-C, H-2-C,), 3.31-3.27 (m, 2H, H-4-C, H-3-B), 3.33-3.27 (m, 3H, C*H*H Linker), 3.17-3.11 (m, 4H, CH*H* Linker, CH_2 Linker), 2.97 (m, 1H, CH*H* Linker), 2.97-2.95 (m, 1H, H-5-C), 2.62-2.54 (m, 4H, 2 x CH_2 Lev), 2.20 (dd, 1H, *J* = 4.8 Hz, *J* = 13.2 Hz, H-3a-A), 2.03-1.95 (m, 7H, 2 x CH_3, H-3b-A), 1.65-1.58 (m, 2H, CH_2 Linker), 1.32 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.02 (s, 9H, $C(CH_3)_3$), 0.94 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): d 206.0, 171.7, 171.1, 167.8, 156.3, 154.5, 138.2, 138.0, 137.7, 137.5, 136.6, 134.1, 135.1, 133.1, 132.9, 129.7-125.3, 109.6, 101.5, 101.2, 101.1, 100.9,

100.6, 99.1, 97.9, 79.4, 79.3, 75.5, 75.1, 74.3, 74.3, 73.2, 73.1, 72.6, 72.5, 71.9, 71.5, 71.1, 70.4, 70.4, 70.3, 70.3, 69.0, 68.4, 67.8, 67.6, 67.4, 67.1, 67.1, 67.0, 66.7, 66.4, 61.4, 50.0, 38.3, 38.1, 38.0, 37.8, 37.7, 32.4, 30.8, 29.6, 29.5, 29.2, 28.0, 27.5, 27.3, 26.7, 24.6, 23.2, 20.9, 20.7, 20.6; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{104}H_{123}Cl_3N_2O_{29}Si$, 2019.6944; found, 2019.6948.

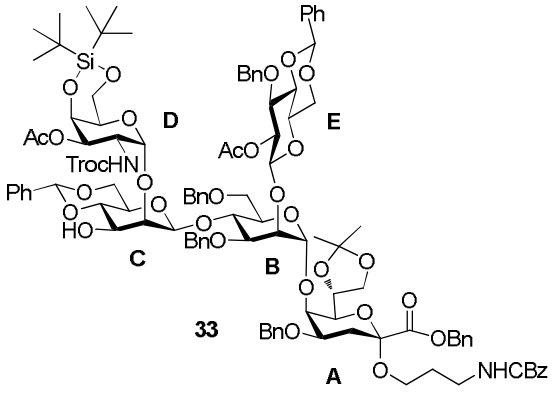
3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-α-D-galactosamine-(1→2)-4,6-di-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-α-D-mannopyranosyl-(1→5)-Benzyl [*N*-benzyloxycarbonyl-3-amino-propyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-manno-octulopyranosid] onate (31). **30** (0.35 g, 0.17 mmol) was dissolved in a mixture of EtOH (2 mL) and Toluene (1 mL) and Hydrazinium acetate (24 mg, 0.26 mmol) was added. The resulting mixture was stirred for 30 min at rt. Acetone (0.1 mL), EtOAc (15 mL) and water (5 mL) were added and the organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - Acetone in Toluene) of the residue afforded **31** (0.27 g, 78%) as a white foam. TLC: (Acetone/Toluene, 20/80 v/v): R_f = 0.20; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73-6.98 (m, 38 H, CH Ar), 6.07 (d, 1H, *J* = 9.0 Hz, N*H*), 5.51 (s, 1H, H-7-C), 5.22-5.28 (m, 2H, CH_2 Bn), 5.14 (H-1-B), 5.03-4.97 (m, 4H, CH_2 Bn, CH_2 Troc), 4.88-4.75 (m, 5H, H-1-D, 2 x CH_2 Bn), 4.63-4.32 (m, 8H, 2 x CH_2 Bn, H-3-D, H-4-D, H-2-D, H-5-D), 4.12-4.11 (m, 2H, H-1-C, H-5-A), 4.05-3.94 (m, H-2-B, H-3-B, H-7A), 3.90-3.73 (m, 11H, H-4-A, H-6-D, H-4-C, H-4-B, H-5-B, H-6-B, H-5-C, H-6-C), 3.57 (t, 1H, *J* = 10.2 Hz, H-2-C), 3.44-3.36 (m, 2H, H-8-A), 3.29-3.26 (m, 2H, C*H*H, H-6-A), 3.16-3.15 (m, 1H, H-3-C), 3.08-3.01 (m, 1H, CH*H*), 2.90-2.81 (m, CH_2 Linker, H-5-C), 2.19 (dd, 1H, *J* = 3.6 Hz, *J* = 12.6 Hz, H-3a-A), 1.96 (s, 3H, CH_3), 1.92 (t, 1H, *J* = 12.0 Hz, H-3b-A), 1.53-1.52 (m, 2H, CH_2 Linker), 1.26 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 0.98 (s, 9H, $C(CH_3)_3$), 0.89 (s, 9H, $C(CH_3)_3$); ^{13}C

