METHODOLOGICAL AND MECHANISTIC STUDIES OF CHIRAL AUXILIARY ASSISTED STEREOSELECTIVE GLYCOSYLATIONS AND THE DEVELOPMENT OF GLYCOCONJUGATE VACCINES FOR α-DYSTROGLYCAN

by

TAO FANG

(Under the Direction of Geert-Jan Boons)

ABSTRACT

Oxathiane ethers have been developed as stable, versatile and easily accessible precursors for sulfonium ion mediated 1,2-*cis*-stereoselective glycosylations. The preparation of glycosyl 1,2-oxathiane ethers starts from the regioselective intramolecular cyclization and stereoselective reduction of 1-thio-β-D-glucopyranosyl acetophenone in a one-pot fashion. Due to the stability of oxathiane ether under acidic, basic and reductive conditions, orthogonally protected donors can be prepared efficiently. Subsequent sulfoxidation, triflation and nucleophilic aromatic substitution by trimethoxylbenzene generate β-sulfonium ions. The S_N2 displacement of β-sulfonium ion by various *O*-nucleophiles resulted excellent to exclusive 1,2-*cis*-stereoselectivity. The utility of this methodology was further tested for the stereoselective assembly of a branched α-glucan derived from *P. Boydii* with immune activation properties.

The mechanism of β-sulfonium ion mediated glycosylations was systemically surveyed by modulating the nucleophilicity of neighboring participating moieties on

chiral auxiliaries or by reversing the chirality of auxiliaries. Results suggested strong dependence of stereoselectivity on the participation and the chirality of the auxiliary. Further computational studies found that there is a shift from S_N2-like to S_N1-like reaction pathway by reversing the chirality of auxiliaries from (*S*) to (*R*). This observation solved the previous puzzle for the inferior *trans*-stereoselectivity after reversing the chirality of auxiliaries.

The stereoselective glycosylation was further pursued for the synthesis of a α-dystroglycan tetrasaccharide SiaAα(2-3)Galβ(1-4)GlcNAcβ(1-2)Manα-threonine and its truncated library with implication in the pathology of muscular dystrophy. The resulted glycosylated amino acids were either incorporated into fully synthetic tripartite vaccines or conjugated to various carrier proteins for eliciting the immune response in mice. Abundant antibodies against synthetic carbohydrate epitopes have been detected. Further characterization and production of monoclonal antibodies are currently ongoing.

INDEX WORDS: Glycosylation, Chiral Auxiliary, Oxathiane, Sulfonium Ion, Stereoselectivity, Mechanism, Vaccine, Dystroglycan, Glycoconjugate

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DEDICATION

To my family for their unconditional love and support.

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LIST OF ABBREVIATIONS

Aβ ..... Amyloid-β
Ac ..... Acetyl
AD ..... Alzheimer's Disease
ADCC ..... Antibody-Dependent Cell-Mediated Cytotoxicity
Ac_2O ..... Acetic Anhydride
AcOH ..... Acetic Acid
Alloc ..... Allyloxycarbonyl
APP ..... Amyloid Precursor Protein
ATIII ..... Antithrombin III
BACE ..... β-site APP-Cleaving Enzyme
BCR ..... B-Cell Receptor
BF_3-Et_2O ..... Boron Trifluoride Diethyl Etherate
Bn ..... Benzyl
BnBr ..... Benzyl Bromide
BSA ..... Bovine Serum Albumin
Bz ..... Benzoyl
cBSA ..... cationized Bovine Serum Albumin
CIP ..... Contact Ion Pair
CMD ..... Congenital Muscular Dystrophy
COSY ..... Correlation Spectroscopy
CS ..... Chondroitin Sulfate
CSA ..... Camphorsulfonic Acid
CSPG ..... Chondroitin Sulfate Proteoglycan
CTL ..... Cytotoxic T Lymphocyte
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
DTT ..... Dithiothreitol
DFT ..... Density Functional Theory
DHB ..... 2,5-Dihydroxybenzoic Acid
DIC ..... *N,N*'-Diisopropylcarbodiimide
DIPEA ..... Diisopropylethylamine
DMAP ..... 4-*N,N*'-Dimethylaminopyridine
DMDO ..... Dimethyldioxirane
DMF ..... *N,N*'-Dimetylformamide
DTBMP 2,6-Di-*tert*-Butyl-4-Methyl-Pyridine
ECM ..... Extracellular Matrix
ER ..... Endoplasmic Reticulum
F6P ..... Fructose 6-Phosphate
FBP ..... Fructose 1,6-bisphosphate
Fmoc 9-Fluorenylmethyloxycarbonyl

FmocCl 9-Fluorenylmethylchloroformate
FUT ..... Fucosyltransferase
GAG ..... Glycosaminoglycan
Gal ..... Galactose
Glc ..... Glucose
GSH ..... Reduced glutathione
GSSG ..... Oxidized glutathione
HA ..... Hemagglutinin
HIV ..... Human Immunodeficiency Virus
HMBC ..... Heteronuclear Multiple Bond Correlation Spectroscopy
HS ..... Heparin Sulfate
HSPG ..... Heprin Sulfate Proteoglycan
HSQC ..... Heteronuclear Single Quantum Coherence Spectroscopy
KDO ..... 3-Deoxy-D-Manno-Octulosonic Acid
KHMDS ..... Potassium bis(trimethylsilyl)amide
KIE ..... Kinetic Isotope Effect
KLH ..... Keyhole Limpet Hemocyanin
KS ..... Keratan Sulfate
Lev ..... Levulinyl
LG ..... Leaving group
LGMD ..... Limb-Girdle muscular dystrophy
LPS ..... Lipopolysaccharide
LSD ..... Liposome storage disease
MAB ..... Monoclonal Antibody
MALDI-TOF ..... Matrix Assisted Laser Desorption Ionization Time-Of-Flight
Man ..... Mannose
*m*CPBA ..... *meta*-Chloroperbenzoic Acid
Me ..... Methyl
MHC ..... Major Histocompatibility Complex
MS ..... Molecular Sieves
NADPH ..... Nicotinamide Adenine Dinucleotide Phosphate
NA ..... Neuraminidase
Nap 2-Methylnaphthyl
NBO ..... Natural Bond Order
Neu5Ac ..... *N*-Acetylneuraminic Acid
NIS ..... *N*-Iodosuccinimide
NMR ..... Nuclear Magnetic Resonance
NPC ..... Niemann–Pick disease type C
OMe ..... Methoxy
OGA ..... *O*-GlcNAcase
OGT ..... *O*-GlcNActransferase
PBS ..... Phosphate Buffered Saline
PFK ..... Phosphofructokinase
POMT ..... Protein *O*-Mannosyl Transferase
PTM ..... Post-Translational Modification
Ph ..... Phenyl
Pse ..... Pseudaminic acid
PTP ..... Protein tyrosine phosphatases
Py ..... Pyridine
R5P Ribose-5-Phosphate
Sia ..... Sialic acid

SSIP ..... Solvent Separated Ion Pair
TACA ..... Tumor-Associated Carbohydrate Antigen
TBAF ..... Tetrabutyl Ammonium Fluoride
TDS ..... dimethyl (1,1,2-trimethylpropyl) silyl
TCA ..... Trichloroacetonitrile
TCEP ..... Tris(2-carboxyethyl)phosphine hydrochloride
TEA ..... Triethylamine
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
TMSOTf ..... Trimethylsilyl Trifluoromethanesulfonate
TMP 2,4,6-Tri-Methoxylphenyl
TOCSY ..... Total Correlation Spectroscopy
Troc 2,2,2-Trichloroethyloxycarbonyl
TS ..... Transition State
SSEA ..... Stage-Specific Embryonic Antigen

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

More than a century ago, the pioneering work of Emil Fisher on determining the stereochemistry of carbohydrates[1] opened an era of wonders and challenges for scientists that even today our knowledge of their biological functions and synthetic manipulations is still in its infancy.[2] But, as one of the four essential life molecules, every step into the unknown world of carbohydrates rewards us with unprecedented understanding of ourselves.[3] This chapter contains a literature overview, in which we will first focus on the current discoveries of the role of carbohydrates in disease pathologies. Then, we will evaluate the potential of carbohydrates and their derivatives as therapeutics. Finally, we will briefly review the synthetic carbohydrate chemistry, with emphasis on the stereocontrol by quasi-stable anomeric intermediates, in accessing these forbidding molecules.

CARBOHYDRATES AS CANCER BIOMARKERS

Carbohydrates are the most abundant protein post-translational modifications (PTMs). It is estimated that more than 50% of the mammalian proteins are modified by carbohydrates. Depending on the glycosidic linkage, PTMs by carbohydrates can be divided into two types: *N*-glycans and *O*-glycans. *N*-glycans are attached to an asparagine side-chain with an underlining sequence of Asn-X-Ser/Thr (where X is any AA except Pro) through an amide linkage in the endoplasmic reticulum. Unlike *N*-glycans, which start from a common dolichol-linked core 14-mer and are transferred *en bloc* to an

asparagine residue for further processing in the Golgi apparatus,[4] *O*-glycans are often attached to the γ-hydroxyl group of Ser/Thr through a variety of core structures (e.g., *O*-GalNAc, *O*-GlcNAc, *O*-Fuc, *O*-Man, etc) and then extended by glycotransferases without consensus sequence.[5]

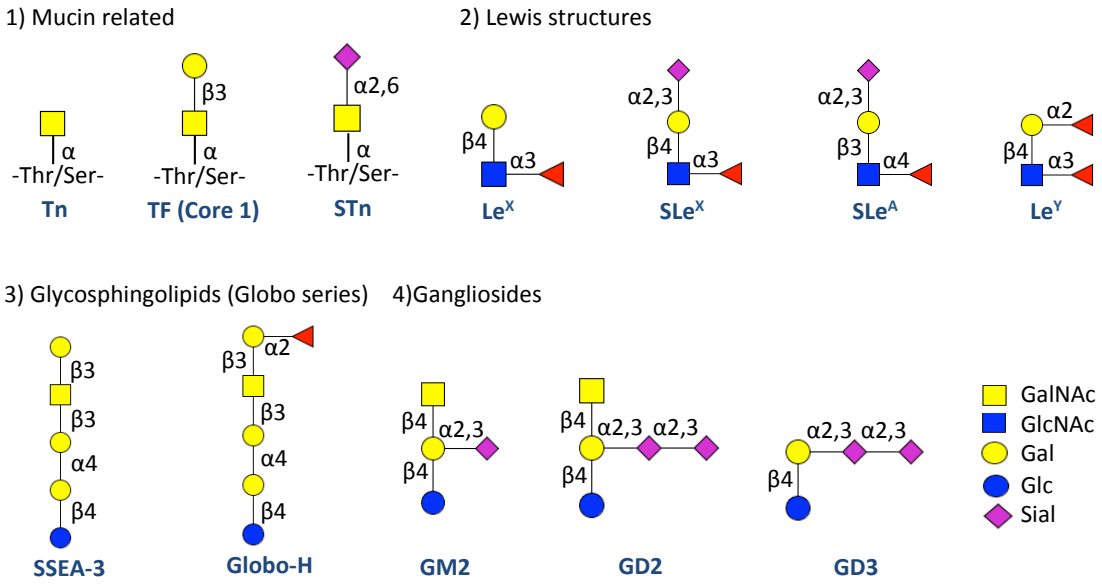

Figure 1.1: Tumor-associated carbohydrate antigens.

Under normal physiological conditions, *O*-glycans in vertebrates are biosynthetically extended beyond Galβ1-3GalNAc- Ser/Thr (Core 1) in all cell types or GlcNAcβ1-3GalNAc- Ser/Thr (Core 3) in the GI track.[3] In pathological situations, however, these complex *O*-glycans are often truncated, resulting in a simple *O*-glycan GalNAc-α-Ser/Thr known as the Tn antigen. The Tn antigen has been found in abundance on 70~90% carcinomas, but no or little expression has been detected in normal adult tissue. A single mutation (G301T) or epigenetic silencing of *Cosmc*, a molecular chaperone preventing the aggregation and subsequent proteasome aggregation of T-synthase, has been

suggested as the molecular basis for the elevated expression of the Tn antigen.[6,7] Although utilization of the Tn antigen is impeded by the dysfunctional T-synthase, ppGlcNAcT[8] and ST6GalNAc[9] also act on the Tn antigen as a substrate, and the outcome of product depends on the competition between these two enzymes. Studies have demonstrated that ppGlcNAcT is down regulated in colon cancer but ST6GalNAc is not, so the alleviated level of STn may correlate with oncogenic transformation.[10] Recent studies from Bertozzi's group further demonstrated that overexpression of the sialylic acid epitope on cancer cell surface is not simply the outcome of oncogenic transformation, but actively benefits the tumor cell growth by suppressing the immune surveillance of NK cells through Siglec-7.[11]

Thomsen-Friedenriech (TF, or T) antigen represents another important mucin related cancer biomarker because of its pancarcinoma expression and roles in mediating cell adhesion and thus cancer metastasis.[12] The reason for overexpression of the TF antigen is multifaceted and could be attributed to increased production levels of the sugar nucleotide Gal-UDP and abnormal glycotransferase activities beyond the synthesis of the Tn epitope. including elevated T-synthase activity or decreased activity of subsequent enzymes. However, there does not appear to be increases in the amount of T-synthase in cancer cells, so the cause of the TF antigen overexpression could be attributed to the malfunction of subsequent enzymes resulting the accumulation of the Tn antigen as the substrate for T-synthase. Newly synthesized TF antigen could also remain unmodified due to decreased subsequent glycosylations. The more acidic Golgi environment of cancer cells may be responsible for this inhibition of enzymes.

Glycosphingolipids and gangliosides are another set of carbohydrate cancer biomarkers widely found on eukaryotic cell membranes.[13] They are glycolconjugates covalently bound to lipid ceramide and clustered on the cell membrane lipid raft. Presumably, the most well known glycosphingolipid is Globo-H hexasaccharide.[14] It was first isolated from human MCF-7 breast cancer cell line,[15,16] and was then further recognized on small-cell lung, prostate, pancreas, gastric ovarian and endometrial carcinomas by using anti-Globo-H monoclonal antibody MBr1.[15,17] Interestingly, Globo-H was also found on normal tissues, but only on apical surfaces, generally considered inaccessible to immune cells, making Globo-H an attractive target for cancer immune therapy.[18]

α-(1,2)-Fucosyltransferase is involved in the biosynthesis of Globo-H at the last stage. It transfers the fucose to stage-specific embryonic antigen-3 (SSEA-3), which is a pentasaccharide that exists on both normal and cancerous cells and lacks the fucose at its non-reducing end. Healthy people possess a strong antibody response to SSEA-3 making it an unsuitable target for cancer immune therapy. Two genes FUT1 and FUT2 have been identified as responsible for α-(1,2)-fucosyltransferase activities, and their activities are cell-line dependent. Studies in breast cancer cell lines MCF-7 and MB-157 have revealed that the FUT2 expression is negligible, suggesting FUT1 is responsible for the synthesis of Globo-H. In another breast cancer cell line, T47D, however, FUT2 was unregulated and confirmed by siRNA silencing of FUT2.[19]

Protein *O*-GlcNAcylation, the covalent attachment of GlcNAc to the γ-hydroxyl group of Ser/Thr, is a unique type of PTM first discovered by Hart in the early 1980s.[20] Compared to other carbohydrate PTMs, it is a dynamic and reversible process mediated

by the *O*-GlcNActransferase OGT and the hydrolysase OGA.[21,22] Unlike other glycotransferases, OGT is pansubstrate selective and responsible for all *O*-GlcNAcylation, which occurs almost exclusively in the cytosolic and nuclear. Significantly, *O*-GlcNAc modification is generally not extended to other complex glycans.

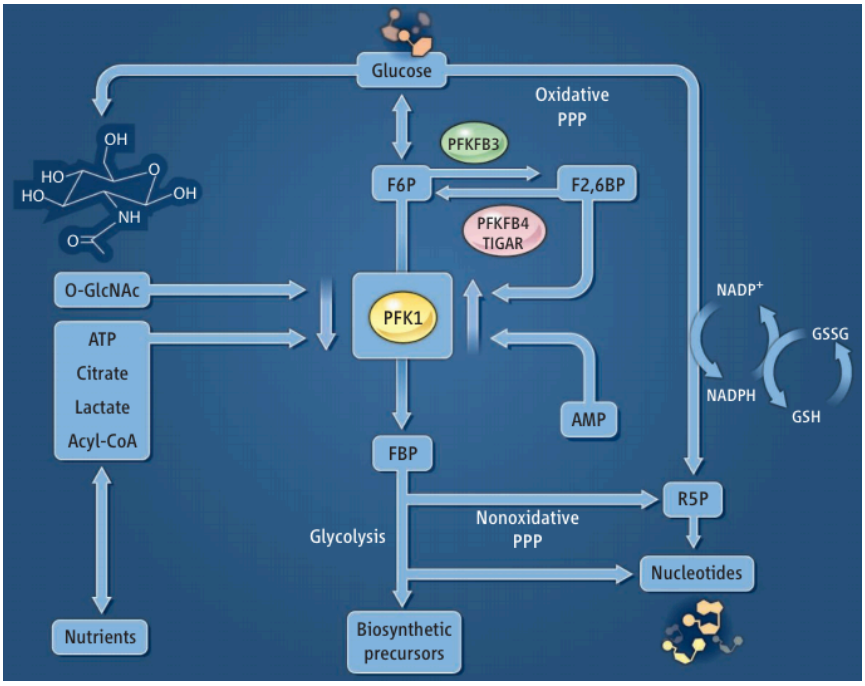

Figure 1.2: Converging on PFK1. PFK1 catalyzes the formation of FBP from F6P in glycolysis. Decreased PFK1 activity diverts glucose carbon from glycolysis and downstream biosynthetic pathways to the oxidative pentose phosphate pathway (PPP). This allows production of NADPH to maintain reduced glutathione pools (GSH) and allows cells to counteract oxidative stress. R5P, ribose-5-phosphate; GSH/GSSG, reduced/oxidized glutathione.[23]

O-GlcNAcylation is expected to be as abundant as Ser/Thr phosphorylation, and extensive crosstalk exists between them.[24] It allows cells to link nutrient availability and

cellular metabolism to other critical processes such as cell cycle regulation, stress response and gene expression. No cancer has yet been identified as being caused by the mutation of either OGT or OGA, probably because of the lethality of such mutations. But subtle changes in *O*-GlcNAcylation patterns have been linked to cancer oncology. Recent studies[25] from Hsieh-Wilson's team found *O*-GlcNAcylation of PFK1 was increased in cells exposed to hypoxia and several human tumors cell lines, but not detected in rapidly proliferating normal cells. By employing chemoenzymatic labeling, computational and functional studies, they revealed that metabolic enzyme phosphofructokinase 1 (PFK1) is inhibited by blocking a binding site of an allosteric activator through the *O*-GlcNAcylation of a serine residue. This results in the rerouting of metabolic flux from the glycolytic pathway to the oxidative pentose phosphate pathway providing essential metabolites for DNA synthesis and protection from oxidative stress (Figure 1.2). This work highlights a new regulatory mechanism in glycolysis with important implications for cancer treatment.

In conclusion, overwhelming evidence has suggested that the aberrant glycosylation is a hallmark of cancer cells that reflects their gene mutations or changes in their micro- and macro-cellular environment. Therefore, tumor-associated carbohydrate antigens (TACAs) have become an attractive target for cancer diagnosis and immune therapy.

O-MAN GLYCAN AND DYSTROPHY

The diversity of protein *O*-glycosylations is implicating their multiple roles in various normal and pathological processes. Protein *O*-mannosylation is emerging as an attractive target closely related to certain types of viral infections,[26] cancer metastases[27] and more

importantly, the congenital muscular dystrophy (CMD)[28]. Unlike most of the *O*-glycans, the expression *O*-Man glycan is more tissue specific with preference for neural and muscular tissues. Although *N*- and mucin type *O*-glycans both exist on these tissues, studies have suggested that the *O*-Man initiated glycans are the binding moieties of the extracellular matrix (ECM) and are responsible for maintaining the integrity of the integrin-mediated cytoskeleton-ECM complex. The malfunction of enzymes in the protein *O*-mannosylation pathway results in dystroglycanopathies (Figure 1.3). [29]

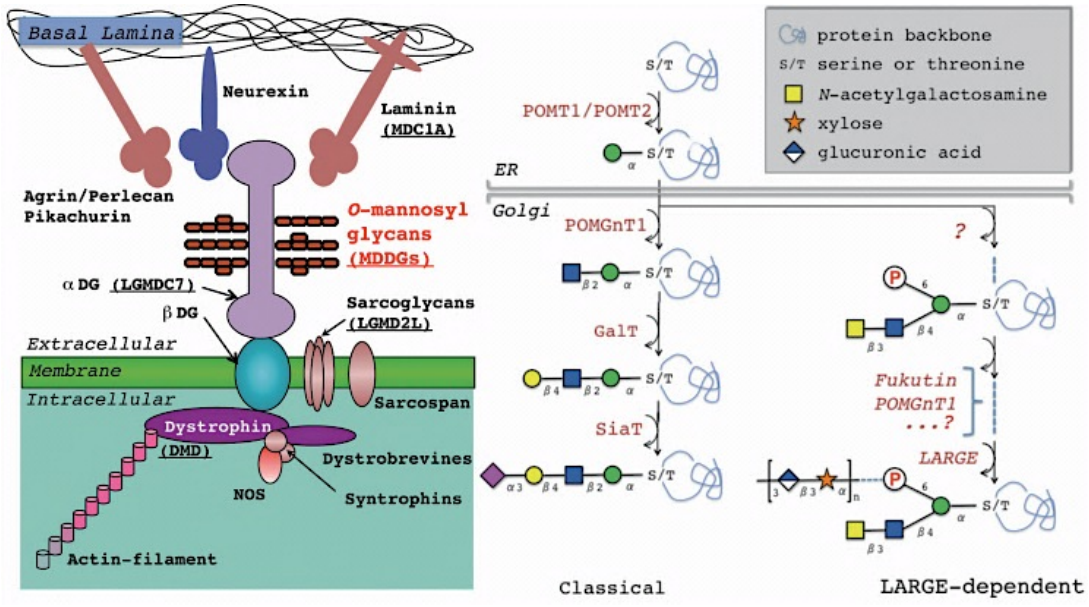

Figure 1.3: Dystrophin glycoprotein complex (DGC) and representative structure of *O*-mannosyl glycans of α-DG.[31]

Dystroglycanopathies range in severity from Walker-Warburg syndrome (WWS), which progresses aggressively, casuing muscle weakness, atrophy and death, usually before age 3, to less severe forms such as Limb-Girdle Muscular Dystrophy (LGMD), which usually involves later onset and no cognitive impairment. In the majority of

patients, it is still difficult to diagnosis the causative genes from clinical phenotypes due to the fact that these disorders are not caused by gene mutations of dystroglycan itself but rather by the posttranscriptional glycosylation of the protein.[30]

Recent results have shown delightful progresses toward identification of the functional glycosyl determinants of dystroglycans. The first and most abundant *O*-Man glycan separated was NeuAcα(2-3)-Galβ(1-4)-GlcNAcβ(1-2)-Manα1-Ser/Thr from bovine peripheral nerve tissue.[32] Controversies still surround the function of this *O*-Man tetrasaccharide, but convincing evidence has suggested the critical role in ECM binding activity of a unique and less abundant *O*-Man trisaccharide, GalNAc-β(1-3)-GlcNAc-β(1-4)-Man α1-Thr, which bears a phosphodiester at the C-6 position of mannose with extension of an unknown moiety.[30,33] Further studies have revealed that the bifunctional glycosyltransferase-like protein LARGE is the corresponding enzyme for introducing the disaccharide repeating unit [-3-Xyl-α(1-3)-GlcUA-β1-] through the rare phosphodiester linkage.[34] Extension at different length serves as a tunable ECM protein scaffold with clear correlation between glycosylation status and phenotype.[35]

CARBOHYDRATES IN NEURODEGENERATIVE DISEASES

Due to the significant increasing in anticipated human life span, senile diseases are no longer neglectable health threats. Alzheimer's disease is the most common form of senile dementia. Although there is currently no effective treatment for these diseases and the etiologies are still not fully illustrated, accumulating results have suggested the crucial roles of glycosylaminoglycans (GAGs) in the formation, aggregation, and proteolysis

resistance of the amyloid fibers that directly cause the damage of brain and nerve system.[36]

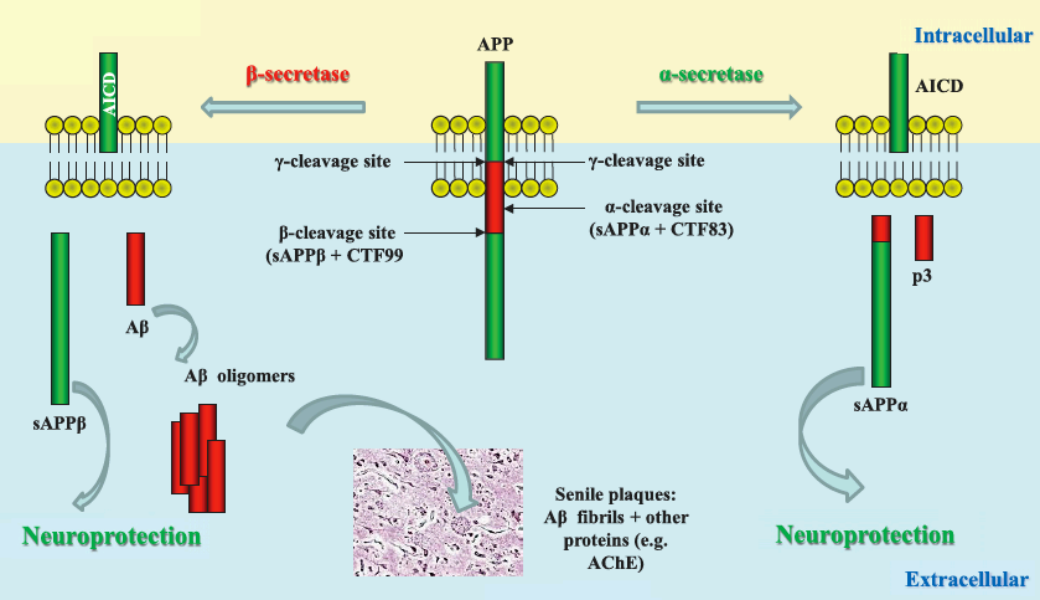

Figure 1.4: Schematic representation of APP processing and the role of its products in AD pathology.[39]

One of the hallmarks of Alzheimer's disease is the Aβ fibrillogenesis. In this process (Figure 1.4), amyloid precursor protein (APP) is processed by the aspartyl protease β-site APP-cleaving enzyme 1 (BACE-1) to generate a highly stable subunit, Aβ42, which tends to adopt ribbon-like β-sheets and form insoluble fibril deposits. Research has indicated that members of the GAG family, such as heparin sulfate (HS), keratan sulfate (KS), and chondroitin sulfate (CS), facilitate the formation of fibril deposits in many ways.[37] For example, the heparin sulfate proteoglycans (HSPG) have been directly associated with increases in the amount, rate of formation and stability of Aβ42. HSPG and CSPG can also bind to the fibrils, thereby preventing their proteolysis. In contrast, recent research has conceived of the role of Aβ fibrils from a very different point of view.

Instead of the insoluble fibril, immature Aβ oligomer are recognizing as highly neurotoxic.[38] GAGs bind to the soluable Aβ oligomer to provide neuroprotective effects by forming less toxic fibril deposits and thus incidentally facilitate the maturation of Aβ fibril. It is worth noting that all of these studies were performed using commercially available GAGs from natural resources; therefore, no precise structure-activity relationship is available.

By applying the state-of-the-art modular synthesis, Boons et al. were able to generate a library of structurally defined heparin derivatives up to hexasaccharide and to test their activities in inhibition of BACE-1 (Figure 1.5).[40] It has been observed that the inhibition is both due to the charge and structure effect. Heparin binding proteins (HBPs) are generally positively charged at physiological pH; therefore, they can tightly bind to negatively charged GAGs by electrostatic interactions.[41] Furthermore, replacing the *N*-sulfates of **8** with acetamido moieties in two glucosamine moieties produces **7**, which demonstrated a ten-fold reduction of inhibitory potency. Structural selection was also seen when just one iduronic acid of **6** was replaced with a glucuronic acid derivative to give **4**, resulting in significant decrease in inhibition potency.

β-D-GlcA(1-4)-α-D-GlcNAc(6S)(1-4)-β-D-GlcA(1-4)-α-D-GlcNAc(6S)(1)-$(CH_2)_5NH_2$ (**1**)

β-D-GlcA(1-4)-α-D-GlcNAS(6S)(1-4)-β-D-GlcA(1-4)-α-D-GlcNS(6S)(1)-$(CH_2)_5NH_2$ (**2**)

β-D-GlcA(1-4)-α-D-GlcNAc(6S)(1-4)-α-L-IdoA(1-4)-α-D-GlcNAc(6S)(1)-$(CH_2)_5NH_2$ (**3**)

β-D-GlcA(1-4)-α-D-GlcNAS(6S)(1-4)-α-L-IdoA(1-4)-α-D-GlcNAS(6S)(1)-$(CH_2)_5NH_2$ (**4**)

α-L-IdoA(1-4)-α-D-GlcNAc(6S)(1-4)-β-D-GlcA(1-4)-α-D-GlcNAc(6S)(1)-$(CH_2)_5NH_2$ (**5**)

α-L-IdoA(1-4)-α-D-GlcNS(6S)(1-4)-β-D-GlcA(1-4)-α-D-GlcNS(6S)(1)-$(CH_2)_5NH_2$ (**6**)

α-L-IdoA(1-4)-α-D-GlcNAc(6S)(1-4)-α-L-IdoA(1-4)-α-D-GlcNAc(6S)(1)-$(CH_2)_5NH_2$ (**7**)

α-L-IdoA(1-4)-α-D-GlcNS(6S)(1-4)-α-L-IdoA(2S)(1-4)-α-D-GlcNS(6S)(1)-$(CH_2)_5NH_2$ (**8**)

β-D-GlcA(1-4)-α-D-GlcNAc(6S)(1-4)-α-L-IdoA(2S)(1-4)-α-D-GlcNAc(6S)(1)-$(CH_2)_5NH_2$ (**9**)

β-D-GlcA(1-4)-α-D-GlcNS(6S)(1-4)-α-L-IdoA(2S)(1-4)-α-D-GlcNS(6S)(1)-$(CH_2)_5NH_2$ (**10**)

Figure 1.5: Putative synthetic HS ligands for BACE-1.[40]

A modulation effect similar to that of GAG on fibrillogensis was also observed in the case of α-synuclein, which is the major component of Lewy bodies and causes Lewy body pathologies as seen in many neurodegenerative disorders such as Parkinson's diseases, Alzheimer's diseases, and Down's syndrome.[42] Elevated expression and impaired degradation pathways are both responsible for the local accumulation of α-synuclein. GAGs not only accelerate the formation of fibrils, but they are also integrated into those fibrils. The *N*-terminal of α-synuclein contains the repeating consensus sequence KTKEGV with multiple lysines serving as a GAG binding region. The central region of α-synuclein also contains an aggregation-prone non-Aβ component.[43]

Chondroitin sulfates (CS), another member of the GAG family, have implicated crucial roles in neural growth and regeneration. For example, CS-B and CS-E share the same sulfation level but have different patterns. Interestingly, only CS-E but not CS-B is able to participate in neural precursor migration during cortical development. By taking advantage of synthetic carbohydrate chemistry, subtle difference among sulfation patterns

have been observed for CS-A, -C, and -E in the regeneration of axons after CNS injury.[44] Axon growth was potently inhibited by 4,6-di-sulfated CS-E, while the 4- and 6-monosulfated CS-A and -C were less potent by at least 50%. The molecular mechanism underlying this observation can be attributed to the selective binding of protein tyrosine phosphatase PTPσ, thereby triggering the downstream pathway of inhibition (Figure 1.6). The inhibition effect can be significantly attenuated by deletion of PTPσ or blockage of CS-E using specific antibodies.

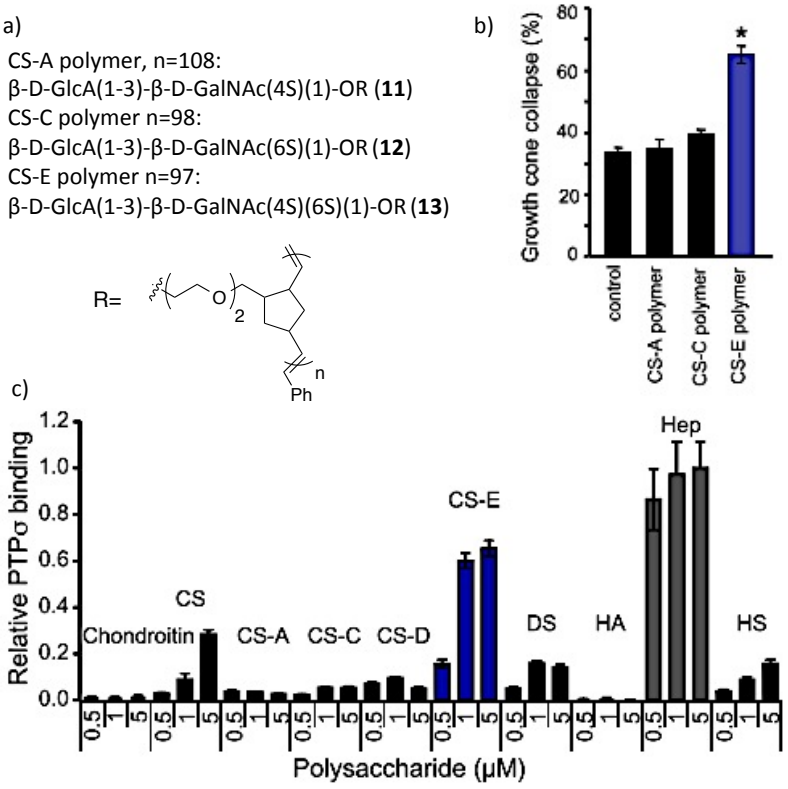

Figure 1.6: The CS-E motif is a potent inhibitor of axon growth via PTPσ. (a) Structures of synthetic glycopolymers displaying pure CS-A, CS-C, and CS-E disaccharides; (b) The synthetic CS-E glycopolymer induces DRG growth cone collapse; (c) PTPσ binds selectively to CS-E-enriched polysaccharides on glycosaminoglycan microarrays.[44]

CARBOHYDRATES IN INFECTIOUS DISEASES

Our rapidly growing body of knowledge on bacterial and viral glycomics suggests the indispensable role of glycosylation for their survivals, infectivities and immune evasions.[45] In eukaryotes, the monosaccharide component is more conserved, but prokaryotes have a larger reservoir of rare sugars and more complex structures, making the characterization of eukaryotic glycan modification more difficult. It is now clear that gram-negative bacteria are heavily *O*-glycosylated at their cell surfaces, and some gram-positive bacteria have also been found to be glycosylated at their surface layers. Regarding *N*-glycosylation, currently only *Campylobacter jejuni*, the major causes of diarrheal worldwide, has been described as having a well-characterized *N*-glycosylation pathway with all enzymes reconstituted in *E. coli*. [46]

Pseudaminic acid (Pse), a nonulopyranoside that is similar to sialic acid, and its derivatives are particularly intriguing targets since they have been directly linked to flagellin integrity and bacterial motility, which are key factors for survival and colonization.[47–49] Many bacterial species including *Legionella*, *Pseudomonas*, *Campylobacter*, *Neisseria*, *Clostridium* and *Aeromonas* have been found to contain Pse and its derivatives as cell surface compositions. In *Helicobacter pylori*, a human gastric pathogen, its flagellin is composed by a major component FlaA, and a base component, FlaB, with seven and ten sites of glycosylations, respectively. Surprisingly, the glycosylation profile is quite simple with Pse5Ac7Ac capping at Ser/Thr residues (Figure 1.7a). Mutagenesis of genes related to flagellar glycosylation resulted in a non-motile phenotype with no structural flagella filament and very little flagellin protein. Instead, recombinant HP0518 protein decreased glycosylation level of *H. Pylori* flagellin *in vitro*,

indicating its function in deglycosylation of FlaA protein.[50] *H. Pylori* HP0518 mutant contained approximately threefold more Pse on its fallellin, and exhibited modulated motility compared to its parental strain. Therefore, pathogen motility can be regulated by the glycosylation status of its flagellin.

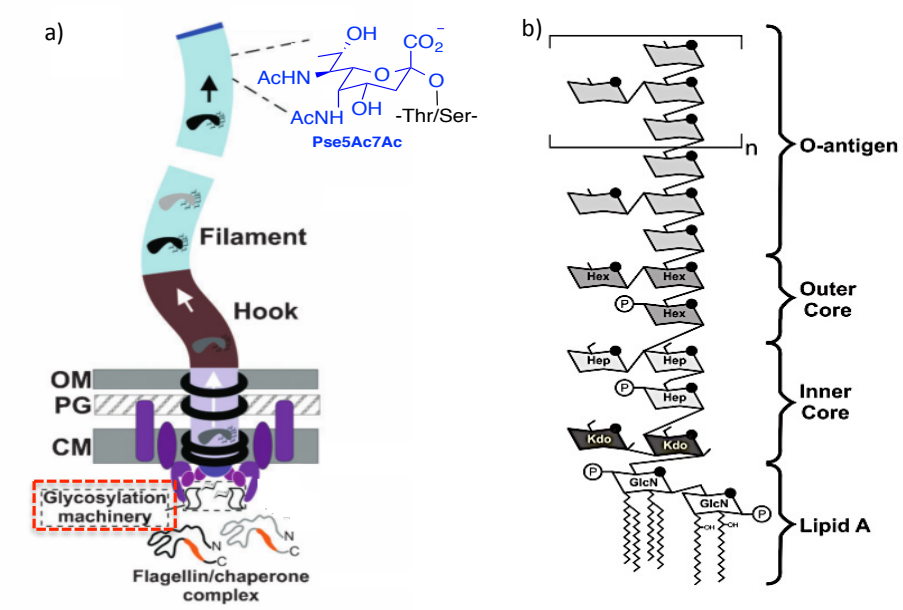

Figure 1.7: Carbohydrates in bacteria. a) Kdo as common component of LPS; b) Pse derivative is critical for maintaining filament structure and *H. Pylori* motility.[48]

Another attractive sugar moiety is 3-deoxy-D-manno-oct-2-ulosonic acid (KDO). It is the key component of lipopolysaccharide (LPS), which affects the pathogenicity of gram-negative bacteria. It functions as a bridge connecting the outmost *O*-antigen and the inner lipid A anchor (Figure 1.7b).[51] The α(2-6) ketosidic bond between lipid A and KDO is susceptible to mild acid cleavage,[52] and the liberated *O*-polysaccharide can induce severe host immune responses, such as septic shock, with mortality rate between 25% and 50%.

Furthermore, KDO and lipid A form the minimal LPS structure neccessary for the gram-negative bacterial growth. No bacteria without KDO have been isolated and no analogues are present in humans, making KDO an ideal target for developing antibacterial drugs.

Unlike prokaryotes, viruses have very limited genetic information. They need to hijack multiple host cell machineries for protein synthesis or posttranscriptional modification in order to successfully infect and replicate.[53] The HIV envelope spike protein gp120 is probably the most intensively studied and the most heavily glycosylated viral glycoprotein. It is believed that more than 50% of the molecule is covered by carbohydrates rendering the underlying protein surface invisible to the host immune surveillance. HIV virus is also able to escape specific neutralizing antibodies by shifting the locations of glycosylations, thereby affect the conformation of targeting protein and the binding of neutralizing antibodies.[54] Fortunately, antibodies with cross-neutralizing ability recognizing the conserved region of gp120 have been generated. Among them, 2G12 is a carbohydrate specific antibody with nanomolar affinity to clustered α(1-2) high-mannose oligosaccharides at the silent face of gp120 outer domain.[55] To mimic the 2G12 epitope by chemical synthesis of high-mannose and its multivalent derivatives has only achieved moderate success with micromolar binding affinity indicating a unique way of presentating carbohydrate epitopes on gp120.[56]

Similar to HIV spike protein gp120 with glycosylation at high density, the influenza surface proteins hemagglutinin (HA) and neuraminidase (NA) also benefit from glycosylation to various degrees and conservation between strains is generally not observed.[57] The sites of glycosylations for HA have been described from 5 to 11 and process subtle effects for virus infectivity. For example, the HA of H3N2, a subtype that

both infect birds and mammals, is glycosylated to a greater extent at its globular head region. This change renders a decrease in virus binding affinity but does not affect the fusion activity.[58] Importantly, the carbohydrate shields the virus from antibody recognition therefore making it more invasive. Over the past half century, a general increase in glycosylations for HA has been observed. However, the effect of additional glycosylations on influenza viruses can be both beneficial and detrimental since the proper glycosylation of the stalk region is crucial to the folding of HA and subsequent binding to host receptors. Indeed, the additional glycosylation of H2 HA abolished its receptor binding property. As a consequence, the glycosylation status of H2 has barely changed since this subtypes were first encountered.[59]

CARBOHYDRATE CANCER VACCINES

We have a glorious history of vaccine invention in which some of the most notorious diseases have been eliminated, but cancer immune therapy has mainly stayed in its infancy.[60] The only FDA approved therapeutic cancer vaccine so far is Sipuleucel-T (Provenge), which is used to treat advanced prostate cancer and projects an average increase in survival time of 4 months.[61] The primary reason for this disappointing situation is due to the endogenous nature of tumor cells. Compared to exogenous causative agents like bacterial cell walls, tumor cells possess components identical to those of healthy cells and are therefore tolerated by our immune systems. Tumor-associated carbohydrate antigens (TACAs), as reviewed in the previous section, are emerging vaccine targets for distinguishing tumor cells from healthy ones.[62] However, the production of "good" antibodies for most immunogens depends on the cooperative

interaction of B and helper T lymphocytes. Saccharides alone cannot activate helper T cells and therefore have limited immunogenicity.[63]

The conjugation of synthetic TACAs with carrier proteins as semisynthetic vaccines has been widely tested as a method of overcoming T-cell independency (Figure 1.8).[64] The first generation of glycoconjugate vaccines was based on a monomeric design, in which a single carbohydrate epitope was connected to the carrier protein via a linker with one copy. In a series of important studies, Danishefsky's team chemically synthesized TACA Globo-H hexasaccharide and conjugated it to KLH. The resulting vaccine construct proved to be safe and effective in generating both IgM and IgG antibodies against Globo-H.[65] Encouragingly, this vaccine is now in phase III clinical trial for treating breast, prostate, and ovarian cancers.

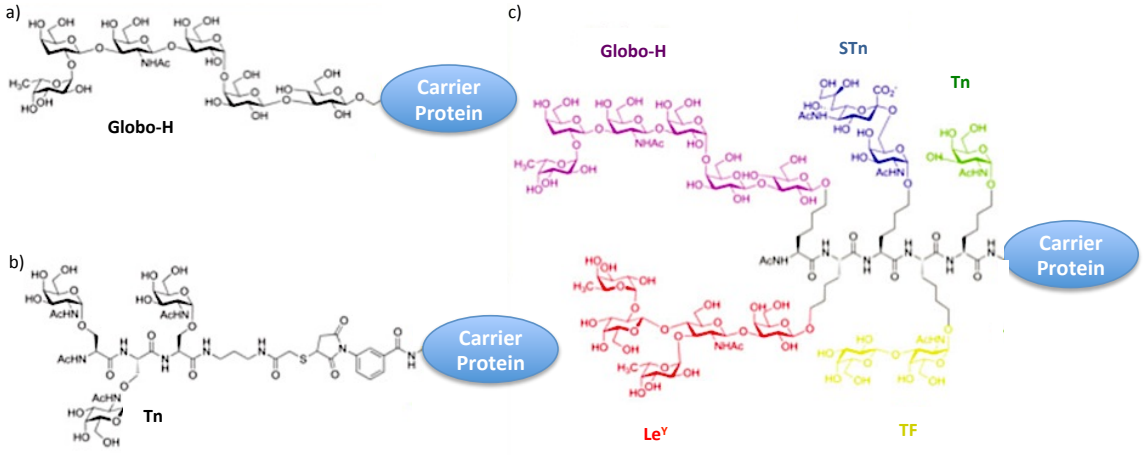

Figure 1.8: Evolution of semi-synthetic glycoconjugate vaccines. a) monovalent glycoconjugate; b) homo-multivalent glycoconjugate; c) hetero-multivalent glycoconjugate.

The second generation of carbohydrate vaccines, instead of using big synthetic oligosaccharides, were composed of smaller carbohydrate antigens, such as Tn, STn, and TF, and were conjugated in a homo-multivalent fashion to mimic the glycoclusters as frequently found in mucins. Multivalent presentation of carbohydrate epitopes has been generally accepted as a requirement for a robust and efficient immune response.[66,67] Vaccines for adenocarcinoma and HIV have been designed using multivalent STn or high-mannose.

Hetero-multivalent presentation is also an attractive strategy, because cancer cell is highly mutagenic and considerable variation among TACAs has been found even within the same tumor site. A multifaceted immune response is necessary for optimal targeting of a heterogeneous population of malignant cells. By linking different carbohydrate epitopes to a small peptide and conjugating it with the carrier protein KLH, Danishefsky and co-workers have prepared several unimolecular multivalent vaccines containing Globo-H, Le^Y, STn, TF, Tn, or GM2. Vaccination with these glycoconjugates produced corresponding antibodies response to all epitopes, and their binding to cancer cells were confirmed by flow cytometry.[68]

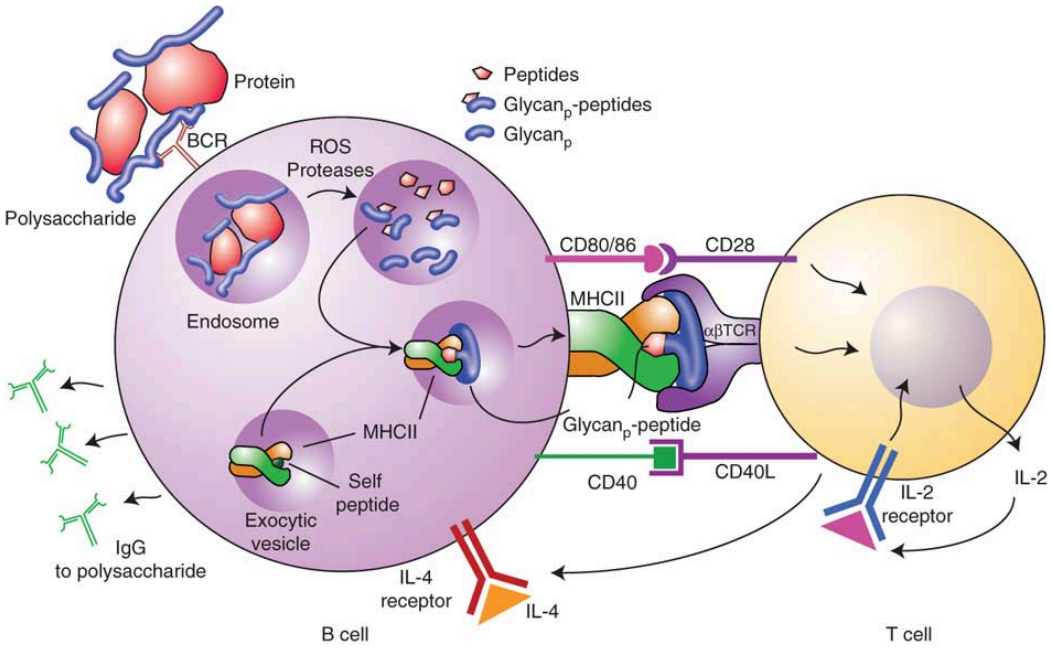

Figure 1.9: A schematic representation showing the steps in antigen processing and presentation of glycoconjugate vaccines resulting in helper $CD4^+$ T cell induction of B cell production of IgG antibodies to the polysaccharide.[69]

Recently, the mechanism of immune response to glycoconjugate vaccine has been studied by Kasper and co-worker.[69] It builds up the foundation of rational glycoconjugate vaccine design. Briefly, glycoconjugates can be recognized, internalized and processed by antigen processing cells (Figure 1.9). Carbohydrates are tolerated during proteasome degradation, generating a glycan-conjugated peptide via processing of glycoconjugates. MHC II binding of the peptide portion allows the presentation of the carbohydrate portion to a specific subset of T-cell receptors, initiating of subsequent cascades of cytokine secretion and B-cell maturation.

One of the drawbacks of using foreign carrier proteins is the inevitable presentation of exogenous components that may elicit strong B-cell response and suppress the antibody

response to the carbohydrate epitope.[70,71] This is especially the case when consider self-antigens like TACAs are employed. Other drawbacks include safety and cost issues of producing recombinant carrier proteins in a bacterial host. For these reasons, there is a trend of evolution from semisynthetic vaccine to fully synthetic vaccine in the past decade.[72,73] Boons and co-workers have developed a fully synthetic vaccine with the minimum structural features required for a focused and effective T-cell dependent immune response.[74] The vaccine is composed of three components namely B- and helper T- epitopes and a lipopeptide as the TLR-2 ligand. The B-epitope is derived from the Tn antigen, which is overexpressed on the surface of human epithelial tumor cells of the breast, colon and prostate. The helper T-epitope is derived from *Neisseria meningitides* as an MHC class II restricted site for human T cells. The lipopeptide Pam_3Cys interacts with TLR-2 and introduces the secretion of pro-inflammatory cytokines and chemokines, which stimulate the maturation of dendritic cells. As they further developed this construct, a tumor-associated MUC1 glycopeptide was chosen as the B-epitope, as well as a well-characterized T-helper epitope from poliovirus as the helper-T epitope and a TLR2 agonist Pam_3CysSK_4 for inducing extra "danger" signals.[75] Immunization of mice with this tripartite vaccine elicited CTL and ADCC-mediating antibodies, which recognized tumor-associated MUC1 (Figure 1.10). [76]

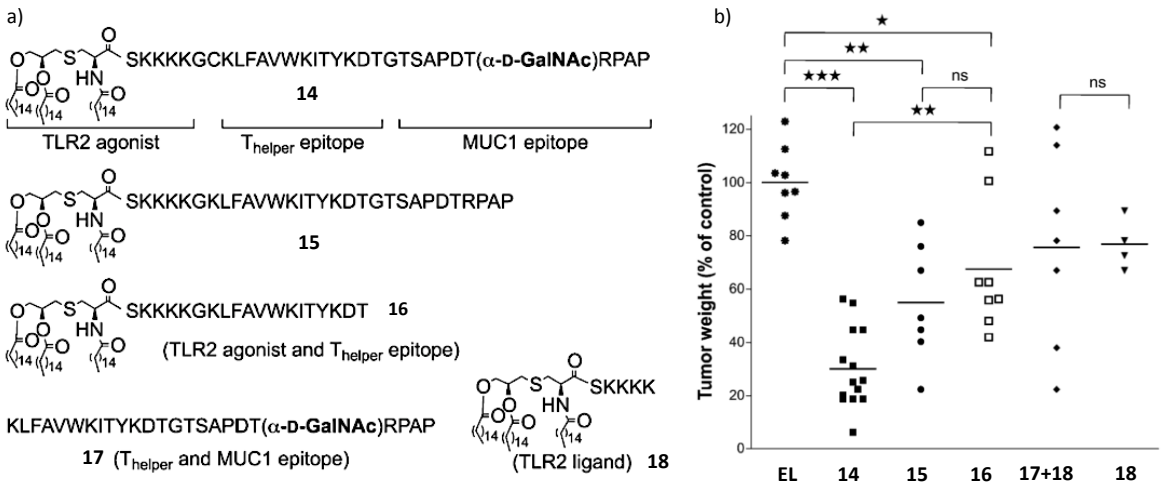

Figure 1.10: Determine dominant immune responsive component of tripartite vaccine. a) Structures of vaccine and its derivatives. b) Comparison of MMT tumor burden reduction in MUC1.Tg mice immunized with structure **14-18**.[76]

CARBOHYDRATE AND GLYCOMIMETIC DRUGS

More than 80 pathophysiologically important carbohydrate-binding proteins have been identified, but only a very small percentage have been exploited as drug targets. The glycosylations of many pathogen proteins have also been shown to perform functions critical to the survival and infectivity of those pathogens. In contrast to the vast range of biological functions, carbohydrate derived drugs only make up a small percentage of the world therapeutics with around 20 approved drugs currently on the market.

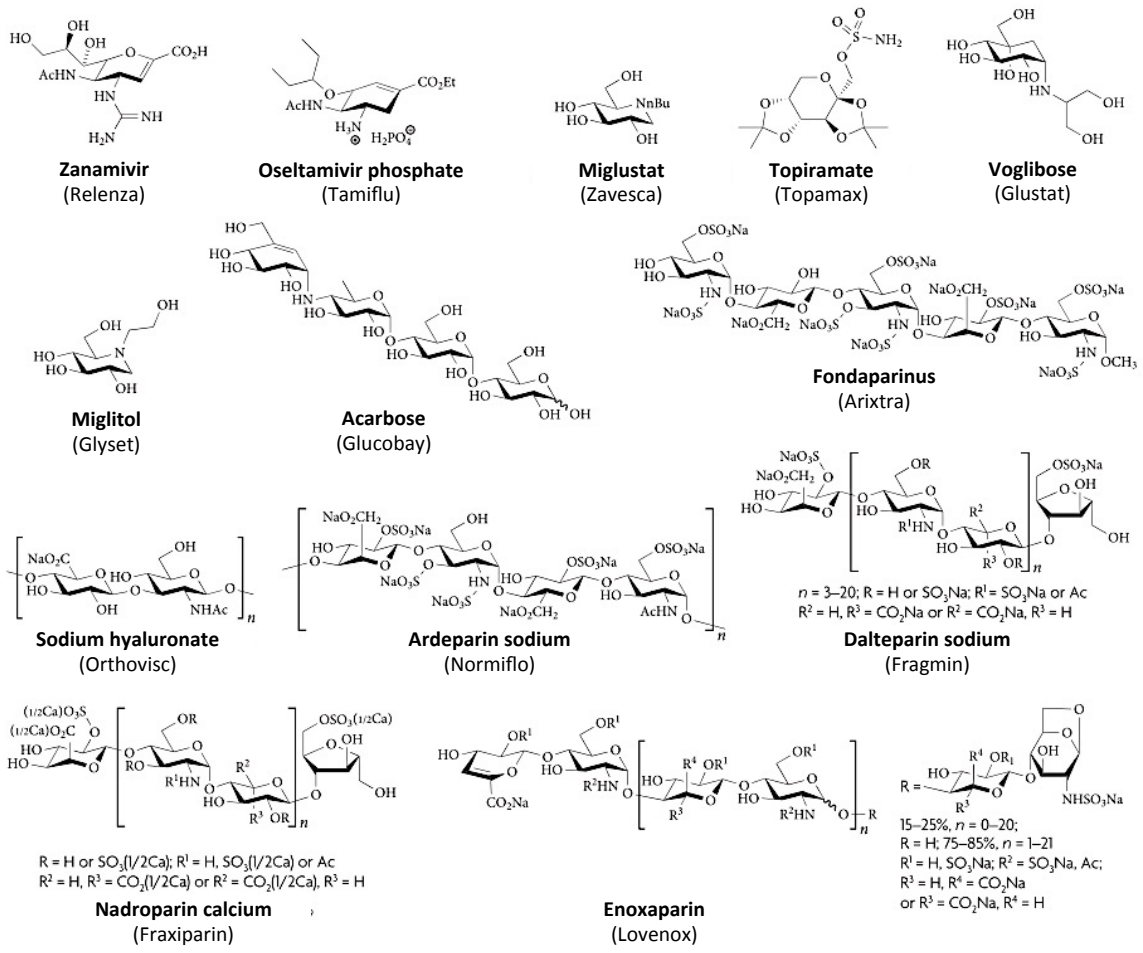

Figure 1.11: Structures of carbohydrate and carbohydrate-derived drugs.[77]

Heparins, anticoagulants for the prevention and treatment of venous thromboembolism, are complex mixtures of alternating glucosamine and uronic acid with different sulfation patterns ranging in molecular weight from 3000 to 30,000. They have been shown to exert the anticoagulant activity by binding to antithrombin III (AT III) through a unique pentasaccharide sequence (A-domain) randomly distributed along the backbone. Heparins with at least 18 saccharides units are also able to inactivate thrombin by forming a ternary complex between AT III and thrombin. However, shorter backbones can only bind antithrombin to activate factor Xa.[78,79] By conducting controlled enzymatic

or chemical depolymerization, low-molecular-weight heparins with heparin with a mean molecular weight around 5000 have been prepared and have demonstrated advantageous bioavailability, anticoagulant response and longer half-life.[80] Since the heparin contamination accident of 2008, a fully synthetic heparin sulfate pentasaccharide Arixtra, which resembles the effective antithrombin binding pentasaccharide epitope, has generated attention by providing a structurally defined heparin sulfate with only factor Xa inhibitory activity; thus, ensuring greater safety comparing to heparins from animal tissue.[81] The success of this drug also represents the state of the art of synthetic carbohydrate chemistry that the pentasaccharide was synthesized with more than 50 steps and 36 the longest linear steps.

The design of glycomimetics is a fruitful area of research. Various α-glucosidase inhibitors, including the carbasugar derivative Voglibose, iminosugar Miglitol and the transition state mimic Acarbose, have been synthesized and are currently used for the treatment of diabetes. The paradigm of glycomimetic drugs has also proved effective in treating infectious disease. Zenamivir, a sialic acid derivative, has been applied for the inhibition of influenza neuraminidase, an enzyme responsible for cleaving sialic acid residues on newly formed virions as they bud off from the host cell. Further systematical optimization by eliminating unnecessary polar groups and metabolically vulnerable spots produced Oseltamivir, a leading drug for treating influenza.[82]

Glycomimietics have also provided versatile strategies for treating lysosome storage disorders (LSDs).[83,84] The *N*-alkylated deoxynojirimycin (DNJ) derivative Zavesca (Miglustate) has been licensed for the treatment of type I Gaucher's disease and Niemann–Pick disease C (NPC) with progressive neurological manifestations. The

proposed mechanism of action is inhibition of glucosylceramide synthase, which reduces the accumulation of substrate. This is known as substrate reduction therapy (SRT). The ability of iminosugars to bind defective enzymes and function as molecular chaperons that help regain functional conformation of defective enzymes has stimulated their application as active-site-specific-chaperons (ASSCs) for treating LSDs and providing an alternative strategy to SRT. In treating type I Gaucher's diseases, Isofagomine AT 2101 has been shown to bind to misfolded glucocerebrosidase, facilitating the processing and trafficking to the lysosome by ER, thereby restoring the normal depredating function of this enzyme.[85] Unfortunately, though well tolerated by patients, no statistically significant improvement was observed in phase II clinic trial of isofagomine. However, Migalastat, a glycomimetic used to treat Fabry's disease, has entered phase III clinic trial.[86]

DEVELOPMENT OF SYNTHETIC CARBOHYDRATE CHEMISTRY

We have reviewed the fundamental impact of carbohydrates on our understanding of diseases and the design of therapeutics. These achievements can be attributed to the rapid growth of glycoscience, which has provided us unprecedented insight into this "sweet molecule".[87] Although sugar molecules, such as starch or cellulose, are among the most abundant molecules on earth, the development of biology and chemistry of carbohydrate has lagged behind that of other life molecules such as DNAs and proteins.[88] This lag is due primarily to the unique features during carbohydrate synthesis either biologically or chemically.[89]

Specifically, the biosynthesis of carbohydrate is not template driven. Therefore the ultimate structures of complex oligosaccharides usually depend on the availability and

activity of related glycotransferases or glycosidases as well as the local concentration of activated nucleotide sugars. This often results in minute structural differences, called microheterogeneities, among different tissues, organs, and even on the same cell, which complicates the separation and SAR study.[90,91] Moreover, because no amplification reaction is available for carbohydrates due to the non-templated feature and the separation of enough well-defined standard material from natural sources is often impossible, the enzymatic synthesis of complex oligosaccharide has achieved, at certain extent, remarkable progress.[92–95] In general, this method is specific and efficient, but the availability of durable enzymes with suitable substrate specificity is usually limited. Generation of the required enzymes can become an independent project that may not fit into the timeline of desired research.

Compared to the biosynthesis, chemical synthesis or combined with enzymatic synthesis of targeted complex oligosaccharides, though challenging, presents several advantages,[96] including well-defined structure, relative large quantity of final product and flexible target modifications. But, as mentioned, chemical synthesis is still not mainstreamed and can be only preformed in certain specialized laboratories. Each target may become a completely new synthetic challenge that requires considerable experience and strategic planning. The development of efficient, selective and generalized glycosylation reactions is the key aspect governing the success of a routine synthesis of complex oligosaccharide and this area remains an active field of research.[89,97,98]

Aside from the challenges surrounding glycosylation reactions themselves, synthetic carbohydrate chemistry is also a laborious task in its own right. The preparation of building blocks requires steps of protection and deprotection manipulations in order to

differentiate multiple hydroxyl groups. The removal of temporary protecting groups between each glycosylation requires extra steps and purifications. Notable progresses have been made in accelerating the process of oligosaccharide assembly, including automated solid-phase synthesis,[99,100] fluorous-tag-assisted solution-phase synthesis,[101] and programmable one-pot oliogosaccharide synthesis.[102,103] These refinements have significantly reduced the time required for purification and the intermediate deprotection. The complexity of targets synthesized by these methods has researched an impressive level,[104,105] though intensive optimization may be still required in advance.

MECHANISTIC OVERVIEW OF CHEMICAL GLYCOSYLATIONS

Glycosylation reactions are at the heart of oligosaccharide synthesis. They are the coupling reactions between two properly protected building blocks: glycosyl donors and glycosyl acceptors (Figure 1.12). The glycosyl donors **19** are usually fully blocked at their hydroxyl groups by protecting groups[106] and the anomeric center is equipped with a leaving group,[98] while the glycosyl acceptors **21** often contain only one free hydroxyl group. During glycosylation, an activator/promoter, usually an electrophile, will be added resulting in the activation of donors followed by the departure of the anomeric leaving group and the accumulation of positive charge at the anomeric center. Depending on the molecularity and the type of activation, the anomeric carbon cation can be stabilized by the endocyclic oxygen, forming an oxocarbenium ion as a reactive species. Without any intramolecular participation, the flattened oxocarbenium ion **20** can be readily attacked by acceptors (nucleophiles) either from the bottom or the top with the formation of two

possible stereoisomers **22** and **23** in an S_N1-like mechanism. The actual stereooutcome may favor the anomeric effect on a case-by-case manner delivering unreliable results.

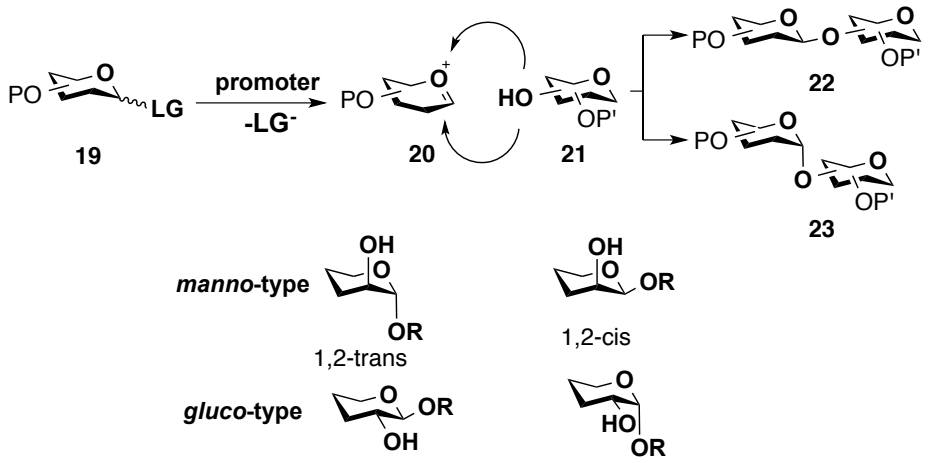

Figure 1.12: General schematic presentation of chemical glycosylations without neighboring group participating.

It has been widely accepted that 1,2-*trans* glycosides can be reliably obtained by employing neighboring participating functionalities such as acetates. However, the formation of 1,2-*cis* glycosides or C-2 deoxy glycosides usually requires the absence of C-2 participating functionality. Therefore, the stereooutcome is a summation of many factors, such as the spatial orientation of donors and acceptors, protecting groups, promoters, and solvents.[107] Optimized stereoselectivity generally requires the combination of two or more effects. Often, protecting groups, promoter counterions, or solvents with nucleophilic properties can compete with acceptors and trap the oxocarbenium ions, leading to the formation of quasi-stable intermediates as new active species for glycosylation coupling. In particular, the active species possess desirable leaving potency and anomeric orientation such that the formation of glycosidic bonds and

the cleavage of the C-1—LG bond is nearly synchronized, resulting in a shift from an S_N1-like mechanism to an S_N2-like mechanism with observed increasing in stereoselectivity.

Traditionally, great emphasis has been placed on the importance of protecting group effect on stereoselectivity. But recent research has a growing appreciation on the contribution of the leaving group to the stereoselectivity.[108] Many quasi-stable active species generated by preactivation or in the presence of acceptors have shown promising properties, providing exceptional stereoselecttivity that cannot achieve by protecting group effect alone. The term "quasi-stable intermediates" is intended to distinguish reactive intermediate governing the formation and stereoselectivity of glycosylation reactions from normally used glycosyl donors, and it is further elaborated below.

STEREOSELECTIVE GLYCOSYLATIONS USING ANOMERIC BROMIDES

In 1975, Lemieux and co-workers found that the addition of tetrabutylammonium bromide as a counterion source of Br^- can trap the oxocarbenium ion as an anomeric bromide. Subsequent S_N2-like displacement of the anomeric bromide by acceptors results in the inversion of anomeric stereochemistry.[109] To allow substitution of the β-bromide, a conformational change to the high-energy boat-like intermediate is required so that the antibonding orbital σ* of C1-Br is periplanar to the lone of the endocyclic oxygen. In contrast, α-bromide has its σ* of C1-Br already in place, so a comformational change is not necessary, thereby less reaction. More importantly, the anomeric bromide is under a rapid equilibrium between β-bromide **24** and α-bromide **25**. In a Curtin-Hamlet scenario, the more reactive β-bromide preferentially reacts with acceptors with the formation of α-

glycosides. Depending on the rate of equilibrium, α-glycosides can be major or exclusive product.

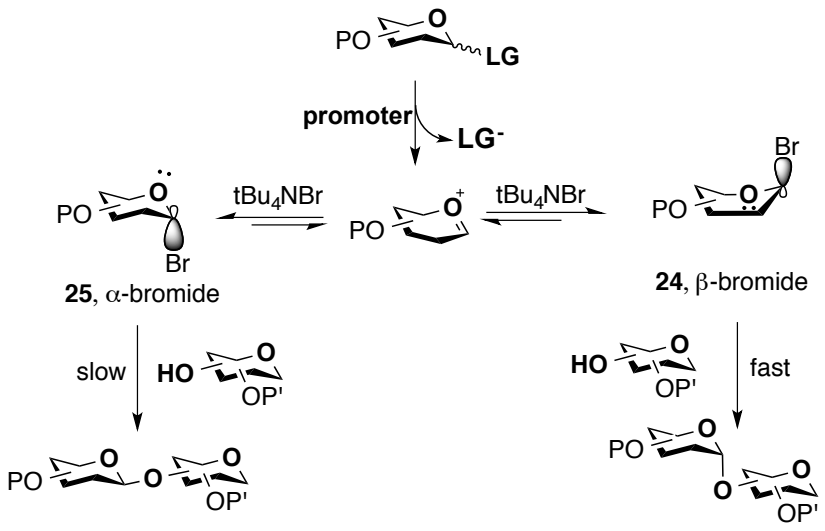

Figure 1.13: *Cis*-glycosylation by *in-situ* anomerization.

In-situ anomerization has proven to be very useful in preparation of α-linked *O*-glycosides without assisting functionality at C-2. But, this process generally requires armed donors and extended reaction time. To overcome this limitation, new lyophilic salts or couterions, such as mercury bromide or silver perchlorate, are introduced and successfully applied on less armed donors.[110–112]

STEREOSELECTIVE GLYCOSYLATIONS USING ANOMERIC TRIFLATES

The breakthrough in applying quasi-stable intermediate for stereoselective glycosylation came from Crich's team, who discovered that preactivation of mannosyl sulfoxides or thioglycosides with triflic anhydride or benzenesulfenyl triflate, respectively, followed by the addition of alcohols led to the efficient formation of β-mannosides.[113] Later,

comprehensive mechanistic studies revealed that this extraordinary β-selectivity relies on three primary factors: (a) conformational locking and deactivating by 4,6-benzylidene, (b) formation of covalent linked anomeric α-triflate, and (c) the use of non-participating protecting groups on O-2 and O-3 of the donors.[114]

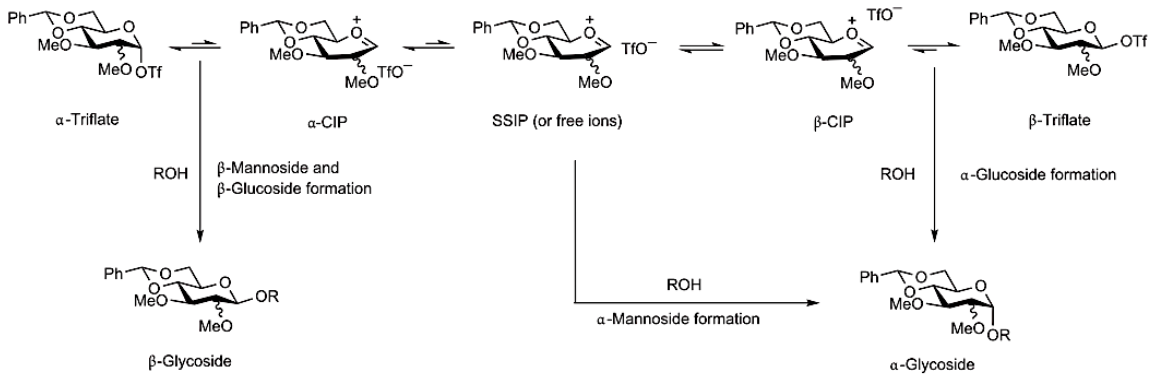

Figure 1.14: Mechanistic picture for the 4,6-*O*-benzylidene-directed formation of α- and β-*gluco*- and mannopyranosides. At the extreme left and right, a series of equilibria connect two covalent glycosyl triflates with the corresponding CIPs and the more loosely associated SSIPs. In three of four cases studied, reaction occurs in the 'grey area' defined by the equilibria between the covalent triflates and the CIPs. Formation of a-mannoside, however, clearly occurs by a dissociative mechanism. [115]

Extensive NMR studies have characterized α-triflate in detail.[116] The existence of this quasi-stable intermediate is a strong indication of S_N2-like displacement. During the displacement (Figure 1.14), triflate is in a continuous change of status from covalent triflate to contact ion pair (CIP) and solvent separated ion pair (SSIP) in accordance with the increasing distance between the triflate and the positively charged anomeric center. As distance increases, anomeric stereocontrol becomes less restricted and a greater

conformational demand is placed on donors, which change from chair to half-chair conformer in order to accommodate more sp^2 character at the anomeric center. By fusing 4,6-bezylidene to the donor, it locks the donor in $^4C_1$ conformation making the equilibrium toward covalent triflate more favorable. By examining the secondary ^2H and primary ^{13}C kinetic isotope effect as indicators of bond order in the transition state (TS),[115,117] Crich and co-workers unambiguously proved that the formation of β-mannoside occurred via an associative TS, by which the formation of α-product does not possess any associative characteristic in the TS. It is worth noting, however, that the KIE value for β-mannoside falls on the lower end of S_N2 reactions, again, supporting the previous argument for continuous equilibrium during the dissociation of triflate.

A similar α-triflate intermediate was also observed in glycosylation employing mannuronic acid donor **26** (Figure 1.15). But, in contrast to the single conformation in the case of 4,6-benzylidene protected mannosyl donors, the α-triflate detected by low temperature NMR for mannuronic acid donors was a mixture of $^4C_1$ **27** and $^1C_4$ **28** conformers.[118] In particular, the $^1C_4$ conformer **28** placed all its three substitutions at axial orientation, and the anomeric triflate adopted a unique equatorial position lacking the stabilization of anomeric effect. The existence of this surprisingly unfavorable conformation can be attributed to the demand of extra electron donation to the positively charged anomeric center in electron-depleted mannuronic acid donors, in which the C-5 carboxylic acid of **29** adopts pseudoaxial position, placing carbonyl group close to the oxocarbenium ion center during the evolution from the $^1C_4$ resting state to the $^3H_4$ TS, the most favorable conformation for the oxocarbenium ion.[119] Direct S_N2-like displacement of **28** and facial selective addition to oxocarbenium ion **29** by avoiding skewed product

31, can both give β-glycoside **32**. The adoption of high-energy conformation for α-triflate with mannuronic donors may contribute to the high reactivity observed for this type donor compared to other uronic acid donors.[120] Accordingly, the α-triflate is also more labile and readily decomposes at higher temperature.

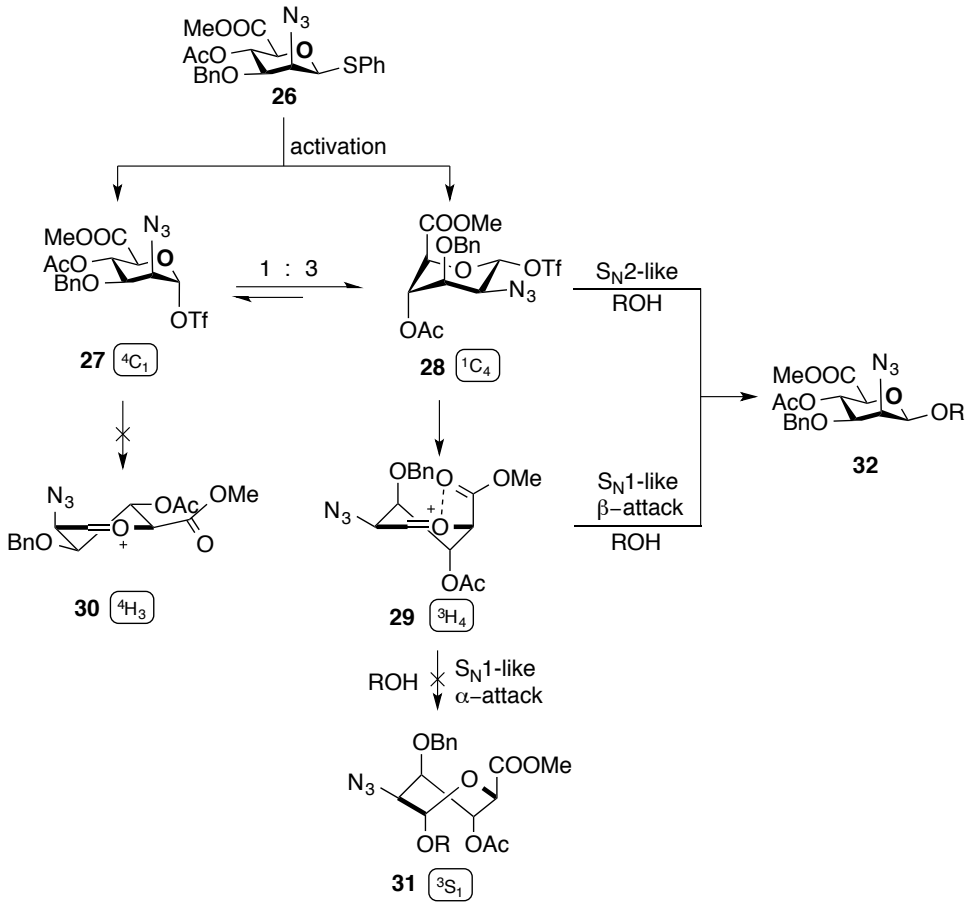

Figure 1.15: β-Mannosylation with mannuronic acid donor goes through a mix of S_N1-like and S_N2-like mechanisms.

STEREOSELECTIVE GLYCOSYLATIONS USING ANOMERIC OXOSULFONIUM TRIFLATES

The ubiquity of triflates as counter ions in promoters has made them extremely useful in synthetic carbohydrate chemistry. Nevertheless, other species of active quasi-stable intermediates are also available under different circumstances. Though it usually takes at least two steps to prepare suitable donors equipped with leaving groups at their anomeric centers, Gin et. al. elegantly designed the dehydrative glycosylation for direct coupling of donor hemiacetals with acceptors.[121]

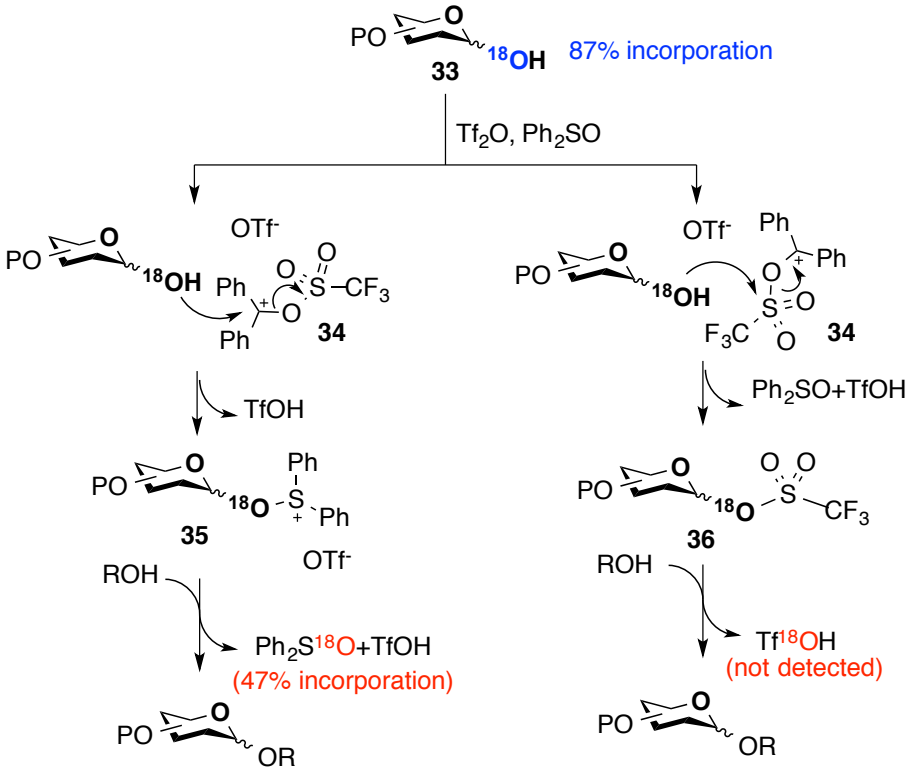

Figure 1.16: Mechanistic identification of oxosulfonium triflate mediated dehydrative glycosylation.

In this process (Figure 1.16), stoichiometric amount diphenyl sulfoxide and triflic anhydride were added and immediately converted to diphenyl sulfide bis(triflate) **34**. This highly reactive intermediate activates the hemiacetal **33** by the electrophilic addition of C-1 OH to the sulfonium center, leading to the formation of oxosulfonium triflate **35**. The possible addition of hemiacetal to another electrophilic sulfonyl center of diphenyl sulfide bis(triflate) with the formation of **36** has been excluded by ^{18}O labeling experiment in which no incorporation of ^{18}O into triflate acid was observed.[122,123] Oxosulfonium triflate has been shown a desirable balance between reactivity and stability compared to triflate intermediates. In case of sialidation, dehydrative glycosylation through oxosuflonium triflate yielded sialglycoside with moderate α-selectivity without any β-elimination.[124] However, activation of thiosialglycoside donors through putative triflate intermediation yielded β-eliminated compound as the exclusive product.

STEREOSELECTIVE GLYCOSYLATIONS USING ANOMERIC ACYOXONIUM ION

Neighboring group participation is widely applied in stereocontrol of glycosylations. Typically, a C-2 acyl group can ensure the formation of *trans*-glycosides (Figure 1.17a). During the reaction, the carbonyl moiety of the acyl group functions as a nucleophile trapping the oxocarbenium ion as an acyloxonium intermediate that can be subsequently displaced by the acceptor in an S_N2 fashion, resulting in the inversion of anomeric stereochemistry. The modulation of the model and the nucleophilic head for neighboring participation has created a dynamic area of research for stereoselective glycosylations, especially the challenging 1,2-*cis*-glycosylations.

Chiral auxiliary, envisioned and developed by Boons and co-workers for 1,2-*cis*-glycosylations, is one of the cases in which both factors have been systematically studied. The first generation of chiral auxiliary employed commercially available and optically pure ethyl mandelate as the C-2 participating group, in which the carbonyl group acted as a nucleophilic head.[125] After activation and the formation of the oxocarbenium ion, participation of the nucleophilic moiety leads to the formation of a putative *trans*- or *cis*-decalin system depending on the chirality of the mandelate. It was expected that the use of (*S*)-mandelate would favor the formation of *trans*-decalin, because the *cis*-fused system would place the phenyl substituent in an axial position. The subsequent substitution of the *trans*-decalin acyoxonium ion with an *O*-nucleophile was anticipated to give excellent 1,2-*cis*-glycosides (Figure 1.17b). Indeed, a survey of glycosylations with various acceptors resulted in good to excellent stereoselectivities. The proposed model of intramolecular cyclization was further supported by the observation of reversed stereoselectivity of product when the chirality of auxiliary was changed.[126]

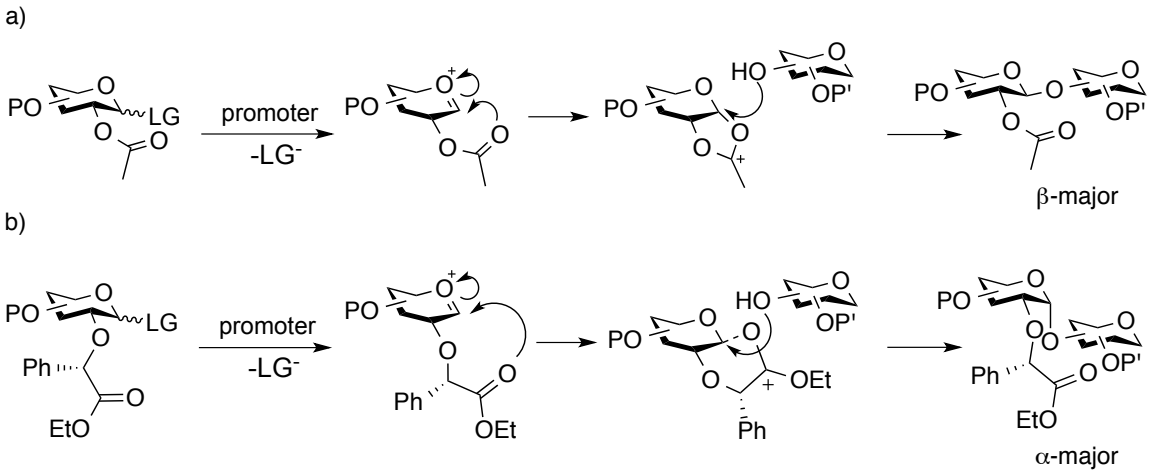

Figure 1.17: General schematic presentation of chemical glycosylations with neighboring group participation for the synthesis of *cis*- and *trans*-glycoside. a)

traditional neighboring participation with 5-membered acyoxonium ion for *trans*-glycosylation; b) putative neighboring participation with 6-membered acyoxonium ion for *cis*-glycosylation.

STEREOSELECTIVE GLYCOSYLATIONS USING ANOMERIC SULFONIUM IONS

The success of the first generation of auxiliary prompted us to screen new nucleophilic heads (Figure 1.18). Sulfur atom is an attractive candidate due to its increased nucleophilicity and bigger atomic radius compared to oxygen. Derived from ethyl mandelate, second-generation chiral auxiliary was installed by reacting sugar C-2 alcohol with acetic acid (1*S*)-phenyl-2-(phenylsulfanyl)ethyl ester in the presence of BF_3-OEt_2. This reaction proceeds by a BF_3-OEt_2 promoted departure of the acetate with concomitant formation of an episulfonium ion. Subsequently, nucleophilic attack at the benzylic position of the episulfonium ion by a sugar hydroxyl leads to the required substituted benzyl ether with overall retention of configuration. Preactivation of donor **37** with a catalytic amount of TMSOTf in an NMR tube at low temperature revealed the formation of *trans*-decalin sulfonium ion **43**. The identity of the covalent linkage was further confirmed by HMBC experiment showing three bond coupling between C1 and H8. The *trans*-decalin conformation was confirmed by NOE experiment.[127] The nucleophilic substitution of the β-sulfonium ion in *trans*-decalin conformation with various acceptors resulted in the exclusive formation of α-glycosides. The attractiveness of this method is further demonstrated on the solid phase platform in the synthesis of a fully *cis*-linked and branched α-glucan involved in the host innate immune response.[128]

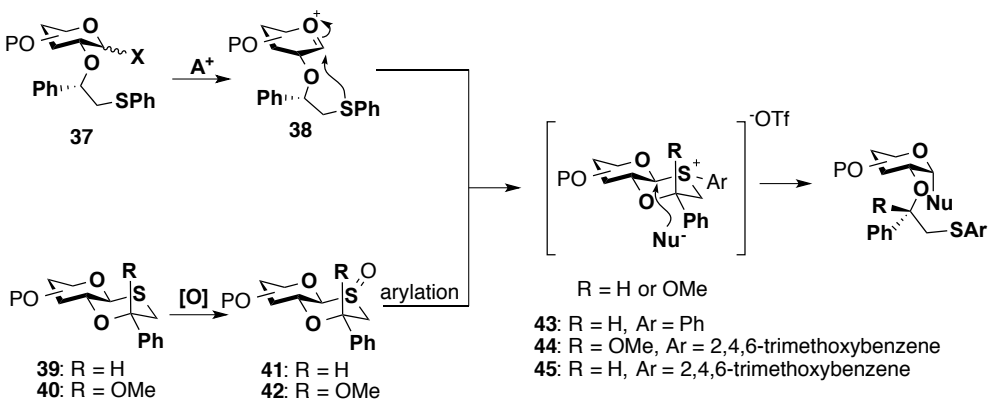

Figure 1.18: α-Selective glycosylations mediated by sulfonium ions from different precursors.

Further optimization of auxiliary systems has focused on tackling the acid liability and the synthetic challenge of chiral auxiliaries. Turnbull and co-workers strategically utilized the stereo- and regio-selective acetal formation reaction for constructing oxathiane acetal **40** as the precursor of a sulfonium ion.[129] The prefused oxathiane acetal has already existed in the trans-decalin conformation. Upon oxidation and preactivation, the sulfoxide **42** was first triflated and then substituted by the electron rich trimethoxylbenzene. The generated sulfonium ions **44** were more stable compared to the second-generation sulfonium ion **43** due to the electron donation and the stabilization by trimethoxybenzene. Therefore, the glycosylation reactions were observed to occur at higher temperature.

One drawback of the oxathiane acetal moiety is its acid liability, which limits the building block manipulations and complicates the glycosylations with C-2 glycosylated side products. We carried out the reduction of oxathiane acetal to its ether **39**, which possesses superior stability under various acidic, basic and reductive conditions, making oxathiane ether an attractive alternative to oxathiane acetal.[130] Methodology studies have

shown oxathiane ether donors to be capable of stereoselective glycosylation with a wide range of acceptors, including primary and secondary hydroxyl acceptors, thioglycoside, and properly protected amino acid. Benefiting from superior compatibility with protecting group manipulations, these highly orthogonally protected oxathiane ether donors were prepared and applied to the preparation of a cell surface oligosaccharide extract from *P. boydii* using a latent activation strategy.

Despite the exceptional stereoselectivity of sulfonium ion mediated glycosylations, no deemed mechanistic explanations are currently available.[131–133] We have previously probed the nature of neighboring group participation by synthesizing donors with both stereoisomers of chiral auxiliaries or without chiral substitution. It was observed that reversing the stereochemistry from the desired (*S*)-isomer to the (*R*)-isomer cause a significant erosion of α/β selectivity. This can be rationalized by the unfavorable spatial orientation of bulky phenyl substitution that destabilizes the *trans*-decalin. Without the chiral substitution, it was anticipated that the preference between *trans*-and *cis*-decalin would be diminished due to the reduction of steric hindrance. This was supported by the observation of a slightly impaired selectivity with α/β=8/1.

Later, Woerpel and Whitefield tried to dissect the stereodirecting effect from the neighboring group participation and facial-selective addition using simplified systems. They found that the sulfonium ion arose from 4-sulfur substituted acetal in a simple tetrahydropyran system serving as a resting state, in which the nucleophilic addition, instead of going through S_N2-like displacement, prefers oxocarbenium ion.[134] However, only carbon nucleophiles, which are six times less nucleophilic than *O*-nucleophiles, were tested in their studies. It is quite possible that a stronger nucleophile would have

been able to react along an S_N2 pathway without opening up the bridged sulfonium ion. In another study, Whitefield and co-workers found that introducing a nonparticipating chiral protecting group at the C-2 position of glucose donors could also contribute to the stereoselectivity of glycosylation.[135] Computational studies from this group suggest that a big rotation barrier along the C2-O2 δ-bond may position the C-2 protecting group in a *syn*-fashion to H2, thereby blocking the β-face of the donor.[136] Nevertheless, these studies suggested that multiple factors might govern the chiral auxiliary assisted sulfonium ion mediated stereoselective glycosylations.

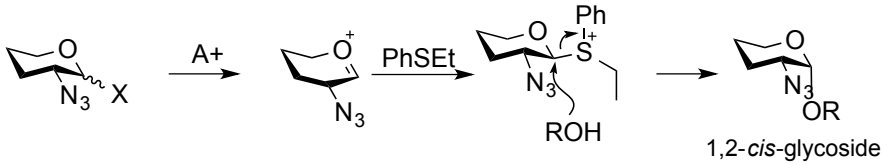

Figure 1.19: α-Selective glycosylation with C-2 deoxy donor mediated by sulfonium ion formed by adding sulfur-containing reagent.

The demand for stereoselective glycosylation of C-2 deoxy sugar presented challenges and opportunities for sulfonium ion mediated glycosylations. Though it is not possible to use C-2 auxiliaries on C-2 deoxy sugar, the addition of other sulfur-containing reagents, such as ethyl phenyl sulfide or thiophenol, has produced 2-deoxy-glycoside with excellent α-selectivity (Figure 1.19).[137] Similar to the mechanism of auxiliary mediated glycosylations, the sulfur-containing additives trap oxocarbenium ions as sulfonium ions during preactivation. The positively charged sulfonium ion tends to adopt the equatorial position due to the reversed anomeric effect, and the subsequent S_N2-like displacement resulted good α-selectivity. The β-sulfonium ion intermediate was also detected and confirmed by NMR studies.

STEREOSELECTIVE GLYCOSYLATIONS USING ANOMERIC SULFONATES

Comparing with sulfoniums ions, sulfonates as glycosyl intermediates are less studied. Recent studies by Bennett and co-workers revealed its usefulness as a valuable intermediate for β-specific dehydrative glycosylation reactions with 2-deoxy sugars (Figure 1.20).[138] Remarkably, the stereoselectivity is reagent controlled and complimentary to sulfonium ion based methodology in the exclusive formation of β-glycosides. In the reaction, hemiacetal **49** is deprotonated by KHMDS and forms sulfonate esters **50** and **51** with tosyl 4-nitroimidazole. The glycosyl tosylates undergo rapid conversion to the more stable α-anomer **51** and are displaced by *O*- or *S*-nucleophiles upon the addition of acceptors, resulting in the inversion of anomeric stereochemistry.

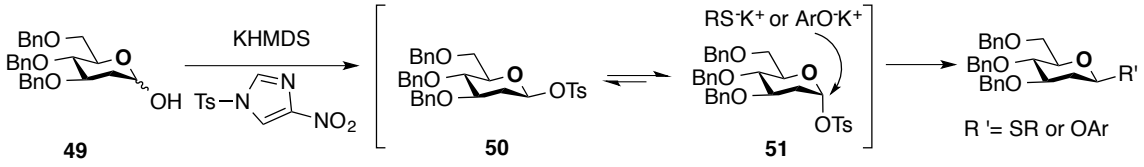

Figure 1.20: Anomeric sulfonate for reagent controlled β-glycosylation.

STEREOSELECTIVE GLYCOSYLATIONS USING ANOMERIC IMIDINIUM IONS.

Stereoselective control by solvent participations is perhaps the most widely applied method in glycosylations. Ether and nitrile are two typical solvents used for α and β-selective glycosylations, respectively. However, solvent is usually used in large excess and may be limited by solubility or melting point issues. Recently, Mong et al. demonstrated that DMF could be used as a nucleophilic participating additive in slightly

excess for α-selective glycosylations (Figure 1.21).[139,140] By using low temperature NMR, they observed the formation of α-glycosyl imidinium ion **53**, which presumably underwent a rapid equilibrium with the more reactive β-glycosyl imidinium ion **52**. Again, in a Curtin-Hamlete scenario, substitution of the β-imidinium ion provided the α-glycoside.

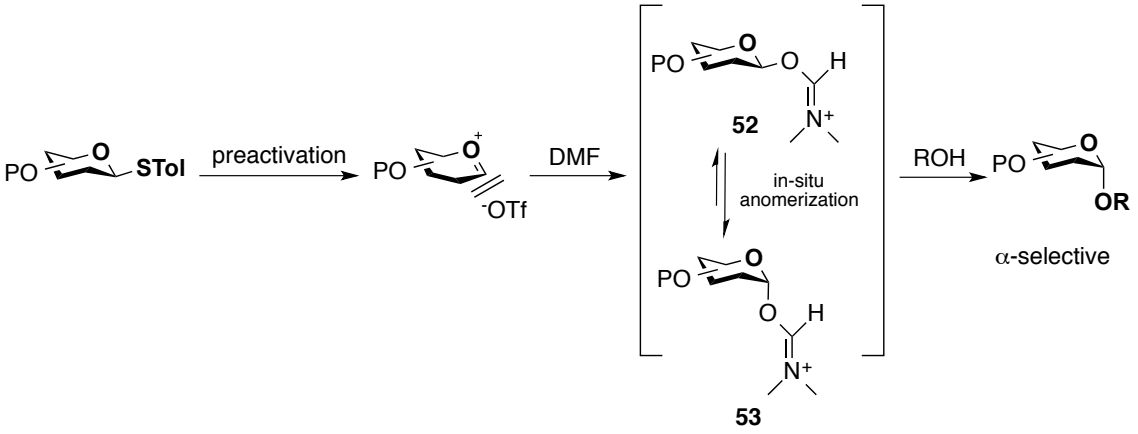

Figure 1.21: α-Selective glycosylation modulated by glycosyl imidinium ion.

CONCLUSION

The introduction was trying to emphasis the diverse roles of carbohydrates, especially in health related fields. We are encouraged by the tremendous advances in glycoscience. The achievements in illustrating biological functions and developing new analytical technologies and synthetic methodologies are pushing the boundaries of our understanding of carbohydrates, and new challenges inevitably emerge. The aims of the work described in this dissertation are to optimize the chiral auxiliary as a reliable tool for accessing complex oligosaccharides and further probing the essential elements of chiral auxiliary in regulating stereoselectivity. In the other aspect, synthetic

oligosaccharides have also been conjugated to different carrier constructs for testing immune response.

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CHAPTER 2

STEREOSELECTIVE ASSEMBLY OF COMPLEX OLIGOSACCHARIDES USING ANOMERIC SULFONIUM IONS AS GLYCOSYL DONORS[†]

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ABSTRACT

The development of selectively protected monosaccharide building blocks that can reliably be glycosylated with a wide variety of acceptors is expected to make oligosaccharide synthesis a more routine operation. In particular, there is an urgent need for the development of modular building blocks that can readily be converted into glycosyl donors for glycosylations that give reliably high 1,2-*cis*-anomeric selectivity. We report here that 1,2-oxathiane ethers are stable under acidic, basic, and reductive conditions making it possible to conduct a wide range of protecting group manipulations and install selectively removable protecting groups such as levulinoyl (Lev) ester, fluorenylmethyloxy- (Fmoc) and allyloxy- (Alloc) carbonates, and 2-methyl naphthyl ethers (Nap). The 1,2-oxathiane ethers could easily be converted into bicyclic anomeric sulfonium ions by oxidization to sulfoxides and arylated with 1,3,5-trimethoxybenzene. The resulting sulfonium ions gave high 1,2-*cis* anomeric selectivity when glycosylated with a wide variety of glycosyl acceptors including properly protected amino acids, primary and secondary sugar alcohols and partially protected thioglycosides. The selective protected 1,2-oxathianes were successfully employed in the preparation of a branched glucoside derived from a glycogen-like polysaccharide isolated form the fungus *Pseudallescheria boydii*, which is involved in fungal phagocytosis and activation of innate immune responses. The compound was assembled by a latent-active glycosylation strategy in which an oxathiane was employed as an acceptor in a glycosylation with a sulfoxide donor. The product of such a glycosylation was oxidized to a sulfoxide for a subsequent glycosylation. The use of Nap and Fmoc as temporary protecting groups made it possible to install branching points.

INTRODUCTION

Complex carbohydrates are involved in a wide range of biological processes such as cell-cell recognition, fertilization, embryogenesis, neuronal development, hormone activities, the proliferation of cells and their organization into specific tissues, viral and bacterial infection, and tumor cell metastasis.[1] Furthermore, carbohydrates are capable of inducing a protective antibody response, which is a major contributor to the survival of an organism during infection.[2] Oligosaccharides have also been found to control the development and defense mechanisms of plants.[3] The increased appreciation of the role of carbohydrates in the biological and pharmaceutical sciences has resulted in a revival of interest in carbohydrate chemistry.[4]

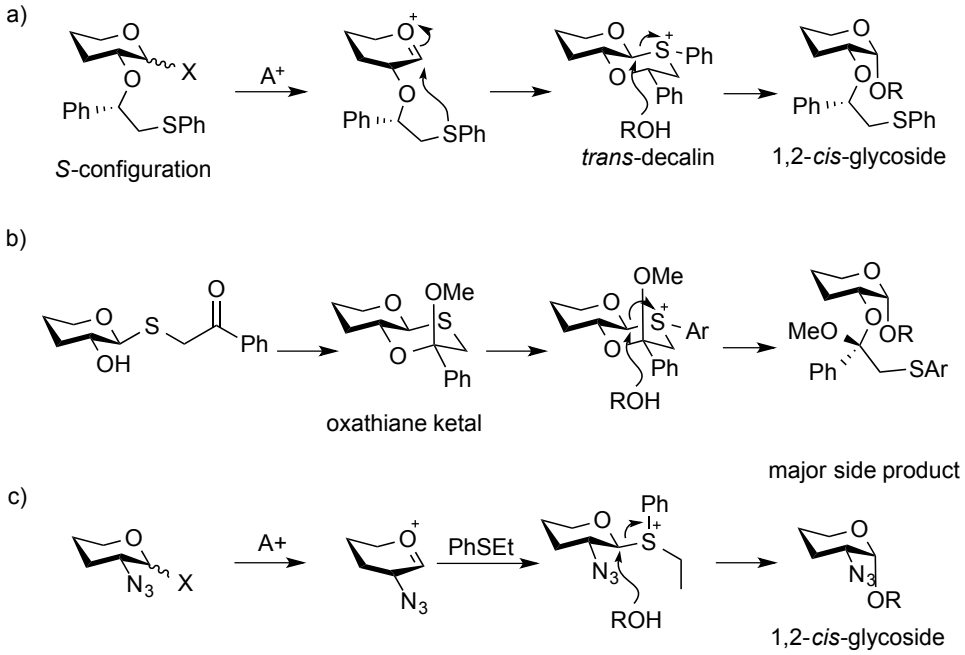
A major obstacle to advances in glycobiology and glycomedicine is the lack of pure and structurally well-defined carbohydrates and glycoconjugates. These compounds are often found in low concentrations and in microheterogeneous forms, greatly complicating their isolation and characterization. In many cases, well-defined oligosaccharides can only be obtained by chemical or enzymatic synthesis.[5] Unfortunately, no general method is available for the preparation of complex carbohydrates of biological importance.[6] As a result the chemical synthesis of each target compound is a challenging and time-consuming endeavor.

To speed up the process of oligosaccharide synthesis, efforts are underway to identify limited numbers of monosaccharide building blocks that can repeatedly be employed for the synthesis of a wide range of target structures.[7] Key features of such building blocks include modification at key positions with selectively removable protecting groups and providing reliably glycoside products in high yield with excellent anomeric control. In

respect to the latter, 1,2-*trans*-glycosides can reliably be introduced by employing a glycosyl donor modified at C-2 with a protecting group that can perform neighboring group participation during glycosylation. On the other hand, conventional methods to introduce 1,2-*cis* glycosides require glycosyl donors having a non-assisting functionality at C-2 and in these cases, reaction conditions such as solvent, temperature, and promoter as well as constitution of the glycosyl donor and acceptor (*e.g.* type of saccharide, leaving group at the anomeric center, protection, and substitution pattern) determine anomeric selectivity.[8] 1,2-*Cis* glycosylations give often mixtures of anomers, which requires time-consuming purification protocols resulting in loss of material, as well as limits the use of one-pot multi-step glycosylations[9] and automated polymer-supported synthesis.[10] Recent advances in anomeric control include the use of protecting groups that sterically shield the β-face of galactosyl donors[11] or locking a glycosyl donor in a conformation that allows nucleophilic attack from only one face of an anomeric oxa-carbenium ion.[12]

We have introduced a stereoselective glycosylation approach based on neighboring group participation by a (*S*)-phenylthiomethylbenzyl moiety at C-2 of a glycosyl donor (Scheme 2.1a).[13-15] Upon formation of an oxacarbenium ion, the nucleophilic thiophenyl moiety of the C-2 functionality participates leading to the formation of an intermediate sulfonium ion. The formation of the *trans*-decalin stereoisomer is strongly favored because of the absence of unfavorable gauche interactions. In addition, the alternative *cis*-decalin system places the phenyl-substituent in an axial position inducing further unfavorable steric interactions. Displacement of the equatorial anomeric sulfonium ion by a sugar alcohol leads to the formation of a 1,2-*cis*-glycoside. We have shown that the (*S*)-(phenylthiomethyl)benzyl moiety can readily be introduced by reaction of a sugar alcohol

with (*S*)-(phenylthiomethyl)benzyl acetate in the presence of BF_3-OEt_2 and removed by conversion into an acetyl ester by treatment with BF_3-OEt_2 in acetic anhydride. The attractiveness of chiral auxiliary mediated glycosylations has been shown by solid phase synthesis of several branched pentasaccharides having only 1,2-*cis*-glycosidic linkages.[16] The proposed participation mechanism is supported by low temperature NMR experiments, which unambiguously identified a β-substituted sulfonium ion as a reaction intermediate. Furthermore, the displacement mechanism is supported by the observation that glycosylations with donors having a C-2 auxiliary with incorrect stereochemistry {(*R*)-(phenylthiomethyl)benzyl} give mixtures of anomers.



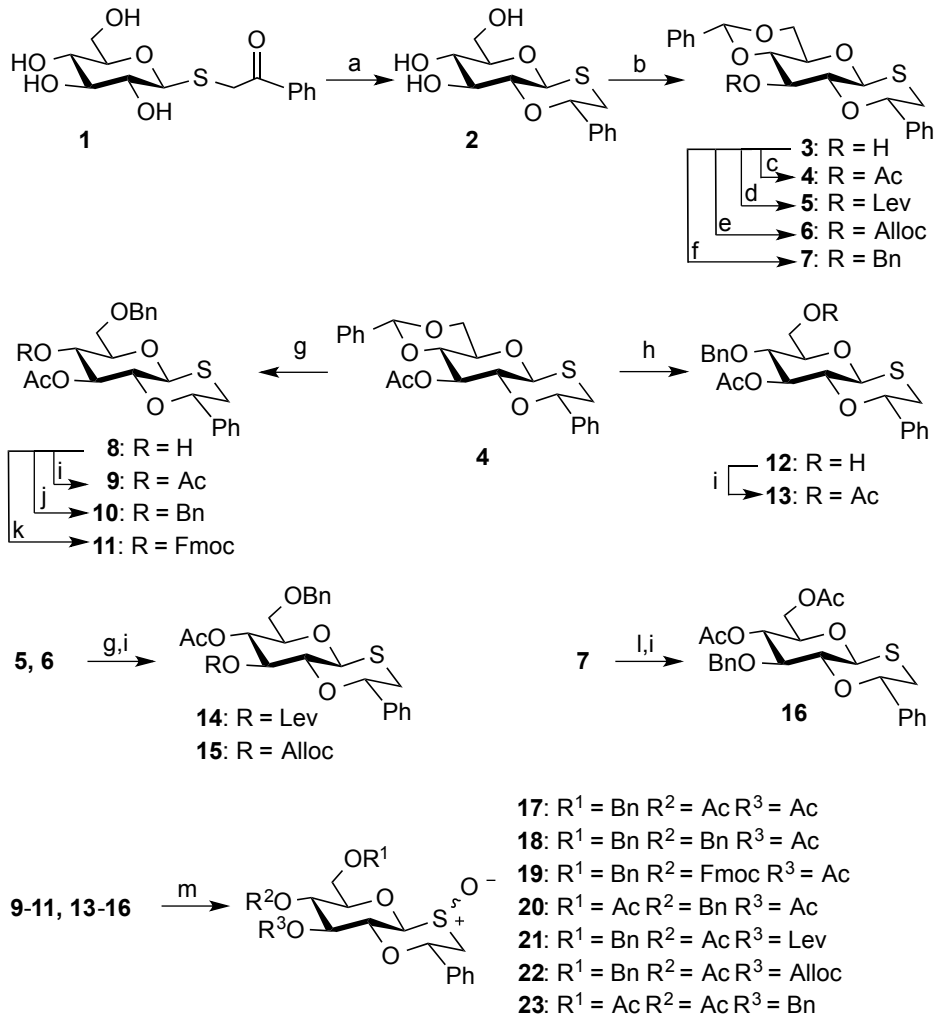
Scheme 2.1: Schematic presentation of sulfonium ion promoted 1,2-*cis* glycosylations. a) Neighboring group participation by C-2 (*S*)-auxiliary leading to 1,2-*cis* glycosides; b) Sulfonium ion formation from precyclized oxathiane ketal; c) Sulfonium ion formation in the presence of thioether.

Several other studies have shown the usefulness of anomeric sulfonium ions for stereoselective glycosylations. In this respect, a number of donors having an achiral thioether at C-2 have been examined and some of these derivatives gave remarkably good α-anomeric selectivity.[13,17] Another interesting approach for forming bicyclic anomeric sulfonium ions involves arylation of 1,2-oxathiane ketals, which can easily be prepared from a thioglycoside (Scheme 2.1b).[18-20] The addition of a thioether to traditional glycosylations or alkylation of thioglycosides can also lead to the formation of anomeric sulfonium ions and enhance alpha-anomeric selectivity (Scheme 2.1c).[21,22] To advance auxiliary mediated glycosylations for building block based oligosaccharide synthesis, it is critical to establish convenient procedures for the preparation of selective protected anomeric sulfonium ions, which can be employed in glycosylations that allow rapid assembly of complex branched compounds. We report here that 1,2-oxathiane ethers are stable under acidic, basic, and reductive conditions making it possible to conduct a wide variety of protecting group manipulations to give panels of selectively protected compounds. The resulting 1,2-oxathiane ethers can easily be converted into bicyclic anomeric sulfonium ions by oxidization to sulfoxides, followed by arylation with 1,3,5-trimethoxybenzene. It is shown that the latter compounds are appropriate glycosyl donors for highly selective 1,2-*cis* glycosylations provided that they are sufficiently deactivated with electron withdrawing protecting groups. The selective protected 1,2-oxathianes were successfully employed for the preparation of a branched glucoside derived from *Pseudallescheria boydii*,[23] which is involved in fungal phagocytosis and Toll-like receptor activation.

RESULT AND DISCUSSION

Synthesis and Glycosylations of Oxathiane. We have observed that the (*S*)-(phenylthiomethyl)benzyl ethers are sensitive to moderately strong acidic conditions complicating a number of important protecting group manipulations. We envisaged that this problem could be addressed by using 1,2-oxathiane ethers as precursors of anomeric sulfonium ions. 1,2-Oxathiane ethers were expected to be stable under acidic conditions because their ring structure prevents the sulfur atom of participating in acid catalyzed cleavage of the benzylic ether linkage, and thus should be compatible with a wide variety of protecting group manipulations. These compounds can, however, be readily converted into an anomeric sulfonium ions by oxidative arylation, for stereoselective 1,2-*cis*-glycosylations.[15,20]

To explore the compatibility of 1,2-oxathiane ethers with a range of protecting group manipulations, compounds **9**-**11** and **13**-**16** were prepared which differ in the pattern of ether and ester protecting groups (Scheme 2.2). Furthermore, several of these derivatives are protected with Alloc, Lev or Fmoc protecting groups, which can be selectively removed under mild conditions providing opportunities for further functionalization. The selectively protected 1,2-oxathianes can be oxidized to the corresponding sulfoxides **17**-**23**, which can then be used for the generation of sulfonium ions for subsequent glycosylations.



Scheme 2.2: Synthesis of 1,4-oxathiane protected donors. a) TMS_2O, TMSOTf, 0 ^oC, 30 min, then Et_3SiH, 3 h (74%); b) $PhCH(OMe)_2$, CSA, reduced pressure, DMF, 50 ^oC,18 h (87%); c) Ac_2O, Py; d) Levulinic acid, DCC, DMAP, DCM (79%); e) AllocCl, TMEDA, DMAP, DCM (87%); f) BnBr, NaH, DMF (79%); g) Et_3SiH, TfOH, DCM, -78 ^oC; h) Et_3SiH, $PhBCl_2$, -78 ^oC; i) Ac_2O, Py(**9**: 85%, g, i 2 steps; **13**: 78%, h, i 2 steps; **14**: 79%, g, i 2 steps; **15**: 92%, g, i 2 steps; **16**: 84%, l, i 2 steps); j) Ag_2O, BnBr (**10**: 55%, g, j 2 steps); k) FmocCl, Py/DCM = 1/1 (v/v) **(11**: 66%, g, k 2 steps); l) EtSH, TsOH, DCM; m) *m*CPBA, DCM, -78 ^oC (**17**: 92%; **18**: 96%; **19**: 98%; **20**: 93%; **21**: 98%; **22**: 82%; **23**: 96%).

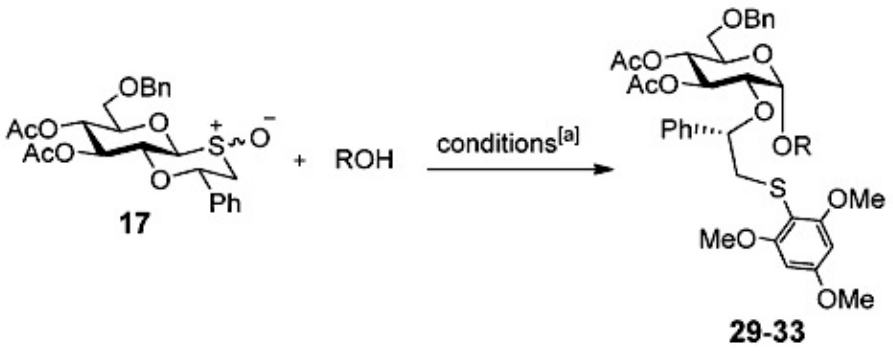
Thus, oxathiane **2** was prepared on large scale by a one-pot two-step reaction involving treatment of **1** with TMS_2O in the presence of TMSOTf to give an intermediate trimethylsilyl acetal, which was reduced by the addition of Et_3SiH. The 4,6-diol of **2** was protected as a benzylidene acetal by treatment with (dimethoxymethyl)benzene in the presence of camphorsulfonic acid (CSA) in DMF under reduced pressure to give **3** in a yield of 87%. The C-3 hydroxyl of compound **3** was protected as an acetyl- and levulinoyl- (Lev) ester,[24] fluorenylmethyloxy- (Fmoc)[25] and allyloxy- (Alloc)[26] carbonate, and benzyl ether using standard conditions to give fully protected **4**, **5**, **6**, and **7**, respectively. The benzylidene acetal of **4** was reductively opened using Et_3SiH and triflic acid (TfOH) in DCM at -78 ^oC[27] to give compound **8** having a C-4 hydroxyl which was acetylated with Ac_2O in pyridine, benzylated under neutral conditions using benzyl bromide and Ag_2O in DMF, or treated with FmocCl in a mixture of pyridine and CH_2Cl_2 to provide selectively protected oxathianes **9**, **10**, and **11**, respectively. Alternatively, the benzylidene acetal of **4** could be opened by treatment with Et_3SiH and $PhBCl_2$ at -78 ^oC[27] to give **12** having a C-6 hydroxyl, which was acetylated to give derivative **13**. The benzylidene acetals of compounds **5** and **6** could also be selectively opened to give derivatives having a C-4 alcohol, which were acetylated using standard conditions to provide compounds **14** and **15**, respectively. Finally, the benzylidene acetal of **7** was removed by treatment with *p*-toluenesulfonic acid in the presence of ethanethiol to give a diol, which was acetylated to provide derivative **16**. The selectively protected oxathianes **9-11** and **13-16** were oxidized by *m*CPBA at -78 ^oC to give sulfoxides **17-23** as mixtures of diastereoisomers. The successful preparation of these compounds demonstrates that

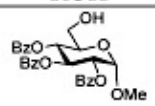
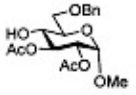
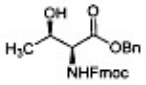
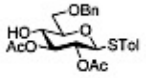
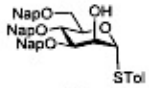
oxathianes can be subjected to a wide variety of protecting group manipulation and withstand acidic, basic and reductive conditions.

Having the sulfoxides **17**-**23** at hand, attention was focused on their conversion into anomeric sulfonium ions for subsequent glycosylations. In this respect, activation of the sulfoxides by triflic anhydride in the presence of trimethoxybenzene will result in arylation of sulfur to give an intermediate sulfonium ion.[15,18] In the first instance, oxathiane **17** was explored as a glycosyl donor for glycosylations with a variety of different glycosyl acceptors (Table 2.1). Thus, **17** was activated with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 1,3,5-trimethoxybenzene in DCM at -10 ^{o}C. After completion of the electrophilic aromatic substitution and formation of the intermediate sulfonium ion, alcohols **24**-**28** were added and after a reaction time of 16 h at room temperature, the disaccharides **29**-**33** were isolated by size exclusion column chromatography and anomeric selectivities determined by careful analysis of ^{1}H NMR spectra. Each glycosylation proceeded with exceptional high alpha-anomeric selectivity, however, in the case of acceptors **24**, **25**, and **27** a trace amount of beta-amomer was detected. The use of primary and secondary sugar alcohols gave the corresponding disaccharides in good to excellent yields. The glycosylation protocol is also compatible with the use of appropriately protected amino acids and for example glycosylated threonine derivative **31** could be prepared in high yield as only the α-anomer. Furthermore, it was also found that thioglycosides can be employed as glycosyl acceptor and for example the use of **27** and **28** led to clean formation of disaccharides **32** and **33**, respectively. The latter type of glycosylation is attractive because it is to be expected that the thioglycosyl products can employed as glycosyl donors in subsequent glycosylations

using an appropriate thiophilic reagent thereby offer a rapid strategy for oligosaccharide assembly.

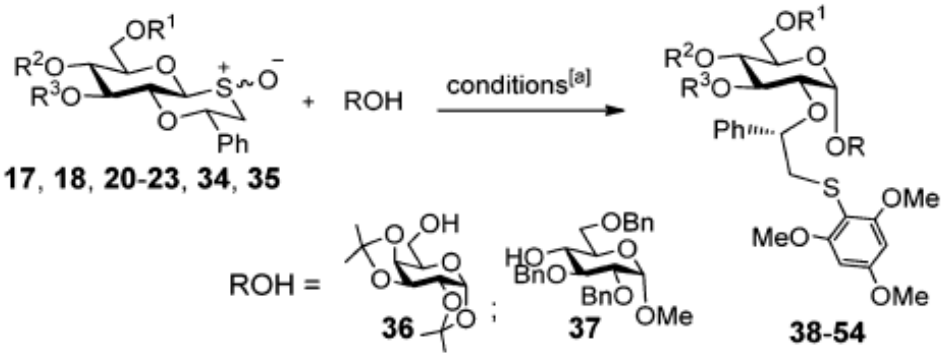
Table 2.1: Stereoselective glycosylations between donor **17** and various acceptors.



Entry	ROH	Product	Yield[b]	α:β[c]
1	 **24**	**29**	91%	>15:1
2	 **25**	**30**	62%	>25:1
3	 **26**	**31**	89%	α only
4	 **27**	**32**	67%	>15:1
5	 **28**	**33**	72%	α only

[a] 1,3,5-Trimethoxybenzene, Tf_2O, DTBMP, molecular sieves 4 Å, -10 ^oC, 30 min, then add acceptor, -40 ^oC to room temperature, 16 h. [b] Isolated yields of the α/β mixture of disaccharide products. [c] The α/β ratios were determined by the integration of key signals in the ^1H NMR spectra of the disaccharide products after purification by LH-20 size exclusion chromatography.

Table 2.2： Protecting group pattern effect on stereoselectivity.



entry	donor	R^1	R^2	R^3	ROH	product	yield[b] (%)	α/β ratio[c]
1	**34**	Ac	Ac	Ac	**36**	**38**	80	α only
2	**34**	Ac	Ac	Ac	**24**	**39**	59	α only
3	**34**	Ac	Ac	Ac	**37**	**40**	48	α only
4	**20**	Ac	Bn	Ac	**36**	**41**	84	α only
5	**20**	Ac	Bn	Ac	**37**	**42**	59	>15:1
6	**17**	Bn	Ac	Ac	**36**	**43**	94	α only
7	**17**	Bn	Ac	Ac	**37**	**44**	67	>25:1
8	**22**	Bn	Ac	Alloc	**36**	**45**	67	α only
9	**22**	Bn	Ac	Alloc	**24**	**46**	78	>15:1
10	**21**	Bn	Ac	Lev	**36**	**47**	85	>15:1
11	**21**	Bn	Ac	Lev	**37**	**48**	64	>15:1
12	**23**	Ac	Ac	Bn	**36**	**49**	98	α only
13	**23**	Ac	Ac	Bn	**37**	**50**	46	7:1
14	**18**	Bn	Bn	Ac	**36**	**51**	95	>15:1
15	**18**	Bn	Bn	Ac	**37**	**52**	66	10:1
16	**35**	Bn	Bn	Bn	**36**	**53**	98	>15:1
17	**35**	Bn	Bn	Bn	**37**	**54**	57	1.5:1

[a] 1,3,5-Trimethoxybenzene, Tf_2O, DTBMP, molecular sieves 4 Å, -10 °C, 30 min, then add acceptor, -40 °C to r.t., 16 h. [b] Isolated yields of the α/β mixture of disaccharide products. [c] The α/β ratios were determined by the integration of key signals in the ^1H NMR spectra of the disaccharide products after purification by LH-20 size exclusion chromatography.

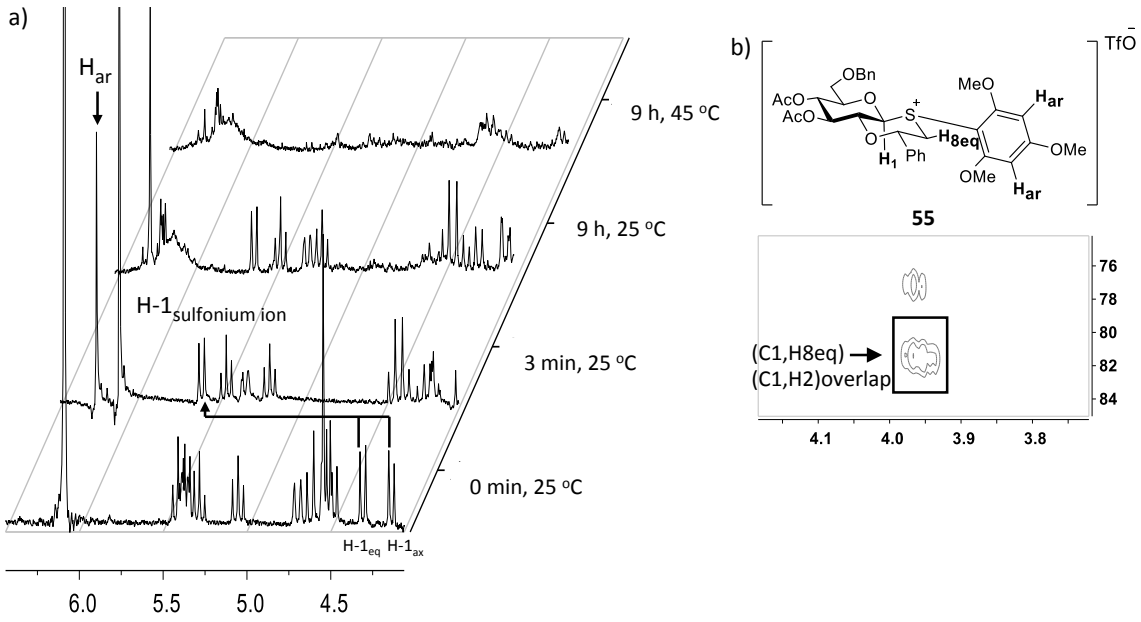
Next, we explored whether protecting groups commonly employed in oligosaccharide synthesis are compatible with the glycosylation protocol. Thus, glycosyl donors **17**, **18**, **20-23**, **34**, and **35** were activated by triflic anhydride in the presence of 1,3,5-trimethoxybenzene to give intermediate sulfonium ions, which were glycosylated with acceptors **36** and **37**. As can be seen in Table 2.2, the expected disaccharides **38-54** were isolated in good to excellent yields. Furthermore, glycosyl donors modified with electron withdrawing protecting groups at C-3, 4, and 6 gave the corresponding disaccharides as only the alpha-anomer (entry 1-4). Glycosyl donors that had an ether function at C-4 or C-6 (entries 5-11) gave exceptional high alpha anomeric selectivities (α:β > 15:1). Highly reactive donors having multiple ether type protecting groups gave in some case disaccharides with modest anomeric selectivities (entries 13 and 17). These observations are in agreement with previous finding[15] that highly reactive anomeric sulfonium ions can react through an oxacarbenium ion resulting in loss of α-anomeric selectivity.

Characterization of Sulfonium Ions by NMR. To ascertain that glycosylations of oxathianes proceed through a sulfonium ion intermediates, compound **17**, trimethoxybenzene, and DTBMP were dissolved in $CDCl_3$, activated with triflic anhydride and ^{1}H, gCOSY, gHSQC, and HMBC spectra were recorded (Figure 2.1). As expected, the chemical shift of H-1 of the newly formed product shifted down field (δ = 4.31 and δ = 4.15 to δ = 5.60) and exhibited $J_{1,2}$ = 9 Hz, which is consistent with a β-anomeric configuration. Full assignment of proton and carbon signals could be made by gCOSY and gHSQC. Careful analysis of proton coupling constants indicated that no conformational distortion of the saccharide ring had occurred. The presence of a carbon-

sulfur linkage of the sulfonium ion was established by an HMBC experiment, which allows the determination of three-bond proton-carbon couplings. In particular, a strong correlation was observed between C-1 and H8eq, confirming the presence of a *trans*-decalin system. Furthermore, the smaller geminal-coupling constant between H8eq and H8ax (12 Hz) indicates that the trimethoxyphenyl substituent of sulfur adopts an equatorial orientation. Comparing chemical shifts of the trimethoxyphenyl (H8eq 3.98, H8ax 4.28 ppm) and phenyl (H8eq 4.32, H8ax 3.66 ppm) substituted sulfonium ion indicates that their aromatic rings adopt different conformations and in particular deshielding of H8ax of the trimethoxylbenzene substituted system indicates that the trimethoxybenzene group is perpendicular to the plane of the sugar ring (see SI for further details).

Interestingly, sulfonium **55** was stable at room temperature for 9 h, while subsequent incubation at 45^{o}C for 5 min resulted in complete decomposition. It was also noticed that the excess of trimethoxylbenzene was further consumed after complete formation of the sulfonium ion, and was no longer present after an incubation time of 9 h.

A number of additional sulfonium ions (**56-61**) were generated and their structure and reactivity studied by NMR. Thus, compounds **55-58** were prepared by arylation of the corresponding sulfoxides and differ in the pattern of protecting groups at C-3, C-4, and C-6. Compounds **59-61** were prepared by methylation of the corresponding sulfoxides with methyl triflate and also differ in hydroxyl protection. Finally, acyclic sulfonium ion **62** was formed by methylation of the corresponding methyl thioglycoside with methyl triflate.



c)

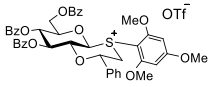
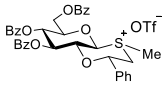
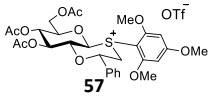
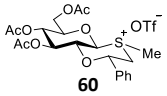
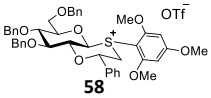
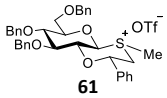
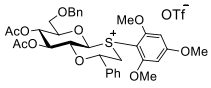
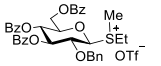
Entry	Sulfonium Ion[a]	$\delta_{H\text{-}1}$ (ppm)	$\delta_{C\text{-}1}$ (ppm)	Entry	Sulfonium Ion[a]	$\delta_{H\text{-}1}$ (ppm)	$\delta_{C\text{-}1}$ (ppm)
1	 **56**	5.81	81.6	5	 **59**	5.78	83.7
2	 **57**	5.67	81.5	6	 **60**	5.47	83.4
3	 **58**	5.61	81.7	7	 **61**	5.31	83.7
4	 **55**	5.60	81.5	8[b]	 **62**	5.31	82.3

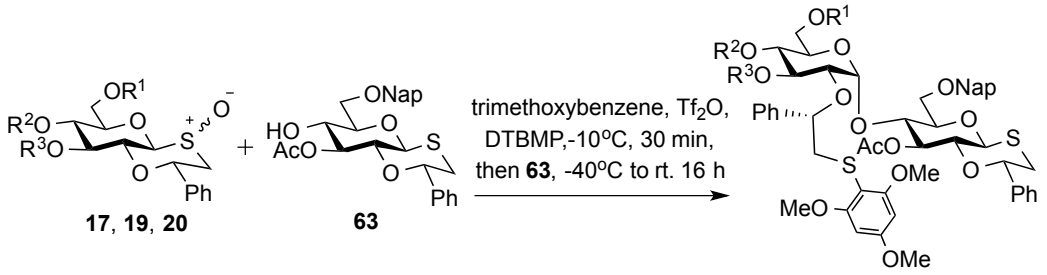
Figure 2.1: NMR study of sulfonium ions. a) thermostability of sulfonium ion **55**; b) HMBC spectrum of sulfonium ion **55**. c) Comparison of electronic properties of different sulfonium ions by NMR chemical shift (all chemical shifts were referred to TMS). [a] Stereochemistry at sulfur was assigned by empirical rules[28] using H-8ax,eq geminal coupling. [b] Cited data.[22]

As expected sulfonium ions **55-58** are stable at room temperature but readily react with alcohols to give mainly or exclusively α-glucosides. Interestingly, exposure of sulfonium ion **59** to an excess of methanol did not lead to glucoside formation and this compound was unaltered after a reaction time of 24 h. Benzylated sulfonium ion **61** was slightly more reactive and exposure to an excess of **24** gave the corresponding glucoside in a low yield of 21% as a mixture of anomers. These results clearly demonstrate that the nature of the sulfonium ion is a major determinant of anomeric reactivity. It was also found that the cyclic nature of sulfonium ions influences anomeric reactivity and for example within 15 min acyclic sulfonium ion **62** reacted with excess methanol to give a methyl glycoside whereas the corresponding cyclic sulfonium ion **59** is unreactive under these conditions.[22]

It is well known that carbon chemical shifts are mainly determined by local electronic environment.[29] Interestingly, it was observed that the chemical shift of C-1 of the arylated and alkylation sulfonium ions differ by approximately 2 ppm indicating a lower electronic density at C-1 of alkylated sulfonium ion, which surprisingly did not result a higher reactivity towards alcohols. Probably, the higher reactivity of the arylated sulfonium corresponds to its better leaving group ability. In this respect, a weaker base constitutes in general a better leaving group. Furthermore, it has been established that the relative stabilities of sulfonium ions corresponds with the relative basicities of the corresponding leaving group.[30] The fact that thioanisol is a weaker base than dimethyl sulfide[30,31] would indicate that arylated sulfonium ion are less stable and provide a better leaving. This is in agreement with the observations described above.