NMR (125 MHz, $CDCl_3$); δ 171.2, 167.9, 156.5, 138.2, 138.0, 137.7, 137.5, 136.6, 135.2, 133.1, 129.0, 128.7, 128.6-125.3, 109.6, 101.6, 101.0, 100.8, 99.6, 99.1, 95.5, 79.5, 78.8, 77.5, 75.7, 74.3, 74.1, 73.2, 72.7, 72.7, 72.6, 72.1, 71.9, 71.5, 70.7, 70.3, 70.1, 68.9, 68.5, 67.8, 67.5, 67.4, 67.3, 67.2, 67.1, 66.5, 66.5, 61.5, 49.9, 38.2, 32.3, 29.2, 27.6, 27.3, 27.0, 25.1, 23.2, 21.0, 20.7, 20.7; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{99}H_{117}Cl_3N_2O_{27}Si$, 1921.6576; found, 1921.6520.

3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-α-D-galactosamine-(1→2)-4,6-di-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-[2-*O*-acetyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-β-D-glucopyranosyl-(1→2)]-α-D-mannopyranosyl-(1→5)-Benzyl [*N*-benzyloxycarbonyl-3-amino-propyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-manno-octulopyranosid] onate (32). To a cooled (0°C) solution of glycosyl donor **7** (0.15 g, 0.28 mmol) and glycosyl acceptor **31** (0.27 g, 0.14 mmol) in CH_2Cl_2 (3 mL) was added activated MS4Å and the resulting solution was stirred for 30 min. TfOH (4.9 uL, 0.06 mmol) was added and the resulting mixture was stirred for 10 min at 0°C. DTBMP (0.115 g, 0.56 mmol) was added and the mixture was concentrated *in vacuo*. Silica gel column chromatography (0% → 10% - Acetone in Toluene) of the residue afforded **32** (0.26 g, 82%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72-7.00 (m, 48H, CH Ar), 6.34 (d, 1H, *J* = 8.4 Hz, N*H*), 5.48 (s, 1H, H-7), 5.40 (s, 1H, H-7), 5.21 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 5.02-4.97 (m, 6H, CH*H*Ph, CH_2 Bn, H-1-B, H-2-E, H-3-D), 4.91-4.71 (m, 7H, 2 x CH_2 Bn, CH_2 Troc, H-1-D), 4.62-4.13 (m, 8H, 3 x CH_2 Bn, H-4-D, H-2-D), 4.20-4.15 (m, 2H, H-1-C, H-1-E), 4.04-3.99 (m, 5H, H-3-B, H-4-B, H-5-B, H-7-A, H-5-A), 3.92-3.66 (m, 13H, H-2-B, H-5-D, H-3-C, H-8-A, H-6a-C, H-6-B, H-5-E, H-6-E, H-6-A), 3.58-3.47 (m, H, H-6b-C, H-4-C, H-4-A, H-4-E), 3.45 (t, 1H, *J* = 9.0 Hz, H-3-E), 3.25-3.19 (m, 4H, H-2-C, H-3-C, C*H*H, H-6a-D), 3.06-2.98 (m, 4H, CH_2 Linker, H-6b-

D, CH*H*), 2.84-2.80 (m, 1H, H-5-C), 2.10 (dd, 1H, *J* = 4.2 Hz, *J* = 12.6 Hz, H-3a-A), 1.97 (s, 3H, CH_3), 1.86-1.83 (m, 4H, CH_3, H-3b-A), 1.22 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.94 (s, 9H, $C(CH_3)_3$), 0.87 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$); δ 171.2, 168.8, 167.8, 156.3, 154.6, 138.5, 138.2, 138.1, 138.0, 137.5, 137.1, 136.6, 135.0, 133.1, 133.0, 129.0, 128.9, 128.6-125.5, 109.5, 101.5, 101.3, 101.1, 99.1, 98.0, 81.1, 79.7, 79.4, 77.7, 75.8, 74.4, 74.3, 74.3, 73.0, 72.7, 72.5, 72.2, 71.9, 71.7, 71.3, 68.5, 68.4, 67.8, 67.5, 67.3, 67.1, 66.8, 66.5, 61.5, 50.1, 38.2, 33.4, 32.5, 31.9, 29.6, 29.6, 29.5, 29.3, 36.9, 25.3, 23.2, 23.1, 22.6, 21.0, 20.7, 20.6, 17.8, 14.1; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{121}H_{139}Cl_3N_2O_{33}Si$, 2303.7992; found, 2303.7975.

3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-α-D-galactosamine-(1→2)-4,6-di-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-[2-*O*-acetyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-β-D-glucopyranosyl-(1→2)]-α-D-mannopyranosyl-(1→5)-Benzyl [*N*-benzyloxycarbonyl-3-amino-propyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-manno-octulopyranosid] onate (33).