Chemical Synthesis of an Immuno-active Glycogen-like Component. Having established a range of selective protected oxathiane building blocks suitable for selective 1,2-*cis*-glycosylations, attention was focused on the preparation of tetraglucoside **79**, which is derived from the cell wall polysaccharide of the fungus *Pseudallescheria boydii*.[23] This fungus is found in soil and polluted water and can cause infections in immuno-compromised and immuno-competent hosts. Recent structural studies have shown that the cell wall of *P. boydii* contains a glycogen like component that is composed of a α(1-4)-linked glucopyranoside backbone modified at C-6 with α-Glc*p* moieties.[32] A soluble form of the polysaccharide could inhibit phagocytosis in a dose dependent manner and furthermore enzymatic degradation of the glycogen-like component of *P. boydii* could reduce the phagocytic index demonstrating that it plays a key role in phagocytosis. It has also been shown that the α-glucan can induce cytokine secretion in a TLR2-dependent manner. The minimal structural motif that can induce these properties is difficult to establish due to structural heterogeneity of the polysaccharide. However, it is to be expected that this problem can be addressed by chemically synthesizing a library of glucans differing in C-6 branching patterns.

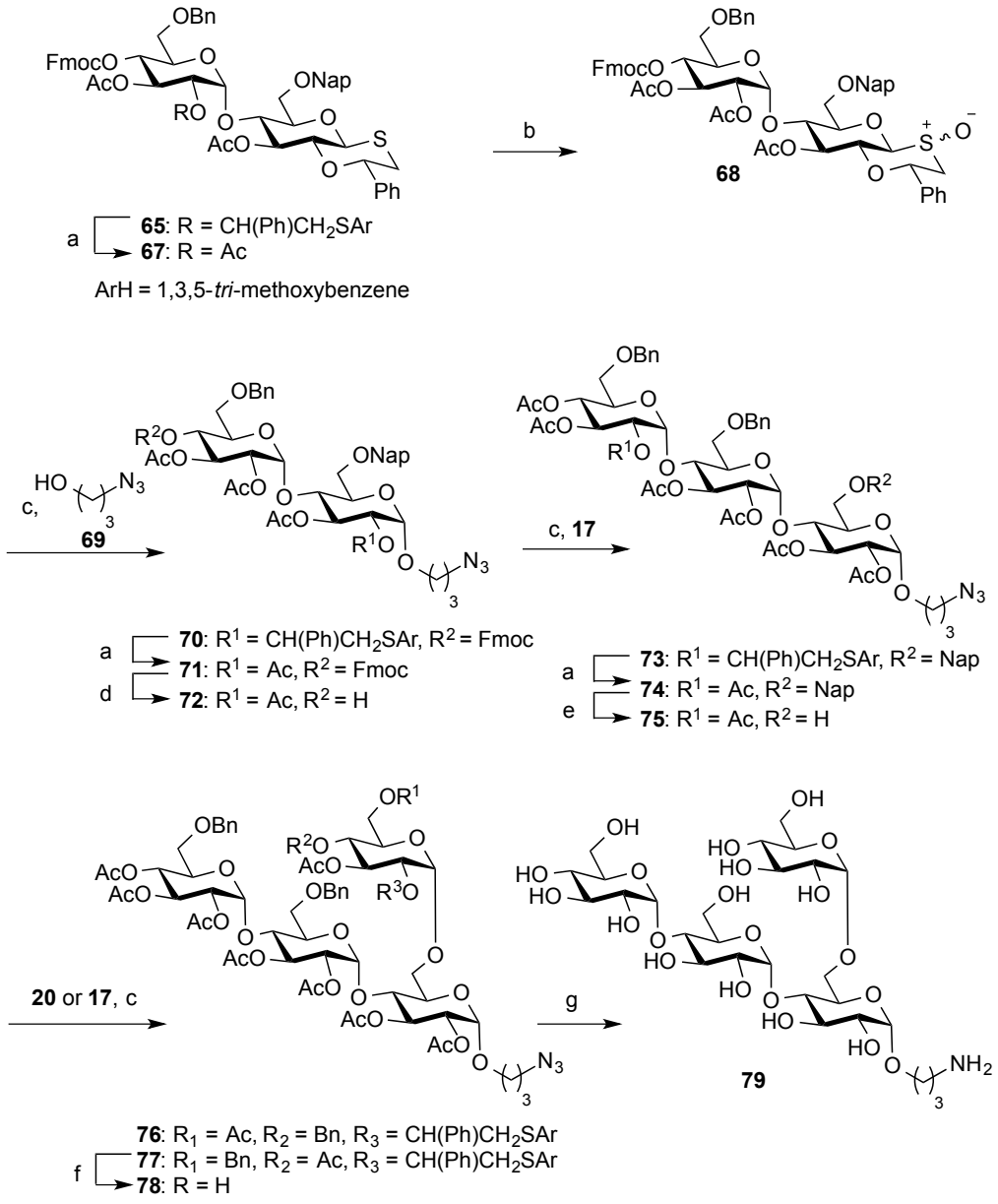
α-Glucans represent a considerable synthetic challenge due to the presence of multiple 1,2-*cis* glycosidic linkages, the low reactivity of C-4 hydroxyls of glucosyl acceptors and the branched nature of the compound. Therefore, this component offered an exciting opportunity to examine the usefulness of oxathianes for the preparation of complex and biological important compounds.



64: R^1 = Bn, R^2 = Ac, R^3 = Ac; α/β>15:1, 68%[a]
65: R^1 = Bn, R^2 = Fmoc, R^3 = Ac; α/β>15:1, 55%[a]
66: R^1 = Ac, R^2 = Bn, R^3 = Ac; α/β>25:1, 55%[a]

Scheme 2.3: Latent-active glycosylation strategy. [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.

We envisaged that α-glucans such as **79** can be assembled by a latent-active glycosylation strategy[33] in which a sulfoxide donor is coupled with an oxathiane acceptor to give a product that can be oxidized to a sulfoxide for further glycosylations (Schemes 3 and 4). To establish the feasibility of such a latent-active glycosylation strategy, sulfoxides **17**, **19**, and **20** were treated with Tf_2O in the presence of 1,3,5-trimethoxybenzene to form an intermediate sulfonium ion, which was glycosylated with oxathiane **63** to give disaccharide **64-66** as mainly alpha-glucosides. These results demonstrate that oxathianes are stable under the condition used for arylation of sulfoxides to give sulfonium ion.



Scheme 2.4: Synthesis of the glycogen-like glucan isolated from *P. boyii*. a) i. 10% TFA in DCM, 0 ^{o}C, 1 h; ii. Ac_2O, Py (**67**: 89%, 2 steps; **71**: 98%, 2 steps; **74**: 76%, 2 steps); b) *m*CPBA, DCM, -78 ^{o}C (98%); c) general glycosylation condition (**70**: 86%, α only; **73**: 65%, α/β>15:1; **76**: 70%, α only; **77**: 73%, α/β=8:1); d) 20% NMP in DMF, 30 min (91%); e) DDQ, H_2O:DCM=1:10 (92%); f) 10% TFA in DCM, 0 ^{o}C, 1 h (85%); g) i. NaOMe, MeOH; ii. H_2, $Pd(OH)_2$/C, *t*BuOH-H_2O-AcOH=40:1:1 (83%, 2 steps).

It was expected that disaccharide **65** would be a suitable substrate for the preparation of target compound **79**. In this respect, the anomeric oxathiane can be oxidized to a sulfoxide and then converted into a sulfonium ion for glycosylation with a properly protected aminopropyl spacer. Furthermore, the Nap[34] ether at C-6 and Fmoc carbonate at C-4 are fully orthogonal and will allow glucosylations at these positions to give after deprotection the expected tetrasaccharide **79**.

First, the C-2 auxiliary of **65** was converted into an acetyl ester to give **67** using a standard procedure. This additional step was required to avoid oxidation of the (2,4,6-trimethoxyphenyl)sulfane moiety of the non-reducing glucoside during the subsequent oxidation step to convert the oxathiane moiety into a sulfoxides. As expected, compound **67** could be cleanly oxidized to the corresponding sulfoxides, which was activated with Tf_2O/1,3,5-trimethoxybenzene to give an anomeric sulfonium ion that was glycosylated with alcohol **69** to provide spacer-containing **70** as only the alpha-anomer. The C-2 auxiliary of **70** was converted into an acetyl ester and the Fmoc group of the resulting compound **71** was cleaved by treatment with *N*-methyl-2-pyrrolidone (NMP) in DMF to give glucosyl acceptor **72**. Next, glycosyl acceptor **72** was coupled with the sulfonium ion derived from sulfoxide **17** using standard conditions to give trisaccharide **73** as mainly the alpha glucoside. The trace amount of unwanted β-anomer could easily be removed by silica gel column chromatography. The C-2 auxilairy of **73** was converted into an acetyl ester by standard procedures to give compound **74**, which was converted into glycosyl acceptor **75** by oxidative removal of the Nap ether using 5,6-dicyano-1,4-benzoquinone (DDQ) in a mixture of DCM and water. A Tf_2O/1,3,5-trimethoxybenzene mediated glycosylation of **17** with **75** gave tetrasaccharide **77** as an 8/1 mixture of

alpha/beta anomers. In order to improve the anomeric selectivity, the glycosylation was repeated with glycosyl donor **20** having an acetyl esters at C-3 and C-6 and a benzyl ether at C-4 and gratifyingly the use of this compound gave tetrasaccharide **76** in a yield of 70% as only the alpha anomer. Deprotection could easily be accomplished by a three-step procedure involving treatment with TFA in DCM to remove the C-2 auxiliary, saponification of the acetyl esters with sodium methoxide in methanol and catalytic hydrogenolysis of the benzyl ether and the reduction of azide using $Pd(OH)_2/C$. The structural identity of α-glucan **77** was confirmed by homo- and heteronuclear two dimensional NMR (gCOSY and gHSQC) experiments and in particular the chemical shifts and coupling constants of the anomeric protons confirmed (1→4) and (1→6)-linked alpha-glucosidic linkages.[35]

CONCLUSIONS

Modular building blocks that can readily be converted into glycosyl donors and acceptors have the potential to speedup the process of oligosaccharide assembly. The potential of such a strategy will, however, only be realized when building blocks will be developed that reliably give high 1,2-*cis*-anomeric selectivities. Previously, we introduced a stereoselective 1,2-*cis*-glycosylation approach based on neighboring group participation by a (*S*)-phenylthiomethylbenzyl moiety at C-2 of a glycosyl donor to give a bicyclic β-sulfonium ion intermediate that can readily be displaced by sugar alcohol leading to the formation of 1,2-*cis*-glycosides. Although the auxiliary mediated approach has many attractive features, the acid sensitivity of the (*S*)-phenylthiomethylbenzyl moiety complicates certain protecting group manipulation, which in turn makes it difficult to

develop robust modular building blocks. We describe here that monosaccharides protected as 1,2-oxathiane ethers are stable to commonly employed protecting groups manipulations making it possible to install a variety of selectively removable protecting groups such as Lev ester, Fmoc and Alloc carbonates, and Nap ether. Furthermore, the 1,2-oxathiane ether could easy be installed by a novel one-pot two-step procedure and it was found that protection of the 1,2-diol facilitated modification of the C-3, C-4 and C-6 alcohols. The resulting 1,2-oxathianes could be employed as glycosyl donors for highly selective 1,2-*cis*-glycosylation by oxidation to sulfoxides followed by arylation with 1,3,5-trimethoxybenzene to give a bicyclic anomeric sulfonium ion. The attractiveness of the new building blocks has been demonstrated by the preparation of a biologically important branched α-glucan, which was assembled by a latent-active glycosylation strategy.

EXPERIMENTAL SECTION

Full experimental is available in Supporting Information online. Compounds **1**,[18] **24**,[36] **25**,[37] **26**,[38] **27**,[39] **34**,[15] **35**,[15] and **37**[40] were prepared following literature procedures.

General Procedure for the Preparation of Sulfoxide Donors 17 - 23 from their Corresponding Oxathianes 9 - 11 and 13 - 16. *m*-CPBA (≤ 77%, l.1 eq.) was dissolved in DCM and slowly injected into a cooled (-78 ^{o}C) solution of oxathiane in DCM. The mixture was stirred at -78 ^{o}C for 30 min, diluted with DCM (50 mL) and then poured into 10% $Na_2S_2O_3$ aqueous solution. The organic layer was washed with saturated $NaHCO_3$,

dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography.

General Glycosylation Procedure for Oxathiane Donors with Various Acceptors. A mixture of sulfoxide donor (1 eq.), 1,3,5-trimethoxybenzene (1.5 eq.), 2,6-di-*tert*-butyl-4-methyl pyridine (2 eq.), and activated molecular sieves (4 Å) in DCM (adjusted donor concentration to 0.15 M) was stirred for 1 h under an atmosphere of argon. After cooling to -10 ^oC, trifluoromethanesulfonic anhydride (1.1 eq.) was added. After 30 min, the reaction mixture was cooled (-40 ^oC), and a solution of acceptor (0.8 eq.) in DCM (adjusted donor concentration to 0.1 M) was added slowly. The temperature of the reaction mixture was kept at -40 ^oC for another 60 min before allowed to warm to room temperature. After 15 h, the reaction mixture was diluted with DCM (10 mL), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography or sephadex® LH20 size exclusion chromatography (DCM/MeOH = 1/1, 0.2 mL/min).

General Procedure for the Removal of C-2 Auxiliary. Trifluoroacetic acid was added dropwise to a solution of glucoside in DCM at 0 ^oC adjusting the final concentration to 10% (v/v). The reaction mixture was stirred for 0.5-3 h until TLC indicated complete consumption of starting material. The reaction mixture was diluted with DCM and poured into saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography.

Procedures for NMR Study of Sulfonium ions. *S*-(2,3,5-trimethoxylphenyl)-oxathianium triflate: A mixture of R/S sulfoxides (10 μmol), 1,3,5-trimethoxybenzene (16 μmol), 2,6-di-*tert*-butyl-4-methyl pyridine (21 μmol), and activated molecular sieves (4 Å, pellets) in $CDCl_3$ (1 mL) was shaken for 30 min under an atmosphere of argon. Then 0.5 mL of the solution was transferred to a 5 mm NMR tube and sealed. After cooling to 0 ^oC, a trifluoromethanesulfonic anhydride stock solution (25 μL, 0.23 M in $CDCl_3$) was added and NMR spectra for **55**–**58** were recorded at room temperature. *S*-methyl-oxathianium triflate: Sulfide (10 μmol) was dissolved in dry $CDCl_3$ (1 mL), methyl triflate (0.1 mmol) was added under the atmosphere of argon at room temperature. The reaction mixture was stirred for 2-16 h and monitored by TLC. After the consumption of sulfide, 0.5 mL of the reaction mixture was transferred to a 5 mm NMR tube and sealed. NMR spectra for **59**–**61** were recorded at room temperature.

2-(*S*)-Phenyl-(1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (2). Compound **1** (11 g, 35 mmol) was dissolved in anhydrous CH_3CN (400 mL) and hexamethyldisiloxane (TMS_2O) (44 mL, 0.21 mol) and TMSOTf (6.6 mL, 37 mmol) were added. After 30 min, Et_3SiH (46 mL, 0.29 mol) was added and the reaction mixture was stirred for another 4 h before quenching by the addition of MeOH (50 mL) and Et_3N (10 mL). The solution was concentrated *in vacuo* and the resulting yellow oil was purified by flash chromatography over silica gel (toluene/acetone, 3/1→1/1, v/v) to give **2** (7.7 g, 74%). Proton chemical shifts are identical to reported data.[18] ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.09 (m, 5H, Ar*H*), 4.67 (dd, J = 10.6, 1.6 Hz, 1H, SCH_2CHPh), 4.35 (d, J = 8.2 Hz, 1H, H-1), 3.84 – 3.71 (m, 2H, H-$6_{a,b}$), 3.70 – 3.43 (m, 3H, H-2, H-3,

H-4), 3.43 – 3.29 (m, 1H, H-5), 3.00 (dd, J = 13.9, 10.8 Hz, 2H, SC*H*HCHPh), 2.69 (d, J = 12.4 Hz, 1H, SCH*H*CHPh).

2-(*S*)-Phenyl-(4,6-*O*-benzylidene-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (3). Compound **2** (3.3 g, 11 mmol) was dissolved in DMF (60 mL) and benzaldehyde dimethyl acetal (2.5 mL, 17 mmol) and camphorsulfonic acid (40 mg, 0.17 mmol) were added. The reaction mixture was heated at 50 ^{o}C under reduced pressure (~15 mm Hg) for 16 h after which it was quenched by adding Et_3N (0.5 mL). The mixture was diluted with DCM (300 mL) and the organic solution was washed with water (2 × 200 mL) and brine (150 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/5→1/2, v/v) to give **3** (3.7 g, 87 %). R_f = 0.26 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +157.1 (c = 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 – 7.27 (m, 10H, Ar*H*), 5.56 (s, 1H, PhC*H*<), 4.73 (dd, J = 10.7, 2.0 Hz, 1H, SCH_2C*H*Ph), 4.54 (d, J = 8.9 Hz, 1H, H-1), 4.37 (dd, J = 10.3, 4.6 Hz, 1H, H-6_a), 3.91 (t, J = 8.8 Hz, 1H, H-3), 3.85 – 3.56 (m, 4H, H-4, H-5, H-2, H-6_b), 3.09 (dd, J = 14.1, 10.8 Hz, 1H, SC*H*HCHPh), 2.77 (dd, J = 14.0, 2.0 Hz, 1H, SCH*H*CHPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ140.20, 137.09, 129.49, 128.86, 128.60, 128.54, 126.56, 126.20, 102.28, 84.67, 81.15, 80.89, 77.69, 77.26, 76.84, 76.47, 72.34, 72.04, 68.64, 35.98; HR MALDI-TOF MS: m/z: calcd for $C_{21}H_{22}O_5S$ $[M+Na]^+$: 409.1086; found: 409.1097.

2-(*S*)-Phenyl-(3-*O*-acetyl-4,6-*O*-benzylidene-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (4). Compound **3** (1.35 g, 3.50 mmol) was dissolved in pyridine (10 mL) and acetic anhydride (5 mL) was added. After stirring for

16 h, the reaction mixture was diluted with DCM (120 mL) and washed with saturated $NaHCO_3$ (2 × 100 mL) and brine (90 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography over silica gel (EtOAc/Toluene, 1 /16→1/8, v/v) to give **4** (1.47 g, 98%). R_f = 0.53 (EtOAc/Toluene, 1/8, v/v); $[\alpha]^d_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +40.0 (*c* = 0.5 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 – 7.16 (m, 10H, Ar*H*), 5.53 (s, 1H, PhC*H*<), 5.42 (t, *J* = 9.4 Hz, 1H, H-3), 4.72 (dd, *J* = 10.6, 1.9 Hz, 1H, SCH_2CHPh), 4.62 (d, *J* = 8.9 Hz, 1H, H-1), 4.39 (dd, *J* = 9.9, 4.1 Hz, 1H, H-6_a), 3.87 – 3.65 (m, 4H, H-2, H-4, H-5, H-6_b), 3.02 (dd, *J* = 14.0, 10.6 Hz, 1H, SC*H*HCHPh), 2.84 (dd, *J* = 14.0, 2.1 Hz, 1H, SCH*H*CHPh), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ170.29, 140.18, 137.03, 129.34, 128.72, 128.47, 128.09, 126.36, 125.52, 101.84, 82.67, 80.10, 79.38, 77.66, 77.24, 76.93, 76.82, 72.48, 71.80, 68.61, 36.10, 21.17; HR MALDI-TOF MS: m/z: calcd for $C_{23}H_{24}O_6S$ $[M+Na]^+$: 451.1192; found: 451.1201.

2-(*S*)-Phenyl-(3-*O*-acetyl-4,6-*O*-benzylidene-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (5). Levulinic acid (464 µL, 4.56 mmol), *N*,*N*'-dicyclohexylcarbodiimide (DCC) (940 mg, 4.56 mmol) and 4-dimethylaminopyridine (DMAP) (44 mg, 0.36 mmol) were added to a stirred solution of **3** (440 mg, 1.14 mmol) in DCM (8 mL). After stirring for 16 h, the reaction mixture was filtered and the organic layer was concentrated *in vacuo*. The resulting oil was purified by flash chromatography over silica gel (toluene/acetone, 15/1→5/1, v/v) to give **5** (436 mg, 79%). R_f = 0.5 (toluene/acetone, 6/1, v/v); $[\alpha]^d_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +66.7 (*c* = 1.2 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 – 7.16 (m, 10H, Ar*H*), 5.53 (s, 1H, PhC*H*<), 5.38 (t, *J* = 9.4 Hz, 1H, H-3), 4.71 (dd, *J* = 10.5, 1.9 Hz, 1H, SCH_2CHPh), 4.61 (d, *J* = 8.9 Hz, 1H, H-1),

4.39 (dd, J = 10.0, 4.3 Hz, 1H, H-5), 3.87 – 3.61 (m, 4H, H-2, H-4, H-$6_{a,b}$), 3.02 (dd, J = 14.0, 10.6 Hz, 1H, SC*H*HCHPh), 2.83 (dd, J = 14.0, 2.1 Hz, 1H, SCH*H*CHPh), 2.71 – 2.45 (m, 4H, 2×CH_2 Lev), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.24, 172.27, 140.12, 137.01, 129.29, 128.68, 128.44, 128.11, 126.37, 125.61, 101.78, 82.67, 80.13, 79.31, 77.67, 77.25, 76.86, 76.83, 72.47, 72.11, 68.59, 38.45, 36.00, 29.82, 28.39.; HR MALDI-TOF MS: m/z: calcd for $C_{21}H_{21}O_4S$ $[M+Na]^+$: 392.1059; found: 392.1051.

2-(*S*)-Phenyl-(3-*O*-allyloxycarbonyl-4,6-*O*-benzylidene-1,2-dideoxyl-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (6). Allyl chloroformate (274 µL, 2.56 mmol), tetramethylethylenediamine (TMEDA) (200 µL, 1.22 mmol) and 4-dimethylaminopyridine (DMAP) (50 mg, 0.41 mmol) were added to a stirred solution of **3** (470 mg, 1.22 mmol) in DCM (10 mL). After stirring for 16 h, the reaction mixture was diluted with DCM (100 mL) and washed with saturated $NaHCO_3$ (2 × 100 mL), brine (90 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography over silica gel (toluene/acetone, 20/1→8/1, v/v) to give **6** (500 mg, 87%). R_f = 0.56 (toluene/acetone, 8/1, v/v); $[\alpha]^d_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +53.8 (c = 1.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.19 (m, 10H, Ar*H*), 5.91 – 5.70 (m, 1H, CH alloc), 5.53 (s, 1H, PhC*H*<), 5.28 – 5.13 (m, 2H, C*H*H alloc, H-3), 5.08 (d, J = 10.5 Hz, 1H, CH*H* alloc), 4.72 (dd, J = 10.6, 1.8 Hz, 1H, SCH_2C*H*Ph), 4.63 (d, J = 8.9 Hz, 1H, H-1), 4.57 (d, J = 5.7 Hz, 1H, CH_2 alloc), 4.40 (dd, J = 10.0, 4.1 Hz, 1H, H-6_a), 3.90 – 3.65 (m, 4H, H-2, H-4, H-5, H-6_b), 3.05 (dd, J = 14.0, 10.7 Hz, 1H, SC*H*HCHPh), 2.83 (dd, J = 14.0, 2.0 Hz, 1H, SCH*H*CHPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ154.59, 140.05, 136.94, 131.41, 129.35, 128.62, 128.43, 128.13, 126.42, 125.70, 119.03, 101.89, 82.57, 80.18, 79.16, 77.66,

77.44, 77.24, 76.82, 76.73, 76.03, 72.35, 68.92, 68.56, 35.98; HR MALDI-TOF MS: m/z: calcd for $C_{25}H_{26}O_7S$ $[M+Na]^+$: 493.1297; found: 493.1288.

2-(*S*)-Phenyl-(3-*O*-benzyl-4,6-*O*-benzylidene-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (7). Benzyl bromide (246 µL, 2.08 mmol) and sodium hydride (124 mg, 3.12 mmol) were added to a stirred solution of **3** (400 mg, 1.04 mmol) in DMF (5 mL). After stirring for 16 h, the reaction mixture was quenched with MeOH (2 mL), diluted with DCM (100 mL) and washed with 1 M HCl solution (100 mL), saturated $NaHCO_3$ (100 mL), and brine (90 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/4 → 1/2, v/v) to give **7** (390 mg, 79%). R_f = 0.28 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +54.5 (c = 1.1 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 – 7.16 (m, 15H, Ar*H*), 5.60 (s, 1H, PhC*H*<), 4.85 (s, 2H, C*H*$_2$Ph), 4.78 (d, J = 10.6 Hz, 1H, SCH$_2$C*H*Ph), 4.53 (d, J = 8.8 Hz, 1H, H-1), 4.37 (dd, J = 10.4, 4.8 Hz, 1H, H-4), 3.88 – 3.72 (m, 4H, H-2, H-3, H-6$_{a,b}$), 3.61 (td, J = 9.5, 4.9 Hz, 1H, H-5), 3.06 (dd, J = 13.9, 10.9 Hz, 1H, SC*H*HCHPh), 2.81 (d, J = 13.9 Hz, 1H, SCH*H*CHPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ140.55, 138.58, 137.42, 129.22, 128.68, 128.46, 128.40, 128.23, 127.76, 126.28, 125.91, 101.65, 84.99, 81.71, 80.40, 78.79, 77.66, 77.24, 76.99, 76.82, 74.83, 72.37, 68.68, 36.09; HR MALDI-TOF MS: m/z: calcd for $C_{28}H_{28}O_5S$ $[M+Na]^+$: 499.1555; found: 499.1562.

2-(*S*)-Phenyl-(3,4-di-*O*-acetyl-6-*O*-benzyl-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (9). A mixture of **4** (550 mg, 1.29 mmol) and activated molecular sieves (4Å) in DCM (5 mL) was stirred for 1 h under an atmosphere of argon. After cooling to -78 ^{o}C, triethylsilane (408 µL, 2.58 mmol) and trifluoromethanesulfonic acid (171 µL,

1.94 mmol) were added. After 1 h, the reaction was quenched by the addition of MeOH (1 mL) and Et_3N (0.5 mL). The mixture was diluted with DCM (10 mL), filtered and the filtrate was concentrated *in vacuo*. The residue was redissolved in pyridine (5 mL) and acetic anhydride (5 mL) was added. After stirring for 16 h, the solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/6 → 1/2, v/v) to afford **9** (516 mg, 85%). R_f = 0.37 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +141.7 (*c* = 1.2 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 – 7.18 (m, 10H, Ar*H*), 5.34 – 5.10 (m, 2H, H-3, H-4), 4.69 (dd, *J* = 10.5, 1.8 Hz, 1H, SCH_2CHPh), 4.58 – 4.44 (m, 3H, CH_2Ph, H-1), 3.86 – 3.66 (m, 2H, H-5, H-2), 3.62 – 3.50 (m, 2H, H-$6_{a,b}$), 2.97 (dd, *J* = 14.0, 10.6 Hz, 1H, SC*H*HCHPh), 2.80 (dd, *J* = 14.0, 2.1 Hz, 1H, SCH*H*CHPh), 1.99 (s, 3H), 1.92 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.65, 169.83, 140.32, 137.84, 128.69, 128.61, 128.22, 128.07, 128.00, 125.57, 81.30, 79.75, 78.81, 77.71, 77.29, 76.86, 76.01, 73.84, 73.38, 69.62, 68.89, 35.86, 21.03, 20.89; HR MALDI-TOF MS: m/z: calcd for $C_{25}H_{28}O_7S$ $[M+Na]^+$: 495.1454; found: 495.1463.

2-(*S*)-Phenyl-(3-*O*-acetyl-4,6-di-*O*-benzyl-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (10). A mixture of **4** (430 mg, 1.00 mmol) and activated molecular sieves (4 Å) in DCM (5 mL) was stirred for 1 h under an atmosphere of argon. After cooling to -78 °C, triethylsilane (316 µL, 2.00 mmol) and trifluoromethanesulfonic acid (132 µL, 1.50 mmol) were added. After 1 h, the reaction was quenched by the addition of MeOH (1 mL) and Et_3N (0.5 mL). The mixture was diluted with DCM (10 mL), filtered and the filtrate was concentrated *in vacuo.* The resulting residue was loaded onto a small plug of silica gel and product fractions were collected and concentrated. The residue was

redissolved in DMF (5 mL) followed by the addition of benzyl bromide (356 μL, 3.00 mmol) and Ag_2O (1.2 g, 5.2 mmol). After stirring for 16 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/6 → 1/3, v/v) to afford **10** (287 mg, 55%). R_f = 0.45 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +66.7 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.09 (m, 15H, Ar*H*), 5.30 (dd, *J* = 11.0, 7.9 Hz, 1H, H-3), 4.72 – 4.50 (m, 5H, 2×C*H*$_2$Ph, SCH$_2$C*H*Ph), 4.46 (d, *J* = 8.9 Hz, 1H, H-1), 3.83 (t, *J* = 9.5 Hz, 1H, H-4), 3.76 (d, *J* = 2.8 Hz, 2H, H-6$_{a,b}$), 3.72 – 3.55 (m, 2H, H-2, H-5), 2.95 (dd, *J* = 14.0, 10.5 Hz, 1H, SC*H*HCHPh), 2.79 (dd, *J* = 14.0, 2.1 Hz, 1H, SCH*H*CHPh) 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ170.34, 140.49, 138.13, 137.99, 128.65, 128.21, 128.10, 128.06, 127.98, 127.91, 125.49, 81.77, 80.59, 79.57, 77.66, 77.24, 76.81, 76.18, 75.93, 75.27, 74.84, 73.85, 68.59, 35.86, 21.21; HR MALDI-TOF MS: m/z: calcd for $C_{30}H_{32}O_6S$ $[M+Na]^+$: 543.1818; found: 543.1824.

2-(*S*)-Phenyl–{3-*O*-acetyl-6-*O*-benzyl-4-*O*-(9-fluorenylmethyloxycarbonyl)-1,2-dideoxy-ß-D-glucopyranoso}[1,2-*e*]-1,4-oxathiane (11). A mixture of **4** (1.05 g, 2.45 mmol) and activated molecular sieves (4 Å) in DCM (10 mL) was stirred for 1 h under an atmosphere of argon. After cooling to -78 ^{o}C, triethylsilane (0.78 mL, 4.90 mmol) and trifluoromethanesulfonic acid (323 μL, 3.68 mmol) were added. After 1 h, the reaction was quenched by the addition of MeOH (1 mL) and Et_3N (0.5 mL). The resulting mixture was diluted with DCM (10 mL), filtered and the filtrate was concentrated *in vacuo*. The resulting residue was redissolved in a mixture of pyridine and DCM (10 mL, 1/1, v/v) and FmocCl (0.95 g, 3.70 mmol) was added. After stirring for 16 h, the reaction mixture was diluted with DCM (50 mL), poured into an aqueous 1 M HCl solution (100 mL) and

washed with H_2O (100 mL) and brine (100 mL). The organic layer dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/6 → 1/3, v/v) to afford **11** (1.06 g, 66%). R_f = 0.47 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +47.5 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 – 7.08 (m, 18H), 5.40 (t, J = 9.5 Hz, 1H, H-3), 5.07 (t, J = 9.7 Hz, 1H, H-4), 4.70 (d, J = 9.3 Hz, 1H, SCH_2CHPh), 4.64 – 4.45 (m, 3H, H-1, CH_2Ph), 4.45 – 4.08 (m, 3H, CH Fmoc, CH_2 Fmoc), 3.98 – 3.83 (m, 1H, H-5), 3.83 – 3.61 (m, 3H, H-2, H-$6_{a,b}$), 2.98 (dd, J = 14.0, 10.7 Hz, 1H, $SCHHCHPh$), 2.81 (dd, J = 13.9, 1.7 Hz, 1H, $SCHHCHPh$), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ171.85, 140.45, 137.87, 128.73, 128.70, 128.12, 128.07, 125.61, 81.28, 80.01, 79.73, 77.77, 77.35, 76.92, 76.03, 75.98, 74.02, 70.95, 70.06, 35.85, 21.29; HR MALDI-TOF MS: m/z: calcd for $C_{38}H_{36}O_8S$ $[M+Na]^+$: 675.2029; found: 675.2017.

2-(*S*)-Phenyl-(3,6-di-*O*-acetyl-4-*O*-benzyl-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (13). A mixture of **4** (610 mg, 1.43 mmol) and activated molecular sieves (4Å) in DCM (8 mL) was stirred for 1 h under an atmosphere of argon. After cooling to -78 ^{o}C, triethylsilane (451 µL, 2.86 mmol) and dichlorophenylborane (280 µL, 2.15 mmol) were added. After 30 min, the reaction was quenched by the addition of MeOH (1 mL) and Et_3N (0.5 mL). The resulting mixture was diluted with DCM (10 mL), filtered and the filtrate was concentrated *in vacuo*. The residue was redissolved in pyridine (5 mL) and acetic anhydride (5 mL) was added. After stirring for 16 h, the mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/4 → 1/3, v/v) to afford **13** (525 mg, 78%). R_f = 0.43 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +80.0 (c = 0.3 in $CHCl_3$); ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.43 – 7.18 (m, 10H, Ar*H*), 5.36 (t, *J* = 9.3 Hz, 1H), 4.73 – 4.53 (m, 3H, SCH_2CHPh, $PHCH_2$), 4.48 (d, *J* = 8.9 Hz, 1H, H-1), 4.38 (dd, *J* = 12.2, 1.8 Hz, 1H, H-6_a), 4.22 (dd, *J* = 12.1, 4.6 Hz, 1H, H-6_b), 3.81 – 3.54 (m, 3H, H-5, H-4, H-2), 2.95 (dd, *J* = 14.0, 10.5 Hz, 1H, SC*H*HCHPh), 2.80 (dd, *J* = 14.0, 2.1 Hz, 1H, SCH*H*CHPh), 2.08 (s, 3H), 1.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.85, 170.20, 140.34, 137.44, 128.80, 128.69, 128.37, 128.27, 128.00, 125.46, 81.70, 79.62, 78.46, 77.70, 77.28, 76.86, 76.17, 75.80, 75.24, 74.91, 63.18, 35.80, 21.23, 21.12; HR MALDI-TOF MS: m/z: calcd for $C_{25}H_{28}O_7S$ $[M+Na]^+$: 495.1454; found: 495.1447.

2-(*S*)-Phenyl-(4-*O*-acetyl-6-*O*-benzyl-3-*O*-levulinoyl-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (14). A mixture of **5** (300 mg, 0.62 mmol) and activated molecular sieves (4 Å) in DCM (5 mL) was stirred for 1 h under an atmosphere of argon. After cooling to -78 ^oC, triethylsilane (196 µL, 1.24 mmol) and trifluoromethanesulfonic acid (82 µL, 0.93 mmol) were added. After 1 h, the reaction was quenched by the addition of MeOH (1 mL) and Et_3N (0.5 mL). The resulting mixture was diluted with DCM (10 mL), filtered and the filtrate was concentrated *in vacuo*. The residue was redissolved in pyridine (5 mL) and acetic anhydride (5 mL) was added. After stirring for 16 h, the mixture was removed *in vacuo*. The resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/4 → 1/2, v/v) to afford **14** (259 mg, 79%). R_f = 0.29 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +105.3 (*c* = 1.9 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 – 7.18 (m, 10H, Ar*H*), 5.23 (t, *J* = 9.6 Hz, 1H, H-3), 5.17 (t, *J* = 9.6 Hz, 1H, H-4), 4.67 (dd, *J* = 10.5, 1.8 Hz, 1H, SCH_2CHPh), 4.63 – 4.43 (m, 3H, CH_2Ph, H-1), 3.86 – 3.66 (m, 2H, H-2, H-5), 3.61 – 3.48 (m, 2H, H-$6_{a,b}$), 2.96 (dd, *J* = 14.0, 10.6 Hz, 1H, SC*H*HCHPh), 2.79 (dd, *J* = 14.0,

2.1 Hz, 1H, SCH*H*CHPh), 2.76 – 2.31 (m, 4H, 2×CH_2 Lev), 2.07 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ206.19, 172.23, 170.06, 140.28, 137.86, 128.66, 128.60, 128.21, 128.06, 127.98, 125.60, 81.39, 79.74, 78.93, 77.69, 77.26, 76.84, 75.94, 73.85, 73.38, 69.20, 68.95, 38.10, 35.80, 29.80, 28.25, 20.92; HR MALDI-TOF MS: m/z: calcd for $C_{23}H_{25}O_5S$ $[M+Na]^+$: 436.1321; found: 436.1329.

2-(*S*)-Phenyl-(4-*O*-acetyl-3-*O*-allyloxycarbonyl-6-*O*-benzyl-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (15). A mixture of **6** (300 mg, 0.64 mmol) and activated molecular sieves (4 Å) in DCM (5 mL) was stirred for 1 h under an atmosphere of argon. After cooling to -78 ^{o}C, triethylsilane (202 µL, 1.28 mmol) and trifluoromethanesulfonic acid (85 µL, 0.96 mmol) were added. After 1 h, the reaction was quenched by the addition of MeOH (1 mL) and Et_3N (0.5 mL), diluted by DCM (10 mL) and filtered. The filtrate was concentrated *in vacuo*. The residue was redissolved in pyridine (5 mL) and acetic anhydride (5 mL) was added. After stirring for 16 h, the solvent was removed. The resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/8 → 1/2, v/v) to afford **15** (302 mg, 92%). R_f = 0.58 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +94.4 (*c* = 3.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.17 (m, 10H, Ar*H*), 5.79 (ddd, *J* = 22.7, 10.8, 5.6 Hz, 1H, C*H* alloc), 5.29 – 4.99 (m, 4H, H-3, H-4, CH_2 alloc), 4.69 (dd, *J* = 10.5, 1.8 Hz, 1H, SCH_2CHPh), 4.64 – 4.45 (m, 5H, CH_2Ph, CH_2 alloc, H-1), 3.89 – 3.71 (m, 2H, H-2, H-5), 3.61 – 3.51 (m, 2H, H-$6_{a,b}$), 2.99 (dd, *J* = 14.0, 10.6 Hz, 1H, SC*H*HCHPh), 2.80 (dd, *J* = 14.0, 2.0 Hz, 1H, SCH*H*CHPh), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.69, 154.84, 140.19, 137.83, 131.45, 128.61, 128.60, 128.21, 128.10, 128.00, 125.77, 125.73, 118.89, 81.32, 79.79, 78.84, 77.70, 77.46, 77.28, 76.85, 75.80, 73.88, 69.45, 69.10, 68.84,

35.72, 20.90; HR MALDI-TOF MS: m/z: calcd for $C_{27}H_{30}O_8S$ $[M+Na]^+$: 537.1559; found: 537.1551.

2-(*S*)-Phenyl-(4,6-di-*O*-acetyl-3-*O*-benzyl-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (16). $TsOH \cdot H_2O$ (80 mg, 0.42 mmol) and EtSH (31 μL, 0.42 mmol) were added to a stirred solution of **7** (200 mg, 0.42 mmol) in DCM (5 mL). After stirring for 2 h, the solvent was removed *in vacuo* and the residue was redissolved in pyridine (5 mL) and acetic anhydride (5 mL). After stirring for 16 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/5 → 1/4, v/v) to afford **16** (167 mg, 84%). R_f = 0.21 (EtOAc/hexanes, 1/4, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +80.0 (c = 0.4 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ7.50 – 7.09 (m, 10H, Ar*H*), 5.11 (t, J = 9.7 Hz, 1H, H-4), 4.80 (t, J = 12.2 Hz, 2H, C*H*HPh, SCH_2CHPh), 4.63 (d, J = 12.0 Hz, 1H, CH*H*Ph), 4.44 (d, J = 8.9 Hz, 1H, H-1), 4.25 – 4.04 (m, 2H, H-$6_{a,b}$), 3.84 (t, J = 9.0 Hz, 1H, H-2), 3.75 – 3.55 (m, 2H, H-5, H-3), 3.05 (dd, J = 13.9, 10.7 Hz, 1H, SC*H*HCHPh), 2.81 (dd, J = 13.9, 1.6 Hz, 1H, SCH*H*CHPh), 2.08 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ171.00, 169.67, 140.51, 138.40, 128.74, 128.49, 128.28, 128.14, 127.87, 125.82, 84.59, 80.05, 79.98, 77.65, 77.55, 77.23, 76.80, 75.92, 74.87, 69.62, 62.68, 35.67, 21.03, 21.00; HR MALDI-TOF MS: m/z: calcd for $C_{25}H28O7S$ $[M+Na]^+$: 495.1454; found: 495.1463.

2-(*S*)-phenyl-(3,4-di-*O*-acetyl-6-benzyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (*R*,*S*)-*S*-oxide (17). Compound **17** (1.4 g, 92 %, *R*/*S* = 1.3/1) was prepared according to the general procedure for the preparation of sulfoxide donors starting from **9** (1.5 g, 3.2 mmol) and using *m*-CPBA (0.79 g, ≤77%, 3.5 mmol). **17*S***: R_f = 0.24

(EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 – 7.19 (m, 10H, Ar*H*), 5.55 – 5.30 (m, 2H, H-3, SCH_2CHPh), 5.05 (t, *J* = 9.8 Hz, 1H, H-4), 4.59 – 4.45 (m, 3H, CH_2Ph, H-2), 4.14 (d, *J* = 9.7 Hz, 1H, H-1), 3.96 – 3.81 (m, 1H, H-5), 3.73 – 3.52 (m, 2H, H-$6_{a,b}$), 3.21 (dd, *J* = 14.5, 1.6 Hz, 1H, $SCH_{eq}HCHPh$), 2.71 (dd, *J* = 14.4, 11.3 Hz, 1H, $SCH_{ax}CHPh$), 2.01 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ170.59, 169.72, 138.87, 137.72, 128.94, 128.65, 128.38, 128.22, 128.07, 125.70, 85.41, 79.27, 77.68, 77.26, 76.83, 73.98, 73.37, 69.40, 69.33, 69.16, 68.51, 53.01, 21.01, 20.82; HR MALDI-TOF MS: m/z: calcd for $C_{25}H_{28}O_8S$ $[M+Na]^+$: 511.1403; found: 511.1397. **17*R***: R_f = 0.18 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 – 7.19 (m, 10H, Ar*H*), 5.47 – 5.20 (m, 2H, H-3, H-4), 4.70 (d, *J* = 10.9 Hz, 1H, SCH_2CHPh), 4.62 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.48 (d, *J* = 12.0 Hz, 1H, CH*H*Ph) 4.31 (d, *J* = 10.0 Hz, 1H, H-1), 3.84 – 3.54 (m, 5H, H-2, H-5, H-$6_{a,b}$, $SCH_{eq}HCHPh$), 3.05 (dd, *J* = 12.7, 11.8 Hz, 1H, $SCH_{ax}CHPh$), 1.99 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ170.32, 169.60, 138.03, 137.69, 129.08, 128.94, 128.81, 128.62, 128.29, 128.21, 128.04, 125.69, 125.60, 95.26, 78.74, 77.65, 77.23, 76.81, 75.74, 75.45, 73.95, 73.47, 68.60, 67.92, 57.81, 20.96, 20.81; HR MALDI-TOF MS: m/z: calcd for $C_{25}H_{28}O_8S$ $[M+Na]^+$: 511.1403; found: 511.1404.

2-(*S*)-Phenyl–(3-*O*-acetyl-4,6-di-*O*-benzyl-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane(*R*,*S*)-*S*-oxide (18). Compound **18** (0.17 g, 96 %, *R*/*S* = 1.1/1) was prepared according to the general procedure for the preparation of sulfoxide donors starting from **10** (0.17 g, 0.33 mmol) and using *m*-CPBA (0.82 g, ≤ 77%, 0.36 mmol). **18*S***: R_f = 0.24 (EtOAc/hexanes, 1/1, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +48.0 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 – 7.13 (m, 15H, Ar*H*), 5.45 (t, *J* = 9.4 Hz,

1H, H-3), 5.35 (d, J = 11.1 Hz, 1H, SCH_2CHPh), 4.66 – 4.49 (m, 4H, 2×CH_2Ph), 4.42 (t, J = 9.6 Hz, 1H, H-2), 4.11 (d, J = 9.6 Hz, 1H, H-1), 3.80 – 3.64 (m, 4H, H-4, H-5, H-$6_{a,b}$), 3.20 (d, J = 14.5 Hz, 1H, $SCH_{eq}HCHPh$), 2.70 (dd, J = 14.3, 11.4 Hz, 1H, $SCH_{ax}CHPh$), 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.11, 138.87, 137.81, 137.40, 128.69, 128.49, 128.43, 128.02, 128.00, 127.78, 125.38, 85.27, 80.83, 77.23, 77.01, 76.80, 75.47, 75.15, 74.81, 73.72, 69.53, 68.60, 68.00, 52.80, 20.98.; HR MALDI-TOF MS: m/z: calcd for $C_{30}H_{32}O_7S$ $[M+Na]^+$: 559.1767; found: 559.1779. **18*R***: R_f = 0.21 (EtOAc/hexanes, 1/1, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +80.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 – 7.12 (m, 15H, ArH), 5.41 (t, J = 9.3 Hz, 1H, H-3), 4.77 – 4.44 (m, 5H, 2×CH_2Ph, SCH_2CHPh), 4.28 (d, J = 9.6 Hz, 1H, H-1), 3.95 – 3.81 (m, 3H, H-4, H-$6_{a,b}$), 3.64 (dd, J = 19.2, 11.4 Hz, 2H, H-5, $SCH_{eq}HCHPh$), 3.52 (t, J = 9.6 Hz, 1H, H-2), 3.02 (t, J = 12.2 Hz, 1H, $SCH_{ax}CHPh$), 1.90 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.72, 137.96, 137.59, 128.79, 128.76, 128.45, 128.44, 128.40, 128.29, 128.05, 128.01, 127.89, 127.86, 125.24, 125.21, 95.05, 80.39, 77.19, 76.98, 76.77, 75.73, 75.26, 74.92, 74.84, 74.73, 73.81, 67.65, 57.46, 20.85; HR MALDI-TOF MS: m/z: calcd for $C_{30}H_{32}O_7S$ $[M+Na]^+$: 559.1767; found: 559.1759.

2-(*S*)-Phenyl–{3-*O*-acetyl-6-*O*-benzyl-4-*O*-(9-fluorenylmethyloxycarbonyl)-1,2-dideoxy-ß-D-glucopyranoso}[1,2-*e*]-1,4-oxathiane(*R*,*S*)-*S*-oxide (19). Compound **19** (1.9 g, 98 %, *R*/*S* = 1/1) was prepared according to the general procedure for the preparation of sulfoxide donors starting from **11** (1.9 g, 2.9 mmol) and using *m*-CPBA (712 mg, ≤77%, 3.2 mmol). **19*S***: R_f = 0.18 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 – 7.08 (m, 18H, ArH), 5.47 (t, J = 9.5 Hz, 1H, H-3), 5.30 (d, J = 10.9 Hz, 1H, SCH_2CHPh), 4.86 (t, J = 9.7 Hz, 1H, H-4), 4.60 – 4.38 (m, 3H, H-2,

CH_2Ph), 4.36 – 4.02 (m, 4H, CH Fmoc, CH_2 Fmoc, H-1), 3.98 – 3.81 (m, 1H, H-5), 3.70 – 3.52 (m, 2H, H-$6_{a,b}$), 3.15 (d, J = 14.1 Hz, 1H, SCH_{eq}HCHPh), 2.64 (dd, J = 14.4, 11.3 Hz, 1H, SCHH_{ax}CHPh), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ170.44, 154.34, 143.38, 143.24, 141.51, 141.49, 138.84, 137.77, 128.97, 128.63, 128.39, 128.24, 128.22, 128.05, 128.03, 127.52, 127.47, 125.69, 125.37, 125.31, 120.36, 120.33, 85.34, 78.88, 77.76, 77.33, 76.91, 74.00, 73.28, 73.11, 70.65, 69.42, 69.37, 68.50, 52.93, 46.77, 21.05; HR MALDI-TOF MS: m/z: calcd for $C_{38}H_{36}O_9S$ $[M+Na]^+$: 691.1978; found: 691.1971. **19*R***: R_f = 0.15 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 – 7.18 (m, 18H), 5.51 (t, J = 9.4 Hz, 1H, H-3), 5.16 (t, J = 9.7 Hz, 1H, H-4), 4.71 (d, J = 11.0 Hz, 1H, SCH_2CHPh), 4.55 (dd, J = 28.1, 12.1 Hz, 2H, CH_2Ph), 4.45 – 4.10 (m, 4H, H-1, CH Fmoc, CH_2 Fmoc), 3.96 – 3.86 (m, 1H, H-5), 3.86 – 3.55 (m, 4H, H-$6_{a,b}$, H-2, SCH_{eq}HCHPh), 3.06 (dd, J = 12.4, 12.0 Hz, 1H, SCHH_{ax}CHPh), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ169.89, 154.01, 143.15, 143.03, 141.27, 137.79, 137.52, 128.87, 128.59, 128.36, 127.99, 127.96, 127.84, 127.75, 127.29, 127.24, 125.34, 125.11, 120.10, 95.02, 78.25, 77.44, 77.22, 77.01, 76.59, 75.52, 75.29, 73.80, 72.93, 72.37, 70.45, 67.85, 57.63, 53.80, 46.51, 30.93, 29.71, 29.28, 20.74; HR MALDI-TOF MS: m/z: calcd for $C_{38}H_{36}O_9S$ $[M+Na]^+$: 691.1978; found: 691.1973.

2-(*S*)-phenyl-(3,6-di-*O*-acetyl-4-benzyl-2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (*R*,*S*)-*S*-oxide (20). Compound **20** (245 mg, 93 %, *R*/*S* = 1/1) was prepared according to the general procedure for the preparation of sulfoxide donors starting from **13** (250 mg, 0.54 mmol) and using *m*-CPBA (133 mg, ≤ 77%, 0.60 mmol). **20*S***: R_f = 0.15 (EtOAc/hexanes, 1/1, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +60.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.20 (m, 10H, ArH), 5.49 (t, J = 9.4 Hz, 1H, H-3), 5.35 (d, J

= 10.5 Hz, 1H, SCH_2CHPh), 4.65 (d, J = 11.2 Hz, 1H, $CHHPh$), 4.58 (d, J = 11.2 Hz, 1H, $CHHPh$), 4.47 – 4.37 (m, 2H, H-2, H-6_a), 4.21 (dd, J = 12.2, 5.5 Hz, 1H, H-6_b), 4.14 (d, J = 9.7 Hz, 1H, H-1), 3.82 (ddd, J = 9.8, 5.5, 2.0 Hz, 1H, H-5), 3.65 (t, J = 9.5 Hz, 1H, H-4), 3.22 (dd, J = 14.5, 1.6 Hz, 1H, $SCH_{eq}HCHPh$), 2.71 (dd, J = 14.4, 11.3 Hz, 1H, $SCH_{ax}CHPh$), 2.07 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ170.82, 170.23, 138.94, 137.17, 128.95, 128.85, 128.48, 128.34, 128.28, 125.56, 85.36, 78.79, 77.67, 77.24, 76.82, 75.52, 75.36, 75.14, 69.67, 68.25, 63.12, 52.98, 21.21, 21.08; HR MALDI-TOF MS: m/z: calcd for $C_{25}H_{28}O_8S$ $[M+Na]^+$: 511.1403; found: 511.1408. **20*R***: R_f = 0.12 (EtOAc/hexanes, 1/1, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +26.7 (c = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 – 7.10 (m, 10H, Ar*H*), 5.48 (t, J = 9.1 Hz, 1H, H-3), 4.69 (d, J = 11.3 Hz, 1H, SCH_2CHPh), 4.60 (q, J = 11.2 Hz, 2H, CH_2Ph), 4.43 (dd, J = 12.4, 1.9 Hz, 1H, H-6_a), 4.31 (dd, J = 13.0, 3.4 Hz, 2H, H-6_b, H-1), 3.85 – 3.73 (m, 1H, H-5), 3.73 – 3.59 (m, 2H, H-4, $SCH_{eq}HCHPh$), 3.52 (t, J = 9.7 Hz, 1H, H-2), 3.12 – 2.96 (m, 1H, $SCH_{ax}CHPh$), 2.08 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.73, 169.82, 138.08, 137.15, 129.08, 128.85, 128.72, 128.50, 128.29, 125.46, 94.99, 78.47, 77.67, 77.25, 76.82, 75.85, 75.62, 75.34, 75.11, 75.07, 62.67, 57.74, 21.13, 21.07; HR MALDI-TOF MS: m/z: calcd for $C_{25}H_{28}O_8S$ $[M+Na]^+$: 511.1403; found: 511.1411.

2-(*S*)-phenyl-(4-*O*-acetyl-6-benzyl-3-levulinoyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (*R*,*S*)-*S*-oxide (21). Compound **21** (0.41 g, 98 %, *R*/*S* = 1.3/1) was prepared according to the general procedure for the preparation of sulfoxide donors using *m*-CPBA (0.24 g, ≤ 77%, 1.1 mmol) and starting from **14** (0.4 g, 0.97 mmol). **21*S***: R_f = 0.19 (EtOAc/hexanes, 1/1, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +87.5 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 – 7.17 (m, 10H, Ar*H*), 5.42 (t, J

= 9.6 Hz, 1H, H-3), 5.36 (d, *J* = 11.0 Hz, 1H, SCH_2CHPh), 5.06 (t, *J* = 9.8 Hz, 1H, H-4), 4.60 – 4.41 (m, 3H, H-2, CH_2Ph), 4.14 (d, *J* = 9.7 Hz, 1H, H-1), 3.97 – 3.79 (m, 1H, H-5), 3.66 (dd, *J* = 11.0, 6.0 Hz, 1H, H-6_a), 3.57 (dd, *J* = 11.0, 2.8 Hz, 1H, H-6_b), 3.21 (d, *J* = 13.5 Hz, 1H, $SCH_{eq}HCHPh$), 2.83 – 2.36 (m, 5H, $SCH_{ax}CHPh$, 2×CH_2 Lev), 2.08 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.04, 171.97, 169.81, 138.01, 137.72, 129.04, 128.77, 128.61, 128.28, 128.02, 125.63, 95.22, 78.85, 77.66, 77.24, 76.81, 75.68, 75.56, 73.96, 73.47, 68.19, 68.01, 57.73, 37.97, 29.79, 28.14, 20.86; HR MALDI-TOF MS: m/z: calcd for $C_{23}H_{25}O_6S$ $[M+Na]^+$: 452.1270; found: 452.1277. **21*R***: R_f = 0.18 (EtOAc/hexanes, 1/1, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +56.0 (*c* = 0.7 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ7.47 – 7.17 (m, 10H, Ar*H*), 5.38 (t, *J* = 9.4 Hz, 1H, H-3), 5.29 (t, *J* = 9.7 Hz, 1H, H-4), 4.70 (d, *J* = 11.2 Hz, 1H, SCH_2CHPh), 4.61 (d, *J* = 12.0 Hz, 1H, $CHHPh$), 4.49 (d, *J* = 12.0 Hz, 1H, $CHHPh$), 4.31 (d, *J* = 10.0 Hz, 1H, H-1), 3.83 – 3.75 (m, 1H, H-5), 3.72 (dd, *J* = 11.1, 2.9 Hz, 1H, H-6_a), 3.69 – 3.53 (m, 3H, H-6_b, H-2, $SCH_{eq}HCHPh$), 3.05 (dd, *J* = 12.8, 11.8 Hz, 1H, $SCH_{ax}CHPh$), 2.78 – 2.37 (m, 4H, 2×CH_2 Lev), 2.08 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ206.12, 172.12, 170.01, 138.84, 137.74, 128.92, 128.64, 128.36, 128.21, 128.06, 125.71, 85.39, 79.41, 77.66, 77.44, 77.23, 76.81, 73.99, 73.35, 69.43, 68.71, 68.46, 52.98, 38.01, 29.79, 28.22, 20.87; HR MALDI-TOF MS: m/z: calcd for $C_{23}H_{25}O_6S$ $[M+Na]^+$: 452.1270; found: 452.1268.

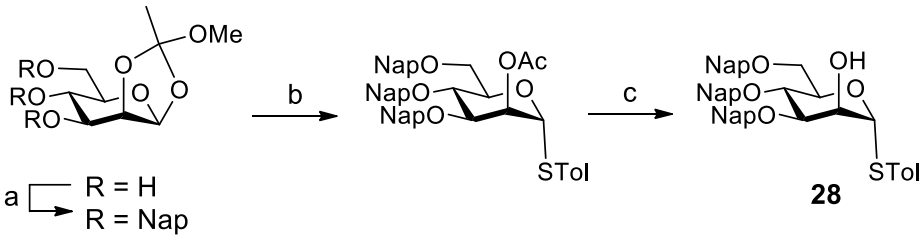
2-(*S*)-phenyl-(3-allyoxycarbonyl-4-*O*-acetyl-6-*O*-benzyl-1,2-dideoxyl-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (*R*,*S*)-*S*-oxide (22). Compound **22** (0.42 g, 82 %, *R*/*S* = 1.5/1) was prepared according to the general procedure for the preparation of sulfoxide donors using *m*-CPBA (0.24 g, ≤ 77%, 0.97 mmol) and starting from **15** (0.50

g, 0.97 mmol). **22*S***: R_f = 0.33 (EtOAc/hexanes, 1/1, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +78.0 (*c* = 4.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 – 7.21 (m, 10H, Ar*H*), 5.92 – 5.64 (m, 1H, CH alloc), 5.37 (d, *J* = 10.0 Hz, 1H, SCH_2CHPh), 5.30 – 5.17 (m, 2H, H-3, C*H*H alloc), 5.17 – 5.00 (m, 2H, H-4, CH*H* alloc), 4.63 – 4.48 (m, 5H, H-2, CH_2 alloc, CH_2Ph), 4.15 (d, *J* = 9.7 Hz, 1H, H-1), 3.97 – 3.81 (m, 1H, H-5), 3.73 – 3.47 (m, 2H, H-$6_{a,b}$), 3.21 (dd, *J* = 14.5, 1.6 Hz, 1H, $SCH_{eq}HCHPh$), 2.72 (dd, *J* = 14.4, 11.3 Hz, 1H, $SCH_{ax}CHPh$), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.60, 154.76, 138.75, 137.72, 131.35, 128.86, 128.65, 128.40, 128.22, 128.08, 125.86, 119.01, 85.23, 79.27, 77.73, 77.60, 77.31, 76.89, 73.99, 69.52, 69.40, 69.01, 68.95, 68.57, 52.87, 20.84.; HR MALDI-TOF MS: m/z: calcd for $C_{27}H_{30}O_9S$ $[M+Na]^+$: 553.1509; found: 553.1500. **22*R***: R_f = 0.31 (EtOAc/hexanes, 1/1, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +81.3 (*c* = 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 – 7.19 (m, 10H, Ar*H*), 5.90 – 5.68 (m, 1H, C*H* alloc), 5.42 – 5.05 (m, 4H, CH_2 alloc, H-3, H-4), 4.71 (d, *J* = 11.0 Hz, 1H, SCH_2CHPh), 4.66 – 4.43 (m, CH_2 alloc, CH_2Ph), 4.32 (d, *J* = 10.0 Hz, 1H, H-1), 3.87 – 3.49 (m, 4H, H-5, H-6, H-2, $SCH_{eq}HCHPh$), 3.07 (t, *J* = 12.0 Hz 1H, $SCH_{ax}CHPh$), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.45, 154.56, 137.93, 137.69, 131.29, 128.99, 128.83, 128.62, 128.28, 128.04, 125.76, 119.07, 95.07, 78.72, 77.69, 77.62, 77.26, 76.84, 75.81, 75.44, 73.97, 69.01, 68.48, 68.15, 57.71, 20.83; HR MALDI-TOF MS: m/z: calcd for $C_{27}H_{30}O_9S$ $[M+Na]^+$: 553.1509; found: 553.1514.

2-(*S*)-phenyl-(4,6-di-*O*-acetyl-3-*O*-benzyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (*R*,*S*)-*S*-oxide (23). Compound **23** (142 mg, 96 %, *R*/*S* = 1.7/1) was prepared as an inseparable mixture of diastereomers according to the general procedure for the preparation of sulfoxide donors using *m*-CPBA (75 mg, ≤77%, 0.33 mmol) and

starting from **16** (140 mg, 0.30 mmol). R_f = 0.27 (EtOAc/hexanes, 2/1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51 – 7.12 (m, 20H, Ar*H*), 5.43 (d, *J* = 10.3 Hz, 1H, SCH_2CHPh^S), 5.12 (t, *J* = 12.0 Hz, 1H, H-4^R), 5.08 (t, *J* = 12.0 Hz, 1H, H-4^S), 4.85 – 4.74 (m, 3H, SCH_2CHPh^R, 2×C*H*HPh), 4.68 – 4.57 (m, 3H, H-2^S, 2×CH*H*Ph), 4.35 – 4.13 (m, 5H, H-1^R, 2×H-$6_{a,b}$) 4.10 (d, *J* = 9.7 Hz, 1H, H-1^S), 3.85 – 3.62 (m, 6H, H-3^S, H-3^R, H-2^R, H-5^S, H-5^R, SC*H*HCHPh^R), 3.20 (dd, *J* = 14.5, 1.5 Hz, 1H, SC*H*HCHPh^S), 3.14 – 3.05 (m, 1H, SCH*H*CHPh^R), 2.79 (dd, *J* = 14.4, 11.3 Hz, 1H, SCH*H*CHPh^S), 2.13 – 2.02 (2×s, 6H), 1.99 – 1.86 (2×s, 6H); selected ^{13}C NMR (gHSQC, $CDCl_3$): δ 94.98 (C-1^R), 85.40 (C-1^S), 79.91, 78.33, 77.58, 75.90, 75.08, 74.42, 68.84, 68.41, 62.66, 61.84, 57.34, 52.51; HR MALDI-TOF MS: m/z: calcd for $C_{25}H_{28}O_8S$ $[M+Na]^+$: 511.1403; found: 511.1411.

Scheme S1. Preparation of **28**



Reagents and conditions: (a) NaH, NapBr, DMF (95%); (b) HgBr (cat.), TolSH, DCE, 60 ^{o}C, 16 h (81%); (c) NaOMe, MeOH (quantitive).

***p*-toluene 3,4,6-tri-*O*-(2-naphthyl)-α-thiomannoside (28):** R_f = 0.53 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +141.5 (*c* = 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 6.89 (m, 25H, Ar*H*), 5.58 (s, 1H, H-1), 5.00 (d, *J* = 11.2 Hz, 1H, NapC*H*H), 4.90 (d, *J* = 11.7 Hz, 1H, NapC*H*H), 4.84 (d, *J* = 11.7 Hz, 1H, NapCH*H*),

4.78 (d, *J* = 12.2 Hz, 1H, NapC*H*H), 4.67 (d, *J* = 11.2 Hz, 1H, NapCH*H*), 4.59 (d, *J* = 12.2 Hz, 1H, NapCH*H*), 4.37 (dd, *J* = 9.1, 2.8 Hz, 1H, H-5), 4.32 (s, 1H, H-2), 4.10 – 3.94 (m, 2H, H-3, H-4), 3.87 (dd, *J* = 10.9, 4.5 Hz, 1H, H-6_a), 3.75 (dd, *J* = 10.8, 1.8 Hz, 1H, H-6_b), 2.25 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.90, 135.91, 135.87, 135.30, 133.49, 133.46, 133.43, 133.32, 133.21, 133.14, 132.44, 130.16, 130.04, 128.67, 128.32, 128.24, 128.21, 128.14, 127.95, 127.91, 127.84, 127.05, 126.91, 126.60, 126.47, 126.33, 126.27, 126.25, 126.19, 126.05, 126.03, 126.01, 87.96, 80.60, 77.68, 77.26, 76.83, 75.41, 74.84, 73.73, 72.51, 72.43, 70.11, 69.07, 21.29; HR MALDI-TOF MS: m/z: calcd for $C_{46}H_{42}O_5S$ $[M+Na]^+$: 729.2651; found: 729.2638.

Methyl 3,4-di-*O*-acetyl-6-*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 (29). Compound **29** was prepared according to the general glycosylation procedure using glycosyl donor **17** (45 mg, 0.09 mmol) and glycosyl acceptor **24** (39 mg, 0.08 mmol). Purification by LH20 size exclusion chromatography afforded compound **29** (80 mg, 91%). R_f = 0.45 (acetone/toluene, 1/9, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +86.7 (*c* = 3.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 – 6.98 (m, 25H, Ar*H*), 6.18 (t, *J* = 9 Hz, 1H, H-3^I), 6.04 (s, 2H, Ar*H*), 5.51 (d, *J* = 3.3 Hz, 1H, H-1^{II}), 5.44 (t, *J* = 9 Hz, 1H, H-4^I), 5.38 (t, *J* = 9 Hz, 1H, H-3^{II}), 5.30 – 5.16 (m, 2H, H-1^I, H-2^I), 4.99 (t, *J* = 9.7 Hz, 1H, H-4^{II}), 4.66 – 4.36 (m, 4H, CH_2Ph, H-5^I, SCH_2CHPh), 4.30 – 4.08 (m, 2H, H-5^{II}), 4.03 – 3.91 (m, 2H, H-$6^I_{a,b}$), 3.81 (s, 3H, OMe), 3.74 (s, 6H, 2 × OMe), 3.66 – 3.37 (m, 6H, OMe, H-2^{II}, H-$6^{II}_{a,b}$), 2.99 – 2.71 (m, 2H, SCH_2CHPh), 1.83 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.26, 169.79, 165.89, 165.67,

165.54, 161.68, 161.60, 142.02, 137.88, 133.29, 133.14, 132.97, 129.95, 129.79, 129.64, 129.34, 129.15, 128.74, 128.39, 128.32, 128.22, 128.15, 127.94, 127.61, 127.41, 126.20, 101.82, 97.36, 96.50, 90.89, 84.33, 78.82, 77.44, 77.22, 77.02, 76.60, 73.39, 72.42, 72.04, 70.67, 69.86, 69.47, 68.83, 68.30, 67.98, 67.08, 55.89, 55.47, 55.34, 43.33, 20.68, 20.32; HR MALDI-TOF MS: m/z: calcd for $C_{62}H_{64}O_{19}S$ $[M+Na]^+$: 1167.3660; found: 1167.3655.

Methyl 3,4-di-*O*-acetyl-6-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-*O*-benzyl-α-D-glucopyranoside (30). Compound **30** was prepared according to the general procedure using glycosyl donor **17** (50 mg, 0.10 mmol) and glycosyl acceptor **25** (31 mg, 0.083 mmol). Purification by LH20 size exclusion chromatography afforded compound **30** (52 mg, 62%). R_f = 0.34 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +75.0 (*c* = 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 – 6.87 (m, 15H, Ar*H*), 6.12 (s, 2H, Ar*H*), 5.77 (d, *J* = 3.2 Hz, 1H, H-1^{II}), 5.72 (t, *J* = 9.2 Hz, 1H, H-3^{I}), 5.23 (t, *J* = 9.8 Hz, 1H, H-3^{II}), 5.04 – 4.79 (m, 3H, H-1^{I}, H-2^{I}, H-4^{II}), 4.61 (s, 2H, C*H*$_2$Ph), 4.48 (d, *J* = 11.8 Hz, 1H, C*H*HPh), 4.33 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.27 – 4.12 (m, 2H, H-4^{I}, SCH$_2$C*H*Ph), 4.12 – 3.90 (m, 3H, H-5^{I}, H-5^{II}, H-6$^{I}_{a}$), 3.84 (s, 3H, OMe), 3.79 (s, 7H, 2 × OMe, H-6$^{I}_{b}$), 3.66 (dd, *J* = 10.2, 3.2 Hz, 1H, H-2^{II}), 3.41 (s, 3H, OMe), 3.39 – 3.29 (m, 2H, H-6$^{II}_{a,}$ H-6$^{II}_{b}$), 3.02 (dd, *J* = 13.9, 3.8 Hz, 1H, SC*H*HCHPh), 2.77 (dd, *J* = 14.0, 8.7 Hz, 1H, SCH*H*CHPh), 2.08 (s, 3H), 2.06 (s, 3H), 1.84 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.70, 170.30, 170.16, 170.08, 162.11, 162.01, 142.30, 138.46, 138.07, 128.53, 128.50, 128.39, 128.22, 128.06, 127.83, 127.64, 127.53, 127.49, 126.22, 100.99, 96.97, 96.90, 91.16, 84.30, 79.90, 77.70, 77.48, 77.27, 76.85, 74.29, 73.61, 73.58, 72.33,

72.16, 71.17, 69.97, 69.72, 69.25, 68.94, 68.43, 56.21, 55.59, 55.49, 42.99, 21.67, 21.11, 20.94, 20.31; HR MALDI-TOF MS: m/z: calcd for $C_{52}H_{62}O_{18}S$ $[M+Na]^+$: 1029.3555; found: 1029.3541.

N$^{\alpha}$-(9-Fluorenylmethyloxycarbonyl)-*O*-{3,4-di-*O*-acetyl-6-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl}-*L*-threonine benzyl ester (31). Compound **31** was prepared according to the general glycosylation procedure using glycosyl donor **17** (35 mg, 0.070 mmol) and glycosyl acceptor **26** (26 mg, 0.060 mmol). Purification by LH20 size exclusion chromatography afforded compound **31** (57 mg, 89%). R_f = 0.23 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +53.3 (*c* = 1.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 – 6.97 (m, 23H, Ar*H*), 6.25 (d, *J* = 7.7 Hz, 1H, N*H*Fmoc), 6.15 (s, 2H, Ar*H*), 5.70 (d, *J* = 3.5 Hz, 1H, H-1), 5.34 (t, *J* = 9.8 Hz, 1H, H-3), 5.27 (s, 2H, CH_2Ph), 4.95 (t, *J* = 9.8 Hz, 1H, H-4), 4.58 – 4.17 (m, 8H, CH_2Ph, 2 × CH^{Thr}, CH_2^{Fmoc}, CH^{Fmoc}, SCH$_2$C*H*Ph), 4.07 (d, *J* = 10.1 Hz, 1H, H-5), 3.85 – 3.81 (2s, 10H, 3 × OMe, H-2), 3.64 – 3.39 (m, 2H, H-6$_a$, H-6$_b$), 3.09 (dd, *J* = 14.0, 2.6 Hz, 1H, SC*H*HCHPh), 2.86 (dd, *J* = 14.0, 9.6 Hz, 1H, SCH*H*CHPh), 1.87 (s, 3H), 1.40 (d, *J* = 6.4 Hz, 3H, CH_3^{Thr}), 1.18 (d, *J* = 13.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.25, 170.07, 169.87, 161.95, 161.79, 156.78, 144.05, 143.91, 142.38, 141.19, 141.15, 137.84, 135.49, 128.50, 128.41, 128.31, 128.23, 127.80, 127.65, 127.55, 127.18, 125.66, 125.41, 125.33, 119.81, 100.97, 98.93, 91.01, 84.72, 80.40, 77.44, 77.22, 77.02, 76.59, 75.93, 73.45, 72.67, 69.59, 69.08, 68.27, 67.61, 67.41, 59.44, 55.96, 55.37, 47.09, 43.20, 30.13, 20.69, 19.93, 19.35; HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{63}NO_{15}S$ $[M+Na]^+$: 1092.3816; found: 1092.3808.

***p*-Methylphenyl 3,4-di-*O*-acetyl-6-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-1-thio-ß-D-glucopyranoside (32)**. Compound **32** was prepared according to the general glycosylation procedure using glycosyl donor **17** (45 mg, 0.090 mmol) and glycosyl acceptor **27** (35 mg, 0.080 mmol). Purification by LH20 size exclusion chromatography afforded compound **32** (63 mg, 75%). R_f = 0.25 (acetone/toluene, 1/9, v/v); $[\alpha]^{d}_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +68.6 (*c* = 0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 – 6.96 (m, 19H, Ar*H*), 6.12 (s, 2H, Ar*H*), 5.64 (d, *J* = 3.2 Hz, 1H, H-1^{II}), 5.43 (t, *J* = 9.0 Hz, 1H, H-3^{I}), 5.18 (t, *J* = 9.7 Hz, 1H, H-3^{II}), 4.92 (t, *J* = 9 Hz, 2H, H-2^{I}, H-4^{II}), 4.68 (d, *J* = 10.0 Hz, 1H, H-1^{I}), 4.56 (s, 2H, C*H*$_2$Ph), 4.45 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.30 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.19 (dd, *J* = 8.3, 4.2 Hz, 1H, SCH$_2$C*H*Ph), 4.10 (t, *J* = 9.4 Hz, 1H, H-4^{I}), 4.03 – 3.87 (m, 2H, H-5^{I}, H-5^{II}), 3.82 (s, 3H, OMe), 3.78 (s, 6H, 2 × OMe), 3.74 – 3.56 (m, 3H, H-2^{II}, H-6$^{I}_{a,}$ H-6$^{I}_{b}$), 3.32 (dd, *J* = 10.7, 2.4 Hz, 1H, H-6$^{II}_{a}$), 3.25 (dd, *J* = 10.7, 3.4 Hz, 1H, H-6$^{II}_{b}$), 2.99 (dd, *J* = 13.9, 4.1 Hz, 1H, SC*H*HCHPh), 2.82 (dd, *J* = 13.9, 8.3 Hz, 1H, SCH*H*CHPh), 2.31 (s, 3H, C*H*$_3$), 2.09 (s, 3H), 2.04 (s, 3H), 1.82 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.16, 169.99, 169.76, 169.67, 161.91, 161.78, 141.96, 138.42, 138.31, 137.81, 133.57, 129.65, 128.27, 128.23, 128.13, 128.02, 127.86, 127.60, 127.44, 127.39, 127.31, 126.10, 116.18, 100.98, 96.79, 91.03, 85.36, 83.75, 79.16, 79.11, 77.44, 77.22, 77.02, 76.59, 75.26, 73.39, 73.34, 73.18, 72.05, 71.12, 69.34, 69.06, 68.93, 68.05, 56.02, 55.37, 42.76, 30.15, 21.40, 21.16, 20.89, 20.67, 20.14.; HR MALDI-TOF MS: m/z: calcd for $C_{58}H_{66}O_{17}S_2$ $[M+Na]^+$: 1121.3639; found: 1121.3630.

***p*-Methylphenyl 3,4-di-*O*-acetyl-6-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-(2-ethylnaphthyl)-1-thio-α-D-mannopyranoside (33)**. Compound **33** was prepared according to the general glycosylation procedure using glycosyl donor **17** (56 mg, 0.11 mmol) and glycosyl acceptor **28** (68 mg, 0.10 mmol). Purification by LH20 size exclusion chromatography afforded compound **33** (93 mg, 72%). R_f = 0.23 (EtOAc/hexanes, 1/3, v/v); $[\alpha]^{d}_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +100 (c = 0.5 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 – 6.83 (m, 35H, Ar*H*), 6.05 (s, 2H, Ar*H*), 5.88 (d, J = 3.5 Hz, 1H, H-1^{II}), 5.83 (s, 1H, H-1^{I}), 5.47 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.22 – 5.06 (m, 2H, C*H*HNap, C*H*HNap), 4.96 (t, J = 9.8 Hz, 1H, H-4^{II}), 4.82 (d, J = 11.8 Hz, 1H, CH*H*Nap), 4.72 (dd, J = 16.6, 11.8 Hz, 2H, CH*H*Nap, C*H*HNap), 4.67 – 4.55 (m, 2H, H-2^{I}, CH*H*Nap), 4.47 (d, J = 12.2 Hz, 1H, C*H*HPh), 4.42 – 4.26 (m, 4H, CH*H*Ph, SCH_2C*H*Ph^{II}, H-5^{I}, H-5^{II}), 4.23 (t, J = 9.2 Hz, 1H, H-4^{I}), 4.12 (d, J = 8.6 Hz, 1H, H-3^{I}), 3.91 – 3.64 (m, 12H, H-2^{II}, H-6$^{I}_a$, H-6$^{I}_b$, 3 ×OMe), 3.48 – 3.33 (m, 2H, H-6$^{II}_a$, H-6$^{II}_b$), 3.01 (dd, J = 13.8, 4.0 Hz, 1H, SCH*H*CHPh^{II}), 2.76 (dd, J = 13.7, 8.7 Hz, 1H, SC*H*HCHPh^{II}), 2.23 (s, 3H), 1.69 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.44, 170.17, 161.97, 161.88, 142.31, 138.19, 137.63, 136.29, 136.26, 136.20, 133.59, 133.49, 133.20, 133.16, 133.10, 132.77, 132.37, 130.94, 130.01, 129.95, 128.54, 128.48, 128.36, 128.28, 128.23, 128.21, 128.13, 128.09, 128.04, 127.87, 127.76, 127.74, 127.45, 126.80, 126.77, 126.59, 126.44, 126.36, 126.20, 126.13, 126.05, 125.98, 125.89, 125.86, 125.82, 101.69, 99.23, 91.20, 87.52, 84.36, 79.77, 79.44, 77.68, 77.50, 77.25, 76.83, 75.33, 73.38, 72.92, 72.88, 71.24, 69.81, 69.58, 69.03, 68.22, 56.17, 55.55, 43.45, 30.35,

21.27, 20.81, 20.38; HR MALDI-TOF MS: m/z: calcd for $C_{80}H_{80}O_{15}S_2$ $[M+Na]^+$: 1367.4836; found: 1367.4829.

3,4,6-tri-*O*-acetyl-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (38). Compound **38** was prepared according to the general glycosylation procedure using glycosyl donor **34** (55 mg, 0.13 mmol) and glycosyl acceptor **36** (27 mg, 0.10 mmol). Purification by LH20 size exclusion chromatography afforded compound **38** (71 mg, 80%). R_f = 0.14 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +36.4 (c = 2.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.01 (m, 5H, Ar*H*), 6.14 (s, 2H, Ar*H*), 5.58 – 5.47 (m, 2H, H-1^I, H-1^{II}), 5.33 (t, J = 9.6 Hz, 1H, H-3^{II}), 4.94 – 4.76 (m, 1H, H-4^{II}), 4.64 (dd, J = 7.9, 2.3 Hz, 1H, H-3^I), 4.45 – 3.94 (m, 8H, H-4^I, H-2^I, SCH_2C*H*Ph, H-5^I, H-5^{II}, H-$6_{a,b}{}^{II}$, H-$6_a{}^I$), 3.94 – 3.74 (m, 10H, 3×OMe, H-$6_b{}^I$), 3.62 (dd, J = 10.0, 3.6 Hz, 1H, H-2^{II}), 3.01 (dd, J = 13.8, 4.4 Hz, 1H, SC*H*HCHPh), 2.90 (dd, J = 13.8, 8.2 Hz, 1H, SCH*H*CHPh), 2.05 (s, 3H), 1.95 (s, 3H), 1.60 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.94, 170.31, 170.13, 161.96, 161.89, 142.09, 128.34, 127.67, 126.49, 109.48, 108.92, 101.77, 98.63, 96.51, 91.21, 84.38, 79.21, 77.68, 77.25, 76.83, 72.28, 71.33, 70.91, 70.88, 69.15, 68.98, 67.38, 67.22, 62.46, 56.16, 55.60, 42.91, 26.41, 26.24, 25.25, 24.71, 20.98, 20.88, 20.44; HR MALDI-TOF MS: m/z: calcd for $C_{46}H_{58}O_{16}S$ $[M+Na]^+$: 873.2979; found: 873.2991.

Methyl 3,4,6-tri-*O*-acetyl-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 (39). Compound **39** was prepared according to the general glycosylation procedure using glycosyl donor **34** (50 mg, 0.11 mmol) and glycosyl acceptor **24** (48 mg, 0.095 mmol).

Purification by LH20 size exclusion chromatography afforded compound **39** (62 mg, 59%). R_f = 0.12 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +50.0 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 – 6.97 (m, 20H), 6.19 (t, J = 9.3 Hz, 1H, H-2^{I}), 6.07 (s, 2H, Ar*H*), 5.56 (d, J = 3.1 Hz, 1H, H-1^{II}), 5.45 (t, J = 9.9 Hz, 1H, H-3^{I}), 5.40 (t, J = 9.7 Hz, 1H, H-3^{II}), 5.32 – 5.20 (m, 2H, H-1^{I}, H-2^{I}), 4.83 (t, J = 9.7 Hz, 1H, H-4^{II}), 4.57 – 4.46 (m, 1H, H-5^{I}), 4.36 – 4.16 (m, 3H, SCH_2CHPh, H-5^{II}, H-6$_a^{II}$), 4.08 (d, J = 12.0 Hz, 1H, H-6$_b^{II}$), 4.01 – 3.90 (m, 2H, H-6$_{a,b}^{I}$), 3.84 (s, 3H, OMe), 3.77 (s, 6H, 2×OMe), 3.64 – 3.51 (m, 4H, OMe, H-2^{II}), 2.96 – 2.79 (m, 2H, SCH_2CHPh), 2.09 (s, 3H), 1.95 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.56, 184.53, 184.51, 184.50, 184.48, 175.63, 175.04, 174.88, 170.81, 170.62, 170.51, 166.61, 166.58, 146.93, 138.25, 138.14, 137.94, 134.89, 134.74, 134.58, 134.22, 134.05, 133.61, 133.34, 133.20, 133.17, 133.14, 132.41, 131.07, 109.95, 106.66, 102.28, 101.97, 101.47, 95.84, 89.59, 84.03, 82.95, 82.94, 82.16, 81.95, 81.74, 77.28, 76.64, 75.53, 74.76, 73.97, 73.74, 72.21, 72.17, 67.23, 60.81, 60.43, 60.31, 48.31, 34.64, 25.74, 25.60, 25.17; HR MALDI-TOF MS: m/z: calcd for $C_{57}H_{60}O_{20}S$ $[M+Na]^+$: 1119.3296; found: 1119.3288.

Methyl 3,4,6-tri-*O*-acetyl-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 (40). Compound **40** was prepared according to the general glycosylation procedure using glycosyl donor **34** (68 mg, 0.15 mmol) and glycosyl acceptor **37** (60 mg, 0.13 mmol). Purification by LH20 size exclusion chromatography afforded compound **40** (65 mg, 48%). R_f = 0.32 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +35.0 (c = 0.3 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 – 6.80 (m, 20H, Ar*H*), 6.19 – 6.05 (m, 3H, Ar*H*, H-1^{II}), 5.35 (t, J = 9.7 Hz, 1H, H-3^{II}), 5.06 (s, 2H, CH_2Ph), 4.80 (t, J = 9.8 Hz, 1H,

H-4^{II}), 4.70 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.64 (d, *J* = 3.5 Hz, 1H, H-1^{I}), 4.63 – 4.54 (m, 3H, C*H*$_2$Ph, CH*H*Ph), 4.29 – 4.08 (m, 4H, H-3^{I}, H-4^{I}, H-5^{II}, SC*H*HCHPh), 4.03 (dd, *J* = 10.7, 3.5 Hz, 1H, H-6$^{I}_{a}$), 3.98 (dd, *J* = 12.2, 3.3 Hz, 2H, H-5^{I}, H-6$^{II}_{a}$), 3.90 – 3.71 (m, 11H, 3×OMe, H-6$^{I}_{b}$, H-6$^{II}_{b}$), 3.67 – 3.53 (m, 2H, H-2^{I}, H-2^{II}), 3.40 (s, 3H, OMe), 2.90 (dd, *J* = 13.9, 4.0 Hz, 1H, SCH*H*CHPh), 2.77 (dd, *J* = 13.9, 8.7 Hz, 1H, SC*H*HCHPh), 1.96 (s, 3H), 1.91 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.38, 170.13, 169.79, 161.89, 161.77, 142.08, 139.55, 138.21, 138.16, 128.40, 128.27, 128.12, 128.10, 127.84, 127.40, 127.23, 126.86, 126.74, 126.08, 101.15, 97.77, 95.91, 90.98, 84.39, 80.60, 80.10, 79.78, 77.68, 77.23, 77.02, 76.80, 74.18, 73.87, 73.47, 73.27, 71.91, 69.54, 69.21, 69.12, 67.55, 62.04, 55.85, 55.35, 42.77, 20.67, 20.64, 19.97; HR MALDI-TOF MS: m/z: calcd for $C_{57}H_{66}O_{17}S$ $[M+Na]^+$: 1077.3918; found: 1077.3926.

3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (41). Compound **41** was prepared according to the general glycosylation procedure using glycosyl donor **20** (60 mg, 0.12 mmol) and glycosyl acceptor **36** (27 mg, 0.10 mmol). Purification by LH20 size exclusion chromatography afforded compound **41** (79 mg, 84%). R_f = 0.25 (EtOAc/hexanes, 1/2, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.06 (m, 10H, Ar*H*), 6.10 (s, 2H, Ar*H*), 5.52 – 5.44 (m, 2H, H-1^{I}, H-3^{II}), 5.37 (d, *J* = 3.5 Hz, 1H, H-1^{II}), 4.62 (dd, *J* = 7.9, 2.3 Hz, 1H, H-3^{I}), 4.54 – 4.40 (m, 2H, C*H*$_2$Ph), 4.37 (dd, *J* = 7.9, 1.7 Hz, 1H, H-4^{I}), 4.35 – 4.20 (m, 4H, H-2^{I}, H-6$^{II}_{a}$, H-6$^{II}_{b}$, SCH$_2$C*H*), 4.16 (dd, *J* = 10.1, 2.9 Hz, 1H, H-5^{II}), 4.06 (t, *J* = 5.4 Hz, 1H, H-5^{I}), 3.97 – 3.92 (m, 1H, H-6$^{I}_{a}$), 3.88 – 3.79 (m, 10H, 3×OMe, H-6$^{I}_{b}$), 3.51 – 3.34 (m, 2H, H-2^{II}, H-4^{II}), 3.01 (d, *J* = 6.5 Hz, 2H, SC*H*$_2$CH), 2.04 (s, 3H), 1.55 (s, 3H), 1.48 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H);

^{13}C NMR (75 MHz, CDCl3): δ 170.91, 170.01, 161.89, 161.79, 141.83, 137.81, 128.61, 128.25, 128.22, 128.04, 127.75, 126.91, 109.41, 108.92, 101.95, 98.24, 96.51, 91.15, 83.80, 79.03, 77.67, 77.45, 77.24, 76.82, 76.38, 73.25, 73.08, 71.23, 70.91, 70.88, 68.46, 68.02, 67.12, 63.39, 56.16, 55.59, 42.30, 30.37, 26.40, 26.26, 25.21, 24.72, 21.12, 20.92; HR MALDI-TOF MS: m/z: calcd for $C_{46}H_{58}O_{16}S$ $[M+Na]^+$: 921.3343; found: 921.3337.

Methyl 3,6-di-*O*-acetyl-4-*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 (42). Compound **42** was prepared according to the general glycosylation procedure using glycosyl donor **20** (40 mg, 0.082 mmol) and glycosyl acceptor **37** (32 mg, 0.069 mmol). Purification by LH20 size exclusion chromatography afforded compound **42** (45 mg, 59%). R_f = 0.2 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +23.0 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 – 6.80 (m, 25H, Ar*H*), 6.07 (s, 2H, Ar*H*), 5.94 (d, *J* = 3.4 Hz, 1H, H-1^{II}), 5.46 (t, *J* = 6.0 Hz, 1H, H-3^{II}), 5.01 (s, 2H, C*H*$_2$Ph), 4.70 (d, *J* = 12.1 Hz, 1H, C*H*HPh), 4.63 (d, *J* = 3.5 Hz, 1H, H-1^{I}), 4.60 – 4.52 (m, 3H, CH*H*Ph, C*H*$_2$Ph), 4.43 (d, *J* = 11.0 Hz, 1H, C*H*HPh), 4.36 (d, *J* = 11.0 Hz, 1H, CH*H*Ph), 4.18 (t, *J* = 12.0 Hz, 1H, SCH$_2$C*H*Ph), 4.14 – 3.89 (m, 7H, H-3^{I}, H-5^{II}, H-5^{I}, H-4^{I}, H-6$_{a,b}$^{II}, H-6$_a$^{I}), 3.79 (s, 3H, OMe), 3.77 – 3.68 (m, 7H, 2×OMe, H-6$_b$^{I}), 3.62 – 3.54 (m, 1H, H-2^{I}), 3.40 (dd, *J* = 10.1, 3.4 Hz, 1H, H-2^{II}), 3.38 (s, 3H, OMe), 3.36 – 3.31 (m, 1H, H-4^{II}), 2.94 (dd, *J* = 13.7, 7.4 Hz, 1H, SC*H*HCHPh), 2.87 (dd, *J* = 13.6, 5.8 Hz, 1H, SCH*H*CHPh), 1.95 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.38, 169.74, 161.78, 161.60, 141.50, 139.59, 138.19, 138.13, 137.54, 128.44, 128.38, 128.17, 128.13, 128.09, 128.06, 128.01, 127.99, 127.93, 127.85, 127.81, 127.76, 127.43, 127.30, 127.28, 126.86, 126.80, 126.68, 101.35, 97.77, 95.86, 90.83, 83.63, 80.83, 80.34,

79.03, 77.23, 77.02, 76.80, 76.42, 74.06, 74.04, 73.31, 73.29, 73.15, 69.56, 69.03, 68.69, 62.87, 55.81, 55.31, 55.23, 42.10, 20.82, 20.56; HR MALDI-TOF MS: m/z: calcd for $C_{62}H_{70}O_{16}S$ $[M+Na]^+$: 1125.4282; found: 1125.4275.

3,4-di-*O*-acetyl-6-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (43). Compound **43** was prepared according to the general glycosylation procedure using glycosyl donor **17** (70 mg, 0.14 mmol) and glycosyl acceptor **36** (31 mg, 0.12 mmol). Purification by LH20 size exclusion chromatography afforded compound **43** (101 mg, 94%). R_f = 0.33 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{27}$ (deg cm^3 g^{-1} dm^{-1}) = +62.5 (*c* = 1.6 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 – 7.01 (m, 10H, Ar*H*), 6.21 – 6.01 (m, 2H, Ar*H*), 5.52 (d, *J* = 4.7 Hz, 1H, H-1^I), 5.45 (d, *J* = 3 Hz, 1H, H-2^{II}), 5.31 (t, *J* = 9.7 Hz, 1H, H-3^{II}), 4.98 (t, *J* = 9.7 Hz, 1H, H-4^{II}), 4.63 (dd, *J* = 7.9, 2.2 Hz, 1H, H-3^I), 4.57 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.45 – 4.38 (m, 2H, C*H*HPh, H-4^I), 4.31 (dd, *J* = 4.9, 2.3 Hz, 1H, H-2^I), 4.27 (dd, *J* = 7.9, 4.9 Hz, 1H, SCH_2CHPh), 4.19 – 4.00 (m, 2H, H-5^I, H-5^{II}), 3.99 – 3.86 (m, 2H, H-6^{II}_a, H-6^{II}_b), 3.83 (s, 3H, OMe), 3.81 (s, 6H, 2 × OMe), 3.63 (dd, *J* = 10.1, 3.5 Hz, 1H, H-2^{II}), 3.56 (dd, *J* = 10.7, 2.5 Hz, 1H, H-6^I_a), 3.46 (dd, *J* = 10.8, 3.6 Hz, 1H, H-6^I_b), 3.02 (dd, *J* = 13.7, 4.8 Hz, 1H, SC*H*HCHPh), 2.91 (dd, *J* = 13.8, 7.9 Hz, 1H, SCH*H*CHPh), 1.84 (s, 3H), 1.60 (s, 3H), 1.48 – 1.21 (4s, 12H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.29, 169.83, 161.73, 161.62, 141.85, 137.93, 128.27, 128.05, 127.91, 127.56, 127.40, 126.37, 116.19, 109.20, 108.67, 101.53, 98.34, 96.30, 90.94, 83.76, 78.64, 77.45, 77.23, 77.03, 76.60, 73.38, 72.39, 70.97, 70.80, 70.62, 69.52, 68.22, 68.08, 67.99, 66.83, 55.96, 55.36, 42.47, 30.16, 26.24, 26.05, 25.04, 24.53, 20.70, 20.31; HR MALDI-TOF MS: m/z: calcd for $C_{46}H_{58}O_{16}S$ $[M+Na]^+$: 921.3343; found: 921.3351.

Methyl 3,4-di-*O*-acetyl-6-*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 (44). Compound **44** was prepared according to the general glycosylation procedure using glycosyl donor **17** (45 mg, 0.09 mmol) and glycosyl acceptor **37** (36 mg, 0.08 mmol). Purification by LH20 size exclusion chromatography afforded compound **44** (57 mg, 67%). R_f = 0.43 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +50.0 (c = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 – 6.78 (m, 25H, Ar*H*), 6.07 (s, 3H, Ar*H*, H-1^{II}), 5.33 (t, J = 9.7 Hz, 1H, H-3^{II}), 5.05 (s, 2H, CH_2Ph), 4.96 (t, J = 9.8 Hz, 1H, H-4^{II}), 4.78 – 4.49 (m, 5H, 2 × CH_2Ph, H-1^{I}), 4.41 – 4.32 (m, 2H, CH_2Ph), 4.22 – 4.11 (m, 3H, SCH_2CHPh, H-3^{I}, H-4^{I}), 4.10 – 3.85 (m, 3H, H-5^{I}, H-5^{II}, H-$6^{I}_{a,}$), 3.80 (s, 1H, OMe), 3.76 – 3.69 (m, 7H, 2 × OMe, H-6^{I}_{b}), 3.64 (m, 2H, H-2^{I}, H-2^{II}), 3.39 (s, 3H, OMe), 3.28 (d, J = 10.6 Hz, 1H, H-6^{II}_{a}), 3.12 (d, J = 10.9 Hz, 1H, H-6^{II}_{b}), 2.89 (dd, J = 13.9, 4.3 Hz, 1H, SC*H*HCHPh), 2.78 (dd, J = 13.9, 8.2 Hz, 1H, SCH*H*CHPh), 1.81 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.52, 169.94, 162.08, 161.91, 142.24, 139.73, 138.55, 138.40, 138.23, 128.62, 128.43, 128.40, 128.35, 128.31, 128.28, 128.03, 127.70, 127.49, 127.43, 127.36, 127.09, 126.37, 101.28, 97.97, 96.08, 91.09, 84.18, 80.95, 80.49, 79.57, 77.66, 77.43, 77.23, 76.81, 74.26, 73.91, 73.52, 72.46, 69.81, 69.69, 69.51, 68.95, 68.15, 56.10, 55.53, 42.84, 30.38, 20.91, 20.31; HR MALDI-TOF MS: m/z: calcd for $C_{62}H_{70}O_{16}S$ $[M+Na]^+$: 1125.4282; found: 1125.4292.

3-*O*-allyloxycarbonyl-4-*O*-acetyl-6-*O*-benzyl-2-*O*-[(1S)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (45). Compound **45** was prepared according to the general glycosylation procedure using glycosyl donor **22** (76 mg, 0.14 mmol) and

glycosyl acceptor **36** (31 mg, 0.12 mmol). Purification by LH20 size exclusion chromatography afforded compound **45** (76 mg, 67%). R_f = 0.3 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +70.0 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 – 7.06 (m, 10H, Ar*H*), 6.10 (s, 2H, Ar*H*), 5.77 – 5.61 (m, 1H, C*H* alloc), 5.52 (d, *J* = 5.0 Hz, 1H, H-1^{I}), 5.46 (d, *J* = 3.5 Hz, 1H, H-1^{II}), 5.26 – 5.09 (m, 2H, CH_2 alloc), 5.04 (t, *J* = 9.7 Hz, 1H, H-4^{II}), 4.64 (dd, *J* = 7.9, 2.2 Hz, 1H, H-3^{I}), 4.54 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.50 – 4.39 (m, 2H, C*H*HPh, H-4^{I}), 4.36 – 4.29 (m, 2H, H-2^{I}, SCH$_2$C*H*), 4.27 (dd, *J* = 13.1, 5.8 Hz, 1H, CH*H* alloc), 4.09 (t, *J* = 6.6 Hz, 1H, H-5^{I}), 4.08 – 3.99 (m, 2H, H-5^{II}, C*H*H alloc), 3.98 – 3.85 (m, 2H, H-6$^{I}_{a}$, H-6$^{I}_{b}$), 3.83 – 3.80 (2s, 9H, 3×OMe), 3.73 (dd, *J* = 9.9, 3.5 Hz, 1H, H-2^{II}), 3.57 (dd, *J* = 10.8, 2.7 Hz, 1H, H-6$^{II}_{a}$), 3.47 (dd, *J* = 10.8, 3.8 Hz, 1H, H-6$^{II}_{b}$), 3.02 (dd, *J* = 13.9, 4.3 Hz, 1H, SC*H*HCH), 2.85 (dd, *J* = 13.9, 8.2 Hz, 1H, SCH*H*CH), 1.86 (s, 3H), 1.60 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.61, 161.74, 161.66, 154.09, 141.63, 137.94, 131.61, 128.26, 127.95, 127.92, 127.54, 127.21, 126.23, 118.19, 109.20, 108.66, 101.31, 98.48, 96.30, 95.09, 90.95, 83.31, 78.35, 78.09, 78.07, 77.22, 77.01, 76.80, 73.40, 70.92, 70.77, 70.61, 69.36, 68.30, 68.13, 67.82, 66.75, 55.93, 55.36, 42.75, 26.24, 26.05, 25.03, 24.56, 20.70; HR MALDI-TOF MS: m/z: calcd for $C_{48}H_{60}O_{17}S$ $[M+Na]^+$: 963.3449; found: 963.3456.

Methyl 3-*O*-allyoxylcarbonyl-4-*O*-acetyl-6-*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 (46). Compound **46** was prepared according to the general glycosylation procedure using glycosyl donor **22** (50 mg, 0.094 mmol) and glycosyl acceptor **24** (40 mg, 0.079 mmol). Purification by LH20 size exclusion chromatography

afforded compound **46** (73 mg, 78%). R_f = 0.24 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +60.0 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 – 6.97 (m, 25H, Ar*H*), 6.18 (t, *J* = 9.4 Hz, 1H, H-3^I), 6.04 (s, 2H, Ar*H*), 5.77 – 5.60 (m, 1H, C*H* alloc), 5.53 – 5.42 (m, 2H, H-1^{II}, H-4^I), 5.31 – 5.22 (m, 2H, H-1^I, H-2^I), 5.22 – 5.10 (m, 3H, H-3^{II}, CH_2 alloc), 5.04 (dd, *J* = 18.4, 8.9 Hz, 1H, H-4^{II}), 4.59 – 4.39 (m, 3H, CH_2Ph, H-5^I), 4.31 – 4.23 (m, 2H, SCH_2CHPh, C*H*H alloc), 4.19 – 4.11 (m, 1H, H-5^{II}), 4.07 (dd, *J* = 13.2, 5.5 Hz, 1H, CH*H* alloc), 3.98 (dd, *J* = 10.6, 8.3 Hz, 1H, H-6$_a^I$), 3.91 (dd, *J* = 10.6, 1.7 Hz, 1H, H-6$_b^I$), 3.82 (s, 3H, OMe), 3.77 – 3.65 (m, 7H, 2×OMe, H-2^{II}), 3.61 – 3.51 (m, 4H, OMe, H-6$_a^{II}$), 3.45 (dd, *J* = 10.8, 3.7 Hz, 1H, H-6$_b^{II}$), 2.87 (ddd, *J* = 22.8, 14.1, 6.2 Hz, 2H, SCH_2CHPh), 1.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.57, 179.54, 179.51, 169.54, 165.85, 165.67, 165.48, 161.65, 161.60, 154.03, 141.67, 137.87, 133.28, 133.17, 132.97, 131.56, 129.93, 129.80, 129.63, 129.29, 129.12, 128.74, 128.37, 128.28, 128.24, 128.21, 127.99, 127.90, 127.56, 127.18, 126.03, 118.15, 97.36, 96.49, 90.87, 83.84, 78.47, 77.97, 77.20, 76.98, 76.77, 73.37, 72.37, 70.62, 69.77, 69.29, 68.75, 68.33, 68.15, 68.11, 66.93, 55.86, 55.43, 55.32, 43.43, 20.66; HR MALDI-TOF MS: m/z: calcd for $C_{64}H_{66}O_{20}S$ $[M+Na]^+$: 1209.3766; found: 1209.3752.

4-*O*-acetyl-3-*O*-levulinoyl-6-*O*-benzyl-2-*O*-[(1S)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (47). Compound **47** was prepared according to the general glycosylation procedure using glycosyl donor **21** (40 mg, 0.074 mmol) and glycosyl acceptor **36** (16 mg, 0.062 mmol). Purification by LH20 size exclusion chromatography afforded compound **47** (51 mg, 85%). R_f = 0.14 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +27.5 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ

7.38 – 7.00 (m, 10H, Ar*H*), 6.10 (s, 2H, Ar*H*), 5.52 (d, *J* = 5.0 Hz, 1H, H-1^{I}), 5.45 (d, *J* = 3.4 Hz, 1H, H-1^{II}), 5.34 (t, *J* = 9.7 Hz, 1H, H-3^{II}), 4.98 (t, *J* = 9.8 Hz, 1H, H-4^{II}), 4.62 (dd, *J* = 7.9, 2.2 Hz, 1H, H-3^{I}), 4.59 – 4.36 (m, 3H, C*H*$_2$Ph, H-4^{I}), 4.31 (dd, *J* = 4.9, 2.3 Hz, 1H, H-2^{I}), 4.25 (dd, *J* = 7.7, 4.8 Hz, 1H, SCH$_2$C*H*Ph), 4.17 – 3.97 (m, 2H, H-5^{I}, H-5^{II}), 3.97 – 3.72 (m, 11H, H-6$^{I}_{a}$, H-6$^{I}_{b}$, 3×OMe), 3.63 (dd, *J* = 10.0, 3.5 Hz, 1H, H-2^{II}), 3.59 – 3.36 (m, 2H, H-6$^{II}_{a}$, H-6$^{II}_{b}$), 3.02 (dd, *J* = 13.7, 4.9 Hz, 1H, SC*H*HCHPh), 2.90 (dd, *J* = 13.7, 7.8 Hz, 1H, SCH*H*CHPh), 2.44 – 2.08 (m, 3H, 3×C*H*H Lev), 2.06 (s, 3H), 1.88 (s, 3H), 1.68 – 1.62 (m, 1H, C*H*H Lev), 1.59 (s, 3H)1.45 (s, 3H), 1.34 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.39, 172.00, 170.15, 161.94, 161.86, 142.07, 138.15, 128.48, 128.22, 128.15, 127.87, 127.77, 127.52, 126.66, 109.41, 108.87, 101.61, 98.58, 96.51, 91.16, 83.84, 78.85, 77.66, 77.44, 77.23, 76.81, 73.62, 72.57, 71.15, 71.00, 70.83, 69.43, 68.57, 68.37, 68.08, 66.96, 56.18, 55.58, 42.60, 37.83, 29.94, 27.75, 26.46, 26.26, 25.24, 24.76, 20.92; HR MALDI-TOF MS: m/z: calcd for $C_{49}H_{62}O_{17}S$ $[M+Na]^+$: 977.3605; found: 977.3597.

Methyl 4-*O*-acetyl-6-*O*-benzyl-3-*O*-levulinoyl-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 (48). Compound **48** was prepared according to the general glycosylation procedure using glycosyl donor **21** (50 mg, 0.093 mmol) and glycosyl acceptor **37** (36 mg, 0.078 mmol). Purification by LH20 size exclusion chromatography afforded compound **48** (57 mg, 64%). R_f = 0.11 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +40.0 (*c* = 0.8 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 – 6.83 (m, 20H, Ar*H*), 6.07 (s, 3H, Ar*H*, H-1^{II}), 5.38 (t, *J* = 9.8 Hz, 1H, H-3^{II}), 5.04 (s, 2H, C*H*$_2$Ph), 4.95 (dd, *J* = 19.0, 9.3 Hz, 1H, H-4^{II}), 4.70 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.63 (d, *J* = 3.5

Hz, 1H, H-1^{I}), 4.60 – 4.52 (m, 3H, CH*H*Ph, C*H*$_2$Ph), 4.38 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.27 (d, *J* = 11.9 Hz, 1H, CH*H*Ph), 4.19 – 4.10 (m, 3H, H-3^{I}, H-4^{I}, SCH$_2$C*H*Ph), 4.07 – 3.90 (m, 3H, H-5^{I}, H-5^{II}, H-6$_a$^{II}), 3.85 – 3.68 (m, 10H, 3×OMe, H-6$_b$^{II}), 3.65 – 3.56 (m, 1H, H-2^{I}), 3.39 (s, 3H, OMe), 3.29 (dd, *J* = 10.7, 2.5 Hz, 1H, H-6$_a$^{II}), 3.13 (dd, *J* = 10.8, 3.4 Hz, 1H, H-6$_b$^{II}), 2.87 (dd, *J* = 13.9, 4.6 Hz, 1H, SC*H*HCHPh), 2.78 (dd, *J* = 13.9, 8.2 Hz, 1H, SCH*H*CHPh), 2.42 – 2.30 (m, 1H, C*H*H Lev), 2.21 – 2.09 (m, 1H, CH*H* Lev), 2.06 (s, 3H), 2.04 – 1.95 (m, 1H, C*H*H Lev), 1.87 (s, 3H), 1.41 (dt, *J* = 17.4, 6.1 Hz, 1H, CH*H* Lev); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.36, 172.06, 170.05, 162.07, 161.93, 142.22, 139.74, 138.55, 138.42, 138.24, 128.62, 128.43, 128.39, 128.35, 128.29, 128.23, 128.05, 127.70, 127.47, 127.37, 127.31, 127.16, 127.07, 126.49, 101.20, 97.99, 96.27, 91.10, 84.05, 80.87, 80.70, 79.55, 77.67, 77.45, 77.24, 76.82, 74.35, 74.00, 73.52, 72.35, 69.76, 69.48, 69.11, 68.28, 56.10, 55.52, 42.75, 37.83, 29.95, 27.54, 20.92; HR MALDI-TOF MS: m/z: calcd for $C_{65}H_{74}O_{17}S$ $[M+Na]^+$: 1181.4545; found: 1181.4556.

4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (49). Compound **49** was prepared according to the general glycosylation procedure using glycosyl donor **23** (60 mg, 0.12 mmol) and glycosyl acceptor **36** (26 mg, 0.10 mmol). Purification by LH20 size exclusion chromatography afforded compound **49** (88 mg, 98%). R_f = 0.19 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +13.5 (*c* = 0.3 in $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 – 7.05 (m, 10H, Ar*H*), 6.09 (s, 2H, Ar*H*), 5.54 (d, *J* = 5.0 Hz, 1H, H-1^{I}), 5.21 (d, *J* = 3.4 Hz, 1H, H-1^{II}), 4.89 (t, *J* = 9.9 Hz, 1H, H-4^{II}), 4.67 (dd, *J* = 7.9, 2.3 Hz, 1H, H-3^{I}), 4.60 – 4.54 (m, 2H, C*H*HPh, SCH$_2$C*H*Ph), 4.48 – 4.41 (m, 2H, CH*H*Ph, H-4^{I}), 4.34 (dd, *J* = 5.0, 2.4 Hz, 1H, H-2^{I}), 4.22 (dd, *J* = 12.3, 4.4

Hz, 1H, H-6^{II}_a), 4.10 (br t, *J* = 5.8 Hz, 1H, H-5^{I}), 4.05 – 3.71 (m, 14H, H-5^{II}, H-6^{II}_b, H-6^{I}_a, H-6^{I}_b H-3^{II}, 3 × OMe), 3.58 (dd, *J* = 9.5, 3.5 Hz, 1H, H-2^{II}), 3.12 (dd, *J* = 13.3, 7.0 Hz, 1H, SC*H*HCHPh), 3.01 (dd, *J* = 13.3, 5.6 Hz, 1H, SCH*H*CHPh), 2.04 (s, 3H), 1.86 (s, 3H), 1.59 (s, 3H), 1.47 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.08, 169.87, 161.83, 161.79, 141.09, 138.99, 128.36, 128.30, 127.91, 127.85, 127.45, 127.16, 109.53, 108.83, 102.16, 98.24, 96.55, 91.20, 81.73, 79.05, 78.58, 77.66, 77.44, 77.24, 76.81, 75.17, 71.36, 70.92, 70.88, 70.04, 68.28, 67.76, 67.09, 62.61, 56.17, 55.57, 42.37, 30.37, 26.40, 26.31, 25.24, 24.84, 21.02, 20.99; HR MALDI-TOF MS: m/z: calcd for $C_{46}H_{58}O_{16}S$ $[M+Na]^+$: 921.3344; found: 921.3352.

Methyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-D-glucopyranose (50). Compound **50** was prepared according to the general glycosylation procedure using glycosyl donor **23** (30 mg, 0.074 mmol) and glycosyl acceptor **37** (24 mg, 0.063 mmol). Purification by LH20 size exclusion chromatography afforded compound **50** (25 mg, 46%, α/β=7/1). **50α**: R_f = 0.23 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +20.0 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (500 MHz, CDCl3): δ 7.50 – 6.92 (m, 25H, Ar*H*), 6.06 (s, 2H, Ar*H*), 5.86 (d, *J* = 3.4 Hz, 1H, H-1^{II}), 5.09 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 5.02 (d, *J* = 13.5 Hz, 1H, CH*H*Ph), 4.83 (t, *J* = 10.0 Hz, 1H, H-4^{II}), 4.69 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.65 (d, *J* = 3.5 Hz, 1H, H-1^{I}), 4.62 – 4.52 (m, 3H, CH*H*Ph, CH_2Ph), 4.48 (t, *J* = 6.4 Hz, 1H, SCH_2C*H*Ph), 4.42 (d, *J* = 11.6 Hz, 1H, C*H*HPh), 4.34 (d, *J* = 11.6 Hz, 1H, CH*H*Ph), 4.17 (t, *J* = 9.1 Hz, 1H, H-3^{I}), 4.04 (t, *J* = 9.2 Hz, 1H, H-4^{I}), 3.99 (dd, *J* = 12.3, 4.1 Hz, 1H, H-6^{I}_a), 3.96 – 3.83 (m, 3H, H-5^{I}, H-5^{II}, H-6^{II}_a), 3.83 – 3.77 (m, 4H, OMe, H-6^{I}_b), 3.77 – 3.67 (m, 7H, 2×OMe, H-6^{II}_b), 3.61 (dd, *J*

= 9.4, 3.5 Hz, 1H, H-2^{I}), 3.50 (dd, *J* = 9.6, 3.4 Hz, 1H, H-2^{II}), 3.40 (s, 3H, OMe), 3.06 (dd, *J* = 13.3, 6.5 Hz, 1H, SC*H*HCHPh), 2.87 (dd, *J* = 13.3, 6.4 Hz, 1H, SCH*H*CHPh), 1.98 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.62, 169.48, 161.58, 161.55, 140.85, 139.13, 138.55, 138.03, 138.01, 128.59, 128.40, 128.31, 128.25, 128.12, 128.06, 127.99, 127.87, 127.53, 127.45, 127.32, 127.21, 127.09, 126.93, 126.83, 101.36, 97.72, 95.95, 90.88, 81.80, 81.24, 80.36, 78.62, 78.14, 78.09, 77.21, 77.00, 76.78, 74.76, 74.06, 73.40, 73.24, 72.79, 70.02, 69.54, 69.12, 68.10, 62.33, 55.80, 55.27, 55.24, 41.56, 20.77, 20.74.; HR MALDI-TOF MS: m/z: calcd for $C_{62}H_{70}O_{16}S$ $[M+Na]^+$: 1125.4283; found: 1125.4276. The ß anomer was purified by reversed phase HPLC on an analytical C-18 column using a gradient of 40→100% acetonitrile in H_2O over 40 min. **50β**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 – 7.08 (m, 25H, Ar*H*), 6.06 (s, 2H, Ar*H*), 4.99 (t, *J* = 6.7 Hz, 1H, SCH_2C*H*Ph), 4.90 (d, *J* = 11.2 Hz, 1H, C*H*HPh), 4.84 – 4.68 (m, 3H, H-4^{II}, 2×C*H*HPh), 4.68 – 4.54 (m, 4H, H-1^{I}, 2×CH*H*Ph, C*H*HPh), 4.54 – 4.40 (m, 2H, 2×CH*H*Ph), 4.32 (d, *J* = 7.2 Hz, 1H, H-1^{II}), 4.22 (d, *J* = 8.2 Hz, 1H, H-6^{I}_{a}), 4.07 – 3.96 (m, 2H, H-4^{I}, H-6^{II}_{a}), 3.89 – 3.81 (m, 3H, H-6^{II}_{b}, H-3^{I}, H-5^{I}), 3.78 (s, 9H, 3×OMe), 3.71 (d, *J* = 11.0 Hz, 1H, H-6^{I}_{b}), 3.51 (dd, *J* = 9.6, 3.8 Hz, 1H, H-2^{I}), 3.42 (s, 3H, OMe), 3.30 (dd, *J* = 13.2, 6.3 Hz, 1H, SC*H*HCHPh), 3.26 – 3.15 (m, 2H, H-2^{II}, H-3^{II}), 3.11 (d, *J* = 8.5 Hz, 1H, H-5^{II}), 2.82 (dd, *J* = 13.2, 6.8 Hz, 1H, SCH*H*CHPh), 1.92 (s, 3H), 1.85 (s, 3H); selected ^{13}C NMR (gHSQC, $CDCl_3$): δ 102.01 (C-1^{II}), 98.90 (C-1^{I}), 82.61, 82.16, 81.94, 81.66, 80.63, 78.75, 78.02, 75.76, 75.26, 73.72, 70.31, 69.87, 68.27, 67.85, 62.24, 55.92, 55.64, 41.89; HR MALDI-TOF MS: m/z: calcd for $C_{62}H_{70}O_{16}S$ $[M+Na]^+$: 1125.4283; found: 1125.4272.

3-*O*-acetyl-4,6-di-*O*-benzyl-2-*O*-[(1S)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (51). Compound **51** was prepared according to the general procedure using glycosyl donor **18** (40 mg, 0.075 mmol) and glycosyl acceptor **36** (16 mg, 0.062 mmol). Purification by LH20 size exclusion chromatography afforded compound **51** (56 mg, 95 %). R_f = 0.34 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +21.5 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 – 7.01 (m, 15H, Ar*H*), 6.06 (s, 2H, Ar*H*), 5.50 (d, *J* = 5.0 Hz, 1H, H-1^{I}), 5.39 (t, *J* = 9.7 Hz, 1H, H-3^{II}), 5.32 (d, *J* = 3.5 Hz, 1H, H-1^{II}), 4.61 (dd, *J* = 7.4, 2.9 Hz, 2H, H-3^{I}, C*H*HPh), 4.46 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.39 (s, 3H, CH_2Ph, H-4^{I}), 4.29 (dd, *J* = 5.0, 2.3 Hz, 1H, H-2^{I}), 4.25 (t, *J* = 6.6 Hz, 1H, SCH_2CHPh), 4.10 – 4.00 (m, 1H, H-6_a^{I}), 3.97 – 3.92 (m, 1H, H-5^{II}), 3.89 (dd, *J* = 9.9, 7.2 Hz, 1H, H-6_b^{I}), 3.86 – 3.71 (m, 11H, 3×OMe, H-5^{I}, H-6_a^{II}), 3.66 (dd, *J* = 10.8, 1.8 Hz, 1H, H-6_b^{II}), 3.57 (t, *J* = 9.7 Hz, 1H, H-4^{II}), 3.45 (dd, *J* = 10.0, 3.5 Hz, 1H, H-2^{II}), 3.02 (d, *J* = 6.6 Hz, 2H, SCH_2CHPh), 1.55 (s, 3H), 1.44 (2s, 6H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.61, 179.58, 179.57, 169.89, 161.60, 161.47, 141.44, 138.04, 137.98, 128.32, 128.25, 127.95, 127.90, 127.75, 127.66, 127.54, 127.45, 126.79, 109.09, 108.63, 101.58, 98.11, 96.24, 90.81, 83.16, 78.39, 78.03, 78.02, 77.20, 76.99, 76.78, 76.23, 73.72, 73.44, 73.18, 70.79, 70.77, 70.53, 69.66, 68.32, 67.64, 66.57, 55.91, 55.32, 41.63, 26.21, 26.00, 24.96, 24.45, 20.70; HR MALDI-TOF MS: m/z: calcd for $C_{51}H_{62}O_{15}S$ $[M+Na]^+$: 969.3707; found: 969.3718.

Methyl 3-*O*-acetyl-4,6-di-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-D-glucopyranosyl-(1→4)- 2,3,6-tri-*O*-benzyl-D-glucopyranoside (52). Compound **52** was prepared according to the general

glycosylation procedure using glycosyl donor **18** (50 mg, 0.093 mmol) and glycosyl acceptor **37** (36 mg, 0.078 mmol). Purification by LH20 size exclusion chromatography afforded compound **52** (59 mg, 66%, α/β=10/1). **52α**: R_f = 0.39 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +48.0 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 – 6.90 (m, 30H, Ar*H*), 6.03 (s, 2H, Ar*H*), 5.95 (d, *J* = 3.4 Hz, 1H, H-1^{II}), 5.39 (t, *J* = 9.7 Hz, 1H, H-3^{II}), 5.03 (d, *J* = 11.8 Hz, 1H, C*H*HPh), 4.94 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.71 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.63 (d, *J* = 3.5 Hz, 1H, H-1^{I}), 4.58 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.50 (q, *J* = 12.2 Hz, 2H, CH_2Ph), 4.43 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.36 (d, *J* = 11.2 Hz, 1H, C*H*HPh), 4.31 (d, *J* = 11.2 Hz, 1H, CH*H*Ph), 4.27 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.21 (t, *J* = 6.7 Hz, 1H, SCH_2CHPh), 4.15 – 4.08 (m, 2H, H-4^{I}, H-3^{I}), 3.96 (dd, *J* = 10.7, 3.4 Hz, 1H, H-6$_a^{I}$), 3.94 – 3.90 (m, 1H, H-5^{I}), 3.81 (d, *J* = 10.0 Hz, 1H, H-5^{II}), 3.76 (s, 3H, OMe), 3.71 (s, 7H, 2×OMe, H-6$_b^{I}$), 3.60 (dd, *J* = 9.2, 3.5 Hz, 1H, H-2^{I}), 3.52 (t, *J* = 9.6 Hz, 1H, H-4^{II}), 3.43 (dd, *J* = 10.2, 3.4 Hz, 1H, H-2^{II}), 3.37 (s, 3H, OMe), 3.33 (d, *J* = 1.9 Hz, 2H, H-6$_{a,b}^{II}$), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.09, 161.98, 161.78, 161.66, 141.61, 139.65, 138.56, 138.44, 138.30, 128.79, 128.63, 128.52, 128.46, 128.37, 128.35, 128.33, 128.17, 128.06, 127.93, 127.85, 127.75, 127.64, 127.38, 127.36, 127.28, 127.14, 127.00, 101.59, 97.96, 95.91, 91.04, 83.32, 81.17, 80.89, 78.80, 77.68, 77.46, 77.26, 76.83, 76.54, 74.36, 73.54, 73.51, 73.35, 72.86, 70.63, 69.70, 69.37, 68.32, 56.23, 56.09, 55.48, 55.43, 42.10, 20.85; HR MALDI-TOF MS: m/z: calcd for $C_{67}H_{74}O_{15}S$ $[M+Na]^+$: 1173.4646; found:1173.4638. The ß anomer was purified by reversed phase HPLC on an analytical C-18 column using a gradient of 50→100% acetonitrile in H_2O over 40 min. **52ß**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.03 (m, 30H, Ar*H*), 6.01 (s, 2H, Ar*H*), 5.00 (d, *J* = 11.4 Hz, 1H, C*H*HPh), 4.96 (t, *J* = 9.4 Hz, 1H,

H-3^{II}), 4.79 (d, *J* = 12.2 Hz, 1H, C*H*HPh), 4.77 – 4.74 (m, 1H, SCH$_2$C*H*Ph), 4.71 (d, *J* = 11.4 Hz, 1H, CH*H*Ph), 4.66 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.63 – 4.58 (m, 2H, H-1^{I}, CH*H*Ph), 4.49 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.45 – 4.33 (m, 5H, 2×C*H*$_2$Ph, H-1^{II}), 4.09 – 4.02 (m, 1H, H-4^{I}), 3.96 (dd, *J* = 11.0, 2.6 Hz, 1H, H-6$_a^{I}$), 3.87 (t, *J* = 9.4 Hz, 1H, H-3^{I}), 3.80 – 3.73 (m, 10H, H-5^{I}, 3×OMe), 3.63 (dd, *J* = 11.2, 1.7 Hz, 1H, H-6$_a^{II}$), 3.61 (dd, *J* = 11.0, 1.7 Hz, 1H, H-6$_b^{I}$), 3.50 – 3.43 (m, 2H, H-2^{I}, H-6$_b^{II}$), 3.43 – 3.35 (m, 4H, H-4^{II}, OMe), 3.21 – 3.09 (m, 3H, H-5^{II}, H-2^{II}, SC*H*HCHPh), 2.93 (dd, *J* = 13.3, 8.6 Hz, 1H, SCH*H*CHPh), 1.70 (s, 3H); ^{13}C NMR (gHSQC, 150 MHz, $CDCl_3$): δ; HR MALDI-TOF MS: m/z: calcd for $C_{67}H_{74}O_{15}S$ $[M+Na]^+$: 1173.4646; found:1173.4641.

3,4,6-tri-*O*-benzyl-2-*O*-[(1S)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (53). Compound **53** was prepared according to the general glycosylation procedure using glycosyl donor **35** (50 mg, 0.086 mmol) and glycosyl acceptor **36** (18 mg, 0.070 mmol). Purification by LH20 size exclusion chromatography afforded compound **53** (68 mg, 98%). R_f = 0.39 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +6.7 (*c* = 1.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 – 6.98 (m, 20H, Ar*H*), 6.06 (s, 2H, Ar*H*), 5.53 (d, *J* = 5.0 Hz, 1H, H-1^{I}), 5.10 (d, *J* = 3.5 Hz, 1H, H-1^{II}), 4.86 – 4.50 (m, 7H, C*H*$_2$Ph, C*H*HPh, C*H*HPh, SCH$_2$C*H*, H-4^{I}, H-3^{I}), 4.49 – 4.37 (m, 2H, C*H*HPh, C*H*HPh), 4.32 (dd, *J* = 5.0, 2.3 Hz, 1H, H-2^{I}), 4.18 – 3.98 (m, 1H, H-5^{I}), 3.98 – 3.68 (m, 15H, 3×OMe, H-3^{II}, H-5^{II}, H-6$^{I}_a$, H-6$^{I}_b$, H-6$^{II}_a$, H-6$^{II}_b$), 3.62 (dd, *J* = 10.6, 1.9 Hz, 1H, H-4^{II}), 3.57 – 3.44 (m, 1H, H-2^{II}) 3.19 (dd, *J* = 13.1, 6.4 Hz, 1H, SC*H*HCH), 3.02 (dd, *J* = 13.1, 6.5 Hz, 1H, SCH*H*CH), 1.56 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.76, 161.64, 140.94, 139.37, 138.71, 138.25, 128.53, 128.48,

128.30, 128.15, 128.02, 127.88, 127.82, 127.73, 127.44, 127.40, 116.41, 109.39, 108.81, 102.33, 98.07, 96.54, 91.16, 81.79, 80.92, 78.21, 77.80, 77.68, 77.46, 77.25, 76.83, 75.49, 75.08, 73.65, 71.10, 71.01, 70.84, 70.37, 68.72, 67.27, 66.48, 56.15, 55.53, 41.84, 30.38, 26.46, 26.35, 25.21, 24.91; HR MALDI-TOF MS: m/z: calcd for $C_{56}H_{66}O_{14}S$ $[M+Na]^+$: 1017.4071; found: 1017.4063.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-D-glucopyranoside (54). Compound **54** was prepared according to the general glycosylation procedure using glycosyl donor **35** (50 mg, 0.086 mmol) and glycosyl acceptor **37** (33 mg, 0.071 mmol). Purification by LH20 size exclusion chromatography afforded compound **54** (49 mg, 57%, α/β=1.5/1). **54α**: R_f = 0.43 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +21.4 (*c* = 1.4 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 – 7.00 (m, 35H, Ar*H*), 6.01 (s, 2H, Ar*H*), 5.81 (d, *J* = 3.3 Hz, 1H, H-1^{II}), 5.09 (d, *J* = 11.8 Hz, 1H, C*H*HPh), 4.98 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.75 – 4.55 (m, 8H, H-1^{I}, C*H*HPh, CH_2Ph×3), 4.53 – 4.47 (m, 2H, SCH_2C*H*Ph, C*H*HPh), 4.45 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.36 (d, *J* = 11.0 Hz, 1H, CH*H*Ph), 4.26 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.15 (t, *J* = 9.1 Hz, 1H, H-3^{I}), 4.07 (t, *J* = 9.2 Hz, 1H, H-4^{I}), 3.92 – 3.64 (m, 14H, H-5^{I}, H-3^{II}, H-5^{II}, H-6$_{a,b}^{I}$, 3×OMe), 3.61 (dd, *J* = 9.4, 3.5 Hz, 1H, H-2^{I}), 3.51 – 3.46 (m, 1H, H-4^{II}), 3.46 – 3.40 (m, 1H, H-6$_a^{II}$), 3.40 – 3.33 (m, 5H, OMe, H-2^{II}, H-6$_b^{II}$), 3.18 (dd, *J* = 13.0, 5.5 Hz, 1H, SC*H*HCHPh), 2.83 (dd, *J* = 13.0, 7.6 Hz, 1H, SCH*H*CHPh); ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.57, 161.43, 140.61, 139.15, 139.07, 138.64, 138.21, 138.14, 138.04, 128.41, 128.33, 128.28, 128.26, 128.17, 128.15, 128.09, 128.04, 128.01, 127.91, 127.87, 127.71, 127.57, 127.53, 127.49, 127.43, 127.27, 127.25, 127.16, 127.10, 127.02, 101.53, 97.74, 95.70, 90.93,

90.87, 81.77, 81.44, 80.89, 80.52, 77.69, 77.45, 77.26, 77.05, 76.84, 75.07, 74.77, 74.17, 73.37, 73.26, 73.07, 71.43, 70.82, 69.53, 69.03, 68.33, 56.00, 55.81, 55.21, 55.15, 41.15; HR MALDI-TOF MS: m/z: calcd for $C_{72}H_{78}O_{14}S$ $[M+Na]^+$: 1221.5010; found: 1221.5001. The ß anomer was purified by reversed phase HPLC on an analytical C-18 column using a gradient of 50→100% acetonitrile in H_2O over 40 min. **54β**: R_f = 0.35 (EtOAc/hexanes, 1/2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.03 (m, 30H, Ar*H*), 6.05 (s, 2H, Ar*H*), 5.04 (t, *J* = 6.7 Hz, 1H, SCH_2CHPh), 4.93 (d, *J* = 11.2 Hz, 1H, C*H*HPh), 4.79 (d, *J* = 12.4 Hz, 2H, C*H*HPh, CH*H*Ph), 4.73 – 4.57 (m, 6H, H-1^I, 2×CH_2Ph, CH*H*Ph), 4.52 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.49 – 4.42 (m, 2H, C*H*HPh, C*H*HPh), 4.37 (d, *J* = 7.8 Hz, 1H, H-1^{II}), 4.33 (d, *J* = 12.3 Hz, 1H, CH*H*Ph), 4.12 (d, *J* = 8.7 Hz, 1H, H-6$_a^I$), 4.06 (t, *J* = 9.7 Hz, 1H), 3.90 – 3.82 (m, 2H, H-3^I, H-5^I), 3.77 (s, 6H, 2×OMe), 3.75 (s, 3H, OMe), 3.71 – 3.62 (m, 2H, H-6$_b^I$, H-6$_a^{II}$), 3.51 – 3.39 (m, 5H, H-6$_b^{II}$, H-2^I, OMe), 3.38 – 3.27 (m, 3H, H-3^{II}, H-4^{II}, SC*H*HCH), 3.25 – 3.16 (m, 2H, H-2^{II}, H-5^{II}), 2.82 (dd, *J* = 13.3, 7.1 Hz, 1H, SCH*H*CHPh).; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.72, 179.71, 179.71, 179.69, 179.69, 179.68, 179.67, 179.65, 179.61, 179.60, 161.36, 161.32, 140.27, 139.51, 138.92, 138.66, 138.45, 138.31, 137.84, 128.47, 128.30, 128.24, 128.17, 128.14, 128.05, 127.96, 127.90, 127.88, 127.74, 127.70, 127.68, 127.52, 127.49, 127.32, 127.19, 127.02, 102.85, 102.05, 98.76, 97.05, 97.05, 90.92, 84.68, 84.22, 82.04, 80.81, 78.67, 78.13, 78.09, 78.08, 77.20, 76.99, 76.77, 75.47, 75.42, 75.38, 75.22, 74.64, 73.73, 73.41, 73.34, 70.12, 68.93, 68.20, 55.98, 55.69, 55.29, 41.82; HR MALDI-TOF MS: m/z: calcd for C72H78O14S [M+Na]+: 1221.5010; found: 1221.4998.