DDQ (41 mg, 0.18 mmol) was added to a vigorously stirred emulsion of **32** (0.26 g, 0.12 mmol) in DCM (2 mL) and water (0.2 mL). The resulting emulsion was stirred for 3 hrs before the mixture was diluted with CH_2Cl_2 (5 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*. Silica gel column chromatography (0% → 20% - EtOAc in Toluene) afforded **22** (195 mg, 76 %); ^1H NMR (600 MHz, $CDCl_3$); δ 7.40-7.13 (m, 40H, CH Ar), 5.99 (d, 1H, *J* = 9.0 Hz, N*H*), 5.41 (s, 2H, 2 x H-7), 5.24 (d, 1H, *J* = 12.0 Hz, C*H*H), 5.04-4.95 (m, 5H, H-1-B, H-2-E, CH*H*, CH_2 Bn), 4.88-4.86 (m, 2H, H-3-D, C*H*H), 4.64-4.20 (m, 9H, CH*H*, CH_2 Troc, 3 x CH_2 Bn), 4.36-4.28 (m, 4H, H-4-D, H-1-C, H-1-E, H-2-D), 4.06-3.69 (m, 19H, H-4-C, H-

5-D, H-2-B, H-4-A, H-6a-C, H-6-A, H-6-B, H-6-E, H-6-D, H-5-A, H-4-E, H-7-A, H-4-B, H-5-B, H-5-E), 3.56-3.34 (m, 6H, H-6b-C, H-3-C, H-3-E, H-2-C, H-2-B, H-3-B), 3.24-3.22 (m, 2H, C*H*H Linker, H-8a-A), 3.07-3.02 (m, 4H, C*H*H Linker, H-8b-A, CH_2 Linker), 2.93-2.87 (m, 2H, H-5-C, H-8b-A), 2.14 (dd, 1H, *J* = 3.6 Hz, *J* = 12.6 Hz, H-3a-A), 2.00 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 1.90-1.85 (m, 1H, H-3b-A), 1.58-1.52 (m, 2H, CH_2 Linker), 1.25 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 0.94 (s, 9H, $C(CH_3)_3$), 0.87 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.9, 167.8, 156.3, 154.6, 138.7, 138.2, 138.1, 137.9, 137.1, 136.6, 135.1, 129.2-125.9, 109.5, 102.0, 101.3, 101.1, 101.0, 100.8, 99.1, 78.0, 95.7, 81.1, 78.9, 77.7, 76.4, 76.0, 75.7, 74.4, 74.3, 73.4, 73.1, 72.8, 72.1, 71.9, 71.8, 71.5, 71.5, 70.8, 70.5, 60.3, 68.5, 68.4, 68.4, 67.8, 67.3, 67.1, 66.6, 66.5, 61.5, 49.8, 38.2, 32.5, 29.6, 29.3, 27.6, 27.3, 26.9, 25.4, 23.2, 21.0, 20.7, 20.6; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{110}H_{131}Cl_3N_2O_{33}Si$, 2163.7366; found, 2163.7312.

3-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethyloxycarbonyl)-amino-4,6-*O*-(di-*tert*-butylsilanediyl)-α-D-galactosamine-(1→2)-4,6-di-*O*-benzylidene-3-*O*-[2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→3)]-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-[2-*O*-acetyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-β-D-glucopyranosyl-(1→2)]-α-D-mannopyranosyl-(1→5)-Benzyl [*N*-benzyloxycarbonyl-3-amino-propyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-manno-octulopyranosid] onate (34). To a cooled (-30°C) solution of glycosyl donor **5** (127 mg, 0.18 mmol) and glycosyl acceptor **33** (195 mg, 0.09 mmol) in Et_2O (3 mL) was added activated MS4Å and the resulting solution was stirred for 30 min. TfOH (3.1 uL, 0.03 mmol) was added and the resulting mixture was stirred for 10 min at -30°C. DTBMP (74 mg, 0.36 mmol) was added and the mixture was concentrated *in vacuo*. Silica gel column chromatography (0% → 20% - EtOAc in Toluene) of the residue afforded **34** (175 mg, 73%); ^1H NMR (600 MHz, $CDCl_3$) δ 7.44-6.72 (m, 60H, CH Ar), 5.45 (s, 1H, H-7), 5.41 (s, 2H,