4-*S*-(2,3,5-trimethoxylphenyl)-2-(*S*)-phenyl-(3,4,6-tri-*O*-benzoyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathianium triflate (56). Compound **56** was prepared

according to the general procedure as descripted in the paper. Selected ^{1}H NMR (500 MHz, gHSQC, $CDCl_3$): δ 5.99 (H-3), 5.81 (d, *J* = 10 Hz, H-1), 5.74 (H-4), 4.88 (SCH_2CHPh), 4.50 (H-$6_{a,b}$), 4.37 (H-2), 4.30 (H-5), 4.35 (SC*H*HCHPh), 4.19 (SCH*H*CHPh); ^{13}C NMR (125 MHz, gHSQC, $CDCl_3$): δ 81.60 (C-1), 78.68 (C-2), 78.25 (C-5), 76.00 (SCH_2CHPh), 72.79 (C-3), 68.93 (C-4), 62.55 (C-6), 45.44 (SCH_2CHPh).

4-*S*-(2,3,5-trimethoxylphenyl)-2-(*S*)-phenyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathianium triflate (57). Compound **57** was prepared according to the general procedure as descripted in the paper. Selected ^{1}H NMR (500 MHz, gHSQC, $CDCl_3$): δ 5.66 (d, *J* = 10 Hz, H-1), 5.47 (H-3), 5.22 (H-4), 5.07 (SCH_2CHPh), 4.26 (SC*H*HCHPh), 4.17 (H-$6_{a,b}$), 4.13 (SCH*H*CHPh, H-2), 3.92 (H-5); ^{13}C NMR (125 MHz, gHSQC, $CDCl_3$): δ 81.54 (C-1), 78.23 (C-2), 77.59 (C-5), 76.64 (SCH_2CHPh), 72.72 (C-3), 68.06 (C-4), 62.55 (C-6), 45.60 (SCH_2CHPh).

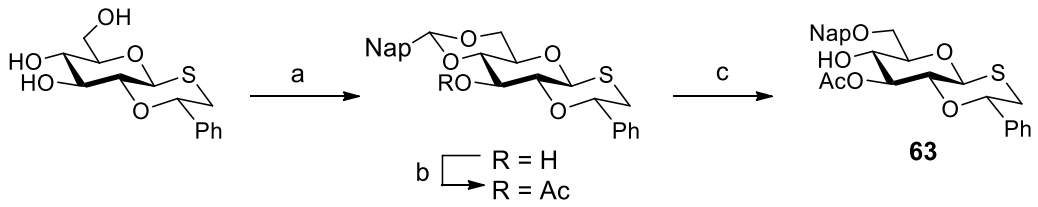
4-*S*-(2,3,5-trimethoxylphenyl)-2-(*S*)-phenyl-(3,4,6-tri-*O*-benzyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathianium triflate (58). Compound **58** was prepared according to the general procedure as descripted in the paper. Selected ^{1}H NMR (500 MHz, gHSQC, $CDCl_3$): δ 5.61 (d, *J* = 10 Hz, 1H, H-1), 5.24 (d, *J* = 15H, 1H, SCH_2CHPh), 4.92 – 4.78 (m, 3H, $PhCH_2$, PhCH*H*), 4.57 (d, *J* = 15 Hz, 1H, SCH_2CHPh), 4.49 – 4.36 (m, 3H, $PhCH_2$, SC*H*HCHPh), 3.99 – 3.97 (m, 3H, H-2, H-3, SCH*H*CHPh), 3.80 (H-4), 3.68 (H-$6_{a,b}$), 3.66 (H-5); ^{13}C NMR (125 MHz, gHSQC, $CDCl_3$): δ 82.53 (C-2, C-3), 81.70 (C-1), 81.39 (C-5), 77.82 (SCH_2CHPh), 76.39 (C-4, $PhCH_2$<), 75.53 ($PhCH_2$<), 73.96 ($PhCH_2$<), 67.82 (C-6), 44.69 (SCH_2CHPh).

4-*S*-methyl-2-(*S*)-phenyl-(3,4,6-tri-*O*-benzoyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathianium triflate (59). Compound **59** was prepared according to the general

procedure as descripted in the paper. Selected ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 – 7.16 (Ar*H*, 20H), 5.99 (t, *J* = 9 Hz, 1H, H-3), 4.81 – 4.74 (m, 2H, H-1, H-4), 5.06 (d, *J* = 10 Hz, 1H, SCH_2CHPh), 4.69 – 4.65 (m, 1H, H-6_a), 4.56 – 4.50 (m, 2H, H-5, H-6_b), 4.30 – 4.27 (m, 2H, H-2, SC*H*HCHPh), 3.72 (t, *J* = 12 Hz, 1H, SCH*H*CHPh); ^{13}C NMR (125 MHz, gHSQC, $CDCl_3$): δ 83.70 (C-1), 78.26 (C-2, C-5), 76.84 (SCH_2CHPh), 72.92 (C-3), 68.78 (C-4), 62.35 (C-6), 46.12 (SCH_2CHPh).

4-*S*-methyl-2-(*S*)-phenyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathianium triflate (60). Compound **60** was prepared according to the general procedure as descripted in the paper. Selected ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.47 (H-1), 5.42 (H-3), 5.15 (H-4), 4.97 (SCH_2CHPh), 4.25 (H-6_a), 4.16 (SC*H*HCHPh), 4.14 (H-6_b), 4.12 (H-5), 3.99 (H-2), 3.63 (SCH*H*CHPh); ^{13}C NMR (125 MHz, gHSQC, $CDCl_3$): δ 83.35 (C-1), 78.05 (C-5, C-2), 76.47 (SCH_2CHPh), 72.35 (C-3), 68.03 (C-4), 62.53 (C-6), 45.85 (SCH_2CHPh).

4-*S*-methyl-2-(*S*)-phenyl-(3,4,6-tri-*O*-benzyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathianium triflate (61). Compound **61** was prepared according to the general procedure as descripted in the paper. Selected ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 – 7.21 (Ar*H*, 20H), 5.31 (d, *J* = 12 Hz, 1H, H-1), 4.89 (d, *J* = 12H, 1H, SCH_2CHPh), 4.83 – 4.78 (m, 2H, PhC*H*H, PhC*H*H), 4.70 (d, *J* = 12 Hz, 1H, PhCH*H*), 4.55 – 4.42 (m, 3H, $PhCH_2$, PhCH*H*), 4.07 (d, *J* = 12H, 1H, SC*H*HCHPh), 3.94 – 3.68 (m, 7H, H-2, H-3, H-4, H-5, H-$6_{a,b}$, SCH*H*CHPh); ^{13}C NMR (150 MHz, gHSQC, $CDCl_3$): δ 83.73 (C-1), 82.70 (C-3), 80.91 (C-2), 80.44 (C-4), 76.50 (SCH_2CHPh), 76.03 (C-5), 75.91 ($PhCH_2$<), 75.55 ($PhCH_2$<), 73.53 ($PhCH_2$<), 67.93 (C-6), 44.94 (SCH_2CHPh).



Scheme S2.2: Preparation of **63**. Reagents and conditions: (a) $NapCH(OMe)_2$, DMF, $TsOH \cdot H_2O$, reduced pressure (78%); (b) Ac_2O, Pyridine; (c) Et_3SiH, TfOH, -78 ^oC (83%, 2 steps).

2-(*S*)-Phenyl-(3-*O*-acetyl-6-*O*-(2-naphthyl)-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (63): R_f = 0.25 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +60.0 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.12 (m, 12H, Ar*H*), 5.11 (t, *J* = 9.3 Hz, 1H, H-3), 4.76 (2H, NapCH_2), 4.67 (dd, *J* = 10.5, 1.7 Hz, 1H, SCH_2CHPh), 4.47 (d, *J* = 8.9 Hz, 1H, H-1), 3.88 – 3.74 (m, 3H, H-4, H-$6_{a,b}$), 3.74 – 3.60 (m, 2H, H-2, H-5), 2.95 (dd, *J* = 14.0, 10.6 Hz, 1H, SC*H*HCHPh), 2.77 (dd, *J* = 14.0, 2.0 Hz, 1H, SCH*H*CHPh), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.90, 140.44, 135.29, 133.47, 133.29, 128.69, 128.56, 128.16, 128.06, 127.94, 126.95, 126.42, 126.24, 125.91, 125.61, 81.24, 80.01, 79.74, 77.71, 77.29, 76.87, 76.08, 76.01, 74.10, 71.03, 70.06, 35.86, 21.27; HR MALDI-TOF MS: m/z: calcd for $C_{27}H_{28}O_6S$ $[M+Na]^+$: 503.1504; found: 503.1521.

2-(*S*)-Phenyl–(3,4-di-*O*-acetyl-6-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-(2-methylnaphthyl)-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (64). Compound **64** was prepared according to the general procedure using glycosyl donor **17**

(53 mg, 0.11 mmol) and glycosyl acceptor **63** (43 mg, 0.091 mmol). Purification by LH20 size exclusion chromatography afforded compound **64** (69 mg, 68 %). R_f = 0.27 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +75.0 (*c* = 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 – 6.94 (m, 22H, Ar*H*), 6.08 (s, 2H, Ar*H*), 5.82 (d, *J* = 3.3 Hz, 1H, H-1^{II}), 5.52 (t, *J* = 9.5 Hz, 1H, H-3^{I}), 5.25 (t, *J* = 9.7 Hz, 1H, H-3^{II}), 4.92 (t, *J* = 9.5 Hz, 1H, H-4^{II}), 4.77 – 4.69 (m, 3H, SCH_2CHPh^{II}, CH_2Nap), 4.54 (d, *J* = 9.0 Hz, 1H, H-1^{I}), 4.45 – 4.30 (m, 2H, H-4^{I}, C*H*HPh), 4.30 – 4.18 (m, 2H, SCH_2CHPh^{I}, CH*H*Ph), 4.11 (dd, *J* = 11.5, 3.8 Hz, 1H, H-6$^{I}_{a}$), 4.06 – 3.91 (m, 2H, H-6$^{I}_{b}$, H-5^{II}), 3.84 (m, 1H, H-5^{I}), 3.81 (s, 3H, OMe), 3.77 (s, 6H, 2× OMe), 3.71 – 3.67 (m, 2H, H-2^{I}, H-2^{II}), 3.35 (dd, *J* = 10.6, 2.6 Hz, 1H, H-6$^{II}_{a}$), 3.26 (dd, *J* = 10.7, 3.7 Hz, 1H, H-6$^{II}_{b}$), 3.07 – 2.67 (m, 4H, SCH_2CHPh^{I}, SCH_2CHPh^{II}), 2.05 (s, 3H), 1.83 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.46, 170.23, 170.04, 162.13, 161.96, 142.19, 140.53, 138.03, 136.09, 133.50, 133.11, 128.66, 128.48, 128.37, 128.18, 128.17, 128.03, 127.96, 127.85, 127.80, 127.53, 126.33, 126.30, 126.15, 125.89, 125.86, 125.45, 101.43, 97.11, 91.17, 84.20, 82.15, 80.71, 79.61, 79.47, 77.67, 77.25, 76.82, 75.64, 74.15, 73.78, 73.50, 72.35, 69.70, 69.29, 69.19, 68.47, 56.21, 55.57, 43.33, 35.76, 21.80, 20.91, 20.39; HR MALDI-TOF MS: m/z: calcd for $C_{61}H_{66}O_{16}S_2$ $[M+Na]^+$: 1141.3690; found: 1141.3697.

2-(*S*)-Phenyl 3-*O*-acetyl-6-*O*-benzyl-4-*O*(9-fluorenylmethyloxycarbonyl)-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-(2-methylnaphthyl)-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (65). Compound **65** was prepared according to the general glycosylation procedure using glycosyl donor **19** (67 mg, 0.09 mmol) and glycosyl acceptor **63** (40 mg, 0.08 mmol). Purification by LH20 size exclusion chromatography afforded compound **65**

(60 mg, 56%). R_f = 0.33 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +56.0 (*c* = 2.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 – 6.97 (m, 30H, Ar*H*), 6.08 (s, 2H, Ar*H*), 5.86 (d, *J* = 3.1 Hz, 1H, H-1^{II}), 5.55 (t, *J* = 9.5 Hz, 1H, H-3^{I}), 5.41 (t, *J* = 9.7 Hz, 1H, H-3^{II}), 4.94 – 4.64 (m, 4H, SCH_2CHPh^I, CH_2Nap, H-4^{II}), 4.55 (d, *J* = 8.9 Hz, 1H, H-1^{I}), 4.48 – 4.19 (m, 5H, SCH_2CHPh^{II}, H-4^{I}, CH_2Ph, C*H*H Fmoc), 4.18 – 4.05 (m, 4H, H-5^{II}, C*H* Fmoc, CH*H* Fmoc, H-6$_a^{I}$), 3.97 (d, *J* = 11.1 Hz, 1H, H-6$_b^{I}$), 3.92 – 3.61 (m, 12H, H-5^{I}, H-2^{I}, H-2^{II}, 3×OMe), 3.51 – 3.29 (m, 2H, H-6$_{a,b}^{II}$), 3.05 – 2.75 (m, 4H, SCH_2CHPh^I, SCH_2CHPh^{II}), 2.07 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.19, 169.79, 161.91, 161.73, 154.28, 143.28, 143.18, 141.95, 141.20, 141.16, 140.30, 137.83, 135.86, 133.27, 132.90, 128.43, 128.20, 128.15, 127.98, 127.85, 127.65, 127.62, 127.51, 127.29, 127.25, 127.21, 126.16, 126.08, 125.89, 125.70, 125.64, 125.25, 125.21, 125.15, 119.96, 101.13, 96.82, 90.93, 84.09, 81.98, 80.41, 79.38, 77.45, 77.02, 76.60, 75.37, 73.95, 73.66, 73.58, 73.32, 71.69, 70.18, 68.90, 68.85, 68.38, 55.97, 55.33, 46.54, 43.11, 35.51, 21.58, 20.16; HR MALDI-TOF MS: m/z: calcd for $C_{74}H_{74}O_{17}S_2$ $[M+Na]^+$: 1321.4265; found: 1321.4659.

2-(*S*)-Phenyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-(2-methylnaphthyl)-1,2-dideoxy-ß-D-glucopyranoso)[1,2-*e*]-1,4-oxathiane (66). Compound **66** was prepared according to the general glycosylation procedure using glycosyl donor **20** (40 mg, 0.082 mmol) and glycosyl acceptor **63** (33 mg, 0.069 mmol). Purification by LH20 size exclusion chromatography afforded compound **66** (42 mg, 55%). R_f = 0.25 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +36.4 (*c* = 1.1 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 – 7.03 (m, 22H, Ar*H*), 6.09 (s, 2H, Ar*H*),

5.71 (d, J = 3.3 Hz, 1H, H-1^{II}), 5.47 (t, J = 9.5 Hz, 1H, H-3^{I}), 5.39 (t, J = 9.5 Hz, 1H, H-3^{II}), 4.76 (s, 2H, CH_2Nap), 4.69 (d, J = 9.3 Hz, 1H, SCH_2CHPh^{II}), 4.51 (d, J = 8.9 Hz, 1H, H-1^{I}), 4.46 (d, J = 11.1 Hz, 1H, CHHPh), 4.39 (d, J = 11.1 Hz, 1H, CHHPh), 4.34 – 4.20 (m, 2H, H-4I, SCH_2CHPh^{I}), 4.19 – 4.09 (m, 2H, H-$6^{II}_{a,b}$), 4.09 – 4.01 (m, 2H, H-5^{II}, H-6^{I}_{a}), 3.96 (d, J = 10.3 Hz, 1H, H-6^{I}_{b}), 3.87 – 3.75 (m, 10H, 3×OMe, H-5^{I}), 3.66 (t, J = 9.3 Hz, 1H, H-2^{I}), 3.46 (dd, J = 10.0, 3.3 Hz, 1H, H-2^{II}), 3.33 (t, J = 9.5 Hz, 1H, H-4^{II}), 3.06 – 2.89 (m, 3H, SCH_2CHPh^{I}, $SCHHCHPh^{II}$), 2.82 (dd, J = 13.9, 1.8 Hz, 1H, $SCHHCHPh^{II}$), 2.08 (s, 3H), 1.96 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.62, 170.46, 169.72, 162.13, 161.92, 141.85, 140.56, 137.71, 135.97, 133.49, 133.11, 128.65, 128.40, 128.21, 128.17, 128.11, 127.87, 127.84, 127.76, 126.78, 126.40, 126.10, 125.89, 125.85, 125.49, 101.85, 96.72, 91.20, 84.11, 82.03, 80.82, 79.57, 79.41, 77.68, 77.46, 77.26, 76.84, 76.53, 75.76, 74.55, 73.93, 73.76, 73.18, 69.30, 68.99, 63.25, 56.22, 55.61, 43.12, 35.80, 21.66, 21.03, 20.83; HR MALDI-TOF MS: m/z: calcd for $C_{61}H_{66}O_{16}S_2$ $[M+Na]^+$: 1141.3690; found: 1141.3685.

2-(*S*)-Phenyl 2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-(9-fluorenylmethyloxycarbonyl)- α-D-glucopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-(2-methylnaphthyl)-1,2-dideoxy-ß-D-glucopyranoso)[1,2-e]-1,4-oxathiane (67). C-2 auxiliary of **65** was removed using general procedure. Then the residue was redissolved in pyridine and an equal volume of acetic anhydride was added. After stirring for 16 h, the solvents were removed and the product was purified by silica column chromatography to afford **67** (89%, 2 steps). R_f = 0.35 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{26}$ (deg cm^3 g^{-1} dm^{-1}) = +23.5 (c = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 – 7.00 (m, 25H, ArH), 5.57 (d, J = 3.9 Hz, 1H, H-3^{II}), 5.52 (t, J = 9.9 Hz, 1H, H-3^{II}), 5.39 (t, J = 9.4 Hz, 1H, H-3^{I}), 5.04 (t, J = 9.9 Hz, 1H, H-

4^{II}), 4.93 – 4.75 (m, 2H, H-2^{II}, C*H*HNap), 4.75 – 4.61 (m, 2H, CH*H*Nap, SCH_2C*H*Ph), 4.51 (d, *J* = 8.9 Hz, 1H, H-1^{I}), 4.41 – 3.95 (m, 8H, H-4^{I}, CH_2 Fmoc, CH Fmoc, CH_2Ph, H-5^{II}, H-6^{I}_{a}), 3.86 (d, *J* = 10.9 Hz, 1H, H-6^{I}_{b}), 3.75 (d, *J* = 9.5 Hz, 1H, H-5^{I}), 3.61 (t, *J* = 9.3 Hz, 1H, H-2^{I}), 3.40 – 3.14 (m, 2H, H-6^{II}_{a}, H-6^{II}_{b}), 2.96 (dd, *J* = 14.0, 10.5 Hz, 1H, SC*H*HCHPh), 2.82 (dd, *J* = 13.9, 2.0 Hz, 1H, SCH*H*CHPh), 2.07 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.81, 170.57, 170.15, 154.24, 143.47, 143.34, 141.47, 140.28, 137.77, 135.79, 133.49, 133.24, 128.70, 128.39, 128.37, 128.21, 128.17, 127.93, 127.84, 127.74, 127.51, 127.46, 126.77, 126.35, 126.15, 126.12, 125.36, 125.32, 120.30, 120.28, 95.25, 81.96, 80.30, 79.74, 77.67, 77.45, 77.25, 76.83, 75.95, 75.83, 74.24, 73.56, 73.07, 71.11, 70.58, 70.53, 69.75, 69.00, 68.76, 67.81, 60.62, 46.77, 35.73, 21.31, 20.94, 20.86; HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{58}O_{15}S$ $[M+Na]^+$: 1061.3394; found: 1061.3387.

3-azidopropyl 2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-(9-fluorenylmethyloxycarbonyl)-α-D-glucopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-(2-methylnaphthyl)-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranoside (70). Compound **67** was oxidized to give sulfoxide donor **68** according to the general procedure. Compound **70** was prepared according to the general glycosylation procedure using glycosyl donor **68** (45 mg, 0.04 mmol) and glycosyl acceptor **69** (22 mg, 0.22 mmol). Purification by LH20 size exclusion chromatography afforded compound **70** (48 mg, 86%). R_f = 0.26 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^{d}_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +80.0 (*c* = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 – 6.97 (m, 25H, Ar*H*), 6.11 (s, 2H, Ar*H*), 5.55 – 5.35 (m, 3H, H-1^{I}, H-3^{I}, H-3^{II}), 5.29 (d, *J* = 3.8 Hz, 1H, H-1^{II}), 4.97 (t, *J* = 9.9 Hz, 1H, H-4^{II}), 4.81 (dd, *J* = 10.5, 3.8 Hz, 1H, H-2^{II}), 4.72 (q, *J* = 12.2 Hz, 2H, CH_2Nap), 4.44 – 4.11 (m, 5H,

SCH_2CHPh, CH_2Ph, CHH Fmoc, CH Fmoc), 4.07 – 3.90 (m, 4H, CHH Fmoc, H-5^I, H-4^I, H-5^{II}), 3.83 (s, 10H, 3×OMe, H-6^I_a), 3.76 – 3.57 (m, 3H, H-6^I_b, CH_2 linker), 3.57 – 3.40 (m, 3H, H-2^I, CH_2 linker), 3.27 (d, J = 2.8 Hz, 2H, H-6^{II}_a, H-6^{II}_b), 2.94 (qd, J = 13.8, 6.3 Hz, 2H, SCH_2CHPh), 2.02 (s, 3H), 2.00 – 1.95 (m, 2H, CH_2 linker), 1.92 (s, 3H) 1.44 (s, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 170.59, 169.82, 161.85, 161.77, 154.03, 143.23, 143.14, 141.46, 141.23, 137.56, 135.61, 133.24, 132.94, 128.22, 128.13, 128.07, 127.91, 127.88, 127.71, 127.54, 127.47, 127.26, 127.21, 126.69, 126.14, 126.11, 125.89, 125.56, 125.13, 120.04, 101.72, 97.24, 94.86, 90.96, 83.93, 78.97, 77.44, 77.22, 77.01, 76.59, 73.76, 73.65, 73.32, 73.07, 71.83, 70.26, 70.19, 69.67, 69.50, 68.86, 68.69, 67.92, 65.31, 56.02, 55.37, 48.53, 46.53, 42.74, 29.00, 20.73, 20.69, 20.67; HR MALDI-TOF MS: m/z: calcd for $C_{71}H_{75}N_3O_{19}S$ $[M+Na]^+$: 1328.4613; found: 1328.4622.

3-azidopropyl 2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-(9-fluorenylmethyloxycarbonyl)-α-D-glucopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-(2-methylnaphthyl)-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranoside (71). The C-2 auxiliary of **70** was removed using the general procedure. The residue was redissolved in pyridine and an equal volume of acetic anhydride was added. After stirring for 16 h, the solvent was removed and the product was purified by silica column chromatography to afford **71** (98%, 2 steps). R_f = 0.44 (EtOAc/hexanes, 1/2, v/v); $[\alpha]^d_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +64.7 (c = 1.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 – 6.98 (m, 20H, ArH), 5.65 – 5.39 (m, 3H, H-1^I, H-3^I, H-3^{II}), 5.09 – 4.99 (m, 2H, H-1^{II}, H-4^{II}), 4.91 – 4.80 (m, 2H, H-2^I, H-2^{II}), 4.74 (dd, J = 28.2, 9.5 Hz, 2H, CH_2Nap), 4.43 – 4.11 (m, 5H, CHH Fmoc, CH Fmoc, CH_2Ph, H-4^I), 4.08 – 3.88 (m, 3H, CHH Fmoc, H-5^I, H-5^{II}), 3.88 – 3.67 (m, 3H, H-6^I_a, CH_2 linker), 3.58 – 3.37 (m, 3H, H-6^I_b, CH_2 linker), 3.27 (s, 2H, H-6^{II}_a, H-6^{II}_b), 2.06 (s,

3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.95 (s, 3H), 1.93 – 1.86 (m, 2H, C*H*$_2$ linker); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.56, 170.33, 170.01, 169.90, 154.01, 143.23, 143.10, 141.25, 137.55, 135.48, 133.25, 133.00, 128.16, 127.94, 127.71, 127.57, 127.51, 127.27, 127.22, 126.34, 126.15, 125.93, 125.70, 125.11, 120.07, 95.86, 95.15, 77.43, 77.21, 77.01, 76.59, 73.90, 73.32, 72.89, 72.75, 71.59, 71.52, 70.44, 70.29, 69.87, 69.46, 68.83, 68.50, 67.73, 65.03, 48.14, 46.54, 28.75, 21.01, 20.70, 20.66, 20.65; HR MALDI-TOF MS: m/z: calcd for $C_{56}H_{59}N_3O_{17}$ $[M+Na]^+$: 1068.3742; found: 1068.3738.

3-azidopropyl 2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-(2-methylnaphthyl)-α-D-glucopyranoside (72). *N*-methyl-2-pyrrolidone (NMP) (0.8 mL) was added to a stirred solution of **71** (130 mg, 0.022 mmol) in DCM (4 mL). After stirring for 1 h, the reaction mixture was diluted with DCM (20 mL) and washed H_2O (2 × 20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/4→1/2, v/v) to give **72** (93 mg, 91%). R_f = 0.24 (EtOAc/hexanes, 1/2, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 – 7.06 (m, 12H, Ar*H*), 5.68 – 5.43 (m, 1H, H-3^{II}), 5.38 (d, *J* = 3.9 Hz, 1H, H-1^{I}), 5.28 – 5.09 (m, 1H, H-3^{I}), 5.01 (d, *J* = 3.7 Hz, 1H, H-1^{II}), 4.93 – 4.63 (m, 4H, H-2^{I}, H-2^{II}, CH_2Nap), 4.28 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.22 – 4.06 (m, 2H, H-4^{II}, CH*H*Ph), 3.92 (d, *J* = 9.2 Hz, 2H, H-5^{I}, H-6$^{I}_a$), 3.87 – 3.59 (m, 4H, H-6$^{I}_b$, H-4^{I}, H-5^{I}, C*H*H linker), 3.57 – 3.36 (m, 4H, C*H*H linker, C*H*$_2$ linker, H-6$^{II}_a$), 3.32 (d, *J* = 10.1 Hz, 1H, H-6$^{II}_b$), 2.63 (s, 1H, O*H*), 2.08 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.00 (s, 2H), 1.97 – 1.81 (m, 2H, C*H*$_2$ linker); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.41, 170.97, 170.54, 170.20, 137.72, 135.73, 133.46, 133.19, 128.60, 128.40, 128.13, 127.98, 127.93, 127.78, 126.39, 126.15, 125.75, 96.06, 95.48,

77.66, 77.43, 77.23, 76.81, 73.84, 73.73, 73.09, 72.33, 71.76, 71.63, 70.95, 70.65, 70.44, 69.96, 69.57, 68.70, 65.22, 48.36, 28.95, 21.22, 21.12, 20.92, 20.88; HR MALDI-TOF MS: m/z: calcd for $C_{41}H_{49}N_3O_{15}$ $[M+Na]^+$: 846.3061; found: 846.3077.

3-azidopropyl 3,4-di-*O*-acetyl-6-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-(2-methylnaphthyl)-α-D-glucopyranoside (73). Compound **73** was prepared according to the general glycosylation procedure using glycosyl donor **17** (20 mg, 0.041 mmol) and glycosyl acceptor **72** (28 mg, 0.034 mmol). Purification by LH20 size exclusion chromatography afforded compound **73** (32 mg, 65%). R_f = 0.51 (acetone/toluene, 1/4, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ7.99 – 6.96 (m, 22H, Ar*H*), 6.10 (s, 2H, Ar*H*), 5.69 (d, *J* = 3.4 Hz, 1H, H-1^{III}), 5.64 (t, *J* = 10.1 Hz, 1H, H-3^{I}), 5.55 (t, *J* = 9.6 Hz, 1H, H-3^{II}), 5.42 (d, *J* = 3.9 Hz, 1H, H-1^{I}), 5.25 (t, *J* = 9.8 Hz, 1H, H-3^{III}), 5.00 (d, *J* = 3.7 Hz, 1H, H-1^{II}), 4.93 (t, *J* = 9.8 Hz, 1H, H-4^{III}), 4.81 (dd, *J* = 10.1, 3.7 Hz, 2H, H-2^{I}, H-2^{II}), 4.76 – 4.63 (m, 2H, C*H*$_2$Nap), 4.39 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.31 – 4.13 (m, 6H, CH*H*Ph, C*H*$_2$Ph SCH$_2$C*H*Ph, H-4^{I}, H-4^{II}), 4.06 – 3.85 (m, 5H, H-5^{I}, H-5^{II}, H-5^{III}, H-6^{III}_a, H-6^{III}_b), 3.85 – 3.63 (m, 12H, 3×OMe, H-2^{III}, C*H*H linker, H-6^{I}_a), 3.53 – 3.34 (m, 4H, C*H*$_2$ linker, CH*H* linker, H-6^{I}_b), 3.27 (d, *J* = 10.8 Hz, 1H, H-6^{II}_a), 3.15 (dd, *J* = 10.6, 3.3 Hz, 1H, H-6^{II}_b), 3.00 (dd, *J* = 13.8, 4.0 Hz, 1H, SC*H*HCHPh), 2.86 (dd, *J* = 13.6, 8.6 Hz, 1H, SCH*H*CHPh), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.92 – 1.80 (m, 5H, CH$_2$ linker, C*H*$_3$), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ171.02, 170.57, 170.23, 169.94, 162.07, 161.93, 142.11, 138.30, 137.96, 135.89, 133.51, 133.21, 128.46, 128.35, 128.28, 128.21, 128.12, 127.91, 127.83, 127.49, 127.31, 126.43, 126.33, 126.20, 125.92,

101.54, 97.21, 96.10, 95.43, 91.17, 83.52, 78.82, 77.65, 77.43, 77.23, 76.81, 73.85, 73.54, 73.25, 73.05, 72.75, 72.44, 71.83, 71.66, 71.49, 69.99, 69.22, 68.76, 68.18, 65.19, 56.16, 55.56, 48.37, 43.04, 28.96, 21.73, 21.25, 20.90, 20.50; HR MALDI-TOF MS: m/z: calcd for $C_{78}H_{87}N_3O_{25}S$ $[M+Na]^+$: 1484.5247; found: 1484.5251.

3-azidopropyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-(2-methylnaphthyl)-α-D-glucopyranoside (74). The C-2 auxiliary of **73** was removed using general procedure as described. The residue was redissolved in pyridine and equal volume of acetic anhydride was added. After stirring for 16 h, the solvents were removed and the product was purified by silica column chromatography to afford **74** (76%, 2 steps). R_f = 0.57 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ7.95 – 7.03 (m, 17H, Ar*H*), 5.54 (t, *J* = 9.6 Hz, 1H, H-3^{I}), 5.49 – 5.29 (m, 4H, H-1^{II}, H-1^{III}, H-3^{II}, H-3^{III}), 5.15 (t, *J* = 9.9 Hz, 1H, H-4^{III}), 5.01 (d, *J* = 3.7 Hz, 1H, H-1^{I}), 4.88 – 4.64 (m, 5H, H-2^{III}, H-2^{II}, H-2^{I}, C*H*$_2$Nap), 4.42 (d, *J* = 12.1 Hz, 1H, CH*H*Ph), 4.23 – 3.88 (m, 7H, C*H*$_2$Ph, C*H*HPh, H-6$_a^{I}$, H-5^{I}, H-4^{II}, H-4^{I}), 3.88 – 3.64 (m, 4H, C*H*H linker, H-6$_b^{I}$, H-5^{III}, H-5^{II}), 3.64 – 3.37 (m, 4H, H-6$_a^{II}$, C*H*$_2$ linker, C*H*H linker), 3.28 (d, *J* = 10.8 Hz, 1H, H-6$_b^{II}$), 3.17 – 3.07 (m, 2H, H-6$_{a,b}^{III}$), 2.09 – 1.97 (4×s, 18H), 1.96 – 1.80 (m, 5H, C*H*$_2$ linker overlap); ^{13}C NMR (75 MHz, CDCl3): δ170.91, 170.74, 170.56, 170.46, 170.18, 170.15, 169.52, 138.17, 137.75, 135.83, 133.51, 133.24, 128.48, 128.42, 128.36, 128.20, 128.17, 127.92, 127.88, 127.67, 127.39, 126.54, 126.30, 126.07, 125.97, 96.12, 95.46, 95.12, 77.66, 77.44, 77.24, 76.81, 74.12, 73.54, 72.85, 72.49, 72.13, 71.75, 71.27, 70.99, 70.81, 70.53, 70.11, 69.15, 69.00, 68.79, 68.48, 67.47, 65.22, 48.35, 28.97, 21.21,

20.96, 20.86, 20.83; HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{71}N_3O_{23}$ $[M+Na]^+$: 1224.4376; found: 1224.4370.

3-azidopropyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-α-D-glucopyranoside (75). 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (9.4 mg, 0.066 mmol) was added to a stirred solution of **74** (27 mg, 0.022 mmol) in DCM (2 mL) and H_2O (0.2 mL). After stirring for 2 h, the reaction mixture was diluted with DCM (20 mL) and washed with saturated $NaHCO_3$ (2 × 20 mL), brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 2/1→1/1, v/v) to give **74** (22 mg, 92%). R_f = 0.37 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ7.41 – 7.16 (m, 10H), 5.55 (t, *J* = 9.6 Hz, 1H, H-3^{II}), 5.46 – 5.25 (m, 3H, H-1^{I}, H-1^{III}, H-3^{III}), 5.08 (t, *J* = 9.8 Hz, 1H, H-4^{III}), 4.97 (d, *J* = 3.7 Hz, 1H, H-1^{II}), 4.83 (dd, *J* = 10.5, 4.0 Hz, 1H, H-2^{III}), 4.80 – 4.69 (m, 2H, H-2^{I}, H-2^{II}), 4.55 (s, 2H, C*H*$_2$Ph), 4.50 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.27 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.01 – 3.88 (m, 3H, C*H*$_2$ linker, H-4^{I}), 3.88 – 3.65 (m, 5H, H-5^{II}, H-5^{III}, H-6$^{I}_a$, C*H*$_2$ linker), 3.58 – 3.38 (m, 3H, H-6$^{I}_b$, H-6$^{III}_a$, H-6$^{III}_b$), 3.33 – 3.19 (m, 2H, H-6$^{II}_a$, H-6$^{II}_b$), 2.72 (dd, *J* = 7.7, 4.9 Hz, 1H, O*H*), 2.04 – 1.9 (6s, 23H, 7×Me, C*H*$_2$ linker overlap); ^{13}C NMR (75 MHz, CDCl3): δ170.95, 170.73, 170.50, 170.32, 170.14, 170.08, 169.57, 137.70, 137.47, 128.69, 128.58, 128.17, 128.14, 128.07, 128.02, 96.20, 95.76, 95.60, 77.65, 77.43, 77.23, 76.80, 74.04, 73.72, 73.11, 72.46, 72.35, 71.86, 71.58, 70.84, 70.76, 70.33, 70.23, 70.04, 69.59, 69.02, 68.92, 67.77, 65.20, 60.84, 48.35, 28.98, 21.22, 21.16, 20.90, 20.86, 20.84, 20.80; HR MALDI-TOF MS: m/z: calcd for $C_{49}H_{63}N_3O_{23}$ $[M+Na]^+$: 1084.3750; found: 1084.3759.

3-azidopropyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-{3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-(2,3,5-trimethoxyphenylsulfanyl)-ethyl]-α-D-glucopyranosyl}-α-D-glucopyranoside (76). Compound **76** was prepared according to the general glycosylation procedure using glycosyl donor **20** (35 mg, 0.072 mmol) and glycosyl acceptor **75** (25 mg, 0.024 mmol). Purification by LH20 size exclusion chromatography afforded compound **76** (28 mg, 70%). R_f = 0.19 (EtOAc/hexanes, 1/1, v/v); $[\alpha]^{d}_{29}$ (deg cm^3 g^{-1} dm^{-1}) = +80.0 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.05 (m, 15H, Ar*H*), 6.14 (s, 2H, Ar*H*), 5.77 (d, *J* = 3.4 Hz, 1H, H-1^{IV}), 5.58 – 5.40 (m, 4H, H-3^{II}, H-3^{I}, H-3^{IV}, H-1^{III}), 5.37 – 5.26 (m, 2H, H-1^{I}, H-3^{III}), 5.17 (t, *J* = 9.9 Hz, 1H, H-4^{III}), 4.98 (d, *J* = 3.8 Hz, 1H, H-1^{II}), 4.87 – 4.77 (m, 3H, H-2^{I}, H-2^{II}, H-2^{III}), 4.64 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.48 – 4.37 (m, 2H, CH*H*Ph, C*H*HPh), 4.34 – 4.16 (m, 5H, SCH_2C*H*Ph, H-4^{II}, H-4^{I}, CH_2Ph), 4.09 – 3.94 (m, 7H, H-5^{I}, H-5^{II}, H-5^{IV}, CH*H*Ph, H-6$^{I}_{a}$, H-6$^{IV}_{a,b}$), 3.94 – 3.78 (m, 13H, 3×OMe, H-5^{III}, H-6$^{I}_{b}$, C*H*H linker, H-6$^{II}_{a}$), 3.68 (dd, *J* = 10.2, 3.4 Hz, 1H, H-2^{IV}), 3.54 – 3.34 (m, 5H, CH_2 linker, CH*H* linker, H-6$^{II}_{b}$, H-4^{IV}), 3.22 – 3.05 (m, 3H, SC*H*HCHPh, H-6$^{III}_{a,b}$), 2.82 (dd, *J* = 14.1, 8.8 Hz, 2H, SCH*H*CHPh), 2.12 – 1.85 (m, 20H, 6×OAc, CH_2 linker), 1.76 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (150 MHz, CDCl3): δ 179.62, 179.60, 179.58, 179.57, 179.55, 170.67, 170.55, 170.45, 170.05, 170.01, 169.91, 169.47, 169.37, 161.79, 161.57, 142.26, 138.62, 137.64, 137.48, 128.33, 128.19, 128.13, 128.11, 127.95, 127.90, 127.82, 127.53, 127.46, 127.27, 127.18, 125.93, 101.25, 98.11, 95.89, 95.54, 95.06, 90.89, 84.21, 80.22, 77.99, 77.21, 76.99, 76.78, 76.52, 74.00, 73.71, 73.64, 73.54, 73.19, 72.56, 72.53, 71.53, 71.16, 71.08, 71.04, 70.25, 70.22, 70.09, 68.87, 68.81, 68.49, 68.43, 66.83, 65.05,

65.00, 63.02, 55.87, 55.36, 48.22, 42.89, 28.70, 20.99, 20.98, 20.84, 20.70, 20.67, 20.64, 20.60, 20.52, 20.31. HR MALDI-TOF MS: m/z: calcd for $C_{83}H_{101}N_3O_{33}S$ $[M+Na]^+$: 1722.5936; found: 1722.5947.

3-azidopropyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-(3,4-di-*O*-acetyl-6-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (78). Compound **77** was prepared according to the general glycosylation procedure using glycosyl donor **17** (19 mg, 0.039 mmol) and glycosyl acceptor **75** (21 mg, 0.020 mmol). Purification by LH20 size exclusion chromatography afforded compound **77** (25 mg, 73%, α/β=8/1). The resulting tetrasaccharide was subjected to general C-2 auxiliary removal condition to give **78** (17 mg, 85%). Isomers were separated by silica gel chromatography. **78α**: R_f = 0.14 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$): δ7.41 – 7.14 (m, 15H, Ar*H*), 5.50 (t, *J* = 9.5 Hz, 1H, H-3^{II}), 5.45 (d, *J* = 4.0 Hz, 1H, H-1^{III}), 5.40 (t, *J* = 9.6 Hz, 1H, H-3^{I}), 5.35 (d, *J* = 4.0 Hz, 1H, H-1^{I}), 5.31 (t, *J* = 9.6 Hz, 1H, H-3^{III}), 5.25 (t, *J* = 9.7 Hz, 1H, H-3^{IV}), 5.19 – 5.08 (m, 3H, H-1^{IV}, H-4^{III}, H-4^{IV}), 4.96 (d, *J* = 3.8 Hz, 1H, H-1^{II}), 4.83 (dd, *J* = 10.5, 4.0 Hz, 1H, H-2^{III}), 4.76 – 4.70 (m, 2H, H-2^{I}, H-2^{II}), 4.60 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.57 (d, *J* = 12.1 Hz, 1H, C*H*HPh), 4.51 – 4.40 (m, 3H, CH*H*Ph, CH*H*Ph, C*H*HPh), 4.16 – 4.08 (m, 2H, CH*H*Ph, H-4^{I}), 4.04 – 4.00 (m, 1H, H-5^{IV}), 4.00 – 3.80 (m, 8H, H-5^{I}, H-5^{II}, H-4^{II}, H-5^{III}, CH_2 linker, H-6$^{I}_{a}$, H-6$^{II}_{a}$), 3.76 – 3.67 (m, 2H, H-2^{IV}, H-6$^{I}_{b}$), 3.57 – 3.42 (m, 5H, H-6$^{IV}_{a,b}$, CH_2 linker, H-6$^{II}_{b}$), 3.26 – 3.05 (m, 2H, H-6$^{III}_{a,b}$), 2.60 (d, *J* = 10.7 Hz, 1H, O*H*), 2.06 – 1.99 (6s, 21H), 1.97 – 1.90 (m, 2H, CH_2 linker), 1.89 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.00, 170.95, 170.52, 170.29, 170.14, 169.86, 169.80, 169.54, 169.30, 138.04, 137.68, 137.50,

128.33, 128.31, 128.30, 128.26, 128.25, 127.97, 127.95, 127.88, 127.87, 127.67, 127.60, 127.41, 127.40, 98.10, 95.75, 95.53, 95.04, 77.20, 76.99, 76.77, 73.92, 73.69, 73.45, 73.44, 73.32, 72.14, 72.08, 71.36, 71.12, 71.10, 71.01, 70.87, 70.22, 69.87, 69.68, 69.03, 68.93, 68.63, 68.59, 68.07, 67.12, 65.11, 48.11, 28.66, 20.94, 20.90, 20.69, 20.64, 20.58; HR MALDI-TOF MS: m/z: calcd for $C_{66}H_{83}N_3O_{30}$ $[M+Na]^+$: 1420.4959; found: 1420.4950. **78β**: R_f = 0.12 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 – 7.16 (m, 15H, Ar*H*), 5.50 (t, *J* = 9.0, 1H, H-3^{I}), 5.44 – 5.37 (m, 3H, H-1^{II}, H-1^{III}, H-3^{II}), 5.40 (t, *J* = 9.6, 1H, H-3^{III}), 5.14 (t, *J* = 9.3 Hz, 1H, H-4^{III}), 5.10 (t, *J* = 9.5 Hz, 1H, H-3^{IV}), 4.99 – 4.91 (m, 2H, H-1^{I}, H-4^{IV}), 4.84 (dd, *J* = 10.5, 4.0 Hz, 1H, H-2^{III}), 4.80 (dd, *J* = 10.2, 3.8 Hz, 1H, H-2^{I}), 4.65 (dd, *J* = 10.2, 3.8 Hz, 1H, H-2^{II}), 4.59 – 4.45 (m, 5H, 2×C*H*$_2$Ph, C*H*HPh), 4.42 (d, *J* = 7.9 Hz, 1H, H-1^{IV}), 4.23 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.12 (dd, *J* = 11.5, 1.9 Hz, 1H, H-6$_a$^{I}), 4.07 – 3.96 (m, 4H, H-6$_b$^{I}, H-4^{II}, H-5^{II}, H-4^{I}), 3.93 – 3.85 (m, 2H, H-5^{I}, H-5^{III}), 3.83 – 3.75 (m, 2H, C*H*H linker, H-6$_a$^{II}), 3.72 (d, *J* = 10.9 Hz, 1H, H-6$_b$^{II}), 3.67 – 3.60 (m, 1H, H-5^{IV}), 3.60 – 3.50 (m, 2H, H-2^{IV}, H-6$_a$^{IV}), 3.47 – 3.38 (m, 3H, C*H*$_2$ linker, C*H*H linker), 3.37 (d, *J* = 3.8 Hz, 1H, H-6$_b$^{IV}), 3.31 – 3.22 (m, 2H, H-6$_{a,b}$^{III}), 2.07 – 1.99 (7×s, 21H), 1.91 – 1.86 (2×s, 8H, C*H*$_2$ linker overlap); selected ^{13}C NMR (150 MHz, gHSQC, $CDCl_3$): δ 102. 46 (C-1^{IV}), 95.90 (C-1^{I}), 95.02 (C-1^{II}, C-1^{III}), 74.80 (C-3^{IV}), 73.42 (C-4^{I}), 73.32 (C-5^{IV}), 72.00 (C-3^{II}), 71.71 (C-3^{I}, C-2^{II}), 71.24 (C-4^{II}), 71.05 (C-2^{I}), 70.10 (C-2^{III}), 69.62 (C-3^{III}), 69.43 (C-4^{IV}, C-5^{II}, C-5^{III}), 69.96 (C-2^{IV}), 68.77 (C-4^{III}), 65.26 (*C*H$_2$), 48.46 (*C*H$_2$), 21.41 (*C*H$_2$) ; HR MALDI-TOF MS: m/z: calcd for $C_{66}H_{83}N_3O_{30}$ $[M+Na]^+$: 1420.4959; found: 1420.4962.

3-aminopropyl-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-6-*O*-(ß-D-glucopyranosyl)-α-D-glucopyranoside (79). Freshly

prepared NaOMe in a methanolic solution (0.2 mL, 1.5 M) was added to a stirred solution of **78α** (8 mg, 5.7 μmol) in methanol (1.5 mL). The reaction mixture was stirred for 2 h and then neutralized by the 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 a mixture of *t*BuOH (4 mL), H_2O (0.1 mL), and AcOH (0.1 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 6 h under and atmosphere of H_2. The progress of the reaction was monitored by MALDI-TOF mass spectrometer. Upon completion, the reaction mixture was purged with Ar gas followed by filtration through a plug of Celite. The filtrate was concentrated *in vacuo* to afford **79** (3.2 mg, 83% over two steps). ^{1}H NMR (600 MHz, D_2O): δ 5.25 (d, J = 3.9 Hz, 1H), 5.19 (d, J = 3.9 Hz, 1H), 4.82 (d, J = 3.6 Hz, 1H), 4.78 (d, J = 3.8 Hz, 1H), 3.87 – 3.20 (m, 26H), 3.11 – 2.94 (m, 2H), 1.91 – 1.81 (m, 2H); selected ^{13}C NMR (150 MHz, gHSQC, $CDCl_3$): δ 99.80 (C-1), 98.44 (C-1), 98.02 (C-1), 78.14, 76.79, 73.66, 72.81, 72.39, 71.96 (C-2), 71.46 (C-2), 71.03, 69.51, 66.21 (*C*H_2, linker), 60.46 (C-6), 37.70 (*C*H_2, linker), 26.70 (*C*H_2, linker). HR MALDI-TOF MS: m/z: calcd for $C_{27}H_{49}NO_{21}$ $[M+Na]^+$: 746.2695; found: 746.2683.

NMR analysis of sulfonium ion 55. Sulfonium ions were prepared according to general procedures. As an example, detailed analysis for 4-*S*-(2,3,5-trimethoxylphenyl)-2-(*S*)-phenyl-(3,4-di-acetyl-6-*O*-benzyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*e*]-1,4-oxathianium triflate (**55**) was discussed here.

A mixture of *R*/*S* sulfoxide **17** (5.0 mg, 10 μmol), 1,3,5-trimethoxybenzene (2.6 mg, 16 μmol), 2,6-di-*tert*-butyl-4-methylpyridine (4.2 mg, 21 μmol) and activated molecular

sieves (4 Å, pellets) in $CDCl_3$ (1 mL) was shaken for 30 min under an atmosphere of argon at room temperature. Then 0.5 mL of the solution was taken out and injected into a 5 mm NMR tube. After cooling to 0 ^oC, trifluoromethanesulfonic anhydride stock solution (25 μL, 0.23 M in $CDCl_3$) was added. After 3 min, NMR spectra of the reaction mixture were recorded (^1H, gCOSY, gHSQC and HMBC were recorded at 25 ^oC, Fig. S2.1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.09 (m, Ar*H*), 6.31 – 6.18 (m, 2H, Ar*H*), 5.63 (d, *J* = 9.7 Hz, 1H, H-1), 5.45 (t, *J* = 9.4 Hz, 1H, H-3), 5.30 (d, *J* = 10.7 Hz, 1H, SCH_2CHPh), 5.22 (t, *J* = 9.7 Hz, 1H, H-4), 4.47 (d, *J* = 11.8 Hz, 1H, C*H*HPh), 4.38 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.28 (t, *J* = 11.6 Hz, 1H, $SCH_{ax}HCHPh$), 4.14 – 3.96 (m, 8H, $SCH_{eq}CHPh$, 2×OMe, H-2), 3.95 – 3.82 (m, 4H, OMe, H-5), 3.67 – 3.46 (m, 2H, H-$6_{a,b}$), 2.02 (s, 3H), 1.94 (s, 3H); selected ^{13}C NMR (200 MHz, gHSQC, $CDCl_3$): δ 81.50 (C-1), 79.38 (C-5), 78.02 (C-2), 76.74 (SCH_2CHPh), 73.62 ($PhCH_2$), 72.02 (C-3), 67.94 (C-4), 67.62 (C-6), 44.33 (SCH_2CHPh). The ^1H NMR spectrum showed that two sets of peaks corresponding to the mixture of *R*/*S* sulfoxide converted into a single set of peaks. Specifically, the anomeric proton (H-1) signal of *R*-sulfoxide (δ = 4.31, d, *J* = 10 Hz) and *S*-sulfoxide (δ = 4.14, d, *J* = 9.7 Hz) shifted downfield (δ = 5.63, d, *J* = 9.7 Hz). The retaining of β anomeric configuration and the shift of H-1 chemical shift indicated that the sulfoxide donors had completely transformed to a new intermediate within 3 min after activation. The rest of the proton signals were assigned from 2D spectra. The HMBC spectrum indicated the presence of three-bond coupling between C-1 and H-8_{eq}, which confirmed the formation of *trans*-decalin sulfonium ion as the reactive intermediate.

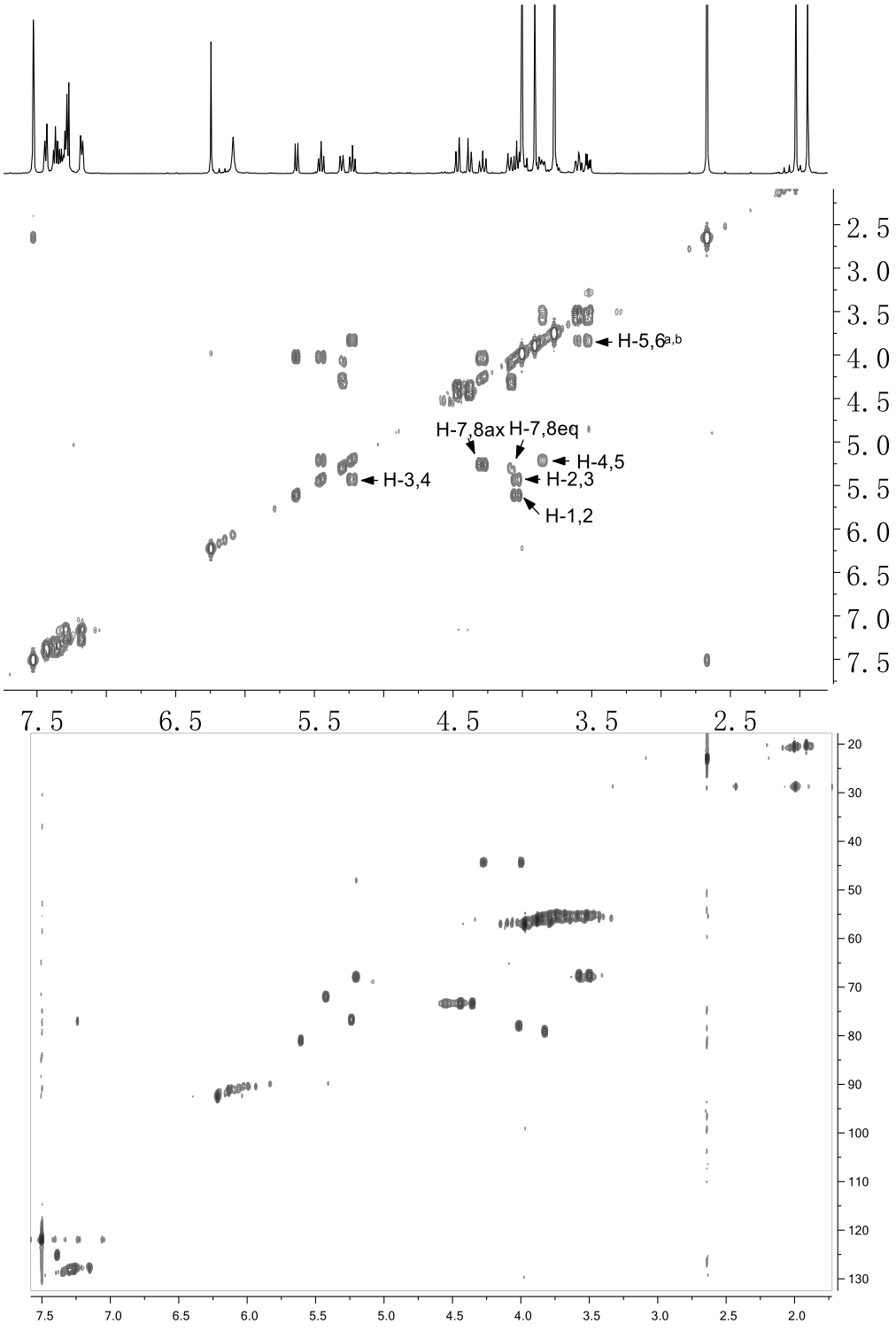


Figure S2.1: 1H, gCOSY, gHSQC spectra of sulfonium ion **55**.

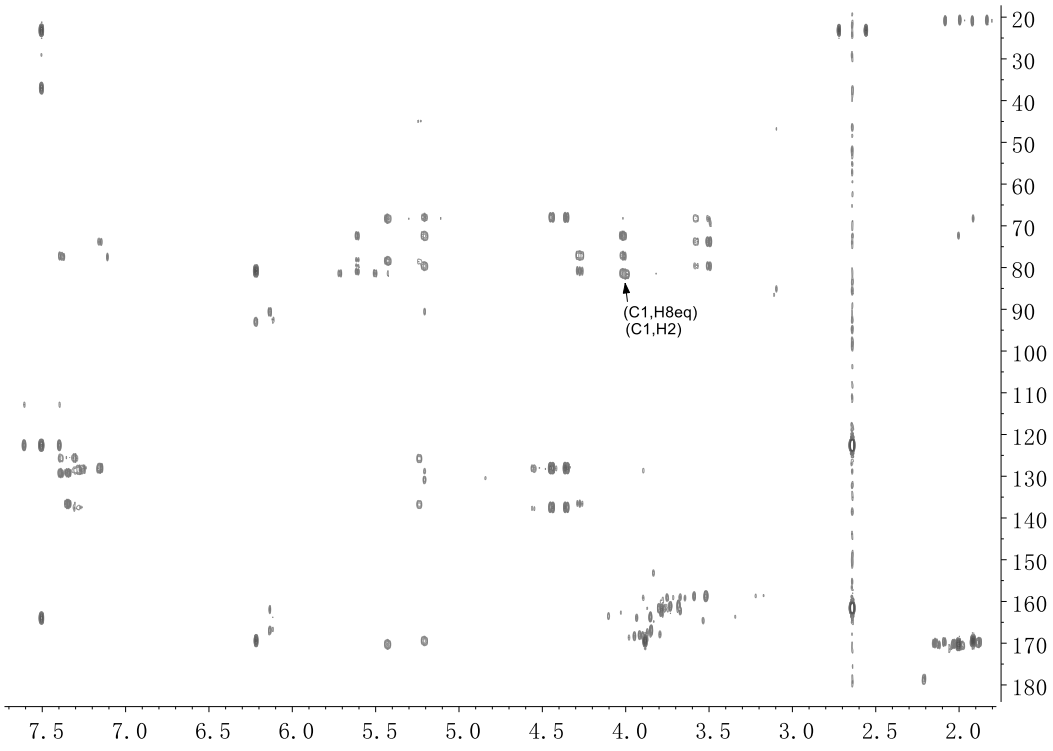


Figure S2.1 (cont'd): HMBC spectrum of sulfonium ion **55**.

Since sulfonium ion was proposed to be the reactive intermediate and responsible for the high stereoselectivity, its stability is of great interest for the purpose of optimizing reaction conditions. So, sulfonium ion **55** was continually monitored by NMR at room temperature (Fig. S2.1). Surprisingly, **55** was stable at this temperature for at least 9 h. During this period of time, the intensity of characteristic sugar peaks remained unchanged while aromatic signal (δ = 6.08) corresponding to trimethoxybenzene decreased. Subsequent heating to 45 ^{o}C in 5 min resulted in prompt decomposition of the sulfonium ion. The temperature sensitivity of the sulfonium ion has also been observed when the glycosylation reaction was heated and resulted in low yield and poor stereoselectivity.

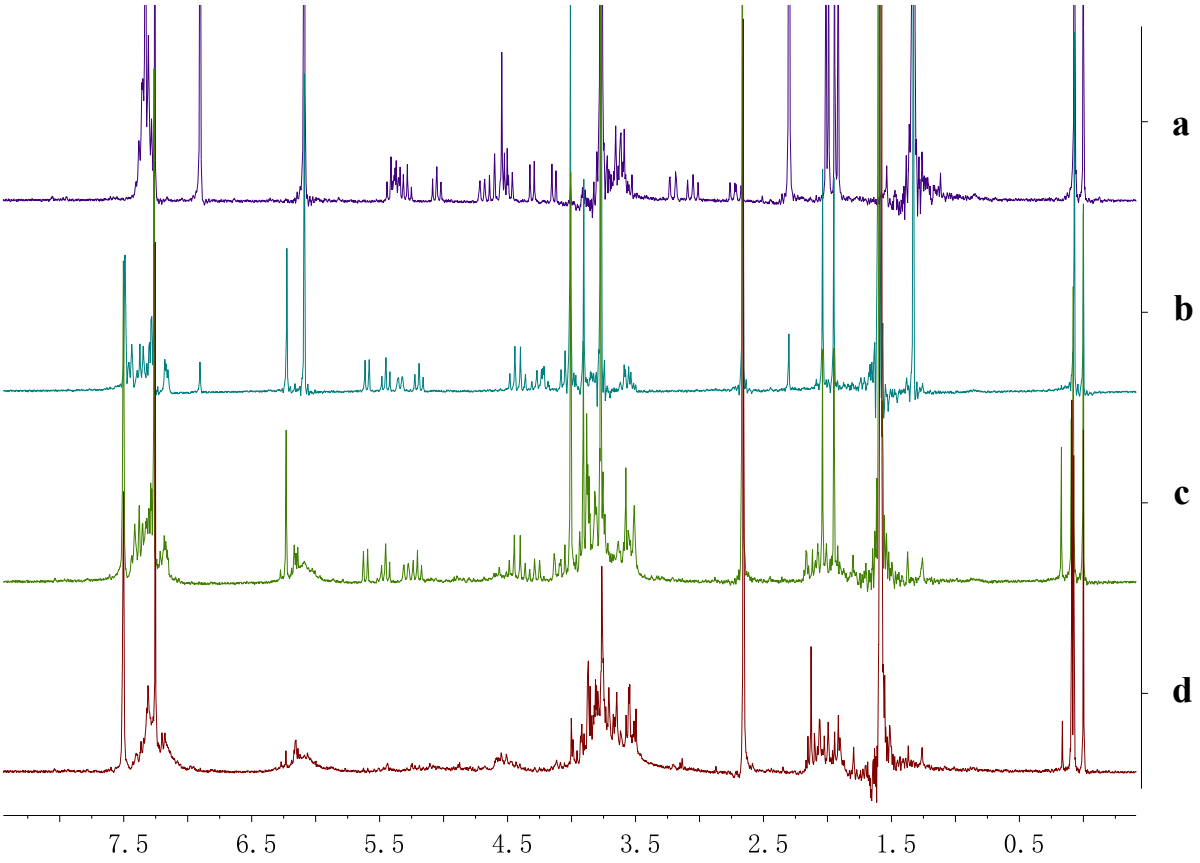


Figure S2.2: Thermostability of sulfonium ion **55**. a) ^{1}H spectrum of a mixture of *R/S* sulfoxide with 1,3,5-trimethoxylbenzene and DTBMP; b) ^{1}H spectrum of the activated reaction mixture after 3 min at 25 ^{o}C; c) ^{1}H spectrum of the activated reaction mixture after 9 h at 25 ^{o}C; d) ^{1}H spectrum recorded after raising to 45 ^{o}C in 5 min.

Assignment and conformational analysis of diastereomeric sulfonium ions. Various criteria have been applied to the assignment of diastereomeric sulfur substituents in a six-member ring system[41]. Usually employed methods include the comparison of the midpoint of chemical shifts for δ_{H8eq} and δ_{H8ax} or the geminal coupling constant for the AB quartet of H8eq and H8ax (Fig. S2.3). Because the substituents on heteroatoms or

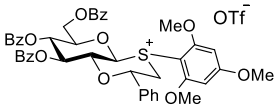
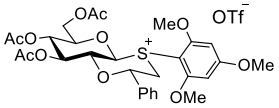
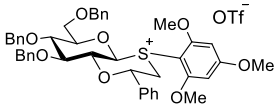
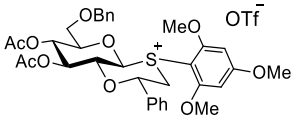
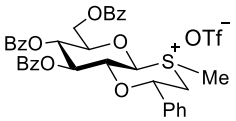
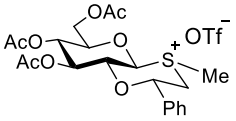
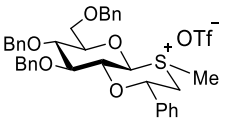
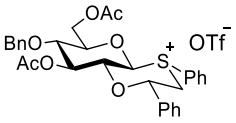
elsewhere on the ring alter, the chemical shift criteria can be overridden. But coupling constant criterion has been proven to hold true regardless of the substitution in the ring[42].

Figure S2.3: Schematic presentation for the interpretation of stereochemistry at sulfur atom using geminal coupling constant of H8eq and H8ax.

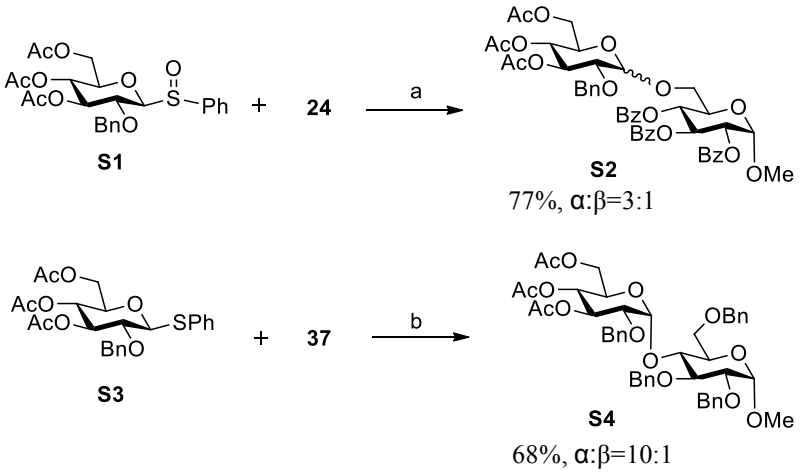
Assignments have also been made for similar oxathiane sulfonium ion systems[13,20,22]. Generally, the equatorial diastereomer with axial lone pair has a smaller geminal coupling constant (~12 Hz) than that of the axial diastereomer with equatorial lone pair (~15 Hz). This trend has also been tested and proven to be effective for similar systems such as sulfoxide donors **17**-**23**, where both diastereomers are available. Therefore, similar rule was applied to the assignment of diastereomeric sulfonium ions **55-61** (Table S1).

Once the stereochemistry at sulfur atom was identified, we could make sure we were comparing sulfonium ions with the same stereochemistry. Then the assignment of the rest of the proton signals can be taken out. Due to the large coupling of H8ax-H9 and small coupling of H8eq-H9, they are showing characteristic splittings that give a triplet and a doublet respectively. Therefore, both H8ax and H8eq can be easily assinged on ^{1}H spectra or gHSQC spectra if there are overlaps of peaks in 1D experiment.

Table S1: List of δ_{H8eq}, δ_{H8ax} and $J_{eq,ax}$.

Entry	Sulfonium Ion	δ_{H8eq} (ppm) doublet	δ_{H8ax} (ppm) triplet	$J_{eq,ax}$ (Hz)	
1	 **56**	4.19	4.35	10.0	
2	 **57**	4.13	4.26	12.5	δ_{Heq} < δ_{Hax}
3	 **58**	3.97	4.36	11.8	
4	 **55**	3.98	4.28	11.6	
5	 **59**	4.27	3.72	11.5	
6	 **60**	4.16	3.63	12.0	δ_{Heq} > δ_{Hax}
7	 **61**	4.07	3.88	10.5	
8[13]		4.32	3.66	11.0	

Control glycosytions using donors without C-2 auxiliary.



Scheme S2.2: Glycosylations using donors without C-2 participation. Reagents and conditions: a) TMSOTf, TEP, - 60 ^{o}C to 0 ^{o}C, 2 h[44]; b) NIS, TfOH, 0 ^{o}C.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (S2). A mixture of glycosyl donor **S1**[22] (60 mg, 0.12 mmol), acceptor **24** (30 mg, 0.059 mmol) and activated molecular sieves (4 Å) in DCM (3 mL) was stirred for 60 min under an atmosphere of argon at room temperature. After cooling to -60 ^{o}C, triethyl phosphite (TEP) (32 µL, 0.20 mmol) and TMSOTf (22 µL, 0.10 mmol) were added and the reaction mixture was allowed to warm to -30 ^{o}C over a period of 30 min. TLC showed donor was not fully consumed. Another 22 µL TMSOTf was added at -30 ^{o}C. Then the reaction mixture was allowed to warm to 0 ^{o}C over 2 h. After diluting with DCM (10 mL), aqueous saturated $NaHCO_3$ (10 mL) was added and the organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by sephadex® LH20 size exlusion chromatography (DCM/MeOH, 1/1) to afford the pure disaccharide **S2** (40 mg, 77%, α:β=3:1). R_f = 0.17

(EtOAc/hexanes, 1/2, v/v); **S2α:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 – 7.05 (m, 20H, Ar*H*), 6.17 (t, *J* = 9.4 Hz, 1H, H-3^{I}), 5.53 – 5.38 (m, 2H, H-5^{II}, H-4^{I}), 5.24– 5.21 (m, 2H, H-1^{I,} H-2^{I}), 4.95 (t, *J* = 9.4 Hz, 1H, H-4^{II}), 4.74 (d, *J* = 3.5 Hz, 1H, H-1^{II}), 4.65 (d, *J* = 12.5 Hz, 1H, C*H*HPh), 4.55 (d, *J* = 12.5 Hz, 1H, CH*H*Ph), 4.43 – 4.29 (m, 1H, H-5^{I}), 4.19 (q, *J* = 4.2 Hz, 2H, H-5^{II}, H-6a^{II}), 4.02 (dd, *J* = 14.2, 4.3 Hz, 1H, H-6$_b^{II}$), 3.83 (dd, *J* = 10.7, 7.6 Hz, 1H, H-6$_a^{I}$), 3.60 – 3.46 (m, 5H, H-2^{II}, H-6$_b^{I}$, OMe), 2.07 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.54, 175.60, 175.00, 174.83, 170.77, 170.67, 170.31, 142.70, 138.50, 138.30, 138.03, 134.87, 134.84, 134.60, 134.12, 133.97, 133.72, 133.43, 133.41, 133.35, 133.21, 132.95, 132.76, 101.60, 101.50, 82.94, 82.16, 81.95, 81.83, 81.74, 78.10, 77.12, 76.63, 75.33, 74.58, 73.55, 73.49, 72.29, 71.69, 66.94, 60.54, 25.79, 25.70, 25.63; HR MALDI-TOF MS: m/z: calcd for $C_{47}H_{48}O_{17}$ $[M+Na]^{+}$: 907.2789; found: 907.2799. The ß anomer was purified by reversed phase HPLC on an analytical C-18 column using a gradient of 50→100% acetonitrile in H_2O over 40 min. **S2ß:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 – 7.21 (m, 20H, Ar*H*), 6.16 (t, *J* = 9.8 Hz, 1H, H-3^{I}), 5.45 (t, *J* = 9.9 Hz, 1H, H-4^{I}), 5.29 – 5.20 (m, 2H, H-2^{I}, H-1^{I}), 5.14 (t, *J* = 9.5 Hz, 1H, H-3^{II}), 4.97 – 4.88 (m, 2H, H-4^{II}, C*H*HPh), 4.59 (dd, *J* = 15.2, 9.8 Hz, 2H, CH*H*Ph, H-1^{II}), 4.37 (t, *J* = 7.9 Hz, 1H, H-5^{I}), 4.23 (dd, *J* = 12.2, 5.2 Hz, 1H, H-6$_a^{II}$), 4.05 (t, *J* = 13.3 Hz, 2H, H-6$_b^{II}$, H-6$_a^{I}$), 3.86 (dd, *J* = 11.2, 7.5 Hz, 1H, H-6$_b^{I}$), 3.73 – 3.59 (m, 1H, H-5^{II}), 3.42 (s, 4H, H-2^{II}, OMe), 2.00 (s, 3H), 1.99 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.48, 184.45, 184.43, 184.42, 175.60, 175.05, 174.64, 170.75, 170.69, 170.39, 142.93, 138.48, 138.32, 138.04, 134.85, 134.79, 134.57, 134.10, 133.94, 133.90, 133.75, 133.56, 133.42, 133.35, 133.31, 133.21, 132.93, 132.71, 118.04, 108.77, 101.95, 101.83, 83.60, 82.96, 82.94, 82.94, 82.16, 81.95, 81.73, 79.33, 78.66,

76.94, 76.50, 75.26, 74.75, 74.01, 73.97, 73.57, 67.06, 60.59, 34.64, 25.63, 25.58; HR MALDI-TOF MS: m/z: calcd for $C_{47}H_{48}O_{17}$ $[M+Na]^+$: 907.2789; found: 907.2781.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (S4). A mixture of glycosyl donor **S3**[22] (60 mg, 0.12 mmol), acceptor **37** (48 mg, 0.10 mmol) and activated molecular sieves (4 Å) in DCM (2 mL) was stirred for 60 min under an atmosphere of argon at room temperature. After cooling to 0 ^oC, NIS (42 mg, 0.31 mmol) was added followed by the addition of TfOH (4 μL, 0.056 mmol). The reaction mixture was stirred for 2 h at 0 ^oC before quenching by the addition of pyridine (0.1 mL) and diluting with DCM (10 mL). The reaction mixture was filtered, and the filtrate was washed with 10% $Na_2S_2O_3$ (20 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The residue was purified by sephadex® LH20 size exlusion chromatography (DCM/MeOH, 1/1) to afford the pure disaccharide **S4** (73 mg, 68%). R_f = 0.16 (EtOAc/hexanes, 1/2, v/v); ^1H NMR (600 MHz, $CDCl_3$): δ 7.41 – 7.01 (m, 20H, Ar*H*), 5.69 (d, *J* = 3.7 Hz, 1H, H-1^{II}), 5.41 (t, *J* = 9.7 Hz, 1H, H-3^{II}), 5.03 (d, *J* = 11.8 Hz, 1H, C*H*HPh), 4.93 (t, *J* = 9.7 Hz, 1H, H-4^{II}), 4.75 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.68 (d, *J* = 12.1 Hz, 1H, C*H*HPh), 4.65 – 4.53 (m, 4H, H-1^I, CH*H*Ph, CH_2Ph), 4.44 (d, *J* = 12.2 Hz, 1H, C*H*HPh), 4.33 (d, *J* = 12.2 Hz, 1H, CH*H*Ph), 4.12 – 4.04 (m, 2H, H-3^I, H-6_a^{II}), 4.04 – 3.97 (m, 2H, H-5^{II}, H-4^I), 3.92 – 3.84 (m, 2H, H-5^I, H-6_a^I), 3.80 (dd, *J* = 12.4, 2.1 Hz, 1H, H-6_b^{II}), 3.67 (dd, *J* = 10.9, 1.6 Hz, 1H, H-6_b^{II}), 3.58 (dd, *J* = 9.4, 3.5 Hz, 1H, H-2^I), 3.47 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2^{II}), 3.39 (s, 3H, OMe), 2.00 (s, 3H), 1.99 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ170.51, 170.02, 169.66, 139.05, 137.92, 137.88, 137.50, 128.56, 128.50, 128.43, 128.37, 128.33, 128.31, 128.20, 128.14, 127.93,

127.76, 127.63, 127.52, 127.39, 127.05, 126.58, 97.70, 96.39, 81.59, 80.13, 77.31, 77.09, 76.88, 76.60, 74.27, 73.47, 73.44, 73.26, 72.93, 71.72, 69.47, 68.93, 68.48, 67.72, 61.81, 55.23, 20.78, 20.72, 20.68; HR MALDI-TOF MS: m/z: calcd for $C_{47}H_{54}O_{14}$ $[M+Na]^+$: 865.3412; found: 865.3403.

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CHAPTER 3

MECHANISTIC INSIGHT INTO SULFONIUM ION MEDIATED GLYCOSYLATIONS: A COMBINATION OF EXPERIMENTAL AND COMPUTATIONAL STUDIES[†]

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ABSTRACT

Sulfonium ions mediated glycosylations are receiving increasing attentions due to its stereocontrol of the outcomes of glycosylations, while the mechanism still remains controversial preventing the rational design of this important type of glycosyl donors. We report here our mechanistic studies on a class of glycosyl donors with (1*S*)-phenyl-2-(phenylsulfanyl)ethyl moiety as the chiral auxiliary at C-2, which after preactivation forms bicyclic β-sulfonium ions. Stereoselectivities of glycosylations with donors replacing the sulfur atom with oxygen atom or methylene group revealed strong dependence of neighboring participation of sulfur atom. Reversing the chirality of the auxiliary from (1*S*) to (1*R*) gave α-sulfonium ion in *cis*-decalin conformation and confirmed by NMR studies. Time-course NMR at various temperatures shows surprisingly different kinetics of α- and β- sulfonium ions illustrating possible different reaction pathways. Results for β-sulfonium ion mediated glycosylation are strongly suggestive of an S_N2-like displacement with late transition state. α-Sulfonium ion, though stable exists during the course of reaction, did not give β-glycoside under the same S_N2-like mechanism. DFT calculation indicated a low energy barrier between S_N1 and S_N2 pathways with slightly S_N1 preference at 0.5 kcal/mol for α-sulfonium ion. The S_N1 TS was further observed to adopt a $^4H_3$ conformation that favors a bottom attack, which is consistent with observed alpha predominance of product.

INTRODUCTION

Complex oligosaccharides and glycoconjugates are increasingly appreciated as the essential molecules in mediating many critical biological processes such as inflammation,

host-virus interaction, embryogenesis, and cancer metastasis.[1,2] A major obstacle to the advance of glycobiology and glycomedicine is the lack of structurally well-defined carbohydrate standards in good quantity, which is caused by glycan microheterogeneity. In many cases, these well-defined carbohydrates can only be obtained by chemical or enzymatic synthesis.[3] Although enzymatic synthesis is generally specific and efficient, the number of durable enzymes with promiscuous substrate specificities is still limited.[4] Often required to address important biomedical problems, the preparation of glycan libraries or readily functionalizable glycan derivatives still largely depends on chemical[5,6] or chemoenzymatic approaches[7–9], in which the enzymatic synthesis is either conducted on a synthetic substrate or prior to chemical diversification. Therefore, chemical synthesis remains the core method of accessing those complex oligosaccharide structures.

Presumably, the most important step in the chemical synthesis of oligosaccharides is the formation of glycosidic bonds, in which two stereoisomers, namely 1,2-*cis* and *trans*, are both possible causing laborious separation and low yield. To address this issue, it has been established that the 1,2-*trans*-glycosidic bond can be reliably synthesized by the assistance of a neighboring participating group. The formation of 1,2-*cis*-glycosidic bonds, on the other hand, requires C-2 nonparticipating functionality, and the stereooutcome is often determined by the sole contribution of the anomeric effect, yielding unpredictable stereoselectivity. Extensive studies have been conducted in order to develop efficient methods of stereocontrolled 1,2-*cis*-glycosylations. [10]

The utility in stereocontrolled glycosylations of trapped covalent glycosyl intermediates,[11] such as glycosyl triflates,[12,13] oxosulfonium triflates,[14] sulfonates,[15] imidinium ions,[16] and sulfonium ions,[17] all of which are reactive enough but also within

the spectroscopic detection limit, has stimulated recent studies. Several groups, including our own, have reported the preparation,[18,19] characterization[20,21] and glycosylation[22–24] of glycosyl sulfonium ions, demonstrating the growing vitality of this field of research since it was first introduced by Schuerch in 1973.[25] We have established that an (*S*)-phenylthiomethylbenzyl moiety at C-2 of a glycosyl donor is capable of trapping the oxocarbenium ion after preactivation, forming bicyclic sulfonium ions in *trans*-decalin conformation that can undergo an S_N2-like displacement of the β-sulfonium ion by *O*-nucleophiles, resulting in inversion of anomeric stereochemistry, which delivers 1,2-*cis*-glycosides. We have further advanced this methodology by transferring it onto a solid phase platform[22] and by employing a latent-active iterative glycosylation in solution[23] for the stereoselective assembly of highly branched glycogen-like glycans with implications in innate immune response activation.

To further streamline the stereoselective synthesis of complex oligosaccharides based on the rational design of the bicyclic sulfonium ion system, studies must illustrate the reaction mechanism of sulfonium ion mediated glycosylation and dissect the elements essential to directing the observed high 1,2-*cis*-stereoselectivity. It is postulated that an S_N2-like displacement of β-sulfonium ions should deliver glycosides with complete inversion of anomeric stereochemistry, thereby delivering α-glycosides exclusively. But, this argument is complicated by the fact that glycosylation reactions usually involve transition states on the borderline between S_N1 and S_N2 and their exact position on the More O'Ferrall-Jencks diagram can be influenced by different reaction conditions and partners.[26,27] This was particular the case when Woerpel and coworkers observed that sulfur atom at a remote position (C-4) in a model tetrahydropyran acetal system did not

significantly impact stereoselectivity and were herefore, against the role of participation. But results like this should be interpreted with caution when the model applied carbon rather than oxygen nucleophiles.[28] Meanwhile, Whitfield and coworker also reported that a C-2 chiral nonparticipating group could exert stereocontrol through a plausible oxocarbenium ion intermediate,[29] raising questions about the dominant stereocontrol component of chiral auxiliaries. However, so far neither the chirality nor the participating nature of sulfur atom of C-2 auxiliary has been systemically studied under real glycosylation conditions.

In this paper, we designed C-2 auxiliary analogues with tunable participation ability by replacing sulfur atom with oxygen atom and methylene group. We also changed the stereochemistry of the auxiliaries to make the corresponding stereoisomers. We conducted extensive experimental studies using donors bearing these analogues at C-2, which enabled us to probe the chiral and participating effects of the auxiliary in a variable-controlled manner. The results are strongly dependent on the participation of the sulfur atom as well as the chirality of the auxiliary. The DFT calculation of the parent donor **19** supports the S_N2-like displacement mechanism with a very late transition state while the stereoisomer **20** appears to slightly favor S_N1.

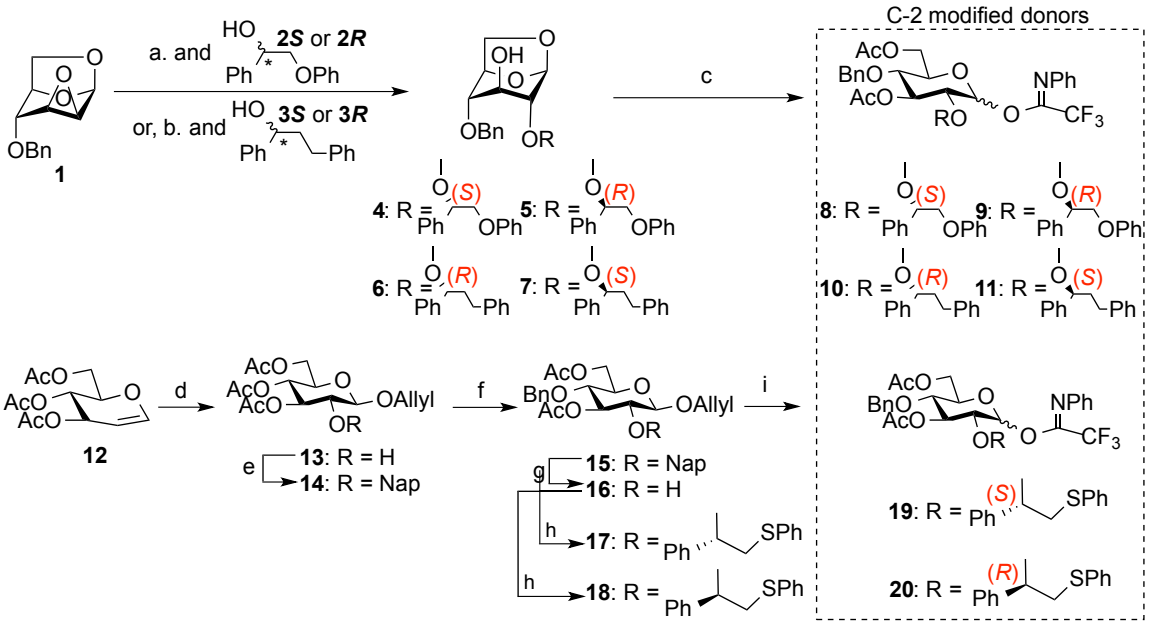
RESULTS AND DISCUSSION

Synthesis and glycosylations of donors with tunable neighboring participation. We have previously demonstrated that bicyclic sulfonium ions, formed either after the preactivation of imidate donors with C-2 (*S*)-(phenylthiomethyl)benzyl ether as the chiral auxiliary[30] or by an umpolung arylation of donors with 1,2-oxathiane ethers as

precyclized sulfonium ion precursors[23], are both capable of α-stereoselective glycosylation with wide substrate and protecting group tolerance. To unambiguously establish the stereoselective origin of bicyclic sulfonium ion mediated glycosylations, it is desired we can selectively turn on and of the participation of sulfonium ions. To this end, we designed donors in such a way that the sulfur atoms of the C-2 (*S*)-(phenylthiomethyl)benzyl ethers of donors **19** and **20** were replaced by oxygen atoms or methylene groups to attenuate or completely eliminate the neighboring group participation while retaining maximum structural similarity.

The synthesis began with the preparation of optically pure auxiliary derivatives. Commercially available optically active styrene oxides were reacted with sodium phenolate and benzyl magnesium chloride to give *O*-auxiliary **2*S*/*R*** and *C*-auxiliary **3*S*/*R*** respectively (see Experimental Section for synthesis). Then regioselectively ring openings of Cerny epoxide **1** by the nucleophilic attacks of **2*S*/*R*** were achieved under acidic condition, using BF_3-Et_2O to give *O*-auxiliary intermediates **4** and **5** in moderate yields with recovery of unreacted Cerny epoxide and auxiliary. The attempt to synthesize *C*-auxiliary derived **6** and **7** failed under the same acidic condition due to the acid liability of **3*S*/*R***. Fortunately, this problem could be circumvented by deprotonating **3*S*/*R*** with NaH followed by the reaction with **1** under a heated condition of 90 ^{o}C for 16 hours to give **6** and **7** in excellent yield.[31] The acetolysis of 1,6-bridged intermediates **4**-**7** was carried out by the treatment of Ac_2O as solvent with a catalytic amount of TMSOTf. Then the anomeric acetate was easily removed by using hydrazine acetate in DMF and subsequently converted to imidate donors using trifluoro *N*-phenyl imodyl chloride and DBU as a base to give donors **8**-**11** with *C*- and *O*- derived auxiliaries.

We also reported an improved synthetic route for donors **19** and **20**. This route enabled the derivatization of C-2 at the late stage. Key intermediate **15** was obtained from triacetyl glucal **12**, which was subjected to epoxidation using *in-situ* generated dimethyldioxirane (DMDO).[32] By stirring with allyl alcohol as solvent, the epoxide can be opened to give **13** and a small amount of *manno*-counterpart, which was easily separated by recrystallization in methanol. Reductive etherification at C-2 with 2-napthaldehyde generated **14**. After protecting group manipulations, the Nap group on **15** was removed with DDQ in a mixture of DCM and water, producing a good yield of **16** with the C-2 hydroxyl group, which was ready for derivatization. In the last, Allyl was removed and the lactol was activated as trifluoro *N*-phenyl imidate.



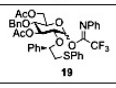
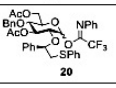
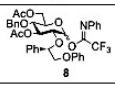
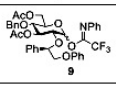
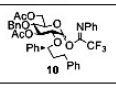
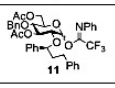
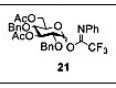
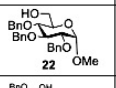
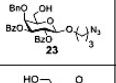
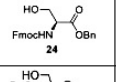
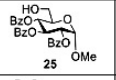
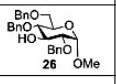
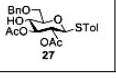
Scheme 3.1: Preparation of various C-2 modified donors. Reagents and conditions: a) BF_3-Et_2O, DCM, r.t., 2 h (**4**: 44%, **5**: 48%); b) NaH, DMF, 90 ^oC, 16 h (**6**: 90%, **7**: 88%); c) i. TMSOTf, Ac_2O, 0 ^oC, 10 min; ii. H_2NNH_2-HOAc, DMF, 45 ^oC, 90 min; iii.

CF_3C=(NPh)Cl, DBU, DCM, r.t., 10 min (3 steps, **8**: 68%, **9**: 73%, **10**: 80%, **11**: 75%); d) i. Oxone™, acetone, aq. $NaHCO_3$, DCM, 0 °C, 4 h; ii. AllylOH, r.t. 16 h, 85%; e) 2-naphthaldehyde, HMDS, TMSOTf, CH_3CN, 0 °C, 30 min, then add Et_3SiH, r.t., 1 h, 31%; f) i. MeONa, MeOH/DCM = 1/2; ii. $PhCH(OMe)_2$, CSA, DMF, 55 °C, reduced pressure, 1 h, then Ac_2O, Py; iii. Cl_2PhB, Et_3SiH, DCM, -78 °C, 1 h, then Ac_2O, Py, 46%, 4 steps; g) DDQ, DCM/H_2O = 10/1, r.t., 1 h, 80%; h) (*R* or *S*) $PhCH(OAc)CH_2SPh$, BF_3-Et_2O, DCM, r.t., 2 h (**17**: 46%, **18**: 47%); i) i. $Pd(PPh_3)_4$, AcOH/DCM = 2/1, r.t. 16 h; ii. CF_3C=(NPh)Cl, DBU, DCM, r.t., 10 min (2 steps, **19**: 86%, **20**: 94%)

Having prepared the necessary donors, we further tested glycosylations with various acceptors, including properly protected amino acids, primary and secondary sugar alcohols, and partially protected thioglycosides (Table 3.1). Donors were divided into four groups (**19** & **20**, **8** & **9**, **10** & **11**, **7**) with different stereochemistry of the C-2 auxiliaries within each group and different participating atoms changing from *S* to *O* and CH_2 among different groups. The last group with donor **21** functioned as a control. We anticipated that by inversing the stereochemistry of the auxiliaries from (*S*) to (*R*) the *trans*-decalin sulfonium ions as formed after preactivation of **19** would not be favored for **20** due to unfavorable steric interaction, resulting in a loss of α-stereoselectivity.[33] The results for donor **19** and **20** were consistent with this prediction. While **19** gave exclusive α-selectivity to all tested acceptors, **20** showed a significant erosion of α-stereoselectivity. Replacing the *S* atom in **19** with *O* atom or *C* atom gave **8** and **10** with decreased nucleophilicity, so the through-space electron donation was weakened. Our observations for donors **19**, **8**, and **10** support the anchimeric assistance model, which holds that

attenuated neighboring group participation results in a partial or complete loss of stereoselectivity.

Table 3.1: Glycosylations for probing C-2 participating effect[a,b,c]

Acceptors	Donors	1	2	3	4	5	6	7
	Yield α/β	 19	 20	 8	 9	 10	 11	 21
a	 22	95% 1:0	85% 2:1	88% 1:0	85% 2:1	91% 5:1	76% 15:1	82% 3:1
b	 23	68% 1:0	70% 3:1	87% 12:1	92% 2:1	100% 2:1	62% 1.5:1	83% 3:1
c	 24	85% 1:0	90% 2:1	94% 1:0	91% 2.5:1	94% 7:1	98% 3:1	88% 7:1
d	 25	93% 1:0	88% 3:1	100% 1:0	81% 4:1	100% 1:0	83% 10:1	74% 10:1
e	 26	50% 1:0	69% 5:1	52% 15:1	48% 10:1	74% 20:1	61% 8:1	88% 14:1
f	 27	56% 1:0	48% 6:1	33% 15:1	53% 7:1	44% 15:1	48% 20:1	51% 15:1

[a]Numberings of products (not shown) are the combination of column's Arabic number and row's alphabetic character. [b]Unless mentioned, glycosylations were conducted by using 1.2 eq. donor and 1 eq. acceptor with 0.4 eq. TMSOTf at -60 ^{o}C. [c]Reaction mixture was separated directly using LH-20 size exclusion column, α/β ratio was determined by comparing integrations of key signals. Minor anomers were further confirmed by 1D TOCSY and coupled HSQCAD experiments. [d]For donors capable of forming sulfonium ions, both preactivation and direct activation were tested and shown the same stereoselective outcome.

Structure identification of *cis*-decalin sulfonium ion. The structure of *trans*-decalin sulfonium ion has been well established,[23,30] where the anomeric leaving group occupies

a equatorial orientation and an S_N2 displacement results α-product in high specificity. Although it was proposed that under the same S_N2 scenario *cis*-decalin sulfonium ion should instead give β-product in high specificity, no structure information about the *cis*-decalin sulfonium ion is available to support this hypothesis. Thus, donor **20** was preactivated in a NMR tube and the reaction process was monitored at low temperature.

It was observed that imidate donor **20** was quickly consumed within 3 min at -20 ^oC forming a single new compound presumably *cis*-decalin sulfonium ion **29**. The characterization of this new compound started from standard 2D experiments including gCOSY, gHSQCAD and gHMBCAD (Figure 3.1a). The overlapped peaks were distinguished by selective irradiation of separated spin system using 1D-zTOCSY experiments. Assignment of peaks was shown in Figure 3.1c. The covalent property of C1-S linkage was established by the observation of three-bond coupling from gHMBCAD experiment (Figure 3.1b). Additionally, the *cis*-decalin configuration was confirmed by NOESY experiment that shows spatial proximity of H-3 and H-7. It is worth noting that a broad H-1 peak for **20** at δ = 5.72, characteristic to *N*-phenyltrifluoroacetimidate,[34,35] was converted into a sharp doublet at δ= 6.72 with coupling constant $J_{1,2}$ = 4.9 Hz indicative for α-configuration. The rest of the coupling constants of the pyranose ring protons are within typical ranges for $^4C_1$ conformation. This is in contrast to acyclic α-sulfonium, which Yoshida and coworkers observed a conformational distortion at C-4 position as well as compromised stereoselectivity of product[20]. This difference between acyclic and cyclic sulfonium ions can be, on one hand, explained by the substitution effect of the thiol nucleophiles, where aryl substituted thioether favor α product,[21] but not dialkyl thioether.[20] On the other hand, the decalin

structure provides favorable stabilization of the chair conformation disfavoring the formation of solvent separated ion pair (SSIP), but shift the equilibrium to more S_N2-like contact ion pair (CIP) or covalent intermediate.[36] In another concept "exploded TS",[37,38] which resemble the S_N2-like mechanism, Jencks argued the bond breaking and formation occur concurrently but with rather weak bond order; therefore, the conformation restraint of decalin sulfonium ions could preorganize the TS in a trigonal bipyramid that both departing leaving group and incoming nucleophile stretched favorably along the long axis.

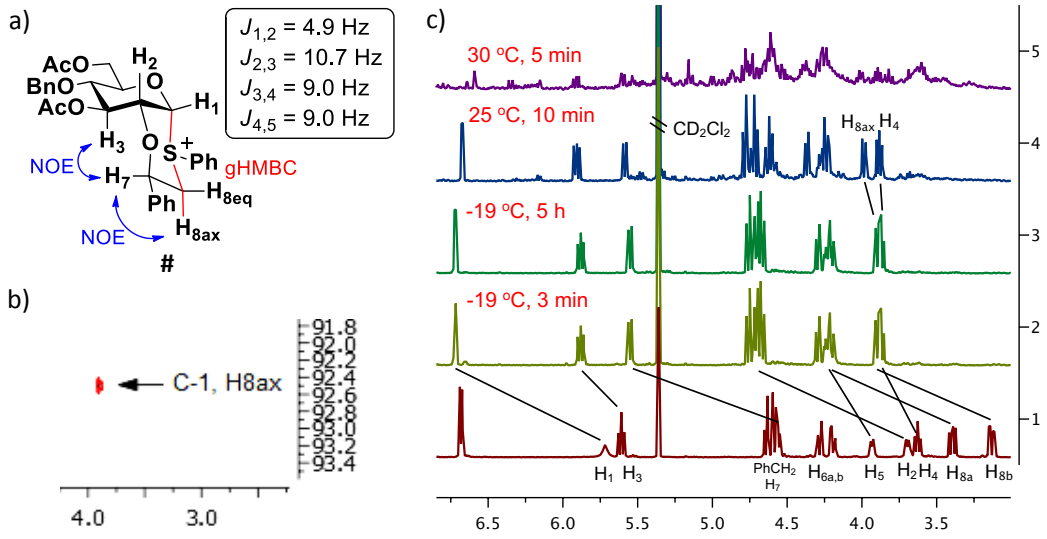


Figure 3.1: NMR structure and thermostability studies of sulfonium ion **29**. a) schematic presentation of NMR structural identifications of **29**; b) gHMBC spectrum of **29** showing C1-H8ax three bond coupling. c) thermostability of **29** (all chemical shifts were referred to CD_2Cl_2).

The thermal stability of the *cis*-decalin sulfonium ion **29** was also studied by raising the NMR probe temperature over a period of time. The compound was first kept at low

temperature for a prolonged time and then the temperature was raised gradually until decomposition was observed. Based on this, the sulfonium ion was stable at -19 ^{o}C for at least 5 h, no sign of decomposition was observed at this point. Then the temperature was raised to 0 ^{o}C and kept for 1 h, still no sign of decomposition. Finally, while kept at 25 ^{o}C for 10 min, the compound started showing decomposition and readily decomposed after rising to 30 ^{o}C. Compared to previously reported *S*-trimethoxylphenyl substituted sulfonium ion, which decomposed at 55 ^{o}C and stable at room temperature for at least 8 h,[23] phenyl substituted sulfonium ion is definitely more labile; and therefore, probably more reactive.

Compare glycosylation rates of *cis*/*trans*-sulfonium ions. To this end, we have established that the chirality and participation of auxiliaries are prerequisites for stereoselectivity. After preactivation, donor **19**, **20** also exist as pure *trans*- and *cis*-decalin sulfonium ions, respectively. Then, it is necessary to show that sulfonium ions indeed exist as reactive intermediate during the course of reaction. For this purpose, we conducted glycosylations side-by-side for both **19** and **20** at different temperatures with **25** as the acceptor. Sanger reagent was used as internal standard due to its inertness under glycosylation conditions and none overlapping characteristic NMR peaks at very low field. During the reaction, the temperature was kept constant. Aliquots of reactions were taken out at specific time interval, and quickly quenched by injecting into excessive methanol. By comparing with integration of product peak from the last sample, which was left overnight and normalized to 100% conversion, we can obtain the relative

percentage of conversion at different reaction time. The percentage of conversion versus time was plotted (Figure 3.2).

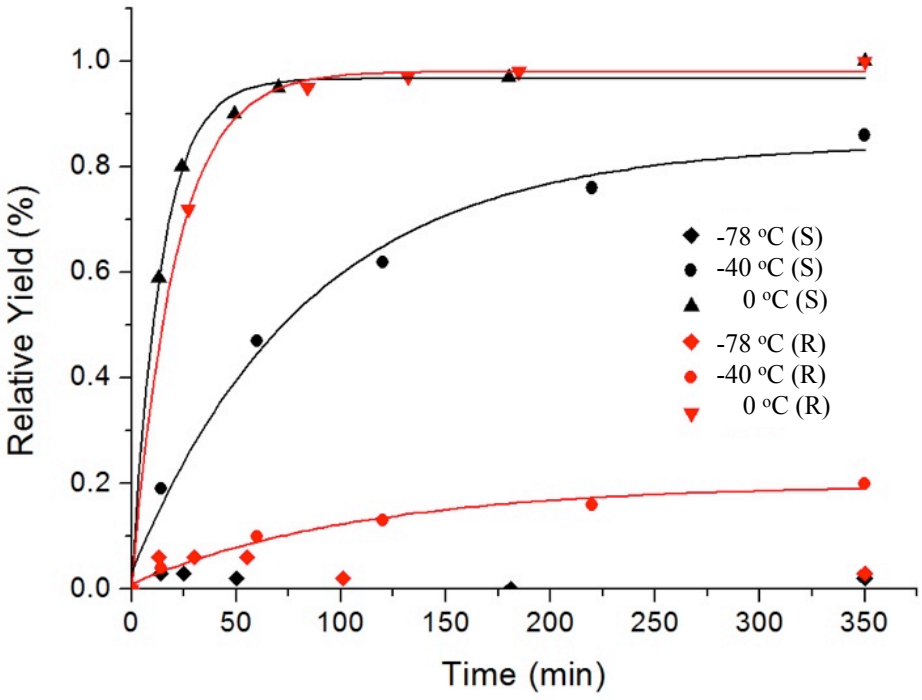
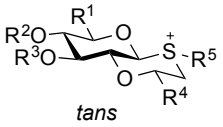


Figure 3.2: Reaction courses of glycosylations using (*R*) or (*S*)-donors at various temperatures. a) glycosylations between donor **19** and acceptor **25**; b) glycosylations between donor **20** and acceptor **25**. (Glycosylations were conducted with final donor and acceptor concentrations adjusted to 8 mM. 1-Fluoro-2,4-dinitrobenzene was added as internal standard. Aliquots of reaction mixture were collected and the time and temperature at that point were recorded.)

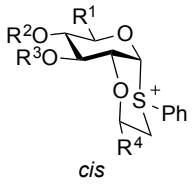
As shown in Figure 3.2, it is surprising that neither **19** nor **20** reacted with **25** after preactivation at –78 °C showing this temperature is too low for sulfonium ion mediated

glycosylations. Based on this observation, more glycosylations were conducted at various temperatures. Further raising the temperature from – 78 to – 60 ^{o}C did not increase the rates of reactions for both donors (data not shown). At – 40 ^{o}C, **19** reached 60% conversion within 2h, while **20** still reacted sluggishly. More studies at 0 ^{o}C showed a very rapid reaction rate that both reactions get close to 100% conversion within 2 h. Therefore, it is reasonable to deduce that the "Optimal Temperature" for **19** and **20** should be close to -20 ^{o}C and -50 ^{o}C, respectively. The reaction temperature is well below the stable temperature of sulfonium ion when significant of conversion of reaction has been reached. This indicates the sulfonium ions exist as the only reactive species along the reaction courses.

Computational studies. It is generally difficult to study the intermediacy of glycosylations under reaction conditions given the fact no direct observation of glycosyl oxocarbenium ion has been reported so far. Kinetic isotopic effect (KIE) is a direct indication of reaction coordination, but it usually requires laborious work to prepare isotope-enriched donors.[39] Other indirect kinetic studies of glycosylation reactions are also rare due to the multicomponent nature of glycosylations. Nevertheless, computational studies have become valuable and practical tools for studying the transition states (TSs) of glycosylation reactions.[40,41] Our studies intended to shed light on the following questions: Why there is no complete reverse of α/β selectivity when changing from β-sulfonium ion to α-sulfonium ion? What are the possible TSs for α/β sulfonium ions mediated glycosylations?



	R^1	R^2	R^3	R^4	R^5
30S:	CH_2OAc	Bn	Ac	Ph	Ph
31S:	CH_2OMe	Me	Me	Ph	Ph
32S:	Me	Me	Me	Ph	Ph
33S:	Me	Me	Me	Me	Ph
34S:	Me	Me	Me	Me	TMP



	R^1	R^2	R^3	R^4
30R:	CH_2OAc	Bn	Ac	Ph
31R:	CH_2OMe	Me	Me	Ph
32R:	Me	Me	Me	Ph
33R:	Me	Me	Me	Me

Figure 3.3: Evolution of model structures.

We first optimized models for sulfonium ions **30S/R** in consideration of balance with accuracy and computer resources (Figure 3.3). **31** was the selected model in which the O-3, O-4 and O-6 acetates were replaced with methyl groups while the rest of the structural features remained intact. Notably, unlike **33S/R** as employed by Turnbull and coworkers,[42] **31** retained both the C-5 methylene and phenyl group of chiral auxiliary. Furthermore, ammonia is usually selected as model acceptor in calculation. But, despite of its simplicity, it may be not considered as a good mimic since its increased nucleophilicity and symmetry compared to alcohols. In our studies, methanol was chosen as the model acceptor instead. Monte Carlo search with MMFF94x force field[43,44] was employed to generate conformers in MOE 2011.[45] The resultant conformers were optimized on the B3LYP/6-31G* level[46,47] in Gaussian 03.[48] Single-point energies were corrected and solvation was modeled at B3LYP/6-31+G** using the IEFPCM method with united atom Kohn–Sham (UAKS) radii.[49] Previous calculations by Turnbull and coworkers indicated generally good correlation between B3LYP and M06 energy values for similar glycosylation reactions.[42] Each transition state was confirmed by intrinsic

reaction coordinate (IRC) scans to ensure that the only negative eigenvalue was responsible for connecting the precursor complex and the product.

Sulfonium ion configurations. Relative energy values for sulfonium ions **31S/R**, **32S**, **34S** were displayed in Table 3.2. As expected, *trans*-sulfonium ions **31S**, **32S**, **34S** were stabilized at 8.82~11.43 kcal/mol compared to their *cis*-isomers. However, the *cis*-sulfonium ion for **31R** was 2.85 kcal/mol more stable than its *trans*-counterpart in agreement of our NMR results. The interconversion of configuration ($\Delta G^{\neq}_{SN1}$) is defined as the cleavage of the anomeric C-S bond, the rotation along C2-O2 bond to a different orientation, and the regeneration of the C-S bond. The high energy barrier ($\Delta G^{\neq}_{SN1}$= 17.72~23.54 kcal/mol), which is much higher than the corresponding $\Delta G^{\neq}_{SN2}$ values making the interconversion impossible before an S_N2-like reaction happens.

Table 3.2: Relative energy and activation energy values of sulfonium ions. (unit: kcal/mol)

Model	*R/S*	R^1	R^2	Ar	$\Delta G_{cis} - \Delta G_{trans}$	$\Delta G^{\neq}_{SN1}$	$\Delta G^{\neq}_{SN1(bnd)}$	$\Delta G^{\neq}_{SN2}$
31S	*S*	Ph	H	Ph	11.43	18.43	14.89	9.86
31R	*R*	H	Ph	Ph	-2.85	14.66	10.71	11.26
32S	*S*	Me	H	Ph	8.87	17.72	14.00	11.90
34S	*S*	Me	H	TMP	8.82	23.54	20.40	13.79

If S_N2 were predominant for all these donors, completely reversed α/β selectivity could have been observed between **19** and **20**. But why did **20** only exhibit compromised

α-selectivity instead of the expected reversal? To solve this problem, one might anticipate this donor's substantial S_N1 characteristic could possibly increase α-selectivity.

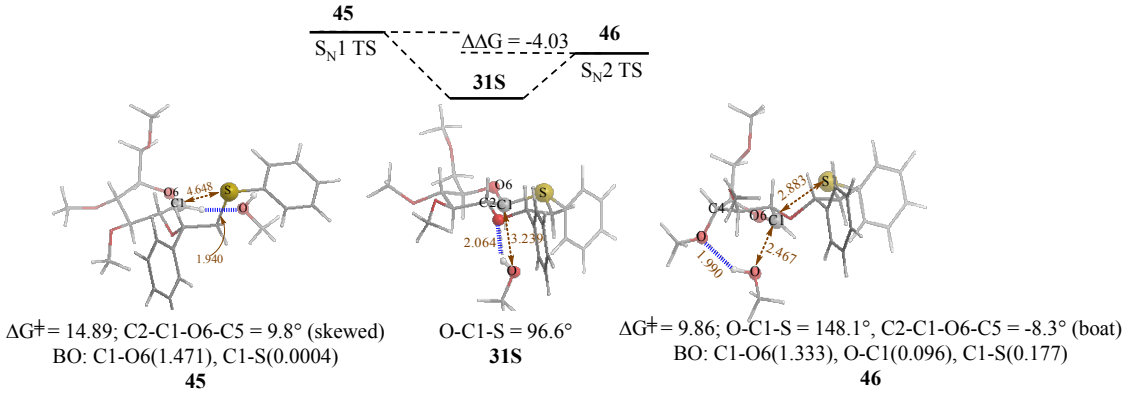
S_N1 vs S_N2: model studies. The computed TSs representing proposed S_N1 and S_N2 pathways for sulfonium ions **31S** and **31R** are shown in Figure 3.4. The S_N2 TS **46** displays a synchronized approaching of the nucleophile and departing of the leaving group, in which the bond length of C1-O_{MeOH} (2.467 Å) is similar to the C1-S bond length (2.883 Å). This concerted TS, however, is very late and posesses cationic characteristics. Natural bond order (NBO) analysis showed that the forming O-C1 bond (B.O. = 0.096), the cleaving C1-S bond (B.O. = 0.177) are weakly bonded, and the C1-O6 bond is partialy doubled (B.O. = 1.333). Consequently, the breaking and formation of bond both happened at very late stage with partial carbon cation character at the anomeric center. Hydrogen bonding (H-bonding) was found between methanol and O-4 in **46** or O-6 in **48** and the H-bond length were determined to be 1.990 Å and 2.064 Å respectively. In fact, all attempts to locate an unbound S_N2 TS ended up with convergence to a bound one. In attempts using Turnbull's method with oversimplified model **32** and ammonia as acceptor, we located both bound and unbound TSs, and the unbound TSs were 1.44~1.73 kcal/mol more stable than their bound counterparts. For a weaker nucleophile like methanol, H-bonding seems important in S_N2 transition states. The impact of H-bonding on facial selectivity is still at dispute. It could be important in directing glycosylation reactions or just act a prerequisite of the obligatory hydrogen transfer of acceptors in the glycosylation reactions.[41,50] In the other aspect, both *O*- and *C*-nucleophiles, with no H-bonding possible for the latter, showed similar stereoselectivity excluded the possibility

of H-bonding in imposing facial selectivity.[51] Indeed, further work is necessary to probe the influence of H-bonding but such weak interaction may be complicated by other factors such as electrostatic attractions.

To draw a fair comparison between S_N1 and S_N2, H-binding was also introduced to the S_N1 transition states. A thorough search of binding sites generated three binding patterns for each S_N1 TS: O-3 or O-4 and H-1, and the H-1 binding provides the greatest stabilization due to the favorable attraction between the methanol oxygen atom and the highly electron-deficient H-1 of the donor. Complexation causes the $\Delta G^{\neq}_{SN1}$ values to drop by 3.14 ~ 3.95 kcal/mol for sulfonium ions included in Table 3.2.

With this decrement of $\Delta G^{\neq}_{SN1}$ values, **32S** is still S_N2 predominant ($\Delta G^{\neq}_{SN2} - \Delta G^{\neq}_{SN1}$ = -4.03 kcal/mol), while **31R** was S_N1 biased ($\Delta G^{\neq}_{SN1} - \Delta G^{\neq}_{SN2}$ = -0.55 kcal/mol). Consequently, **31S** should be α-selective while the stereoselectivity of **31R** could be perplexed and compromised. The S_N1 preference for **31R** raised an alternative explanation for the dominated formation of α-products of this donor based on the two-conformer hypothesis.[52] It states that *gluco*-oxocarbenium ions occupy two half chair conformers namely $^4H_3$ and $^3H_4$. Each conformer is possible for α- (bottom) and β- (up) attacks, but the real preference is determined by the avoidance of strained twist-boat intermediate after addition. The S_N1 TS **47** obtained by calculation with dihedral angle C2-C1-O6-C5 = -0.5° clearly indicated the $^4H_3$ conformation, which favors the α- (bottom) attack. Therefore, the formation of major α-product from *cis*-sulfonium ion could be attributed to a facial selective nucleophilic attack to the oxocarbenium ion.

a) **31S**



b) **31R**

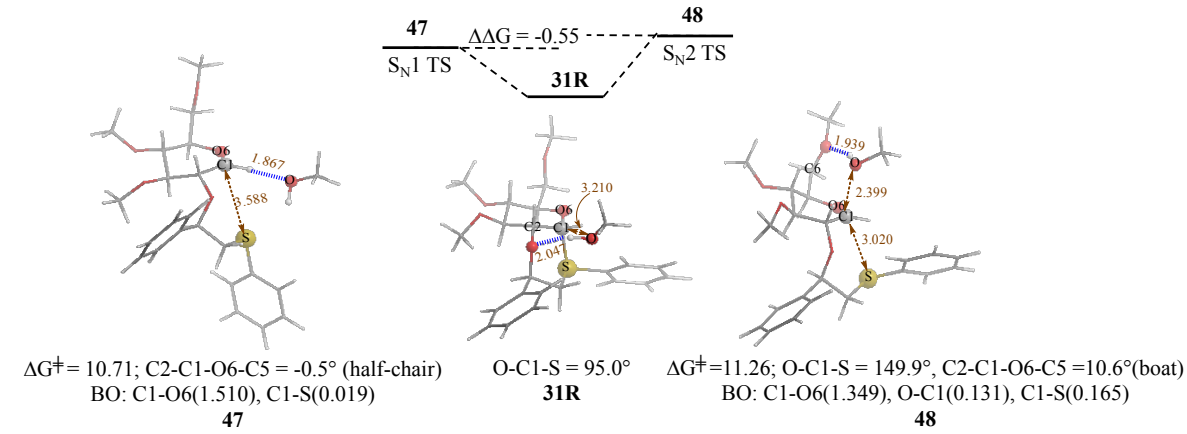


Figure 3.4: Energy profiles for TSs of *trans*-decalin sulfonium ion **31S** and *cis*-decalin sulfonium ion **31R**. (Energy values are quoted in kcal/mol).

Aryl orientation effect. We observed that S-TMP donors like **52** are slightly unreactive compared to the S-Ph donors like **30S**. This phenomenon can be explained by electronic effect that the more electron donating TMP group tends to stabilize the positively charged sulfonium ion better, therefore resulting more stable sulfonium ion that can not be easily displaced especially when the acceptor are of low nucleophilicity. This stabilization

effect was also reflected by looking at the ring-opening energy ($\Delta G^{\neq}S_N1$) that S-TMP sulfonium ion **34S** is 6 kcal/mol higher than S-Ph sulfonium ion **33S**. In the other aspect, this difference in reactivity can be addressed by steric effect. Previous NMR studies of an array of sulfonium ions found that the orientation of aryl substitutions on the sulfur atoms are different with TMP group perpendicular to the decalin ring and Ph group almost parallel to the decalin surface.[23] This difference in orientation placed H8eq and H8ax in completely reversed shielding and deshielding environment of aryl groups, which was indicated by reversed chemical shifts. Our simulation also confirmed this observation. For these two particular donors, conformers were generated by conformation search using the MMFF94x force field with decalin moiety fixed. The resultant conformers were further subjested to structural optimization in Gaussian 03. By comparing the dihedral angles as shown in Figure 3.5, the S-TMP sulfonium ion possesses a more crowded α-face compared to its S-Ph counterpart. This may result difference in reactivity as well as stereoselectivity.

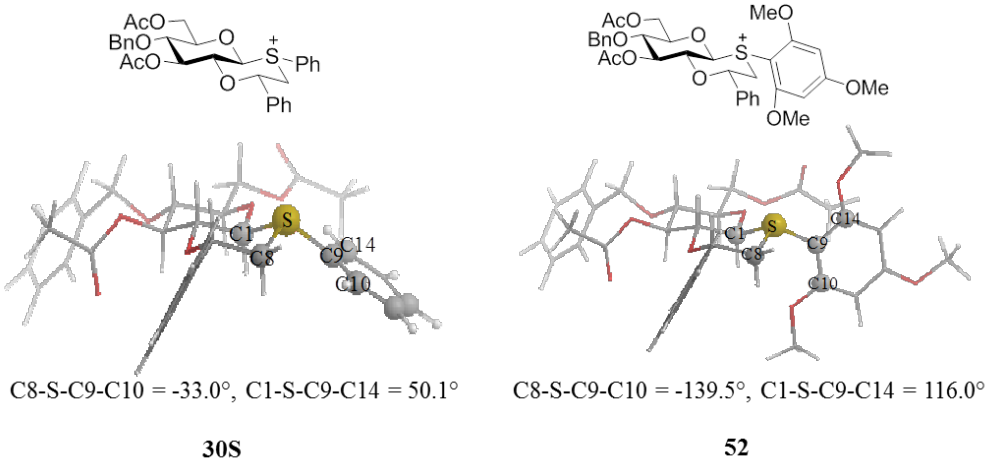


Figure 3.5: Different orientations of S-Aryl substitutions for **30S** and **52.**

Protecting group pattern effect. Previous studies have established an optimized protecting group pattern for sulfonium ion mediated glycosylations.[53] The protecting groups can have profound stereoelectronic influences on the stereochemical outcome of glycosylatios by favoring/disfavoring oxocarbenium ion formation. Indeed, by replacing the C4 Me group in model **31S** to acetyl, the S_N2 TS **46** was destabilized by 1.78 kcal/mol probably due to reduced H-bonding between O4 and the acceptor hydroxyl. On the other hand, replacement of the C3 methyl with acetyl increased the S_N2 preferentiality from 5.03 kcal/mol to 7.57 kcal/mol. The reason for C-3 acetylation improvement remains unclear, but long-range participation seems less likely to happen considering the distance of 4.369 Å between the carbonyl oxygen of C3 OAc and C1.

CONCLUSIONS

Although there are well-established examples of neighboring group participation in chemical glycosylations, the role of sulfonium ions as participating functionalities is still puzzling. We were able to address these problems by designing auxiliary structural mimics with tunable participating ability. Our experimental studies confirmed that sulfonium ion mediated stereoselective glycosylations strongly rely on the participating ability of sulfur atoms and the proper configuration of fused decalin systems. These results answer existing questions about the stereoselective origin of sulfonium ion mediated glycosylations asking the role of C-2 auxiliary in regard of participation and chirality.

By employing DFT calculations and molecular modeling, we were also able to examine the sulfonium ion precursors and their transition states in great detail. Our model

was consistent with our experimental data. The energy barriers between *cis*- and *trans*-sulfonium ions indicated a low tendency toward configuration interconversion, which was supported by the clean formation of *trans*- and *cis*-sulfonium ions in NMR studies. Calculations also suggested a strong preference of S_N2 mechanism for *trans*-decalin sulfonium ions with $\Delta\Delta G^{\neq}$ = -5.03 kcal/mol, while the *cis*-decalin sulfonium ions slightly prefers S_N1 mechanism with $\Delta\Delta G^{\neq}$ = -0.55 kcal/mol. The tendency toward S_N1 reactions for *cis*-decalin sulfonium ions made the two-conformer hypothesis a suitable model for explanation of the preferred α-product formation.

It has been widely accepted that most of the glycosylation reactions go through a continuum of mechanisms between the two extremes of S_N1 and S_N2 depending on the reactivity of leaving groups, nucleophiles, and many other subtle reaction conditions.[54] Based on the current experimental and computational data, we are convinced that bicyclic sulfonium ion mediated glycosylations go through an S_N2-like mechanism and that the role of sulfonium ion displacement is unambiguous.

EXPERIMENTAL SECTION

Reagents and general procedures. Reagents were obtained from commercial sources and used as purchase. Dichloromethane (DCM) was freshly distilled using standard procedures. Other organic solvents were purchased anhydrous and used without further purification. Unless otherwise noted, all reactions were carried out at room temperature in oven-dried glassware with magnetic stirring. Molecular sieves were flame dried under high vacuum prior to use. Organic solutions were concentrated under diminished pressure with bath temperatures < 40^{o} C. Flash column chromatography was carried out on silica

gel G60 (Silicycle, 60-200 μm, 60 Å). Thin-layer chromatography (TLC) was carried out on Silica gel 60 F_{254} (EMD Chemicals Inc.) with detection by UV absorption (254 nm) 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. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-300 (300/75 MHz), a Varian Inova-500 (500 MHz) and a Varian Inova-600 (600/150 MHz) spectrometer equipped with sun workstations. Multiplicities are quoted as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), or multiplet (m). All NMR signals were assigned on the basis of ^{1}H NMR, gCOSY and HSQCAD experiments. Minor anomers were identified by selective irradiation of suspect peaks using 1D-TOCSY experiments. All chemical shifts are quoted on the δ-scale in parts per million (ppm). Signals marked with a superscript Roman numeral I were the reducing end, whereas II was the second sugar from the reducing end. Residual solvent signals were used as an internal reference. Carbon chemical shifts were obtained and assigned from HSQCAD. No tertiary carbons were assigned. For simplicity, aromatic and acetate carbons were not assigned either. Mass spectra were recorded on an Applied Biosystems 5800 MALDI-TOF mass spectrometer using 2,5-dihydroxybenzoic acid (DHB) as matrix and ultamark 1621 as the internal standard. Optical rotations were measured by ATAGO POLAX-2L with 1 ml (5 cm) micro observation tube at 589 nm.

General Glycosylation Procedure for Glycosylations. *Protocol A*: A mixture of donor **19** or **20** (0.06 mmol) and activated molecular sieves (4 Å) in DCM (1.5 mL) was stirred for 30 min under an atmosphere of argon at room temperature. After the mixture was

cooled to -70 °C, trimethylsilyl trifluoromethanesulfonate (TMSOTf) (11 μL, 0.06 mmol) was added, and the reaction mixture was allowed to warm to -20 °C over a period of 30 min. After cooling of the reaction mixture to -70 °C, glycosyl acceptor (0.09 mmol) and 2,6-di-*tert*-butyl-4- methylpyridine (24 mg, 0.12 mmol) were added. The reaction mixture was allowed to warm slowly to room temperature and react for another 14 h. After filtration through a syringe filter, the volume of the filtrate was reduced *in vacuo* and loaded to the size exclusion column LH-20 directly. The obtained disaccharide fractions were collected and the α/β ratio was calculated by ^{1}H NMR integration of key signals. Minor anomer was determined by coupled HSQCAD and 1D-TOCSY.

Protocol B: A mixture of donor **8** – **11** and **21** (0.06 mmol), glycosyl acceptor (0.09 mmol), and activated molecular sieves (4 Å) in DCM (2 mL) was stirred for 30 min under an atmosphere of argon at room temperature. After the mixture was cooled to -70 °C, trimethylsilyl trifluoromethanesulfonate (TMSOTf) (11 μL, 0.06 mmol) was added. The reaction mixture was allowed to warm slowly to -40 °C. After the donor was consumed, the reaction mixture was quenched with pyridine and filtered. The volume of the filtrate was reduced *in vacuo* before loaded to the size exclusion column LH-20. The obtained disaccharide fractions were collected and the α/β ratio was calculated by ^{1}H NMR integration of key signals. Minor anomer was determined by coupled HSQCAD and 1D-TOCSY.

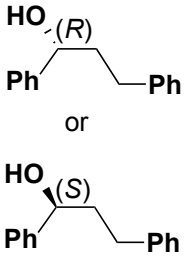
Procedures for NMR kinetic studies. Multiple glycosylations were conducted at different temperatures using the same procedure. In a flame dried flask was added acceptor **25** (10 mg, 0.02 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (15 mg), DCM (0.9

ml), 1-fluoro-2,4-dinitrobenzene stock solution 100 µl (14.8 µl reagent in 2 ml DCM) and activated molecular sieves 4 Å. In a separated flask was added donor **19** or **20** (15 mg, 0.02 mmol), DCM (1.5 ml) and activated molecular sieves 4 Å. After stirring at room temperature for 30 min, the donor was preactivated following general procedure and the temperature was raised to designated value before the addition of acceptor solution. The temperature was regulated for at least 6 h before rising to room temperature gradually. Aliquots of reactions were collected, quenched by quickly injecting into excessive methanol and the time of collection was recorded. Then, the aliquots were centrifuged in order to remove molecular sieves and the clean solution was transferred to another flask before dried under vacuum. Quantitive ^{1}H NMR was conducted with 45° excitation angle, 1 s acquisition time and 5 s acquisition delay. Spectra were processed using MestreNova 7.0. Careful phase/baseline corrections were conducted before integration. The percentage of relative conversion was calculated using equation below:

$$\text{relative conversion } \% = \frac{\mathrm{I}'/\mathrm{N}'}{\mathrm{I}/\mathrm{N}}\%$$

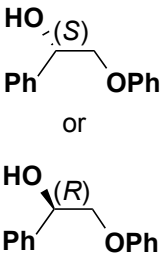
where, I' and N' are the integrations of desired product peak and internal standard at certain point of time; I and N are the integrations of desired product peak and internal standard after overnight reaction and conversion is normalized to 1.

(1*R*),3-diphenyl-propanol or (1*S*),3-diphenyl-propanol (3*S* or 3*R*). (*R*)-Phenyloxirane or (*S*)-Phenyloxirane (500 mg, 4.16 mmol) was dissolved in anhydrous THF (40 ml) at 0°C, then benzylmagnesium chloride (1M in THF) (4.1 ml) was added to the reaction drop-wisely. The reaction was stirred for 1h and quenched with water (5 ml). The reaction was diluted with ethyl acetate and then washed with brine (30 ml). The



mixture was extracted with ethyl acetate and the organic layer was collected and dried by $MgSO_4$. The mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash chromatography over silica gel (EtOAc/ Hexane, 0% to 15%, v/v) to give **3*S*** or **3*R*** (477mg, 58%). (*R*): $[\alpha]_{22}^{d}$ (deg cm^3 g^{-1} dm^{-1}) = +20.8 (*c* = 2.4 in $CHCl_3$); (*S*): $[\alpha]_{22}^{d}$ (deg cm^3 g^{-1} dm^{-1}) = -17.9 (*c* = 2.8 in $CHCl_3$). R_f= 0.56 (EtOAc/Hexane, 1/4, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.08 (m, 10H, Ar*H*), 4.72 (dd, J = 7.8, 5.4 Hz, 1H, C*H*), 2.98 – 2.76 (m, 2H, CH_2), 2.26 – 2.02 (m, 2H, CH_2), 1.97 – 1.84 (broad s, 1H, O*H*); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$) δ 76.84 (*C*H), 45.61 (*C*H_2), 42.67 (*C*H_2); HR MALDI-TOF MS: m/z: calcd for $C_{15}H_{16}O$ $[M+Na]^+$: 235.1099; found: 235.1136.

(1*S*)-phenyl-2-phenoxylethanol or (1*R*)-phenyl-2-phenoxylethanol (2*S* and 2*R*).