H-7, H-1-F), 5.28 (m, 2H, C*H*HPh, H-1-D), 5.07-4.26 (m, 21H, 9 x CH_2 Bn, CH_2 Troc, CH*H*Ph), 4.41-4.35 (m, 4H, H-1-C, H-1-E, H-2-D, H-4-D), 4.17-3.18 (m, 31H, H-4-A, H-5-A, H-6-A, H-7-A, H-8-A, H-2-B, H-3-B, H-4-B, H-5-B, H-6-B, H-2-C, H-3-C, H-4-C, H-6-C, H-5-D, H-6-D, H-3-E, H-4-E, H-5-E, H-6-E, H-2-F, H-3-F, H-4-F, H-5-F, H-6-F), 3.11-3.05 (m, 4H, 2 x CH_2 Linker), 2.80-2.76 (m, 1H, H-5-C), 2.16-2.13 (m, 1H, H-3a-A), 1.97 (s, 3H, CH_3), 1.91-1.85 (m, 4H, CH_3, H-3b-A), 1.58-1.55 (m, 2H, CH_2 Linker), 1.29 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 0.92 (s, 9H, $C(CH_3)_3$), 0.89 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 168.7, 167.7, 156.2, 154.3, 139.1, 138.5, 138.1, 137.9, 137.8, 137.7, 137.3, 137.1, 136.6, 135.0, 129.3-125.9, 109.5, 102.4, 101.1, 100.0, 99.0, 98.4, 98.1, 97.2, 81.5, 81.0, 79.3, 78.1, 77.7, 76.1, 75.5, 75.3, 74.8, 74.4, 74.0, 73.4, 73.4, 73.1, 72.7, 71.6, 71.5, 71.3, 70.5, 70.2, 68.5, 68.5, 68.2, 67.8, 67.3, 67.2, 67.0, 66.9, 66.5, 61.6, 49.0, 38.2, 32.7, 29.6, 29.2, 27.5, 27.3, 27.2, 26.8, 25.2, 23.2, 20.9, 20.6; HR-MALDI-TOF/MS (*m/z*): $[M+Na]^+$ cacld for $C_{144}H_{165}Cl_3N_2O_{38}Si$, 2685.8772; found, 2685.8754.

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CHAPTER 6

CONCLUSIONS

We demonstrated that protecting groups and the chemical nature of the sulfonium ion can have a profound influence on the stereochemical outcome of glycosylations and it has been found that by disfavoring oxacarbenium ion formation by electronic or stereoelectronic effects, exclusive α-anomeric selectivity can be accomplished. These observations can be used as a guide to select glycosyl donors that are expected to give exclusive 1,2-*cis* stereoselectivity and be employed for further improvement of chiral auxiliary mediated glycosylation methodology.

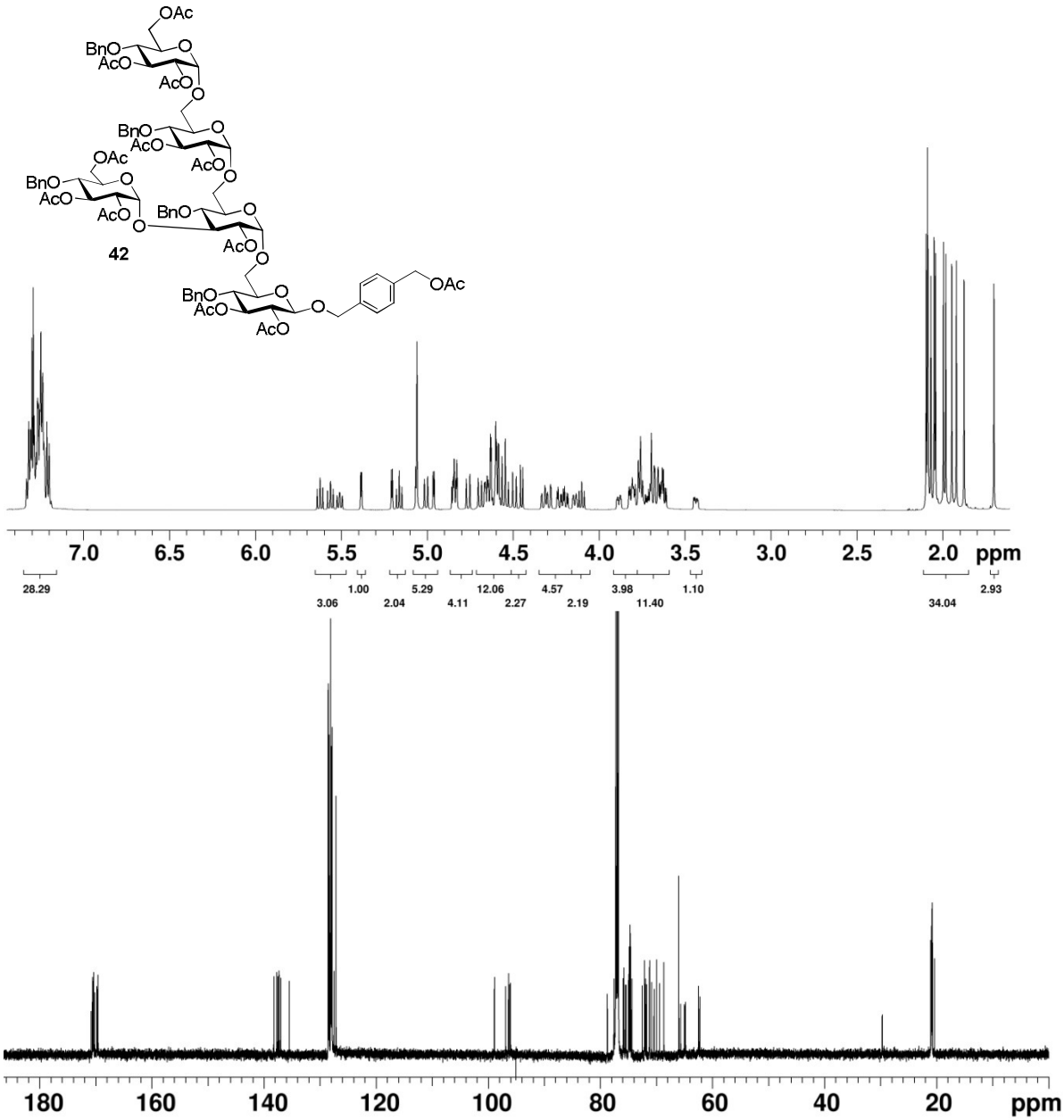
Furthermore, glycosyl donors having an (*S*)-(phenylthiomethyl) benzyl chiral auxiliary at C-2 have been successfully used for the solid supported synthesis of complex branched oligosaccharides. To our knowledge, this is the first example of a stereoselective solid-supported synthesis of an oligosaccharide having multiple 1,2-*cis*-glycosidic linkages. A particularly interesting feature was that a relatively small excess of glycosyl donor was required to drive the glycosylations to completion. It is likely that the intermediate sulfonium ion is sufficiently stable to diffuse into the polymer support for glycosylation of the resin-bound sugar hydroxyls. Furthermore, it has been found that Fmoc and Alloc form an attractive set of orthogonal protecting groups for solid supported synthesis, compatible with the auxiliary-based glycosylation methodology. Deprotection of the fully assembled oligosaccharide could partially be performed when still attached to the resin, thereby further reducing the number of purification steps. The convenient protection of monosaccharides by a one-pot multi-step approach, combined with classical and auxiliarymediated neighbouring group participation for controlling anomeric selectivity, is bringing the fulfillment of routine automated solid supported oligosaccharide synthesis closer. Such an approach could provide the libraries of well-defined oligosaccharides needed for glycomics research.