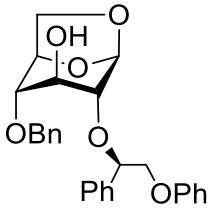


60% Sodium hydride (0.32 g, 8.5 mmol) was mixed with phenol (0.63 g, 6.7 mmol) in anhydrous DMF (50 ml). After stirring for 5 min, (*R*)-phenyloxirane or (*S*)-phenyloxirane (1.10 g, 9.2 mmol) was added to the reaction followed by heating to 60°C. After 5h, the reaction was diluted with DCM (50 ml), and then quenched with water (10 ml) and washed with brine (50 ml). The organic phase was collected and dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash chromatography over silica gel (EtOAc/ Hexane, 0% to 10%, v/v) to give **2*S*** or **2*R*** (0.9 g, 50%). R_f= 0.51 (EtOAc/Hexane, 10%, v/v); (*S*): $[\alpha]_{22}^{d}$ (deg cm^3 g^{-1} dm^{-1}) = +38.4 (*c* = 5.0 in $CHCl_3$); (*R*): $[\alpha]_{22}^{d}$ (deg cm^3 g^{-1} dm^{-1}) = -43.7 (*c* = 4.4 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 6.62 (m, 10H, Ar*H*), 5.24 – 5.10 (m, 1H, C*H*), 4.29 – 3.90 (m, 2H, CH_2), 3.17 (d, J =

2.3 Hz, 1H, O*H*); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$) δ 73.59 (*C*H_2), 72.77 (*C*H); HR MALDI-TOF MS: m/z: calcd for $C_{15}H_{16}O$ $[M+Na]^+$: 237.0891; found: 237.0940.

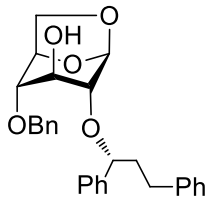
1,6-Anhydro-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenoxyl)-ethyl]-β-D-glucopyranose (4). Under an atmosphere of argon, compound **1** (560 mg, 2.4 mmol) and **2*S*** (900 mg, 4.2 mmol) were dissolved in anhydrous DCM (4 mL) followed by the addition of BF_3-Et_2O (220 μl) at 0 °C. After removing the ice bath and stirring at room temperature for 2 h, the reaction mixture was quenched with Et3N and the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/Hexanes, 1/10→1/3, v/v) to give **4** (470 mg, 44%). R_f = 0.18 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 6.79 (m, 15H, Ar*H*), 5.58 (s, 1H, H-1), 4.88 (dd, J = 8.2, 3.6 Hz, 1H, C*H*^{Aux}), 4.64 (d, J = 12.2 Hz, 1H, C*H*HPh), 4.60 – 4.48 (m, 2H, C*H*HPh, H-5), 4.20 (dd, J = 10.2, 8.3 Hz, 1H, C*H*H^{Aux}), 4.07 (dd, J = 10.2, 3.6 Hz, 1H, C*H*H^{Aux}), 3.79 (dd, J = 9.9, 5.0 Hz, 1H, H-3), 3.72 (d, J = 7.4 Hz, 1H, H-6_a), 3.64 (dd, J = 7.4, 5.4 Hz, 1H, H-6_b), 3.36 (d, J = 4.9 Hz, 1H, H-2), 3.25 (d, J = 5.0 Hz, 1H, H-4); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$) δ 102.01 (C-1), 81.66 (C-2), 821.21 (*C*H^{Aux}), 80.56 (H-4), 75.86 (C-5), 72.51 (*C*H_2^{Aux}), 71.99 (*C*H_2Ph), 71.67 (C-3), 67.08 (C-6); HR MALDI-TOF MS: m/z: calcd for $C_{27}H_{28}O_6$ $[M+Na]^+$: 471.1784; found: 471.1817.

1,6-Anhydro-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenoxyl)-ethyl]-β-D-glucopyranose (5). The same procedure as **4**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 – 6.77 (m, 15H, Ar*H*), 5.28 (s, 1H, H-1), 4.91 (dd, J = 8.2, 3.8 Hz, 1H, C*H*^{Aux}), 4.79 (d, J = 12.2 Hz, 1H, C*H*HPh), 4.69 (d, J = 12.3 Hz, 1H, C*H*HPh), 4.56 (d, J = 5.3 Hz, 1H, H-5), 4.24 (dd, J =



10.1, 8.3 Hz, 1H, C*H*H^{Aux}), 4.06 – 3.98 (m, 2H, C*H*H^{Aux}, H-3), 3.76 (d, J = 7.5 Hz, 1H, H-6$_a$), 3.61 (dd, J = 7.5, 5.4 Hz, 1H, H-6$_b$), 3.37 (d, J = 4.4 Hz, 1H, H-4), 3.31 (d, J = 4.3 Hz, 1H, H-2); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 102.02 (C-1), 81.73 (*C*H^{Aux}), 81.73 (C-5), 80.72 (C-2), 79.67 (C-4), 72.73 (*C*H$_2^{Aux}$), 71.74 (*C*H$_2$Ph), 70.99 (C-3), 66.42 (C-6); HR MALDI-TOF MS: m/z: calcd for $C_{27}H_{28}O_6$ $[M+Na]^+$: 471.1784; found: 471.1859.

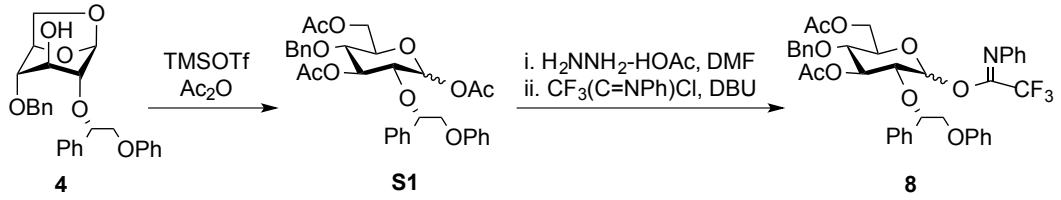
1,6-Anhydro-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-β-D-glucopyranose (6). Under an atmosphere of argon, compound **1** (150 mg, 0.64 mmol) and **3*R*** (440 mg, 1.9



mmol) were dissolved in anhydrous DMF (4 mL) followed by the addition of NaH (80 mg, 60 % dispersion in mineral oil) at 0 ^oC. After removing the ice bath, the mixture was stirred at 90 ^oC for 16 h. Then, the reaction mixture was diluted with DCM (20 mL) and washed with saturated $NaHCO_3$ (2 × 20 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography over silica gel (EtOAc/Hexanes, 1 /8→1/2, v/v) to give **6** (256 mg, 90%). R_f = 0.53 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 6.84 (m, 15H, Ar*H*), 5.37 (s, 1H, H-1), 4.68 – 4.40 (m, 3H, C*H*$_2$Ph, H-5), 4.31 (dd, J = 4.4, 8.1 Hz, 2H, C*H*$_2^{Aux}$), 3.69 – 3.42 (m, 3H, H-3, H-6$_{a,b}$), 3.21 – 3.08 (m, 1H, H-4), 3.02 (d, J = 5.0 Hz, 1H, H-2), 2.83 – 2.45 (m, 2H, C*H*$_2^{Aux}$), 2.27 – 2.05 (m, 1H, C*H*H^{Aux}), 2.04 – 1.82 (m, 1H, CH*H*^{Aux}), 1.50 (broad s, 1H, O*H*); ^{13}C NMR (selected HSQCAD, 75 MHz, $CDCl_3$): δ 101.62 (C-1), 81.40 (*C*H$_2^{Aux}$), 80.43 (C-4), 79.70 (C-2), 76.23 (C-5), 71.78 (*C*H$_2$Ph),

71.66 (C-3), 67.17 (C-6), 39.83 (CH_2^{Aux}), 32.01 (CH_2^{Aux}); HR MALDI-TOF MS: m/z: calcd for $C_{28}H_{30}O_5$ $[M+Na]^+$: 469.1991; found: 469.2064.

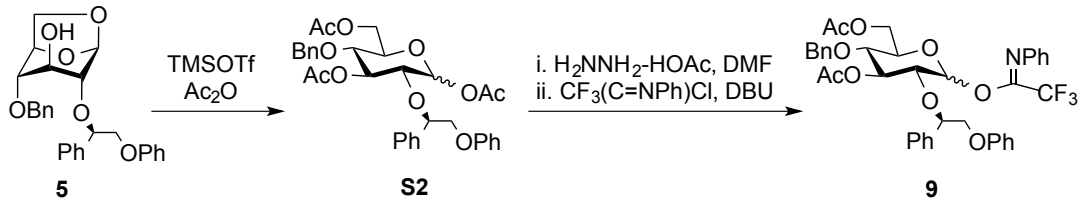
1,6-Anhydro-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-β-D-glucopyranose (7). The same procedure as **6**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 – 6.93 (m, 15H, Ar*H*), 5.17 (s, 2H, CH_2Ph), 4.67 (s, 1H, H-5), 4.58 – 4.44 (m, 1H, CH^{Aux}), 4.40 – 4.29 (m, 1H, CH^{Aux}), 3.86 (s, 1H, H-3), 3.77 (d, J = 7.5 Hz, 1H, H-6_a), 3.60 – 3.48 (m, 1H, H-6_b), 3.30 (s, 1H, H-4), 3.06 (s, 1H, H-2), 2.86 – 2.68 (m, 1H, C*H*H^{Aux}), 2.65 – 2.49 (m, 1H, CH*H*^{Aux}), 2.26 – 2.09 (m, 1H, C*H*H^{Aux}), 1.95 – 1.82 (m, 1H, CH*H*^{Aux}), 1.75 (broad s, 1H, O*H*); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$) δ 101.87 (C-1), 81.85 (*C*H^{Aux}), 78.63 (C-4), 76.83 (C-2), 74.74 (C-5), 71.85 (*C*H_2Ph), 70.14 (C-3), 66.17 (C-6), 39.75 (CH_2^{Aux}), 32.57 (CH_2^{Aux}); HR MALDI-TOF MS: m/z: calcd for **$C_{28}H_{30}O_5$** $[M+Na]^+$: 469.1991; found: 469.2007.



Scheme S3.1: Preparation of **8.**

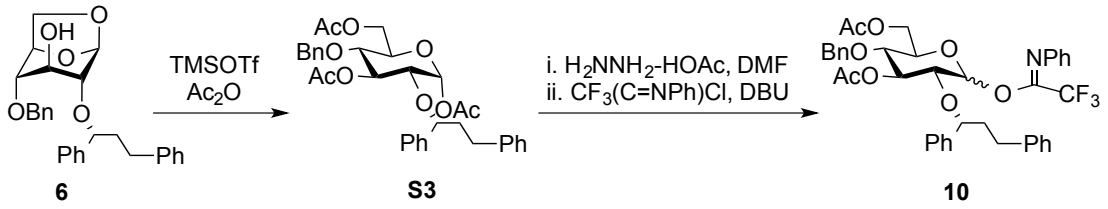
1,3,6-tri-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranoside (S1). Compound **4** (200 mg, 0.45 mmol) was dissolved in Ac_2O (10 mL) followed by the addition of TMSOTf (3 μl) at 0 °C. After stirring for 15 min, the reaction was quenched by the addition of pyridine. Then, the mixture was concentrated *in vacuo* to give **S1** as a mixture of α/β = 7/1. R_f = 0.39 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^1H NMR (300 MHz, $CDCl_3$)

δ 7.51 – 6.71 (m, 15H, Ar*H*), 6.51 (d, J = 3.5 Hz, 1H, H-1), 5.53 (t, J = 9.6 Hz, 1H, H-3), 4.74 (dd, J = 9.1, 3.5 Hz, 1H, C*H*^{Aux}), 4.59 – 4.40 (m, 2H, C*H*$_2$Ph), 4.29 – 4.19 (m, 2H, H-6$_{a,b}$), 4.10 (dd, J = 10.2, 8.3 Hz, 1H, C*H*H^{Aux}), 3.98 (dt, J = 10.1, 3.1 Hz, 1H, H-5), 3.87 (dd, J = 10.2, 3.5 Hz, 1H, C*H*H^{Aux}), 3.63 (dd, J = 10.0, 3.6 Hz, 1H, H-2), 3.51 (t, J = 9.8 Hz, 1H, H-4), 2.08 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.80 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 75 MHz, $CDCl_3$): δ 89.63 (C-1), 81.84 (*C*H^{Aux}), 76.55 (C-2), 76.10 (C-4), 75.08 (*C*H$_2$Ph), 73.51 (C-3), 72.42 (*C*H$_2^{Aux}$), 71.00 (C-5), 62.89 (C-6); HR MALDI-TOF MS: m/z: calcd for **$C_{33}H_{36}O_{10}$** $[M+Na]^+$: 615.2206; found: 615.2292. **1,3,6-tri-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl *N*-phenyl trifluoroacetimidate (8).** The crude was from previous step redissolved in DMF (1.5 ml) followed by the addition of H_2NNH_2-HOAc (62 mg, 68 mmol). The mixture was stirred at 55 ^oC for 2 h before diluted with DCM and washed with saturated $NaHCO_3$. The organic phase was concentrated *in vacuo* and the crude was passed through a short column. After collecting the corresponding fractions, the solvent was removed and the compound was dried under high vacuum for 2 h before redissolving in anhydrous DCM. To this solution, 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (~186 μl, 0.9 mmol) and DBU (~ 68 μl, 0.45 mmol) were added at 0 ^oC and stirred at this temperature until TLC indicated the disappearance of starting material. The reaction mixture was briefly concentrated by air-flow and loaded directly to silica gel column to give **8** (221 mg, 68 % over 3 steps) for direct use without further characterization. R_f = 0.65 (EtOAc/Hexanes, 1/2, v/v).



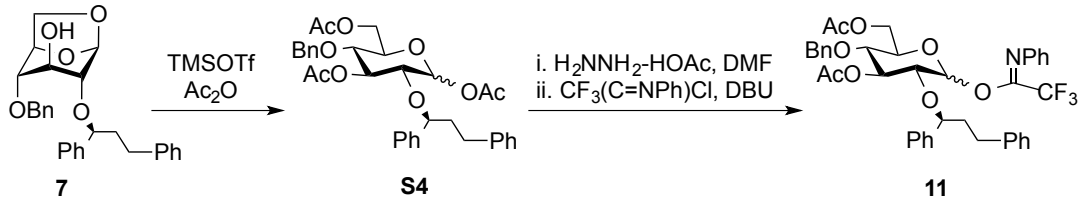
Scheme S3.2: Preparation of **9.**

1,3,6-tri-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranoside (S2). According to the same procedure for **S1**, **S2** was prepared as a mixture of α/β = 4/1, R_f = 0.36 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 6.75 (m, 15H, Ar*H*), 5.88 (d, J = 3.7 Hz, 1H, H-1), 5.65 (t, J = 9.7 Hz, 1H, H-3), 4.80 (dd, J = 8.5, 3.0 Hz, 1H, C*H*^{Aux}), 4.63 – 4.47 (m, 2H, C*H*$_2$Ph), 4.26 – 4.16 (m, 2H, H-6$_{a,b}$), 4.10 – 4.04 (m, 1H, C*H*H^{Aux}), 3.96 – 3.87 (m, 1H, H-5, C*H*H^{Aux}), 3.66 (dd, J = 10.0, 3.7 Hz, 1H, H-2), 3.56 (d, J = 9.9 Hz, 1H, H-4), 2.09 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$) δ 91.13 (C-1), 83.72 (*C*H^{Aux}), 76.75 (C-2, C-4), 75.21 (*C*H$_2$Ph), 74.34 (C-3), 72.76 (*C*H$_2^{Aux}$), 71.02 (C-5), 62.55 (C-6); HR MALDI-TOF MS: m/z: calcd for **$C_{33}H_{36}O_{10}$** [M+Na]$^+$: 615.2206; found: 615.2293. **1,3,6-tri-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl *N*-phenyl trifluoroacetimidate (9).** The crude from previous step was further modified according to the same procedure for **8** to give **9** (73 % over 3 steps) for direct use without further characterization. R_f = 0.61 (EtOAc/Hexanes, 1/2, v/v).



Scheme S3.3: Preparation of **10.**

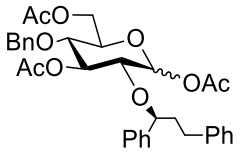
1,3,6-tri-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-D-glucopyranoside (S3). According to the same procedure for **S1**, **S3** was prepared as pure α-anomer. R_f = 0.42 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 6.95 (m, 15H, Ar*H*), 6.44 (d, J = 3.5 Hz, 1H, H-1), 5.50 (t, J = 9.6 Hz, 1H, H-3), 4.49 (dd, J = 24.9, 11.0 Hz, 2H, H-$6_{a,b}$), 4.36 (t, J = 6.8 Hz, 1H, C*H*^{Aux}), 4.24 (d, J = 3.0 Hz, 2H, C*H*$_2$Ph), 3.98 (dt, J = 10.2, 3.0 Hz, 1H, H-5), 3.56 – 3.33 (m, 2H, H-4, H-2), 2.71 – 2.52 (m, 1H, C*H*H^{Aux}), 2.49 – 2.31 (m, 1H, CH*H*^{Aux}), 2.21 (s, 3H, OAc), 2.12 – 2.01 (m, 4H, OAc, CH*H*^{Aux}), 1.97 (s, 3H, OAc), 1.93 – 1.77 (m, 1H, C*H*H^{Aux}); ^{13}C NMR (selected HSQCAD, 75 MHz, $CDCl_3$) δ 88.92 (C-1), 81.11 (*C*H^{Aux}), 75.73 (C-2), 74.99 (C-6), 74.12 (C-4), 73.22 (C-3), 71.02 (C-5), 62.74 (*C*H$_2$Ph),39.93 (*C*H$_2^{Aux}$), 32.13 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{34}H_{38}O_9$ $[M+Na]^+$: 613.2414; found: 613.2547. **1,3,6-tri-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-D-glucopyranosyl *N*-phenyl trifluoroacetimidate (10).** The crude from previous step was further modified according to the same procedure for **8** to give **10** (80 % over 3 steps) for direct use without further characterization. R_f = 0.65 (EtOAc/Hexanes, 1/2, v/v).



7 **S4** **11**

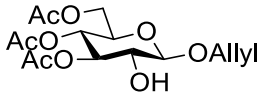
Scheme S3.4: Preparation of **11.**

1,3,6-tri-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-D-glucopyranoside (S4). According to the same procedure for **S1**, **S4** was prepared as a mixture of α/β = 6/1,



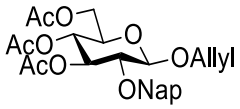
R_f = 0.37 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.03 (m, 15H, Ar*H*), 5.67 (d, J = 3.7 Hz, 1H, H-1), 5.61 (t, J = 9.7 Hz, 1H, H-3), 4.56 (dd, J = 29.6, 11.0 Hz, 1H, *C*H_2Ph), 4.31 (t, J = 6.5 Hz 1H, C*H*^{Aux}), 4.21 (ddd, J = 14.4, 12.2, 3.2 Hz, 1H, H-6$_{a,}$b), 3.90 (ddd, J = 10.0, 3.8, 2.3 Hz, 1H, H-5), 3.58 – 3.44 (m, 2H, H-4, H-2), 2.72 – 2.43 (m, 2H, C*H*$_2^{Aux}$), 2.16 – 2.10 (s, 4H, OAc, C*H*H^{Aux}), 2.03 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.97 – 1.88 (m, 1H, C*H*H^{Aux}); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 90.27 (C-1), 84.24 (*C*H^{Aux}), 75.83 (C-2), 75.80 (C-4), 74.59 (*C*H_2Ph), 73.97 (C-3), 70.43 (C-5), 62.38 (C-6), 39.63 (*C*H_2^{Aux}), 31.75 (*C*H_2^{Aux}); HR MALDI-TOF MS: m/z: calcd for $C_{34}H_{38}O_9$ $[M+Na]^+$: 613.2414; found: 613.2511. **1,3,6-tri-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-glucopyranosyl *N*- phenyl trifluoroacetimidate (11).** The crude from previous step was further modified according to the same procedure for **8** to give **11** (75 % over 3 steps) for direct use without further characterization. R_f = 0.68 (EtOAc/Hexanes, 1/2, v/v)

Allyl 3,4,6-tri-*O*-acetyl-D-glucopyranoside (13). In a 500 ml RB flask was added



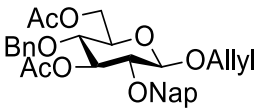
triacetyl D-glucal (5g, mmol), ethyl acetate (75 ml), acetone (10 ml) and saturated $NaHCO_3$ solution (150 ml). After cooling to 0 ^oC, OXONE® (23 g in H_2O) was added dropwisely through a dripping funnel and the biphasic solution was stirred vigoursely. Depanding on the quality of OXONE®, it may need to add more of the reagent before TLC showing the disappearance of starting material. The reaction mixture was dilutted with ethyl acetate and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The resulting colorless oil was directly redisolved in allyl alcohol and stirred at room temperature for 16 h. Then, the solvent was removed in vacuo. The crude was recrystallized in ethyl acetate to give **13** in white crystal (5.4 g, 85 %). R_f = 0.16 (EtOAc/Hexanes, 1/2, v/v), ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (dddd, J = 17.0, 10.3, 6.4, 5.3 Hz, 1H, CH_2=C*H*-), 5.22 (dq, J = 17.2, 1.5 Hz, 1H, CH*H*=CH-), 5.12 (dq, J = 10.7, 1.5 Hz, 1H, C*H*H=CH-), 5.00 (t, J = 9.5 Hz, 1H, H-3), 4.89 (t, J = 9.7 Hz, 1H, H-4), 4.32 (d, J = 7.8 Hz, 1H, H-1), 4.26 (ddt, J = 12.8, 5.3, 1.5 Hz, 1H, C*H*H^{Allyl}), 4.15 (dd, J = 12.3, 4.9 Hz, 1H, H-6_a), 4.04 (ddt, J = 12.8, 6.5, 1.4 Hz, 1H, C*H*H^{Allyl}), 4.03 – 3.91 (m, 1H, H-6_b), 3.58 (ddd, J = 10.0, 5.0, 2.4 Hz, 1H, H-5), 3.48 (dd, J = 9.6, 7.8 Hz, 1H, H-2), 1.97 (s, 3H, OAc), 1.95 (s, 3H, OAc), 1.91 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$) δ 132.70 (CH_2=*C*H-), 117.38 (*C*H_2=CH-), 101.01 (C-1), 73.80 (C-3), 71.18 (C-5, C-2), 69.72 (*C*H_2^{Allyl}), 67.75 (C-4), 61.53 (C-6), HR MALDI-TOF MS: m/z: calcd for $C_{15}H_{22}O_9$ $[M+Na]^+$: 369.1162; found: 369.1202.

Allyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-methyl naphthalene)-β-D-glucopyranoside (14). Compound **13** (12 g, 34 mmol) and 2-naphthaldehyde (10.8 g, 68 mmol) were dissolved



in anhydrous CH_3CN (200 mL) followed by the addition of hexamethyldisiloxane (TMS_2O) (15.3 mL, 68 mmol) and TMSOTf (6.3 mL, 34 mmol) at 0 ^oC. After 30 min, Et_3SiH (27 mL, 0.17 mol) was added and the reaction mixture was stirred for another 4 h at room temperature before quenching by the addition of MeOH (50 mL) and Et_3N (10 mL). The solution was concentrated *in vacuo* and the resulting yellow oil was purified by flash chromatography over silica gel (EtOAc/Hexanes, 4/1→2/1, v/v) to give **14** (5.3 g, 31% with recovering of starting material). R_f = 0.33 (EtOAc/Hexanes, 1/2, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.15 (m, 7H, Ar*H*), 6.11 – 5.85 (m, 1H, CH_2=C*H*-), 5.39 (d, J = 17.1 Hz, 1H, C*H*H=CH-), 5.27 (d, J = 10.5 Hz, 1H, CH*H*=CH-), 5.20 (t, J = 9.5 Hz, 1H, H-3), 5.08 – 4.92 (m, 2H, C*H*H^{Nap}, H-4), 4.82 (d, J = 12.0 Hz, 1H, CH*H*^{Nap}), 4.59 (d, J = 7.8 Hz, 1H, H-1), 4.47 (dd, J = 12.8, 5.3 Hz, 1H, C*H*H^{Allyl}), 4.29 (dd, J = 12.3, 4.8 Hz, 1H, H-6_a), 4.21 (dd, J = 12.8, 6.1 Hz, 1H, CH*H*^{Allyl}), 4.17 – 4.03 (m, 1H, H-6_b), 3.79 – 3.63 (m, 1H, H-5), 3.53 (t, J = 8.1,1H, H-2), 2.09 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.88 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 131.85 (CH_2=*C*H-), 117.91 (*C*H_2=CH-), 102.58 (C-1), 78.39 (C-2), 74.36 (*C*H_2Nap), 73.92 (C-3), 71.65 (C-5), 70.58 (*C*H_2^{Allyl}), 68.74 (C-4), 62.14 (C-6); HR MALDI-TOF MS: m/z: calcd for $C_{26}H_{30}O_9$ $[M+Na]^+$: 509.1788; found: 509.1873.

Allyl 3,6-*O*-diacetyl-4-*O*-benzyl-2-*O*-(2-methyl naphthalene)-β-D-glucopyranoside

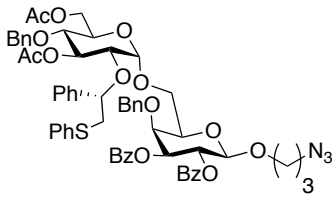


(15). Compound **14** (730 mg, 1.5 mmol) was disolved in anhydrous MeOH (4 ml) and DCM (2 ml) followed by the additioin of freshly prepared NaOMe solution at room temperature. After stirring for 30 min, the reaction was neutralized by the addition of Dowex® 50W X8-200 H^+ resin. The

resin was removed by filtration and the filtrate was concentrated *in vacuo* and dried over high vacuum for 2 h. The resulting solid was redissolved in DMF (5 mL) and benzaldehyde dimethyl acetal (0.33 mL, 2.3 mmol) and camphorsulfonic acid (20 mg, 0.085 mmol) were added. The reaction mixture was heated at 50 ^{o}C under reduced pressure (~15 mm Hg) for 6 h after which it was quenched by the addition of Et_3N (0.1 mL). The solvent was again removed *in vacuo* and the crude was redissolved in pyridine (2 ml) and acetyl anhydride (2 ml). After completion of the reaction, the solvent was removed *in vacuo* and the resulting yellow oil was purified by flash chromatography over silica gel to give allyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-(2-methyl naphthalene)-β-D-glucopyranoside (480 mg, 67 %). R_f = 0.4 (EtOAc/Hexanes, 1/4, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.18 (m, 12H, Ar*H*), 6.09 – 5.90 (m, 1H, CH_2=C*H*-), 5.47 (s, 1H, PhC*H*<), 5.41 (dd, J = 17.2, 1.6 Hz, 1H, C*H*H=CH-), 5.35 (t, J = 9.3 Hz, 1H, H-3), 5.29 (dd, J = 10.4, 1.4 Hz, 1H, CH*H*=CH-), 5.05 (d, J = 12.0 Hz, 1H, C*H*HNap), 4.85 (d, J = 12.1 Hz, 1H, CH*H*Nap), 4.71 (d, J = 7.6 Hz, 1H, H-1), 4.47 (ddt, J = 12.8, 5.3, 1.4 Hz, 1H, C*H*H^{Allyl}), 4.38 (dd, J = 10.5, 4.8 Hz, 1H, H-6$_a$), 4.23 (ddt, J = 12.8, 6.1, 1.3 Hz, 1H, CH*H*^{Allyl}), 3.79 (t, J = 10.1 Hz, 1H, H-6$_b$), 3.62 – 3.49 (m, 3H, H-5, H-4, H-2), 1.93 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 133.99 (CH_2=*C*H-), 118.25 (*C*H_2=CH-), 103.53 (C-1), 101.67 (Ph*C*H<), 79.86 (C-4), 78.98 (C-2), 74.71 (*C*H_2Nap), 72.76 (C-3), 71.02 (*C*H_2^{Allyl}), 68.96 (C-6), 66.37 (C-5); HR MALDI-TOF MS: m/z: calcd for $C_{29}H_{30}O_7$ $[M+Na]^+$: 513.1889; found: 513.1976.A mixture of previously obtained intermediate (480 mg, 0.98 mmol) and activated molecular sieves (4 Å) in DCM (5 mL) was stirred for 1 h under an atmosphere of argon. After cooling to -78 ^{o}C, triethylsilane (0.46 mL, 4.90 mmol) and Cl_2PhB (152 μL, 1.2 mmol) were added. After 1

h, the reaction was quenched by the addition of MeOH (1 mL) and Et_3N (0.5 mL). The resulting mixture was diluted with DCM (10 mL), filtered and the filtrate was concentrated *in vacuo*. The resulting residue was redissolved in a mixture of pyridine (2 ml) and acetyl anhydride (2 ml). After stirring for 16 h, the solvent was removed *in vacuo* and the resulting yellow oil was purified by flash chromatography over silica gel (EtOAc/hexanes, 1/4→1/2, v/v) to give **15** (350 g, 68 %) R_f = 0.4 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.08 (m, 12H, Ar*H*), 6.12 – 5.85 (m, 1H, CH_2=C*H*-), 5.39 (dq, J = 17.2, 1.6 Hz, 1H, CH*H*=CH-), 5.34 – 5.20 (m, 1H, C*H*H=CH-, H-3), 5.03 (d, J = 12.2 Hz, 1H, C*H*HNap), 4.82 (d, J = 12.2 Hz, 1H, CH*H*Nap), 4.62 – 4.41 (m, 4H, H-1, CH_2Ph, C*H*H^{Allyl}), 4.36 (dd, J = 12.0, 2.1 Hz, 1H, H-6$_a$), 4.28 – 4.11 (m, 2H, H-6$_b$, C*H*H^{Allyl}), 3.64 – 3.50 (m, 2H, H-5, H-4), 3.43 (dd, J = 9.6, 7.8 Hz, 1H, H-2), 2.09 (s, 3H, OAc), 1.87 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 133.71 (CH_2=*C*H-), 117.75 (*C*H_2=CH-), 102.62 (C-1), 78.76 (C-2), 75.93 (C-4), 75.61 (C-3), 74.58 (*C*H_2Ph), 74.13 (*C*H_2Nap), 73.27 (C-5), 70.67 (*C*H_2^{Allyl}), 63.05 (C-6); HR MALDI-TOF MS: m/z: calcd for $C_{31}H_{34}O_8$ $[M+Na]^+$: 557.2151; found: 557.2272.

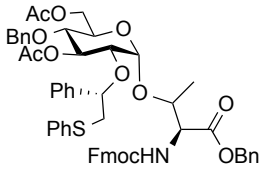
3-azidopropyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dibenzoyl-β-D-galacopyranoside



(1b). R_f = 0.33 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 – 7.01 (m, 30H, Ar*H*), 5.74 (dd, J = 10.5, 7.9 Hz, 1H, H-2^I), 5.51 (t, J = 9.5 Hz, 1H, H-3^{II}), 5.25 (dd, J = 10.5, 3.0 Hz, 1H, H-3^I), 5.05 (d, J = 3.3 Hz, 1H, H-1^{II}), 4.72 (d, J = 11.6 Hz, 1H, C*H*HPh), 4.56 – 4.48 (m, 2H, C*H*HPh, H-1^I), 4.48 – 4.34 (m, 2H, CH_2Ph), 4.32 – 4.19 (m, 2H, H-6$^{II}_{a,b}$), 4.07 – 3.99 (m, 2H, H-5^{II}, H-4^I), 3.93 (dd,

J = 9.8, 7.7 Hz, 1H, H-6^{I}_{a}), 3.89 – 3.73 (m, 1H, C*H*H^{Linker}), 3.69 – 3.58 (m, 1H, H-5^{I}), 3.56 – 3.48 (m, 1H, C*H*H^{Linker}), 3.49 – 3.42 (m, 1H, H-6^{I}_{b}), 3.44 – 3.33 (m, 2H, H-4^{II}, H-2^{II}), 3.29 – 3.13 (m, 1H, C*H*H^{Aux}), 3.14 – 2.96 (m, 3H, C*H*HAux, CH_2^{Linker}), 2.02 (s, 3H, OAc), 1.69 (s, 3H, OAc), 1.66 – 1.59 (m, 1H, C*H*H^{Linker}), 1.54 – 1.46 (m, 1H, C*H*H^{Linker}); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 101.16 (C-1^{I}), 95.96 (C-1^{II}), 82.67 (*C*H^{Aux}), 77.19 (C-2^{II}), 77.16 (C-4^{II}), 74.66 (*C*H_2Ph), 74.47 (C-3^{I}), 74.36 (*C*H_2Ph), 74.12 (C-4^{I}), 73.81 (C-5^{I}), 73.03 (C-3^{II}), 69.99 (C-2^{I}), 68.74 (C-5^{II}), 66.94 (C-6^{I}), 66.67 (*C*H_2^{Linker}), 62.58 (C-6^{II}), 47.87 (*C*H_2^{Linker}), 41.57 (*C*H_2^{Aux}), 28.80 (*C*H_2^{Linker}); HR MALDI-TOF MS: m/z: calcd for $C_{61}H_{63}N_3O_{15}S$ $[M+Na]^+$: 1132.3878; found: 1132.3905.

N$^{\alpha}$-(9-Fluorenylmethyloxycarbonyl)-*O*-{3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenylsulfanyl)-ethyl]-α-D-glucopyranosyl }-*L*-threonine benzyl ester (1c).



R_f = (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 6.96 (m, 28H, Ar*H*), 6.16 (d, J = 8.3 Hz, 1H, N*H*), 5.50 (t, J = 9.6 Hz, 1H, H-3), 5.26 (q, J = 12.4 Hz, 2H, CH_2Ph^{Thr}), 5.19 (d, J = 3.7 Hz, 1H, H-1), 4.61 – 4.18 (m, 9H, C*H*^{Aux}, C*H*$_2^{Fmoc}$, C*H*^{THr}, C*H*$_2^{Thr}$, H-$6_{a,b}$, C*H*^{Fmoc}), 4.01 (d, J = 10.0 Hz, 1H, H-5), 3.45 (dd, J = 9.9, 3.5 Hz, 1H, H-2), 3.42 – 3.30 (m, 2H, C*H*H^{Aux}, H-4), 3.15 (dd, J = 13.5, 5.2 Hz, 1H, C*H*H^{Aux}), 2.06 (s, 3H, OAc), 1.37 (d, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 97.30 (C-1), 82.27 (*C*HAux), 78.11 (C-2), 76.64 (C-4), 74.35 (*C*H_2^{Fmoc}), 73.19 (C-3), 69.13 (C-5), 67.73 (*C*H_2^{Thr}), 67.39 (*C*H_2Ph^{Thr}), 62.88 (C-6), 58.99 (*C*H^{Thr}), 47.15 (*C*H^{Fmoc}), 41.91 (*C*H_2^{Aux}); HR MALDI-TOF MS: m/z: calcd for $C_{57}H_{57}NO_{12}S$ $[M+Na]^+$: 1002.6125; found: 1002. 6197.

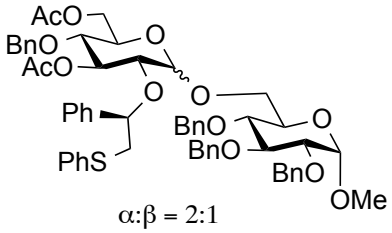
Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (1e). R_f = 0.46 (EtOAc/Hexanes, 1/3, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 6.85 (m, 30H, Ar*H*), 5.78 – 5.54 (m, 2H, H-3^{II}, H-1^{II}), 5.21 (d, J = 11.8 Hz, 1H, CH*H*Ph), 4.79 (d, J = 11.4 Hz, 1H, C*H*HPh), 4.66 – 4.34 (m, 9H, 3 × C*H*$_2$Ph, H-1^I, C*H*^{Aux}, H-5^{II}), 4.34 – 4.23 (m, 2H, H-6$^{II}_a$, H-3^I), 4.10 (dd, J = 12.1, 4.2 Hz, 1H, H-6$^{II}_b$), 3.93 – 3.78 (m, 2H, H-5^I, H-4^I), 3.80 – 3.59 (m, 2H, H-6$^I_{a,b}$), 3.53 (dd, J = 9.3, 3.6 Hz, 1H, H-2^I), 3.47 – 3.28 (m, 5H, OMe, H-2^{II}, H-4^{II}), 3.24 (dd, J = 13.3, 6.2 Hz, 1H, C*H*H^{Aux}), 2.86 (dd, J = 13.3, 7.4 Hz, 1H, C*H*H^{Aux}), 2.03 (s, 3H, OAc), 1.84 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 97.55 (C-1^I), 96.14 (C-1^{II}), 80.22 (*C*H^{Aux}), 79.22 (C-2^I), 78.31 (C-3^I), 77.90 (C-4^I), 76.37 (C-2^{II}), 76.35 (C-4^{II}), 74.12 (*C*H$_2$Ph), 73.58 (*C*H$_2$Ph), 73.53 (*C*H$_2$Ph), 73.37 (*C*H$_2$Ph), 73.04 (C-3^{II}), 69.32 (C-5^I), 68.71 (C-6^I), 68.68 (C-5^{II}), 63.16 (C-6^{II}), 55.13 (OMe), 40.51 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{13}S$ $[M+Na]^+$: 1035.3965; found: 1035.4045.

***p*-Methylphenyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-ß-D-glucopyranoside (1f).** R_f = 0.33 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 – 6.90 (m, 24H, Ar*H*), 5.44 – 5.24 (m, 2H, H-2^I, H-3^{II}), 5.21 (d, J = 3.3 Hz, 1H, H-1^{II}), 4.90 (t, J = 9.4 Hz, 1H, H-3^I), 4.61 – 4.32 (m, 5H, H-1I, C*H*Aux, 2 × CH_2Ph), 4.07 (t, J = 9.3 Hz, 1H, H-4^I), 4.03 – 3.81 (m, 4H, H-6$^{II}_{a,b}$, H-5^{II}, H-6^I_a), 3.75 (d, J = 10.7 Hz, 1H, H-6^I_b), 3.38 (dd, J = 9.6, 1.8 Hz, 1H, H-5^I), 3.35 – 3.17 (m, 3H, H-4^{II}, H-2^{II}, C*H*H^{Aux}), 3.05 (dd, J = 13.8,

5.6 Hz, 1H, C*H*H^{Aux}), 2.29 (s, 3H, Me), 2.09 (s, 3H, OAc), 2.06 (s, 3H, OAc), 1.94 (s, 3H, OAc), 1.78 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 94.44 (C-1^{II}), 85.43 (C-1^{I}), 80.71 (*C*H^{Aux}), 78.94 (C-5^{I}), 76.02 (C-2^{II}, C-4^{II}), 75.67 (C-3^{I}), 74.17 (*C*H$_2$Ph), 73.11 (*C*H$_2$Ph), 72.68 (C-3^{II}), 72.00 (C-4^{I}), 70.75 (C-2^{I}), 69.36 (C-5^{II}), 68.73 (C-6^{I}), 62.67 (C-6^{II}), 41.44 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{55}H_{60}O_{14}S_2$ $[M+Na]^+$: 1031.3322; found: 1031.3441.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenylsulfanyl)-ethyl]-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-galacopyranoside (1g). R_f = 0.48 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 6.87 (m, 30H, Ar*H*), 5.45 (t, J = 9.5 Hz, 1H, H-3^{II}), 4.96 (d, J = 3.4 Hz, 1H, H-1^{II}), 4.89 (d, J = 11.7 Hz, 1H, C*H*HPh), 4.82 (d, J = 11.0 Hz, 1H, C*H*HPh), 4.74 – 4.54 (m, 4H, C*H*$_2$Ph, C*H*HPh, C*H*HPh), 4.43 – 4.26 (m, 3H, CH$_2$Ph, C*H*^{Aux}), 4.25 – 4.09 (m, 3H, H-1^{I}, H-6$^{II}_{a,b}$), 3.94 (dt, J = 10.2, 3.1 Hz, 1H, H-5^{II}), 3.80 (dd, J = 9.7, 6.8 Hz, 1H, H-6$^{I}_{a}$), 3.75 – 3.60 (m, 2H, H-2^{I}, H-3^{I}), 3.50 – 3.37 (m, 4H, OMe, H-4^{I}), 3.37 – 3.25 (m, 2H, H-5^{I}, H-2^{I}), 3.11 (dd, J = 14.0, 8.9 Hz, 1H, C*H*H^{Aux}), 2.98 (dd, J = 14.0, 4.1 Hz, 1H, C*H*H^{Aux}), 1.95 (s, 3H, OAc), 1.59 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 104.79 (C-1^{I}), 96.24 (C-1^{II}), 82.55 (*C*H^{Aux}), 81.99 (C-4^{I}), 79.66 (C-2^{I}), 77.08 (C-2^{II}), 73.41 (C-5^{I}), 73.15 (C-3^{II}), 75.05 (*C*H$_2$Ph), 74.40 (*C*H$_2$Ph), 74.24 (*C*H$_2$Ph), 74.01 (C-3^{I}), 73.50 (*C*H$_2$Ph), 68.40 (C-5^{II}), 67.83 (C-6^{I}), 62.81 (C-6^{II}), 57.09 (OMe), 41.94 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{13}S$ $[M+Na]^+$: 1035.3965; found: 1035.4084.

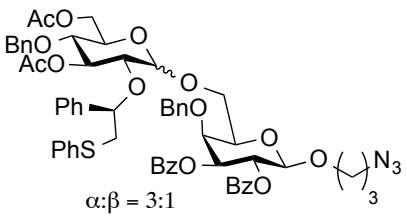
Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenylsulfanyl)-ethyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (2a). R_f = 0.43



α:β = 2:1

(EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.01 (m, Ar*H*), 5.51 (t, J = 9.6 Hz, H-3$^{II\alpha}$), 5.24 (t, J = 9.0 Hz, H-3$^{II\beta}$), 5.03 – 4.86 (m, CH$^{Aux\beta}$, C*H*$_2$Ph), 4.84 – 4.45 (m, C*H*$_2$Ph, CH$^{Aux\alpha}$, H-1$^{I\alpha}$, H-1$^{I\beta}$), 4.35 – 4.17 (m, H-6$^{II\beta}_{a,b}$, C*H*HPh, H-1$^{II\alpha}$, H-1$^{II\beta}$), 4.07 (ddd, J = 16.5, 12.1, 3.2 Hz, H-6$^{II\alpha}_{a,b}$), 3.95 (t, J = 9.2 Hz, H-3$^{I\alpha}$), 3.92 – 3.76 (m, H-5$^{I\alpha}$, H-5$^{II\alpha}$, H-3$^{I\beta}$, H-6$^{I\beta}_a$), 3.71 – 3.22 (m, H-5$^{I\beta}$, H-4$^{II\beta}$, H-6$^{I\alpha}_{a,b}$, H-6$^{I\beta}_b$, H-2$^{I\alpha}$, H-5$^{II\beta}$, H-4$^{I\alpha}$, H-2$^{II\beta}$, H-2$^{I\beta}$, H-2$^{II\alpha}$, H-4$^{I\beta}$, H-4$^{II\alpha}$, OMe$^{\alpha}$, OMe$^{\beta}$, CHHAux$^{\beta}$, C*H*H$^{Aux\alpha}$), 3.12 – 2.97 (m, C*H*H$^{Aux\beta}$, CH*H*$^{Aux\alpha}$), 2.04 (s, OAc$^{\alpha}$), 2.02 (s, OAc$^{\beta}$), 2.02 (s, OAc$^{\beta}$), 1.93 (s, OAc$^{\alpha}$); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 103.12 (C-1$^{II\beta}$), 97.69 (C-1$^{I\beta}$), 97.64 (C-1$^{I\alpha}$), 97.17 (C-1$^{II\alpha}$), 83.50 (*C*H$^{Aux\alpha}$), 82.03 (C-3$^{I\alpha}$), 81.61 (C-3$^{I\beta}$), 80.43 (C-2$^{I\alpha}$), 80.36 (*C*H$^{Aux\beta}$), 80.04 (C-2$^{I\beta}$), 78.15 (C-2$^{II\alpha}$), 77.92 (C-4$^{I\beta}$), 77.37 (C-4$^{I\alpha}$), 76.39 (C-4$^{II\alpha}$), 76.07 (C-4$^{II\beta}$), 75.70 (C-3$^{II\beta}$), 75.35 (*C*H$_2$Ph), 75.25 (*C*H$_2$Ph), 74.57 (*C*H$_2$Ph), 74.53 (*C*H$_2$Ph), 73.12 (C-3$^{II\alpha}$), 72.89 (*C*H$_2$Ph), 72.48 (C-5$^{II\beta}$), 69.89 (C-5$^{II\alpha}$), 69.77 (C-5$^{I\beta}$), 68.39 (C-5$^{I\alpha}$), 68.13 (C-6$^{I\beta}$), 66.62 (C-6$^{I\alpha}$), 62.70 (C-6$^{II\beta}$), 62.52 (C-6$^{II\alpha}$), 55.11 (OMe$^{\beta}$), 55.07 (OMe$^{\alpha}$), 41.41 (*C*H$_2^{Aux\alpha}$), 40.32 (*C*H$_2^{Aux\beta}$); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{13}S$ $[M+Na]^+$: 1035.3965; found: 1035.4072.

3-azidopropyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenylsulfanyl)-ethyl]-D-glucopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dibenzoyl-β-D-galacopyranoside (2b). R_f = 0.5

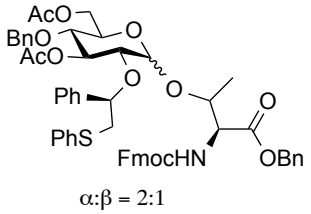


α:β = 3:1

(EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 – 6.93 (m, 30H, Ar*H*), 5.74 (dd, J

= 10.5, 7.9 Hz, 1H, H-2^{I}), 5.57 (dd, J = 13.3, 5.9 Hz, 1H, H-3^{II}), 5.32 (dd, J = 10.6, 3.1 Hz, 1H, H-3^{I}), 4.77 – 4.34 (m, 6H, 2 × CH_2Ph, CH^{Aux}, H-1^{I}), 4.29 – 4.20 (m, 2H, H-$6^{II}_{a,b}$), 4.17 (d, J = 3.1 Hz, 1H, H-1^{II}), 4.02 (t, J = 2.8 Hz, 1H, H-4^{I}), 3.99 – 3.92 (m, 1H, H-5^{II}), 3.91 – 3.75 (m, 2H, H-6^{I}_{a}, H-5^{I}), 3.70 – 3.60 (m, 1H, CHH^{Linker}), 3.59 – 3.36 (m, 3H, H-6^{I}_{b}, H-4^{II}, H-2^{II}), 3.34 – 3.23 (m, 1H, CHH^{Aux}), 3.15 – 3.03 (m, 2H, CH_2^{Linker}), 3.04 – 2.91 (m, 1H, CHH^{Aux}), 2.07 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.73 – 1.53 (m, 2H, CH_2^{Linker}); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 101.18 (C-1^{I}), 96.76 (C-1^{II}), 83.49 (CH^{Aux}), 78.31 (C-2^{II}), 75.97 (C-4^{II}), 74.64 (CH$_2$Ph), 74.46 (C-3^{I}), 74.38 (CH$_2$Ph), 73.90 (C-4^{I}), 73.26 (C-3^{II}), 69.91 (C-2^{I}), 68.54 (C-5^{II}), 66.91 (CH$_2^{Linker}$), 66.60 (C-6^{I}), 62.63 (C-6^{II}), 47.80 (CH$_2^{Linker}$), 41.75 (CH$_2^{Aux}$), 28.78 (CH$_2^{Linker}$); HR MALDI-TOF MS: m/z: calcd for $C_{61}H_{63}N_3O_{15}S$ $[M+Na]^+$: 1132.3878; found: 1132.3986.

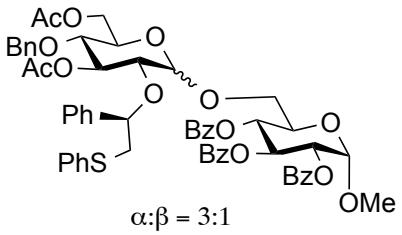
N$^{\alpha}$-(9-Fluorenylmethyloxycarbonyl)-*O*-{3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenylsulfanyl)-ethyl]-D-glucopyranosyl}-*L*-threonine benzyl ester (2c). R_f = 0.41 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.95 – 6.80 (m, ArH), 6.11 (d, J = 7.6 Hz, NH), 5.54 (t, J = 9.6 Hz, H-3^{α}), 5.39 – 5.10 (m, CH_2Ph, H-3^{β}), 4.74 (t, J = 6.2 Hz, $CH^{Aux\beta}$), 4.65 – 4.03 (m, $CH^{Aux\alpha}$, CH_2Ph, H-1^{α}, H-1^{β}, 2 × $CH^{Thr\alpha}$, 2 × $CH^{Thr\beta}$, CH_2^{Fmoc}, H-$6^{\alpha}_{a,b}$, C$H^{Fmoc\alpha}$, C$H^{Fmoc\beta}$), 3.92 (d, J = 5.6 Hz, H-5^{α}), 3.52 (t, J = 9.4 Hz, H-4^{β}), 3.48 – 3.20 (m, 1H, H-4^{α}, H-2^{α}, H-2^{β}, CHH$^{Aux\alpha}$, CH$H^{Aux\beta}$), 3.19 – 2.94 (m, CHH$^{Aux\alpha}$, CHH$^{Aux\beta}$), 2.04 – 1.85 (m, OAc), 1.27 (d, J = 6.2 Hz, $CH_3^{Thr\alpha}$), 0.87 (d, J = 6.0 Hz, $CH_3^{Thr\beta}$); ^{13}C NMR (selected HSQCAD, 150 MHz, CD_2Cl_2): δ 99.64 (C-1^{β}), 98.30 (C-1^{α}), 83.37 (CH$^{Aux\alpha}$), 81.29 (CH$^{Aux\beta}$), 76.45 (C-2^{β}), 75.96 (CH$^{Thr\alpha}$), 75.84 (C-4^{β}), 75.69 (C-3^{β}), 75.25 (C-2^{α}), 74.80 (CH$_2$Ph), 74.42 (CH$^{Thr\beta}$), 73.81 (C-3^{α}), 69.15 (H-5^{α}),



α:β = 2:1

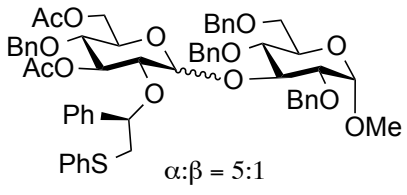
67.21 (*C*H$_2$Ph), 67.02 (*C*H$_2^{Fmoc}$), 62.53 (C-6$^{\alpha}$), 59.24 (*C*H$^{Fmoc\alpha}$), 58.88 (*C*H$^{Fmoc\beta}$), 47.11 (*C*H$^{Thr\alpha}$, *C*H$^{Thr\beta}$), 40.75 (*C*H$_2^{Aux\beta}$), 40.42 (*C*H$_2^{Aux\alpha}$), 18.62 (*C*H$_3^{Thr\alpha}$), 16.20 (*C*H$_3^{Thr\beta}$); HR MALDI-TOF MS: m/z: calcd for $C_{57}H_{57}NO_{12}S$ [M+Na]$^+$: 1002.3499; found: 1002.3528.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenylsulfanyl)-ethyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (2d). R_f = 0.42 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 – 6.60 (m, 30H, Ar*H*), 6.16 (t, J = 9.8 Hz, 1H, H-3^I), 5.58 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.31 (t, 1H, J = 9.4 Hz, H-4^I), 5.23 (dd, J = 10.2, 3.7 Hz, 1H, H-2^I), 5.19 (d, J = 3.7 Hz, 1H, H-1^I), 4.54 (dd, J = 44.7, 11.1 Hz, 2H, C*H*$_2$Ph), 4.32 (dd, J = 8.8, 4.4 Hz, 1H, C*H*^{Aux}), 4.24 (d, J = 10.3 Hz, 1H, H-5^I), 4.20 – 4.09 (m, 2H, H-6$^{II}_{a,b}$), 4.05 – 3.99 (m, 2H, H-5^{II}, H-1^{II}), 3.57 – 3.42 (m, 5H, OMe, H-6^I_a, H-2^{II}), 3.39 (dd, J = 10.0, 3.5 Hz, 1H, H-4^{II}), 3.26 (dd, J = 13.6, 8.7 Hz, 1H, C*H*H^{Aux}), 3.00 – 2.90 (m, 2H, CH*H*^{Aux}, H-6^I_b), 2.08 (s, 3H, OAc), 2.00 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 96.48 (C-1^I), 96.40 (C-1^{II}), 83.62 (*C*H^{Aux}), 79.32 (C-4^{II}), 75.90 (C-2^{II}), 73.75 (*C*H$_2$Ph), 72.74 (C-3^{II}), 72.00 (C-2^I), 70.37 (C-3^I), 69.67 (C-4^I), 68.37 (C-5^I), 68.08 (C-5^{II}), 66.40 (C-6^I), 62.82 (C-6^{II}), 55.50 (OMe), 41.80 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{58}O_{16}S$ [M+Na]$^+$: 1077.3343; found: 1077.3427.



α:β = 3:1

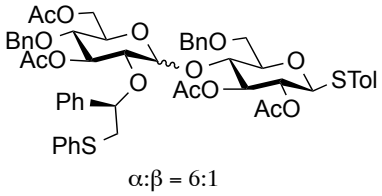
Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenylsulfanyl)-ethyl]-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (2e). R_f = 0.41 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.47 – 7.01 (m, 30H, Ar*H*), 5.68 (t, J = 9.9 Hz, 1H, H-3^{II}), 5.09 (d, J = 12.4 Hz, 1H, C*H*HPh), 5.00



α:β = 5:1

(d, J = 3.4 Hz, 1H, H-1^{II}), 4.72 (d, J = 3.6 Hz, 1H, H-1^{I}), 4.66 – 4.41 (m, 5H, C*H*^{Aux}, 2 × C*H*$_2$Ph), 4.37 (ddd, J = 10.2, 3.8, 1.9 Hz, 1H, H-5^{II}), 4.08 (dd, J = 12.2, 2.0 Hz, 1H, H-6^{II}_a), 4.05 – 3.90 (m, 1H, H-3^{I}), 3.83 (dd, J = 12.2, 4.0 Hz, 1H, H-6^{II}_b), 3.74 (ddd, J = 10.0, 3.5, 2.2 Hz, 1H, H-5^{I}), 3.70 – 3.58 (m, 3H, H-4I, H-$6^{I}_{a,b}$), 3.51 (dd, J = 9.5, 3.6 Hz, 1H, H-2^{I}), 3.42 – 3.29 (m, 5H, H-4^{II}, H-2^{II}, OMe), 3.20 (dd, J = 13.4, 6.8 Hz, 1H, C*H*H^{Aux}), 2.91 (dd, J = 13.4, 6.5 Hz, 1H, C*H*H^{Aux}), 1.95 (2s, 6H, 2 × OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, CD_2Cl_2): δ 97.81 (C-1^{II}), 97.11 (C-1^{I}), 82.41 (*C*H^{Aux}), 78.69 (C-2^{I}), 78.13 (C-4^{I}), 77.54 (C-3^{I}), 76.70 (C-2^{II}), 74.01 (C-3^{II}), 73.98 (*C*H$_2$Ph), 73.34 (*C*H$_2$Ph), 73.11 (*C*H$_2$Ph), 69.72 (C-5^{I}), 68.97 (C-6^{I}), 68.61 (C-5^{II}), 62.56 (C-6^{II}), 54.92 (OMe), 40.70 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{13}S$ $[M+Na]^+$: 1035.3965; found: 1035.4024.

***p*-Methylphenyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenylsulfanyl)-ethyl]-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-ß-D-glucopyranoside (2f).** R_f = 0.42 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 6.78 (m, 19H, Ar*H*), 5.46 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.18 (t, J = 9.0 Hz, 1H, H-3^{I}), 4.87 (t, J = 9.3 Hz, 1H, H-2^{I}), 4.65 – 4.36 (m, 3H, H-1I, H-1II, C*H*^{Aux}, C*H*$_2$Ph), 4.11 – 3.97 (m, 2H, C-$6^{II}_{a,b}$), 3.97 – 3.86 (m, 1H, C-5^{II}), 3.81 (dt, J = 15.6, 7.8 Hz, 1H, H-6^{I}_a), 3.78 – 3.63 (m, 2H, H-6^{I}_b, H-4^{I}), 3.50 – 3.24 (m, 4H, H-5^{I}, H-4^{II}, H-2^{II}, C*H*H^{Aux}), 3.06 (dd, J = 13.4, 5.7 Hz, 1H, C*H*H^{Aux}), 2.36 (s, 3H, Me), 2.13 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.96 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 96.70 (C-1^{II}), 85.25 (C-1^{I}), 84.08 (*C*H^{Aux}), 79.17 (C-5^{I}), 78.12 (C-2^{II}), 76.33 (C-4^{II}), 74.97 (C-3^{I}), 73.96 (*C*H$_2$Ph), 73.14 (C-3^{II}), 73.11 (C-4^{I}), 70.89 (C-2^{I}),



α:β = 6:1

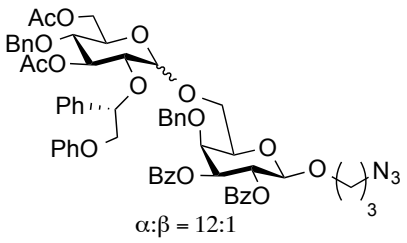
69.02 (C-5^{II}), 68.31 (C-6^{I}), 62.85 (C-6^{II}), 41.08 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{55}H_{60}O_{14}S_2$ $[M+Na]^+$: 1031.3322; found: 1031.3422.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenylsulfanyl)-ethyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-galacopyranoside (2g). R_f = 0.46 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 6.95 (m, 30H, Ar*H)*, 5.54 (t, J = 9.6 Hz, 1H, H-3^{II}), 4.95 – 4.88 (m, 1H, CH*H*Ph), 4.87 – 4.79 (m, 1H, CH*H*Ph), 4.77 – 4.58 (m, 4H, CH*H*Ph, CH*H*Ph, C*H*$_2$Ph), 4.55 – 4.42 (m, 2H, C*H*$_2$Ph), 4.41 – 4.29 (m, 1H, C*H*^{Aux}), 4.22 (d, J = 8.9 Hz, 1H, H-1^{I}), 4.18 – 4.14 (m, 2H, H-6$^{II}_{a,b}$), 4.13 (d, J = 3.7 Hz, 1H, H-1^{II}), 3.86 (ddd, J = 8.2, 6.2, 2.8 Hz, 1H, H-5^{II}), 3.75 – 3.65 (m, 2H, H-4^{I}, H-2^{I}), 3.59 – 3.28 (m, 8H, H-5^{I}, H-3^{I}, H-2^{II}, H-4^{II}, H-6$^{I}_{a}$, OMe), 3.25 – 3.13 (m, 1H, CH*H*Aux), 3.08 (dd, J = 9.5, 5.5 Hz, 1H, H-6$^{I}_{b}$), 2.91 (dd, J = 13.5, 5.1 Hz, 1H, C*H*H^{Aux}), 2.00 (s, 3, OAc), 1.95 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 104.94 (C-1^{I}), 97.18 (C-1^{II}), 83.60 (*C*H^{Aux}), 82.01 (C-3^{I}), 79.68 (C-2^{I}), 77.93 (C-2^{II}), 76.25 (C-4^{II}), 75.20 (*C*H$_2$Ph), 74.38 (*C*H$_2$Ph), 74.21 (*C*H$_2$Ph), 73.79 (C-4^{I}), 73.64 (*C*H$_2$Ph), 73.63 (C-3^{II}), 73.13 (C-5^{I}), 67.35 (C-6^{I}), 62.78 (C-6^{II}), 68.36 (C-5^{II}), 57.14 (OMe), 41.55 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{13}S$ $[M+Na]^+$: 1035.3965; found: 1035.3827.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenoxyl)-ethyl]-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (3a). R_f = 0.39 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 6.62 (m, 30H, Ar*H*), 5.57 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.28 (d, J = 3.4 Hz, 1H, H-1^{II}),

4.91 (dd, J = 11.1, 4.8 Hz, 2H, 2 × C*H*HPh), 4.86 – 4.74 (m, 2H, C*H*HPh, C*H*^{Aux}), 4.69 (d, J = 11.2 Hz, 1H, C*H*HPh), 4.61 – 4.37 (m, 4H, 2 × CH_2Ph), 4.29 (d, J = 3.6 Hz, 1H, H-1^{I}), 4.21 (ddd, J = 16.4, 12.1, 3.2 Hz, 2H, H-6$^{II}_{a,b}$), 4.03 – 3.85 (m, 4H, H-5^{II}, H-3^{I}, CH_2^{Aux}), 3.86 – 3.67 (m, 4H, H-6$^{I}_{a,b}$, H-5^{I}, H-4^{I}), 3.62 (dd, J = 10.0, 3.5 Hz, 1H, H-2^{II}), 3.52 – 3.37 (m, 3H, H-4^{II}, H-2^{I}), 3.25 (s, 3H, OMe), 2.02 (s, 3H, OAc), 1.61 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.82 (C-1^{I}), 97.46 (C-1^{II}), 82.24 (C-3^{I}), 81.69 (*C*H^{Aux}), 79.90 (C-2^{I}), 78.79 (C-2^{II}), 77.75 (C-4^{I}), 76.11 (C-4^{II}), 75.56 (*C*H_2Ph), 74.93 (*C*H_2Ph), 73.94 (*C*H_2Ph), 73.69 (*C*H_2Ph), 73.42 (C-3^{II}), 73.11 (*C*H_2^{Aux}), 70.50 (C-5^{I}), 68.37 (C-5^{II}), 65.96 (C-6^{I}), 62.98 (C-6^{II}), 55.09 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{14}$ $[M+Na]^+$: 1019.4194; found: 1019.4280.

3-azidopropyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dibenzoyl-β-D-galacopyranoside (3b). R_f = 0.35 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 – 6.66 (m, 30H, Ar*H*), 5.73 (dd, J = 10.5, 7.9 Hz, 1H, H-2^{I}), 5.62 – 5.50 (m, 1H, H-3^{II}), 5.25 (dd, J = 10.5, 3.1 Hz, 1H, H-3^{I}), 5.13 (d, J = 3.4 Hz, 1H, H-1^{II}), 4.72 (dd, J = 8.7, 3.0 Hz, 1H, C*H*^{Aux}), 4.67 – 4.60 (m, 1H, C*H*HPh), 4.56 (d, J = 7.9 Hz, 1H, H-1^{I}), 4.52 – 4.39 (m, 3H, C*H*HPh, CH_2Ph), 4.30 (ddd, J = 16.3, 12.1, 3.2 Hz, 2H, C-6$^{II}_{a,b}$), 4.09 – 4.02 (m, 2H, H-5^{II}, C*H*H^{Aux}), 4.01 (d, J = 3.0 Hz, 1H, H-4^{I}), 3.97 – 3.92 (m, 1H, H-6$^{I}_{a}$), 3.92 – 3.83 (m, 2H, C*H*H^{Aux}, C*H*H^{Linker}), 3.77 (dd, J = 7.0, 4.8 Hz, 1H, C-5^{I}), 3.62 (dd, J = 10.0, 3.4 Hz, 1H, H-2^{II}), 3.55 – 3.40 (m, 3H, C*H*H^{Linker}, H-6$^{I}_{b}$, H-4^{II}), 3.10 (t, J = 6.8 Hz, 2H, CH_2^{Linker}), 2.06 (s, 3H, OAc), 1.73 – 1.64 (m, 1H, C*H*H^{Linker}), 1.61 – 1.49 (m, 4H, C*H*H^{Aux}, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ

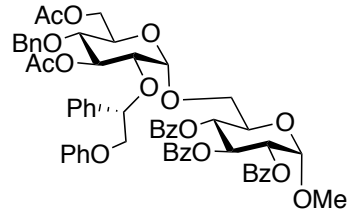


α:β = 12:1

101.29 (C-1^{I}), 96.81 (C-1^{II}), 83.21 (CH^{Aux}), 79.60 (C-2^{II}), 76.24 (C-4^{II}), 74.39 (C-3^{I}), 74.69 (CH_2Ph), 74.19 (CH_2Ph), 74.18 (C-4^{I}), 73.57 (C-5^{I}), 73.36 (C-3^{II}), 72.42 (CH_2^{Aux}), 70.09 (C-2^{I}), 68.48 (C-5^{II}), 67.02 (C-6^{I}), 66.55 (CH_2^{Linker}), 62.75 (C-6^{II}), 47.91 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{61}H_{63}N_3O_{16}$ $[M+Na]^+$: 1116.4106; found: 1116.4137.