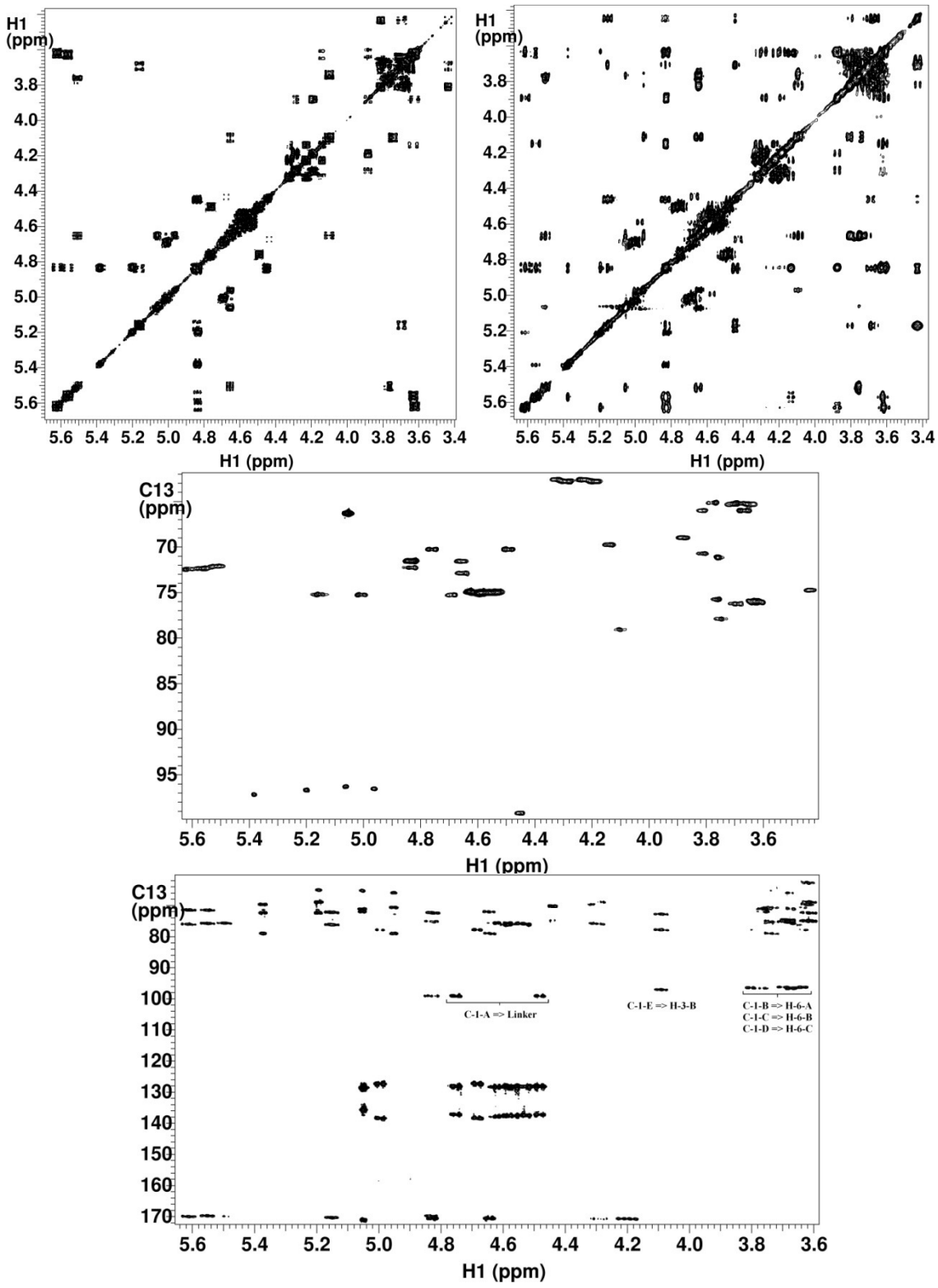
The inner core LPS hexasaccharide of *Francisella tularensis* was prepared using a flexible strategy that can easily enable the synthesis of truncated derivatives. Key to this approach was a β-D-Man-(1→4)-D-Man disaccharide, modified with four orthogonal protecting groups, the DEIPS, 2-methynaphthyl, and allyl ether and a levulinyl ester. The order of introduction and nature of the glycosyl donors was found to be critical in glycosylation of the β-mannoside. Further, sequential deprotection and glycosylation followed by global deprotection afforded the native hexasaccharide. Comparison of the ^{1}H NMR spectra of isolated material and the synthetic derivative confirmed that the reported structural assignment of the isolated LPS fragment is correct and that the synthetic analogue is of the right composition. A selective modification of the aminopropyl linker with biotin or KLH-protein was achieved.

APPENDIX A

SUPPLEMENTARY DATA CHAPTER 3

^{1}H and ^{13}C NMR and HPLC Data

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H1 (ppm)
H1 (ppm)
H1 (ppm)
C13 (ppm)
H1 (ppm)
C13 (ppm)
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C-1-B => H-6-A
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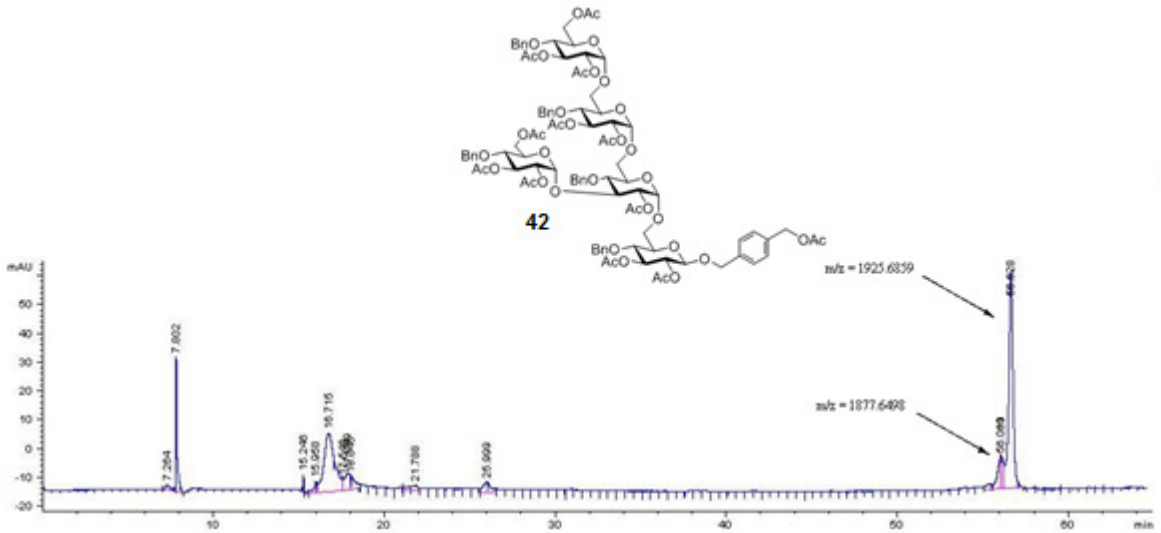
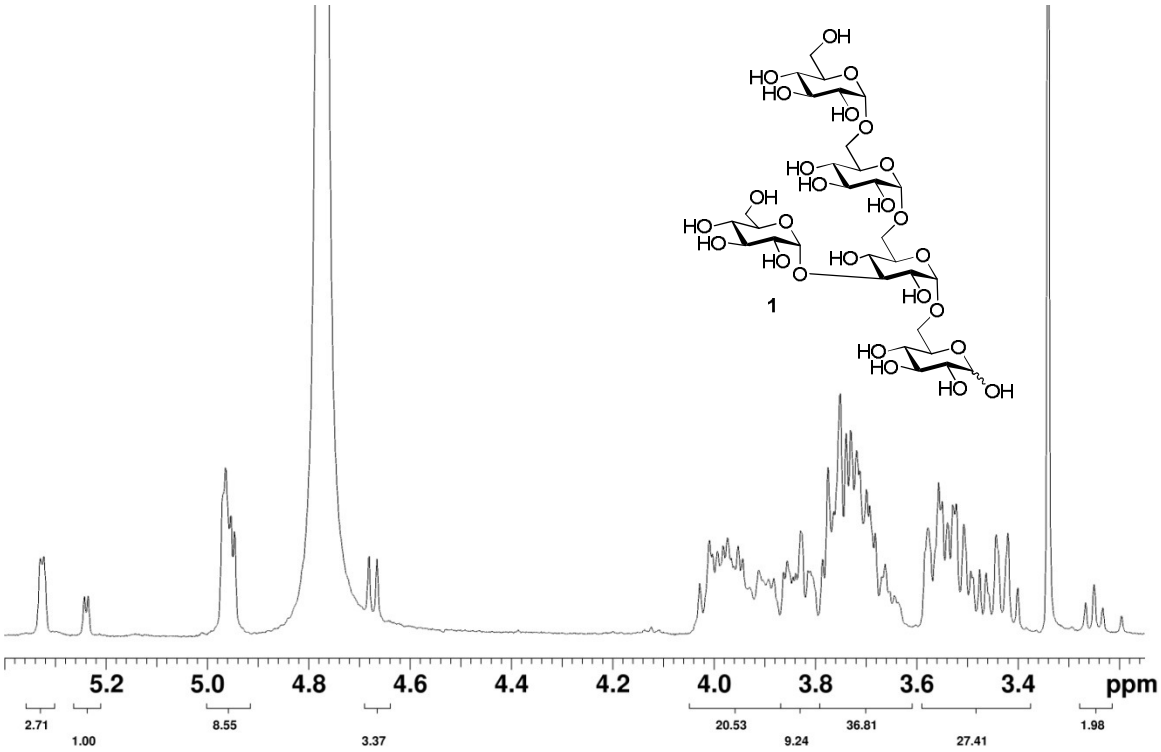
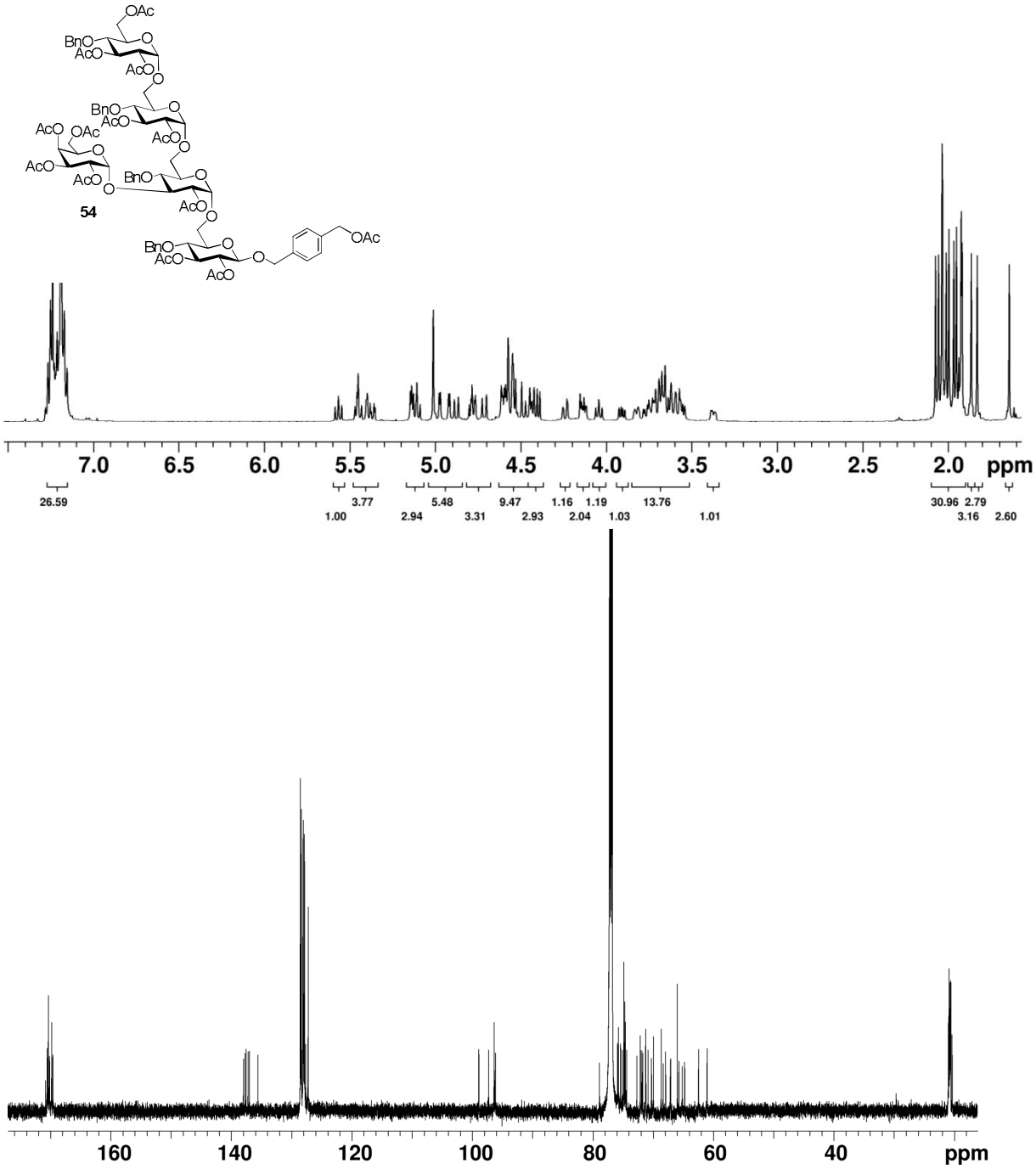
C-1-D => H-6-C
H1 (ppm)



HPLC trace of compound **42** after LH-20 size exclusion chromatography.

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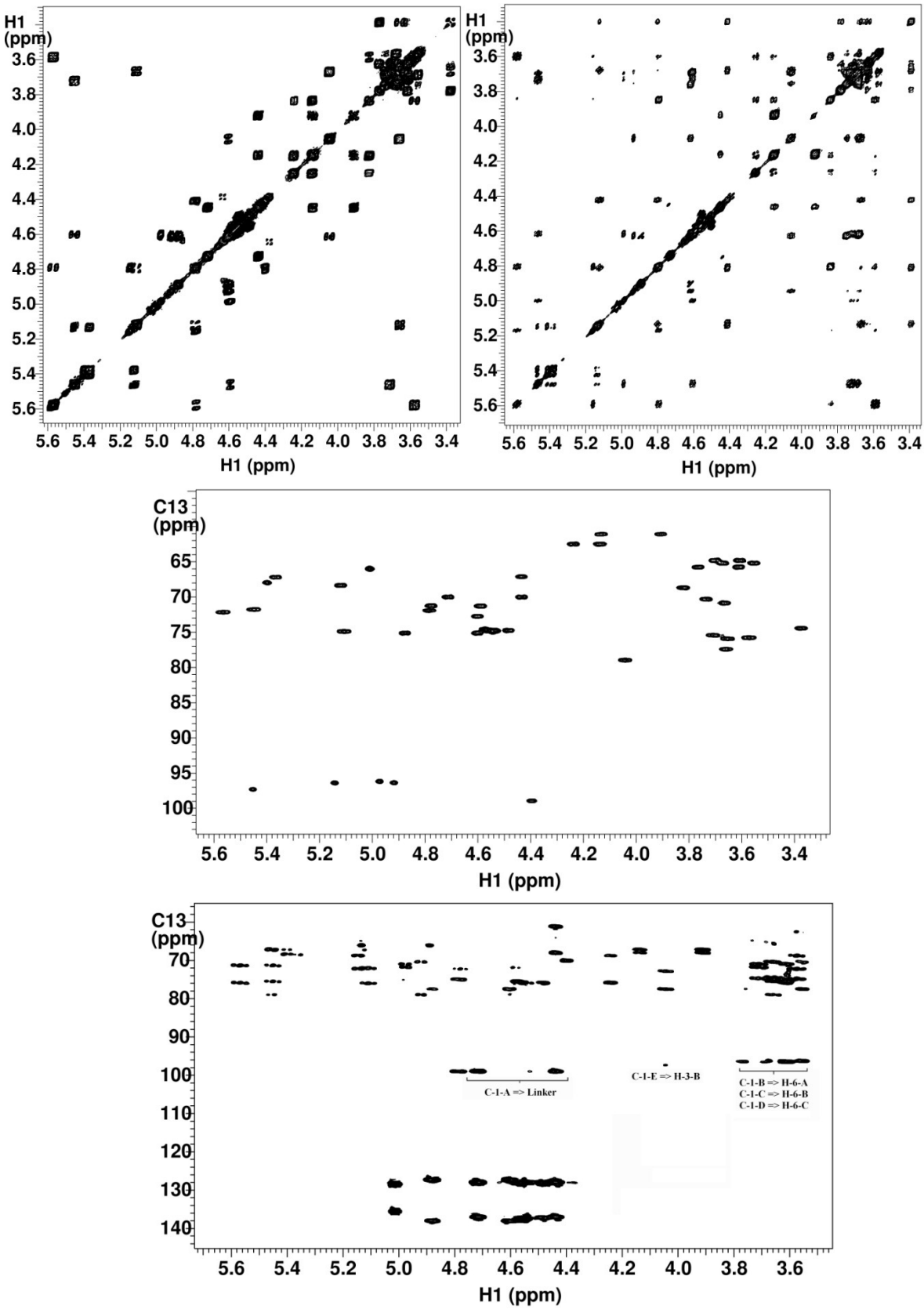
H1 (ppm)
H1 (ppm)
C13 (ppm)
H1 (ppm)
C13 (ppm)
C-1-A => Linker
C-1-E => H-3-B
C-1-B => H-6-A
C-1-C => H-6-B
C-1-D => H-6-C
H1 (ppm)