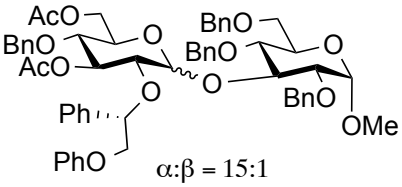
N$^{\alpha}$-(9-Fluorenylmethyloxycarbonyl)-*O*-{3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2- phenoxyl)-ethyl]-α-D-glucopyranosyl }-*L*-threonine benzyl ester (3c). R_f = 0.42 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 – 6.68 (m, 28H, Ar*H*), 6.11 (d, J = 8.0 Hz, 1H, N*H*), 5.54 (t, J = 9.6 Hz, 1H, H-3), 5.16 (d, J = 3.6 Hz, 1H, H-1), 5.04 (d, J = 12.4 Hz, 1H, C*H*HPh), 4.92 (d, J = 12.4 Hz, 1H, CH*H*Ph), 4.81 (dd, J = 8.4, 3.2 Hz, 1H, CH^{Aux}), 4.56 – 4.41 (m, 2H, CH_2Ph), 4.41 – 4.12 (m, 8H, 2 × CH^{Thr}, CH_2^{Fmoc}, H-$6_{a,b}$, CH^{Fmoc}, C*H*H^{Aux}), 4.03 (ddd, J = 10.0, 4.5, 2.2 Hz, 1H, H-5), 3.97 (dd, J = 10.2, 3.3 Hz, 1H, CHH^{Aux}), 3.68 (dd, J = 10.1, 3.6 Hz, 1H, H-2), 3.45 (t, J = 9.6 Hz, 1H, H-4), 2.05 (s, 3H, OAc), 1.57 (s, 3H, OAc), 1.32 (d, J = 6.1 Hz, 3H, CH_3); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.97 (C-1), 82.83 (CH^{Aux}), 79.29 (C-2), 76.61 (C-4), 75.81 (CH^{Thr}), 74.25 (CH_2Ph), 73.98 (C-3), 72.92 (CH_2^{Aux}), 69.61 (C-5), 67.48 (CH_2^{Fmoc}), 67.14 (CH_2Ph), 62.99 (C-6), 59.03 (CH^{Thr}), 47.12 (CH^{Fmoc}), 19.03 (CH_3); HR MALDI-TOF MS: m/z: calcd for $C_{57}H_{57}NO_{13}$ $[M+Na]^+$: 986.3728; found: 986.3785.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenoxyl)-ethyl]-α-D-glucopyranosyl-(1→6)- 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (3d). R_f = 0.35 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 – 6.70 (m, 30H, Ar*H*), 6.12 (t, J = 9.8 Hz, 1H, H-3^{I}), 5.58 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.44 (t, J = 9.9 Hz, 1H, H-4^{I}),



5.23 (dd, J = 10.2, 3.7 Hz, 1H, H-2^{I}), 5.15 (d, J = 3.3 Hz, 1H, H-1^{II}), 5.11 (d, J = 3.6 Hz, 1H, H-1^{I}), 4.72 (dd, J = 8.4, 3.4 Hz, 1H, C*H*^{Aux}), 4.49 (dd, J = 32.4, 11.2 Hz, 2H, C*H*$_2$Ph), 4.37 – 4.08 (m, 4H, H-5^{I}, H-$6^{II}_{a,b}$, C*H*H^{Aux}), 4.00 – 3.79 (m, 2H, H-6^{I}_{a}, C*H*H^{Aux}), 3.67 (d, J = 9.5 Hz, 1H, H-6^{I}_{b}), 3.58 (dd, J = 10.0, 3.4 Hz, 1H, H-2^{II}), 3.51 – 3.32 (m, 4H, H-4^{II}, OMe), 2.06 (s, 3H, OAc), 1.60 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 96.94 (C-1^{II}), 96.57 (C-1^{I}), 82.54 (*C*H^{Aux}), 79.19 (C-2^{II}), 76.11 (C-4^{II}), 73.83 (*C*H$_2$Ph), 73.06 (C-3^{II}), 72.53 (*C*H$_2^{Aux}$), 72.21 (C-2^{I}), 70.64 (C-3^{I}), 69.70 (C-4^{I}), 68.64 (C-5^{I}), 68.39 (C-5^{II}), 66.91 (C-6^{I}), 63.10 (C-6^{II}), 57.63 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{58}O_{17}$ $[M+Na]^+$: 1061.3572; found: 1061.3676.

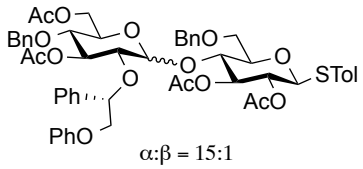
Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (3e). R_f = 0.43 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 – 6.49 (m, 30H, Ar*H*), 5.79 – 5.52 (m, 2H, H-3^{II}, H-1^{II}), 5.23 (d, J = 12.0 Hz, 1H, C*H*HPh), 4.79 (d, J = 11.4 Hz, 1H, C*H*HPh), 4.70 – 4.39 (m, 9H, C*H*^{Aux}, H-1^{I}, H-5^{II}, 2 × C*H*HPh, 2 × C*H*$_2$Ph), 4.37 – 4.19 (m, 2H, H-3^{I}, H-6^{II}_{a}), 4.09 (dd, J = 12.1, 4.1 Hz, 1H, H-6^{II}_{b}), 3.99 (dt, J = 26.7, 13.4 Hz, 1H, C*H*H^{Aux}), 3.87 – 3.59 (m, 5H, H-4^{I}, H-5^{I}, C*H*H^{Aux}, H-$6^{I}_{a,b}$), 3.61 – 3.40 (m, 3H, H-2^{I}, H-2^{II}, H-4^{II}), 3.31 (s, 3H, OMe), 2.05 (s, 3H, OAc), 1.81 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.46 (C-1^{I}), 96.57 (C-1^{II}), 79.99 (*C*HAux), 79.61 (C-2^{I}), 78.50 (C-3^{I}), 77.96 (C-4^{I}), 77.24 (C-4^{II}), 76.35 (C-2^{II}), 73. 98 (*C*H$_2$Ph), 73.72 (*C*H$_2$Ph), 73.61 (*C*H$_2$Ph), 73.22 (*C*H$_2$Ph), 73.15 (C-3^{II}), 71.58



α:β = 15:1

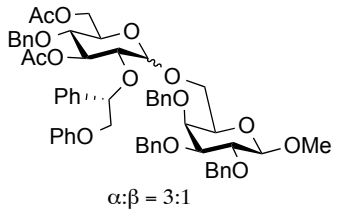
(CH_2^{Aux}), 69.32 (C-5^I), 68.75 (C-6^I), 68.59 (C-5^{II}), 63.33 (C-6^{II}), 55.00 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{14}$ $[M+Na]^+$: 1019.4194; found: 1019.4264.

***p*-Methylphenyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-ß-D-glucopyranoside (3f).** R_f = 0.42 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 6.80 (m, 24H, Ar*H*), 5.37 (t, 1H, H-3^{II}), 5.33 (d, J = 3.3 Hz, 1H, H-1^{II}), 5.28 (t, J = 9.0 Hz, 1H, H-3^I), 4.78 – 4.71 (m, 1H, H-2^I), 4.67 (dd, J = 8.1, 3.1 Hz, 1H, C*H*^{Aux}), 4.59 – 4.38 (m, 5H, H-1^I, 2 × CH_2Ph), 4.17 – 4.13 (m, 2H, H-4^I, C*H*H^{Aux}), 4.08 – 4.05 (m, 2H, H-$6^{II}_{a,b}$), 3.98 – 3.88 (m, 3H, H-5^{II}, C*H*H^{Aux}, H-6^I_a), 3.83 (dd, J = 11.4, 1.5 Hz, 1H, H-6^I_b), 3.47 (dd, J = 10.0, 3.3 Hz, 1H, H-2^{II}), 3.41 – 3.34 (m, 2H, H-5^I, H-4^{II}), 2.29 (s, 3H, C*H*$_3$), 2.05 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.95 (s, 3H, OAc), 1.67 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 95.54 (C-1^{II}), 85.66 (C-1^I), 81.73 (*C*H^{Aux}), 78.94 (C-5^I), 78.16 (C-2^{II}), 76.11 (C-4^{II}), 75.37 (C-3^I), 74.03 (*C*H_2Ph), 73.44 (*C*H_2Ph), 73.10 (C-4^I), 72.66 (C-3^{II}), 72.31(*C*H_2^{Aux}), 70.90 (C-2^I), 69.41 (C-5^{II}), 68.61 (C-6^I), 62.58 (C-6^{II}); HR MALDI-TOF MS: m/z: calcd for $C_{55}H_{60}O_{15}S$ $[M+Na]^+$: 1015.3551; found: 1015.3590.



α:β = 15:1

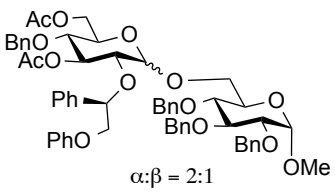
Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-galacopyranoside (3g). R_f = 0.41 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 6.67 (m, 30H, Ar*H*), 5.56 (t, J = 9.6, 1H, H-3^{II}), 5.10 (d, J = 3.4 Hz, 1H, H-1^{II}), 4.93 – 4.41 (m, 9H, C*H*^{Aux}, 4 × CH_2Ph), 4.34 – 4.16 (m, 3H, H-$6^{II}_{a,b}$, H-1^I), 4.08 – 3.95 (m, 2H, H-5^{II}, C*H*H^{Aux}), 3.92 – 3.84 (m, 2H, CH*H*^{Aux}, H-6^I_a), 3.79 – 3.68 (m, 2H, H-



α:β = 3:1

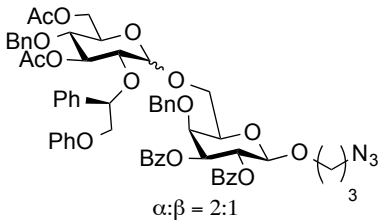
4^{I}, H-2^{I}), 3.68 – 3.57 (m, 1H, H-2^{II}), 3.55 – 3.32 (m, 6H, OMe, H-5^{I}, H-4^{II}, H-3^{I}), 2.04 (s, 3H, OAc), 1.57 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 104.82 (C-1^{I}), 97.00 (C-1^{II}), 82.92 (*C*H^{Aux}), 82.09 (C-3^{I}), 79.57 (C-2^{I}), 79.38 (C-2^{II}), 75.99 (C-4^{II}), 74.74 (*C*H$_2$Ph), 74.30 (*C*H$_2$Ph), 74.04 (*C*H$_2$Ph), 73.87 (C-4^{I}), 73.39 (C-3^{II}),73.22 (*C*H$_2$Ph, C-5^{I}), 72.67 (*C*H$_2^{Aux}$), 68.54 (C-5^{II}), 67.57 (C-6^{I}), 62.81 (C-6^{II}), 57.12 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{14}$ $[M+Na]^+$: 1019.4194; found: 1019.4245.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenoxyl)-ethyl]-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (4a). R_f = 0.38 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) α-anomer: δ 7.38 – 6.82 (m, Ar*H*), 5.63 (t, J=9.6, 1H, H-3^{II}), 4.96 – 4.49 (m, C*H*$_2$Ph, C*H*^{Aux}, H-1^{I}, H-1^{II}), 4.18 – 4.07 (m, 3H, H-6$^{II}_{a,b}$, C*H*H^{Aux}), 3.99 – 3.80 (m, H-3^{I}, CH*H*^{Aux}, H-5^{II}), 3.60 – 3.40 (m, H-5^{I}, H-6$^{II}_{a,b}$, H-4^{I}, H-4^{II}, H-2^{II}, H-2^{I}, OMe), 2.02 (s, 3H, OAc), 1.96 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.66 (C-1^{I}), 97.55 (C-1^{II}), 82.80 (*C*H^{Aux}), 82.29 (C-3^{I}), 80.07 (C-2^{I}), 79.14 (C-4^{II}), 77.79 (C-2^{II}), 76.11 (C-4^{I}), 73.45 (C-3^{II}), 72.45 (*C*H$_2^{Aux}$), 69.95 (C-5^{II}), 69.91 (C-5^{I}), 66.40 (C-6^{II}), 62.78 (C-6^{II}), 55.18 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{14}$ $[M+Na]^+$: 1019.4194; found: 1019.4203.



α:β = 2:1

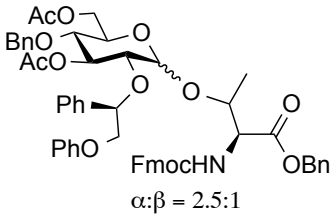
3-azidopropyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dibenzoyl-β-D-galacopyranoside (4b). R_f = 0.43 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 – 6.63 (m, Ar*H*), 5.74 (dd, J = 10.5, 7.9 Hz, 1H, H-2^{I}), 5.69 – 5.54 (m, 1H, H-3^{II}), 5.38 – 5.25 (m, 1H, H-3^{I}), 5.11 – 4.94 (m, 1H, H-4^{II}), 4.79 –



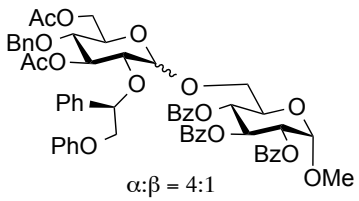
α:β = 2:1

4.67 (m, 1H, C*H*^{Aux}), 4.71 – 4.42 (m, 3H, C*H*$_2$Ph, H-1^{I}), 4.37 (d, J = 3.5 Hz, 1H, H-1^{II}), 4.35 – 4.15 (m, 2H, H-6$^{II}_{a,b}$), 4.09 – 3.93 (m, 3H, C*H*H$_{Aux}$, H-4^{I}, H-5^{II}), 3.91 – 3.80 (m, 3H, H-6$^{I}_{a}$, C*H*H^{Linker}, H-5^{I}), 3.80 – 3.71 (m, 1H, H-6$^{I}_{a}$), 3.62 – 3.34 (m, 3H, H-2^{II}, H-6$^{I}_{b}$, C*H*H^{Linker}), 3.26 – 3.14 (m, 1H, C*H*H^{Linker}), 3.09 (t, J = 6.8 Hz, 1H, C*H*H^{Linker}), 2.02 (s, 6H, 2×OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 101.31 (C-1^{I}), 97.18 (C-1^{II}), 82.96 (*C*H^{Aux}), 81.76 (C-4^{II}), 77.06 (C-2^{II}), 74.79 (C-3^{I}), 74.71 (*C*H$_2$Ph), 74.70 (*C*H$_2$Ph), 74.15 (C-4^{I}), 73.72 (C-5^{I}), 73.66 (C-3^{II}), 72.04 (*C*H$_2^{Aux}$), 70.05 (C-2^{I}), 68.63 (C-5^{II}), 67.07 (C-6^{I}), 66.59 (*C*H$_2^{Linker}$), 62.72 (C-6^{II}), 47.89 (*C*H$_2^{Linker}$); HR MALDI-TOF MS: m/z: calcd for $C_{61}H_{63}N_3O_{16}$ $[M+Na]^+$: 1116.4106; found: 1116.4198.

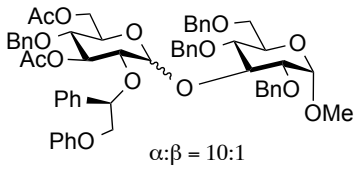
N$^{\alpha}$-(9-Fluorenylmethyloxycarbonyl)-*O*-{3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2- phenoxyl)-ethyl]-D-glucopyranosyl }-*L*-threonine benzyl ester (4c). R_f = 0.46 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 6.53 (m, 28H, Ar*H*), 6.15 (d, J = 8.2 Hz, 1H, N*H*), 5.68 (t, J = 9.7 Hz, 1H, H-3), 5.21 (d, J = 12.4 Hz, 1H, C*H*HPh), 5.05 (d, J = 12.3 Hz, 1H, C*H*HPh), 4.85 (dd, J = 8.4, 2.7 Hz, 1H, C*H*^{Aux}), 4.67 – 4.46 (m, 3H, C*H*$_2$Ph, H-1), 4.42 – 4.03 (m, 8H, 2 × C*H*^{Thr}, C*H*$_2^{Fmoc}$, C-6$_{a,b}$, C*H*H^{Aux}, C*H*^{Fmoc}), 3.97 (dd, J = 11.1, 6.3 Hz, 1H, C-5), 3.83 (dd, J = 10.2, 3.1 Hz, 1H, C*H*H^{Aux}), 3.49 – 3.25 (m, 2H, H-4, H-2), 2.11 (s, 1H, OAc), 2.00 (s, 1H, OAc), 1.27 (d, J = 6.9, 3H, CH$_3^{Thr}$); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 98.88 (C-1), 82.98 (*C*H^{Aux}), 76.81 (*C*H^{Thr}), 76.28 (C-4), 76.13 (C-2), 74.67 (*C*H$_2$Ph), 73.95 (C-3), 71.82 (*C*H$_2^{Aux}$), 68.86 (C-5), 67.35 (*C*H$_2^{Fmoc}$), 67.26 (*C*H$_2$Ph), 62.76 (C-6), 59.28 (*C*H^{Thr}), 46.98 (*C*H^{Fmoc}), 18.60 (*C*H$_3^{Thr}$); HR MALDI-TOF MS: m/z: calcd for $C_{57}H_{57}NO_{13}$ $[M+Na]^+$: 986.3728; found: 986.3783.



Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (4d). R_f = 0.45 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 – 6.74 (m, 30H, Ar*H*), 6.16 (t, J = 9.8 Hz, 1H, H-3^I), 5.62 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.34 (t, J = 9.9 Hz, 1H, H-4^I), 5.23 (dd, J = 10.1, 3.7 Hz, 1H, H-2^I), 5.19 (d, J = 3.7 Hz, 1H, H-1^I), 4.65 (dd, J = 8.3, 3.4 Hz, 1H, C*H*^{Aux}), 4.55 (dd, J = 40.1, 11.1 Hz, 2H, C*H*$_2$Ph), 4.28 (dd, J = 17.2, 8.7 Hz, 1H, H-5^I), 4.26 – 4.04 (m, 5H, H-6$^{II}_{a,b}$, H-5^{II}, C*H*H^{Aux}, H-1^{II}), 3.83 (dd, J = 10.3, 3.4 Hz, 1H, CH*H*^{Aux}), 3.62 (dd, J = 10.4, 8.1 Hz, 1H, H-6^I_a), 3.55 – 3.43 (m, 5H, OMe, H-4^{II}, H-2^{II}), 3.10 (d, J = 9.3 Hz, 1H, H-6^I_b), 2.02 (s, 3H, OAc), 1.99 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 96.92 (C-1^{II}), 96.59 (C-1^I), 83.25 (*C*H^{Aux}), 79.15 (C-2^{II}), 75.76 (C-4^{II}), 73.76 (*C*H$_2$Ph), 73.03 (C-3^{II}), 72.27 (*C*H$_2$Aux), 72.13 (C-2^I), 70.45 (C-3^I), 69.92 (C-4^I), 68.64 (C-5^{II}), 68.54 (C-5^I), 66.67 (C-6^I), 63.07 (C-6^{II}), 55.68 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{58}O_{17}$ $[M+Na]^+$: 1061.3572; found: 1061.3668.

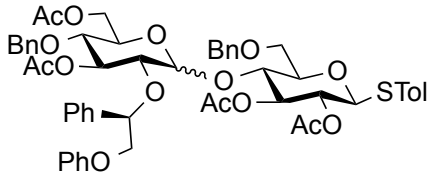


Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4e). R_f = 0.44 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 6.65 (m, 30H, Ar*H*), 5.87 (t, J = 9.7 Hz, 1H, H-3^{II}), 5.24 (d, J = 3.4 Hz, 1H, H-1^{II}), 4.98 (d, J = 12.3 Hz, 1H, C*H*HPh), 4.87 (dd, J = 6.6, 3.1 Hz, 1H, C*H*^{Aux}), 4.73 (d, J = 11.6 Hz, 1H, C*H*HPh), 4.62 (d, J = 3.7 Hz, 1H, H-1^I), 4.60 – 4.35 (m, 9H, H-5II, 2 × C*H*HPh, 2 × C*H*$_2$Ph), 4.22 (d, J = 12.2 Hz, 1H, H-6^I_a), 4.14 (t, J = 9.0 Hz, 1H, H-3^I), 4.07 (dd, J =



12.2, 4.0 Hz, 1H, H-6^{II}_{b}), 4.00 (dd, J = 10.0, 7.7 Hz, 1H, C*H*H^{Aux}), 3.85 (dd, J = 10.1, 4.1 Hz, 1H, C*H*H^{Aux}), 3.78 – 3.71 (m, 1H, H-5^{I}), 3.71 – 3.65 (m, 1H, H-4^{I}), 3.65 – 3.46 (m, 5H, H-$6^{I}_{a,b}$, H-2^{II}, H-4^{II}, H-2^{I}), 3.31 (s, 3H, OMe), 2.05 (s, 3H, OAc), 1.99 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.59 (C-1^{II}), 97.44 (C-1^{I}), 81.52 (*C*H^{Aux}), 79.08 (C-2^{I}), 78.18 (C-4^{I}), 77.82 (C-3^{I}), 76.77 (C-2^{II}), 76.49 (C-4^{II}), 73.94 (C-3^{II}), 73.71 (*C*H_2Ph), 73.55 (*C*H_2Ph), 73.30 (*C*H_2Ph), 73.12 (*C*H_2Ph), 72.24 (*C*H_2Aux), 69.30 (C-5^{I}), 68.53 (C-6^{I}), 68.44 (C-5^{II}), 63.03 (C-6^{II}), 54.95 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{14}$ $[M+Na]^+$: 1019.4194; found: 1019.4226.

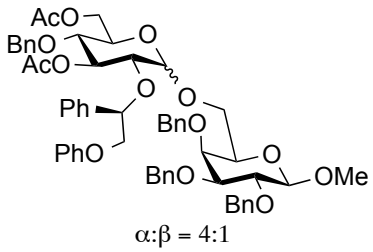
***p*-Methylphenyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-ß-D-glucopyranoside (4f).** R_f = 0.38 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 – 6.71 (m, 24H, Ar*H*), 5.50 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.21 (t, J = 9.0 Hz, 1H, H-3^{I}), 4.87 (t, J = 9.3 Hz, 1H, H-2^{I}), 4.74 (dd, J = 8.7, 2.9 Hz, 1H, C*H*^{Aux}), 4.67 (d, J = 3.4 Hz, 1H, H-1^{II}), 4.58 (d, J = 9.6 Hz, 1H, H-1^{I}), 4.55 – 4.51 (m, 1H, C*H*HPh), 4.49 – 4.45 (m, 1H, C*H*HPh), 4.43 (s, 2H, CH_2Ph), 4.09 – 3.97 (m, 3H, H-$6^{II}_{a,b}$, C*H*H^{Aux}), 3.97 – 3.91 (m, 1H, H-5^{II}), 3.90 – 3.81 (m, 3H, H-6^{I}_{a}, CH*H*^{Aux}, H-4^{I}), 3.69 (d, J = 11.3 Hz, 1H, H-6^{I}_{b}), 3.45 (dd, J = 9.6, 1.7 Hz, 1H, H-5^{I}), 3.42 – 3.31 (m, 2H, H-4^{II}, H-2^{II}), 2.34 (s, 3H, CH_3), 2.07 (s, 6H, 2 × OAc), 1.96 (s, 3H, OAc), 1.92 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.08 (C-1^{II}), 85.25 (C-1I), 83.04 (*C*H^{Aux}), 79.08 (C-5^{I}), 77.71 (C-2^{II}), 75.83 (C-4^{II})74.20 (C-3^{I}), 73.96 (*C*H_2Ph), 73.63 (C-4^{I}), 73.60 (*C*H_2Ph), 73.06 (C-3^{II}), 71.62 (*C*H_2Aux), 70.46 (C-2^{I}), 68.84 (C-5^{II}),



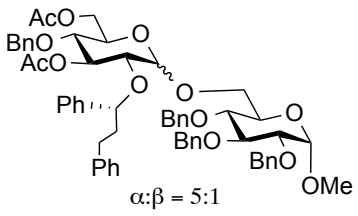
α:β = 7:1

68.04 (C-6^{I}), 62.80 (C-6^{II}), 21.09 (*C*H$_3$); HR MALDI-TOF MS: m/z: calcd for $C_{55}H_{60}O_{15}S$ $[M+Na]^+$: 1015.3551; found: 1015.3628.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*)-phenyl-2-phenoxyl)-ethyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-galacopyranoside (4g). R_f = 0.36 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 6.73 (m, 30H, Ar*H*), 5.64 (t, J = 9.6 Hz, 1H, H-3^{II}), 4.93 – 4.84 (m, 2H, 2 × C*H*HPh), 4.76 – 4.48 (m, 9H, C*H*^{Aux}, 2 × C*H*HPh, 2 × C*H*$_2$Ph), 4.37 (d, J = 3.4 Hz, 1H, H-1^{II}), 4.28 – 4.18 (m, 3H, H-6$^{II}_{a,b}$, H-1^{I}), 4.00 (t, J = 9.3 Hz, 1H, C*H*H^{Aux}), 3.96 – 3.91 (m, 1H, H-5^{II}), 3.83 (dd, J = 10.4, 3.7 Hz, 1H, CH*H*^{Aux}), 3.78 (d, J = 5.4 Hz, 1H, H-4^{I}), 3.77 – 3.71 (m, 1H, H-2^{I}), 3.70 – 3.63 (m, 1H, H-6$^{I}_{a}$), 3.55 – 3.44 (m, 6H, OMe, H-5^{I}, H-2^{II}, H-3^{I}), 3.28 (dd, J = 9.5, 5.8 Hz, 1H, H-6$^{I}_{b}$), 2.04 (s, 1H, OAc), 2.00 (s, 1H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 104.77 (C-1^{I}), 97.30 (C-1^{II}), 82.73 (*C*H^{Aux}), 81.68 (C-3^{I}), 79.46 (C-2^{I}), 76.97 (C-2^{II}), 75.62 (*C*H$_2$Ph), 74.22 (*C*H$_2$Ph), 74.12 (*C*H$_2$Ph), 73.74 (C-4^{I}), 73.68 (C-3^{II}), 73.57 (*C*H$_2$Ph), 72.96 (C-5^{I}), 72.04 (*C*H$_2^{Aux}$), 68.28 (C-5^{II}), 67.03 (C-6^{I}), 62.67 (C-6^{II}), 57.01 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{59}H_{64}O_{14}$ $[M+Na]^+$: 1019.4194; found: 1019.4160.

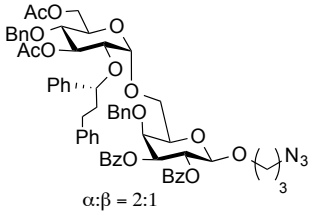


Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (5a). R_f = 0.37 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.00 (m, 30H, Ar*H*), 5.52 (t, *J* = 9.5 Hz, 1H, H-3^{II}), 5.03 (d, *J* = 3.4 Hz, 1H, H-1^{II}), 5.00 (d, *J* = 11.3 Hz, 1H, C*H*HPh), 4.95 (d, *J* = 11.0 Hz, 1H,



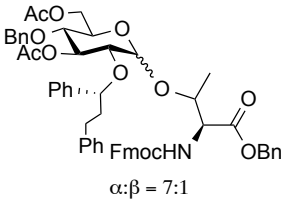
C*H*HPh), 4.80 (d, *J* = 11.0 Hz, 1H, C*H*HPh), 4.66 (d, *J* = 11.4 Hz, 1H, C*H*HPh), 4.55 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.51 (d, *J* = 3.6 Hz, 1H, H-1^{I}), 4.49 (d, *J* = 11.1 Hz, 1H, C*H*HPh), 4.44 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.40 (d, *J* = 11.0 Hz, 1H, C*H*HPh), 4.32 (dd, *J* = 8.1, 5.0 Hz, 1H, C*H*^{Aux}), 4.13 (dd, *J* = 12.1, 2.2 Hz, 1H, H-6^{II}_{a}), 4.07 (dd, *J* = 12.1, 4.3 Hz, 1H, H-6^{II}_{b}), 3.98 (t, *J* = 9.3 Hz, 1H, H-3^{I}), 3.88 – 3.78 (m, 3H, H-5^{I}, H-5^{II}, H-6^{I}_{a}), 3.69 – 3.64 (m, 2H, H-6^{I}_{b}, H-4^{I}), 3.47 (dd, *J* = 9.4, 3.4 Hz, 1H, H-2^{I}), 3.37 (m, 4H, OMe, H-4^{II}), 3.32 (dd, *J* = 9.9, 3.4 Hz, 1H, H-2^{II}), 2.80 (ddd, *J* = 14.0, 11.0, 5.4 Hz, 1H, C*H*H^{Aux}), 2.53 (ddd, *J* = 13.9, 10.8, 5.4 Hz, 1H, C*H*H^{Aux}), 2.11 – 2.05 (m, 1H, C*H*H^{Aux}), 1.97 (s, 3H, OAc), 1.91 (s, 3H, OAc), 1.89 – 1.81 (m, 1H, C*H*H^{Aux}); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.87 (C-1^{I}), 96.27 (C-1^{II}), 82.16 (C-3^{I}), 80.26 (C-2^{I}), 80.10 (*C*H^{Aux}), 77.71 (C-4^{I}), 76.00 (C-4^{II}), 75.67 (*C*H_2Ph), 75.06 (*C*H_2Ph), 74.98 (C-2^{II}), 74.06 (*C*H_2Ph), 73.33 (*C*H_2Ph), 73.11 (C-3^{II}), 69.15 (C-5^{II}), 66.29 (C-6^{I}), 62.74 (C-6^{II}), 40.13 (*C*H_2^{Aux}), 32.10 (*C*H_2^{Aux}); HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{66}O_{13}$ $[M+Na]^+$: 1017.4401; found: 1017.4460.

3-azidopropyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-D-glucopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dibenzoyl-β-D-galacopyranoside (5b). R_f = 0.44 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 – 6.98 (m, 30H, Ar*H*), 5.88 – 5.68 (m, 2H, H-2^{I}, H-3^{I}), 5.50 (t, *J* = 9.5 Hz, 1H, H-3^{II}), 4.91 (d, *J* = 3.3 Hz, 1H, H-1^{II}), 4.80 – 4.72 (m, 1H, C*H*HPh), 4.66 (d, *J* = 7.9 Hz, 1H, H-1^{I}), 4.59 – 4.36 (m, 5H, C*H*HPh, C*H*$_2$Ph, CH_2^{Linker}), 4.35 – 4.19 (m, 3H, H-$6^{II}_{a,b}$, C*H*^{Aux}), 4.15 – 4.09 (m, 1H, H-4^{I}), 4.04 (ddd, *J* = 10.2, 4.4, 2.2 Hz, 2H, H-5^{II}), 4.01 – 3.85 (m, 7H, H-5^{I}, H-6^{I}_{a}), 3.62 – 3.44 (m, 1H, H-6^{I}_{b}), 3.43 – 3.31 (m, 2H, H-4^{II}, H-2^{II}),



3.25 – 3.15 (m, 1H, C*H*H^{Linker}), 3.08 (t, *J* = 6.8 Hz, 1H, C*H*H^{Linker}), 2.71 – 2.42 (m, 2H, CH_2^{Aux}), 2.23 – 2.06 (m, 1H, C*H*H^{Aux}), 2.03 (m, 4H, OAc, C*H*H^{Aux}), 1.98 – 1.90 (m, 1H, C*H*H^{Aux}), 1.87 (s, 3H, OAc), 1.75 – 1.48 (m, 2H, CH_2^{Linker}); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 101.27 (C-1^{I}), 95.68 (C-1^{II}), 80.73 (*C*H^{Aux}), 75.82 (C-2^{II}, C-4^{II}), 74.78 (*C*H_2Ph), 74.83 (*C*H_2Ph), 74.32 (*C*H_2^{Linker}), 73.85 (C-4^{I}), 73.60 (C-5^{I}), 73.06 (C-3^{II}), 69.95 (C-2^{I}, C-3^{I}), 68.62 (C-5^{II}), 66.77 (C-6^{I}), 62.65 (C-6^{II}), 47.84 (*C*H_2^{Linker}), 39.49 (*C*H_2^{Aux}), 31.80 (*C*H_2^{Aux}), 28.79 (*C*H_2^{Linker}); HR MALDI-TOF MS: m/z: calcd for $C_{62}H_{65}N_3O_{15}$ $[M+Na]^+$: 1114.4313; found: 114.4465.

N$^{\alpha}$-(9-Fluorenylmethyloxycarbonyl)-*O*-{3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-α-D-glucopyranosyl }-*L*-threonine benzyl ester (5c). R_f = 0.37 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 – 6.95 (m, 28H, Ar*H*), 6.08 (d, *J* = 8.6 Hz, 1H, N*H*), 5.48 (t, *J* = 9.6 Hz, 1H, H-3), 5.30 – 5.11 (m, 2H, CH_2Ph), 4.96 (d, *J* = 3.5 Hz, 1H, H-1), 4.52 (d, *J* = 10.9 Hz, 1H, C*H*HPh), 4.48 – 4.35 (m, 3H, C*H*^{Thr}, C*H*^{Thr}, C*H*HPh), 4.36 – 4.26 (m, 2H, C*H*^{Aux}, C*H*H^{Thr}), 4.28 – 4.15 (m, 3H, H-6$_{a,b}$, C*H*H^{Thr}), 4.08 (t, *J* = 7.5 Hz, 1H, C*H*^{Fmoc}), 3.95 (dt, *J* = 10.0, 3.5 Hz, 1H, H-5), 3.35 (t, *J* = 9.6 Hz, 1H, H-4), 3.29 (dd, *J* = 10.1, 3.5 Hz, 1H, H-2), 2.59 – 2.44 (m, 1H, C*H*H^{Aux}), 2.39 – 2.21 (m, 2H, C*H*H^{Aux}, C*H*H^{Aux}), 2.09 – 1.95 (m, 4H, C*H*H^{Aux}, OAc), 1.34 (d, *J* = 6.4 Hz, 3H, CH_3^{Thr}); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 96.40 (C-1), 81.50 (*C*H^{Aux}), 76.35 (C-4), 75.52 (C-2), 74.70 (*C*H^{Thr}), 74.59 (*C*H_2Ph^{Thr}), 72.86 (C-3), 69.03 (C-5), 67.42 (*C*H_2^{Fmoc}), 67.40 (*C*H_2Ph), 62.82 (C-6), 58.66 (*C*H^{Thr}), 46.99 (*C*H^{Fmoc}), 39.33 (*C*H_2^{Aux}), 31.51 (*C*H_2^{Aux}), 19.11 (*C*H_3^{Thr}); HR MALDI-TOF MS: m/z: calcd for $C_{58}H_{59}NO_{12}$ $[M+Na]^+$: 984.3935; found: 984.3999.



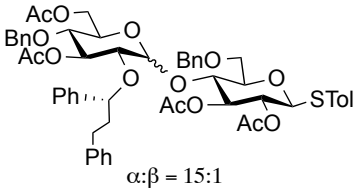
Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (5d). R_f = 0.28 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 6.99 (m, 30H, Ar*H*), 6.19 (t, J = 9.8 Hz, 1H, H-3^I), 5.70 – 5.46 (m, 2H, H-3^{II}, H-4^I), 5.29 (dd, J = 10.1, 3.5 Hz, 1H, H-2^I), 5.19 (d, J = 3.4 Hz, 1H, H-1^I), 4.94 (d, J = 2.9 Hz, 1H, H-1^{II}), 4.61 – 4.34 (m, 3H, C*H*$_2$Ph, H-5^I), 4.32 – 4.02 (m, 4H, H-6$^{II}_{a,b}$, H-5^{II}, C*H*^{Aux}), 3.94 (dd, J = 10.3, 7.5 Hz, 1H, H-6^I_a), 3.65 (d, J = 10.5 Hz, 1H, H-6^I_b), 3.51 (s, 3H, OMe), 3.46 – 3.26 (m, 2H, H-2^{II}, H-4^{II}), 2.93 – 2.66 (m, 1H, C*H*H^{Aux}), 2.67 – 2.44 (m, 1H, C*H*H^{Aux}), 2.25 – 2.07 (m, 1H, C*H*H^{Aux}), 2.03 (s, 3H, OAc), 1.90 (s, 4H, C*H*H^{Aux}, OAc); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 96.73 (C-1^I), 95.95 (C-1^{II}), 80.50 (*C*H^{Aux}), 76.06 (C-4^{II}), 75.59 (C-2^{II}), 73.82 (*C*H$_2$Ph), 72.85 (C-3^{II}), 72.43 (C-2^I), 70.62 (C-3^I), 69.70 (C-4^I), 68.95 (C-5^I), 68.38 (C-5^{II}), 67.00 (C-6^I), 62.86 (C-6^{II}), 55.70 (OMe), 39.69 (*C*H$_2$Aux), 31.99 (*C*H$_2$Aux); HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{60}O_{16}$ $[M+Na]^+$: 1059.3779; found: 1059.3852.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (5e). R_f = 0.41 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 6.78 (m, 30H, Ar*H*), 5.63 (t, *J* = 9.6 Hz, 1H, H-3^{II}), 5.59 (d, *J* = 3.4 Hz, 1H, H-1^{II}), 5.11 (d, *J* = 11.7 Hz, 1H, C*H*HPh), 4.78 (d, *J* = 11.4 Hz, 1H, C*H*HPh), 4.61 (d, *J* = 3.7 Hz, 1H, H-1^I), 4.60 – 4.36 (m, 7H, 3 × C*H*$_2$Ph, H-5^{II}), 4.32 – 4.20 (m, 3H, H-6$^{II}_a$, C*H*^{Aux}, H-3^I), 4.08 (dd, *J* = 12.2, 4.3 Hz, 1H, H-6$^{II}_b$), 3.86 – 3.73 (m, 2H, H-5^I, H-4^I), 3.72 – 3.62 (m, 2H, H-6$^I_{a,b}$),

α:β = 20:1

3.57 (dd, J = 9.3, 3.6 Hz, 1H, H-2^{I}), 3.43 – 3.34 (m, 1H, H-4^{II}), 3.33 – 3.26 (m, 4H, H-2^{II}, OMe), 2.44 (ddd, J = 14.0, 11.4, 5.5 Hz, 1H, C*H*H^{Aux}), 2.26 (ddd, J = 14.0, 11.3, 5.0 Hz, 1H, C*H*H^{Aux}), 2.10 – 2.03 (m, 1H, C*H*H^{Aux}), 2.01 (s, 3H, OAc), 1.93 (s, 3H, OAc), 1.84 – 1.74 (m, 1H, C*H*H^{Aux}); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.45 (C-1^{I}), 95.79 (C-1^{II}), 80.33 (*C*H^{Aux}), 79.57 (C-2^{I}), 77.89 (C-4^{I}), 77.74 (C-3^{I}), 76.28 (C-4^{II}), 75.28 (C-2^{II}), 74.35 (*C*H_2Ph), 73.97 (*C*H_2Ph), 73.39 (*C*H_2Ph), 73.13 (*C*H_2Ph), 72.95 (C-3^{II}), 68.96 (C-5^{I}), 68.63 (C-6^{I}, C-5^{II}), 63.14 (C-6^{II}), 55.09 (OMe), 39.08 (*C*H_2^{Aux}), 31.37 (*C*H_2^{Aux}); HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{66}O_{13}$ $[M+Na]^+$: 1017.4401; found: 1017.4496.

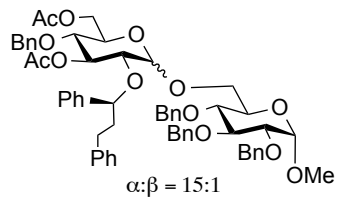
***p*-Methylphenyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-ß-D-glucopyranoside (5f).** R_f = 0.5 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 6.92 (m, 24H, Ar*H*), 5.37 – 5.22 (m, 2H, H-3^{I}, H-3^{II}), 5.15 (d, J = 3.5 Hz, 1H, H-1^{II}), 4.93 (t, J = 9.5 Hz, 1H, H-2^{I}), 4.61 (d, J = 10.0 Hz, 1H, H-1^{I}), 4.58 – 4.31 (m, 4H, 2 × *C*H_2Ph), 4.20 (t, J = 6.6 Hz, 1H, C*H*Aux), 4.08 – 3.87 (m, 5H, H-4^{I}, H-5^{II}, H-6^{I}_{a}, H-$6^{II}_{a,b}$), 3.79 (dd, J = 11.6, 1.6 Hz, 1H, H-6^{I}_{b}), 3.50 (ddd, J = 9.6, 3.4, 1.7 Hz, 1H, H-5^{I}), 3.29 (t, J = 9.5 Hz, 1H, H-4^{II}), 3.19 (dd, J = 9.9, 3.4 Hz, 1H, H-2^{II}), 2.58 (ddd, J = 13.8, 10.3, 6.2 Hz, 1H, C*H*H^{Aux}), 2.44 (ddd, J = 14.4, 10.3, 5.1 Hz, 1H, C*H*H^{Aux}), 2.29 (s, 3H, Me), 2.23 – 1.84 (m, 14H, 4 × OAc, C*H*$_2^{Aux}$); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 94.28 (C-1^{II}), 85.35 (C-1^{I}), 80.02 (*C*H^{Aux}), 79.05 (C-5^{I}), 75.78 (C-4^{II}), 75.77 (C-3^{I}), 74.68 (C-2^{II}), 73.82 (*C*H_2Ph), 73.35 (*C*H_2Ph), 72.50 (C-3^{II}), 71.42 (C-4^{I}), 70.67 (C-2^{I}), 69.01 (C-5^{II}), 68.22 (C-6^{I}),



62.73 (C-6^{II}), 39.35 (*C*H$_2^{Aux}$), 31.53 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{56}H_{62}O_{14}S$ [M+Na]$^+$: 1013.3758; found: 1013.3845.

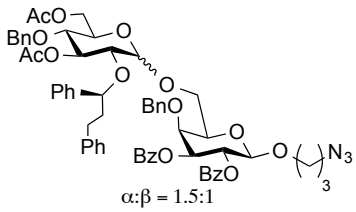
Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*R*),3-diphenyl-propyl]-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-galacopyranoside (5g). R_f = 0.38 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 6.94 (m, 30H, Ar*H*), 5.49 (t, *J* = 9.5 Hz, 1H, H-3^{II}), 4.97 (d, *J* = 11.7 Hz, 1H, C*H*HPh), 4.91 – 4.84 (m, 2H, C*H*HPh, CH-1^{II}), 4.77 – 4.60 (m, 5H, C*H*$_2$Ph, CH*H*Ph, CH*H*Ph, CH*H*Ph), 4.52 – 4.36 (m, 2H, C*H*$_2$Ph), 4.29 (d, *J* = 7.6 Hz, 1H, H-1^I), 4.25 – 4.17 (m, 3H, C*H*^{Aux}, H-6$^{II}_{a,b}$), 3.97 (ddd, *J* = 10.2, 4.0, 2.6 Hz, 1H, H-5^{II}), 3.89 – 3.67 (m, 3H, H-6^I_a, H-4^I, H-2^I), 3.60 (t, *J* = 5.7 Hz, 1H, H-3^I), 3.58 – 3.44 (m, 5H, OMe, C-6^I_b, H-5^I), 3.42 – 3.34 (m, 1H, H-4^{II}), 3.33 (dd, *J* = 10.0, 3.4 Hz, 1H, H-2^{II}), 2.60 (ddd, *J* = 13.9, 10.4, 5.8 Hz, 1H, C*H*H^{Aux}), 2.41 (ddd, *J* = 13.9, 10.3, 5.6 Hz, 1H, C*H*H^{Aux}), 2.12 – 2.03 (m, 1H, C*H*H^{Aux}), 2.00 (s, 3H, OAc), 1.91 – 1.81 (m, 4H, OAc, C*H*H^{Aux}); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 104.80 (C-1^I), 95.86 (C-1^{II}), 82.11 (C-5^I), 80.73 (*C*H^{Aux}), 79.45 (C-2^I), 75.91 (C-4^{II}), 75.46 (C-2^{II}), 74.64 (*C*H$_2$Ph), 74.18 (*C*H$_2$Ph), 74.16 (*C*H$_2$Ph), 73.85 (C-4I), 73.29 (*C*H$_2$Ph), 73.23 (C-3^I), 73.07 (C-3^{II}), 68.34 (C-5^{II}), 67.62 (C-6^I), 62.72 (C-6^{II}), 57.06 (OMe), 39.72 (*C*H$_2^{Aux}$), 31.83 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{66}O_{13}$ [M+Na]$^+$: 1017.4401; found: 1017.4505.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (6a). R_f = 0.42 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 – 7.05 (m, 30H, Ar*H*), 5.72 (t, *J* = 9.7 Hz, 1H, H-3^{II}), 5.16 – 4.54 (m, 9H, 4 × C*H*$_2$Ph, H-1^I), 4.46 – 4.31 (m, 2H,



H-1^{II}, C*H*^{Aux}), 4.30 – 4.17 (m, 2H, H-6$_{a,b}$), 4.12 (td, *J* = 9.1, 2.8 Hz, 1H, H-3^{I}), 4.07 – 3.99 (m, 1H, H-5^{II}), 3.96 (dd, J = 10.2, 6.3 Hz, 1H, H-5^{I}), 3.71 – 3.31 (m, 9H, OMe, H-6$_{a,b}{}^{I}$, H-2^{I}, H-2^{II}, H-4^{I}, H-4^{II}), 2.77 (ddd, J = 14.8, 10.0, 6.1 Hz, 1H, C*H*H^{Aux}), 2.65 (ddd, J = 14.5, 9.9, 5.7 Hz, 1H, CH*H*^{Aux}), 2.23 – 1.89 (m, 8H, 2 × OAc, C*H*$_2{}^{Aux}$); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.67 (C-1^{I}), 97.49 (C-1^{II}), 84.17 (*C*H^{Aux}), 82.20 (C-3^{I}), 80.00 (C-2^{I}), 78.06 (C-4^{I}), 77.73 (C-4^{II}), 76.21 (C-2^{II}), 75.68 (*C*H$_2$Ph), 75.05 (*C*H$_2$Ph), 73.98 (*C*H$_2$Ph), 73.64 (C-3^{II}), 73.26 (*C*H$_2$Ph), 68.11 (C-5^{I}), 62.84 (C-5^{II}), 66.50 (C-6^{I}), 62.64 (C-6^{II}), 40.15 (*C*H$_2{}^{Aux}$), 31.98 (*C*H$_2{}^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{66}O_{13}$ $[M+Na]^+$: 1017.4401; found: 1017.4456.

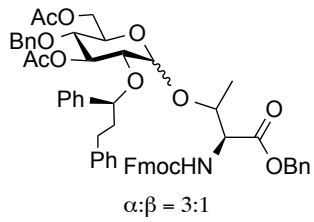
3-azidopropyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-D-glucopyranosyl -(1→6)-4-*O*-benzyl-2,3-*O*-dibenzoyl-β-D-galacopyranoside (6b). *R*$_f$ =



0.34 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 7.01 (m, 30H, Ar*H*), 5.78 (dd, J = 10.5, 7.9 Hz, 1H, H-2^{I}), 5.61 (t, 1H, H-3^{II}), 5.34 (t, 1H, C-3^{I}), 4.79 – 4.45 (m, 5H, 2 × C*H*$_2$Ph, H-1$^{\alpha}$), 4.35 – 4.11 (m, 4H, H-6$_{a,b}$, CH^{Aux}, H-1^{II}), 3.99 (ddd, J = 10.1, 4.1, 2.3 Hz, 1H, H-5^{II}), 3.94 – 3.81 (m, 1H, C*H*H^{Linker}), 3.61 – 3.32 (m, 3H, C*H*H^{Linker}, H-4^{II}, H-2^{II}), 3.28 – 3.18 (m, 1H, C*H*H^{Linker}), 3.17 – 3.05 (m, 1H, C*H*H^{Linker}), 2.72 – 2.49 (m, 2H, C*H*$_2{}^{Aux}$), 2.27 – 2.07 (m, 1H, C*H*H^{Aux}), 2.09 – 1.94 (m, 6H, 2 × OAc), 1.94 – 1.66 (m, 3H, C*H*H^{Aux}, C*H*$_2{}^{Aux}$); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 101.02 (C-1^{I}), 97.09 (C-1^{II}), 84.37 (*C*H^{Aux}), 78.36 (C-2^{II}), 76.32 (C-4^{I}), 76.27 (C-4^{II}), 74.79 (C-3^{I}), 74.46 (*C*H$_2$Ph), 70.00 (C-3^{II}), 69.96 (C-2^{I}), 68.34 (C-5^{II}), 66.48 (*C*H$_2{}^{Linker}$),

62.77 (C-6^{II}), 47.88 (CH$_2$^{Linker}), 39.43 (CH$_2$^{Aux}), 31.35 (CH$_2$^{Aux}), 29.00 (CH$_2$^{Linker}); HR MALDI-TOF MS: m/z: calcd for $C_{62}H_{65}N_3O_{15}$ $[M+Na]^+$: 1114.4313; found: 1114.4414.

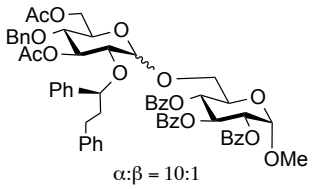
N$^{\alpha}$-(9-Fluorenylmethyloxycarbonyl)-*O*-{3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-α-D-glucopyranosyl }-*L*-threonine benzyl ester (6c). R_f = 0.38



α:β = 3:1

(EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 6.85 (m, 28H, Ar*H*), 6.18 (d, J = 7.5 Hz, 1H, N*H*), 5.64 (t, J = 9.6 Hz, 1H, H-3), 5.35 – 5.14 (m, 2H, CH_2Ph), 4.63 – 4.45 (m, 2H, CH_2^{Fmoc}), 4.43 – 4.08 (m, 7H, H-1, C*H*Aux, 2 × C*H*^{Thr}, H-6$_{a,b}$, C*H*^{Fmoc}), 4.02 – 3.89 (m, 1H, H-5), 3.45 – 3.38 (m, 1H, H-4), 3.34 (dd, J = 10.0, 3.7 Hz, 1H, H-2), 2.62 – 2.40 (m, 2H, CH_2^{Aux}), 2.33 – 2.18 (m, 1H, CH*H*^{Aux}), 2.18 – 1.82 (m, 7H, 2 × OAc, C*H*H^{Aux}), 1.28 (d, J = 6.3 Hz, 3H, CH_3^{Thr}); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 98.77 (C-1), 84.19 (CH^{Aux}), 76.43 (C-4), 76.16 (*C*H^{Thr}), 75.62 (C-2), 74.57 (*C*H$_2$^{Fmoc}), 74.35 (C-3), 69.03 (C-5), 67.40 (*C*H$_2$Ph), 62.83 (C-6), 59.32 (*C*H^{Thr}), 47.03 (*C*H^{Fmoc}), 38.92 (*C*H$_2$^{Aux}), 31.52 (*C*H$_2$^{Aux}), 18.92 (*C*H$_3$^{Thr}); HR MALDI-TOF MS: m/z: calcd for $C_{58}H_{59}NO_{12}$ $[M+Na]^+$: 984.3935; found: 984.4026.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (6d). R_f = 0.33



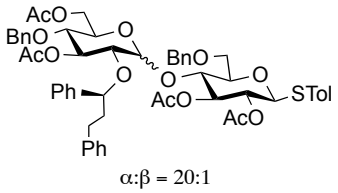
α:β = 10:1

(EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 – 6.70 (m, 30H, Ar*H*), 6.13 (t, J = 9.8 Hz, 1H, H-3^{I}), 5.55 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.28 (t, J = 9.9 Hz, 1H, H-4^{I}), 5.20 (dd, J = 10.2, 3.7 Hz, 1H, H-2^{I}), 5.15 (d, J = 3.8 Hz, 1H, H-1^{I}), 4.57 – 4.44 (m, 2H, CH_2Ph), 4.30 – 4.20 (m, 1H, H-5^{I}), 4.20 – 4.05 (m, 3H, H-6$^{II}_{a,b}$, C*H*^{Aux}), 4.04 – 3.97 (m,

2H, H-5^{II}, H-1^{II}), 3.53 – 3.47(s, 4H, OMe, H-6$^{I}_{a}$), 3.46 – 3.35 (m, 1H, H-4^{II}), 3.33 (dd, *J* = 10.0, 3.5 Hz, 1H, H-2^{II}), 2.97 (dd, *J* = 10.6, 1.7 Hz, 1H, H-6$^{I}_{b}$), 2.61 (ddd, *J* = 14.0, 9.6, 6.0 Hz, 1H, C*H*H^{Aux}), 2.49 (ddd, *J* = 13.9, 9.4, 6.0 Hz, 1H, C*H*H^{Aux}), 2.12 – 2.00 (m, 1H, C*H*H^{Aux}), 1.99 (s, OAc), 1.97 (s, OAc), 1.82 – 1.72 (m, 1H, C*H*H^{Aux}); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 96.82 (C-1^{II}), 96.56 (C-1^{I}), 84.85 (*C*H^{Aux}), 78.87 (C-2^{II}), 76.14 (C-4^{II}), 73.72 (*C*H_2Ph), 73.45 (C-3^{II}), 72.32 (C-2^{I}), 70.63(C-3^{I}), 69.79 (C-4^{I}), 68.55 (C-5^{I}), 68.30 (C-5^{II}), 66.48 (C-6^{I}), 55.50 (OMe), 40.18 (*C*H_2^{Aux}), 32.00 (*C*H_2^{Aux}); HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{60}O_{16}$ $[M+Na]^+$: 1059.3779; found: 1059.3828.

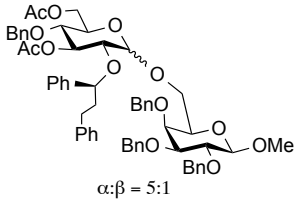
Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (6e). R_f = 0.43 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 6.82 (m, 30H, Ar*H*), 5.69 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.09 – 4.95 (m, 2H, H-1^{II}, CH*H*Ph), 4.67 – 4.52 (m, 2H, H-1I, CH*H*Ph), 4.53 – 4.25 (m, 8H, 3 × C*H*$_2$Ph, H-5^{II}, C*H*^{Aux}), 4.10 – 3.97 (m, 2H, H-6$^{II}_{a}$, H-3^{I}), 3.88 (dd, J = 12.1, 4.0 Hz, 1H, H-6$^{II}_{b}$), 3.72 – 3.58 (m, 2H, H-5^{I}, H-4^{I}), 3.58 – 3.49 (m, 2H, H-6$^{I}_{a,b}$, H-2^{I}), 3.45 (dd, J = 9.4, 3.7 Hz, 1H, H-2^{I}), 3.37 – 3.25 (m, 2H, H-2^{II}, H-4^{II}), 3.23 (s, 3H, OMe), 2.37 (t, J = 7.8 Hz, 2H, C*H*$_2^{Aux}$), 2.08 – 1.95 (m, 1H, C*H*H^{Aux}), 1.92 (s, 3H, OAc), 1.82 (s, 3H, OAc), 1.78 – 1.66 (m, 1H, C*H*H^{Aux}); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 97.90 (C-1^{II}), 97.43 (C-1^{I}), 82.44 (*C*H^{Aux}), 78.78 (C-2^{I}), 78.14 (C-4^{I}), 77.37 (C-3^{I}), 76.45 (C-4^{II}), 75.31 (C-2^{II}), 73.74 (*C*H_2Ph), 73.66 (*C*H_2Ph), 73.49 (*C*H_2Ph), 73.23 (C-3^{II}), 72.99 (*C*H_2Ph), 69.52 (C-5^{I}), 68.51 (C-6^{I}), 68.29 (C-5^{II}), 62.87 (C-6^{II}), 55.00 (OMe), 38.99 (*C*H_2^{Aux}), 31.60 (*C*H_2^{Aux}); HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{66}O_{13}$ $[M+Na]^+$: 1017.4401; found: 1017.4460.

***p*-Methylphenyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-ß-D-glucopyranoside (6f).** R_f = 0.39



(EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 – 6.96 (m, 24H, Ar*H*), 5.40 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.18 (t, J = 9.1 Hz, 1H, H-3^{I}), 4.85 (t, J = 9.5 Hz, 1H, H-2^{I}), 4.57 (d, J = 9.8 Hz, 1H, H-1^{I}), 4.53 – 4.33 (m, 7H, 2 × C*H*$_2$Ph, H-1^{II}), 4.18 (t, J = 6.9 Hz, 2H, C*H*^{Aux}), 4.08 – 3.94 (m, 3H, H-6$^{II}_{a,b}$), 3.89 (ddd, J = 10.4, 5.1, 2.4 Hz, 1H, H-5^{II}), 3.78 (dd, J = 11.3, 3.7 Hz, 1H, H-6$^{I}_{a}$), 3.72 – 3.61 (m, 2H, H-6$^{I}_{b}$, H-4^{I}), 3.43 (ddd, J = 9.5, 3.7, 1.8 Hz, 1H, H-5^{I}), 3.41 – 3.30 (m, 1H, H-4^{II}), 3.24 (dd, J = 10.1, 3.4 Hz, 1H, H-2^{II}), 2.55 – 2.37 (m, 2H, C*H*$_2^{Aux}$), 2.33 (s, 3H, C*H*$_3$), 2.18 – 1.84 (m, 14H, 4 × OAc, C*H*$_2^{Aux}$); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.02 (C-1^{II}), 85.27 (C-1^{I}), 84.57 (*C*H^{Aux}), 79.47 (C-5^{I}), 77.70 (C-2^{II}), 76.24 (C-4^{II}), 74.80 (C-3^{I}), 74.05 (*C*H$_2$Ph), 73.38 (C-3^{II}), 73.17 (*C*H$_2$Ph), 73.00 (C-4^{I}), 70.40 (C-2^{I}), 68.87 (C-5^{II}), 68.31 (C-6^{I}), 62.93 (C-6^{II}), 39.26 (*C*H$_2^{Aux}$), 31.72 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{56}H_{62}O_{14}S$ $[M+Na]^+$: 1013.3758; found: 1013.3865.

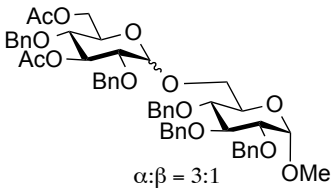
Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-[(1*S*),3-diphenyl-propyl]-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-galacopyranoside (6g). R_f = 0.41



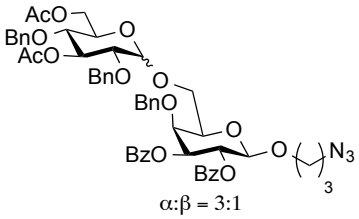
(EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.02 (m, 30H, Ar*H*), 5.61 (t, J = 9.6 Hz, 1H, H-3^{II}), 4.98 (d, J = 11.7 Hz, 1H, C*H*HPh), 4.90 (d, J = 11.0 Hz, 1H, C*H*HPh), 4.81 – 4.67 (m, 4H, 2 × C*H*$_2$Ph), 4.60 – 4.48 (m, 2H, C*H*$_2$Ph), 4.29 (d, J = 7.7 Hz, 1H, H-1^{I}), 4.27 – 4.20 (m, 3H, C*H*^{Aux}, H-6$^{II}_{a,b}$), 4.18 (d, J = 3.6 Hz, 1H, H-1^{II}), 3.98 – 3.91 (m, 1H, H-5^{II}), 3.84 – 3.74 (m, 2H, H-4^{I}, H-2^{I}), 3.67 – 3.59 (m, 1H, H-6$^{I}_{a}$), 3.59 –

3.42 (m, 6H, OMe, H-3^{I}, H-4^{II}, H-5^{I}), 3.38 (dd, J = 10.1, 3.5 Hz, 1H, H-2^{II}), 3.20 (dd, J = 9.4, 5.5 Hz, 1H, H-6$^{I}_{b}$), 2.70 – 2.47 (m, 2H, CH_2^{Aux}), 2.19 (s, 3H, OAc), 2.17 – 2.06 (m, 1H, CHH^{Aux}), 2.03 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.92 – 1.78 (m, 1H, CHH^{Aux}); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 104.88 (C-1^{I}), 97.37 (C-1^{II}), 84.28 (*C*H^{Aux}), 82.16 (C-5^{I}), 79.59 (C-2^{I}), 77.73 (C-2^{II}), 76.33 (C-4^{II}), 75.13 (*C*H$_2$Ph), 74.36 (*C*H$_2$Ph), 74.22 (*C*H$_2$Ph), 73.97 (C-3^{II}), 73.82 (C-4^{I}), 73.65 (C-3^{I}), 73.37 (*C*H$_2$Ph), 68.28 (C-5^{II}), 67.09 (C-6^{I}), 62.79 (C-6^{II}), 56.95 (OMe), 39.61 (CH$_2^{Aux}$), 31.95 (*C*H$_2^{Aux}$); HR MALDI-TOF MS: m/z: calcd for $C_{60}H_{66}O_{13}$ $[M+Na]^+$: 1017.4401; found: 1017.4499.

Methyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (7a). R_f = 0.40 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.05 (m, 25H, Ar*H*), 5.55 (t, *J* = 9.6 Hz, 1H, H-3^{II}), 4.96 (d, *J* = 3.5 Hz, 1H, H-1^{II}), 4.92 (dd, *J* = 16.5, 11.2 Hz, 2H, CH_2Ph), 4.79 (d, *J* = 10.9 Hz, 1H, C*H*HPh), 4.65 (dd, *J* = 28.4, 11.6 Hz, 2H, CH_2Ph), 4.57 – 4.53 (m, 3H, C*H*HPh, CH$_2$Ph), 4.51 (d, *J* = 3.6 Hz, 1H, H-1^{I}), 4.49 – 4.44 (m, 2H, CH_2Ph), 4.25 – 4.13 (m, 2H, H-6$^{II}_{a,b}$), 3.98 – 3.92 (m, 1H, H-3^{I}), 3.90 (ddd, *J* = 10.0, 4.2, 2.2 Hz, 1H, H-5^{II}), 3.79 – 3.63 (m, 3H, H-5^{I}, H-6$^{I}_{a,b}$), 3.57 (t, *J* = 9.4 Hz, 1H, H-4^{I}), 3.53 – 3.43 (m, 1H, H-4^{II}), 3.42 – 3.34 (m, 5H, OMe, H-2^{II}, H-2^{I}), 2.00 (s, 3H, OAc), 1.97 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 98.05 (C-1^{I}), 96.62 (C-1^{II}), 82.03 (C-3^{I}), 79.74 (C-2^{I}), 77.65 (C-4^{I}), 76.93 (C-2^{II}), 76.09 (C-4^{II}), 75.55 (*C*H$_2$Ph), 74.80 (*C*H$_2$Ph), 74.03 (*C*H$_2$Ph), 73.22 (C-3^{II}), 73.16 (*C*H$_2$Ph), 72.46 (C-5^{I}), 71.82 (*C*H$_2$Ph), 68.31 (C-5^{II}), 66.01 (C-6^{I}), 62.82 (C-6^{II}), 55.22 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{52}H_{58}O_{13}$ $[M+Na]^+$: 913.3775; found: 913.3796.

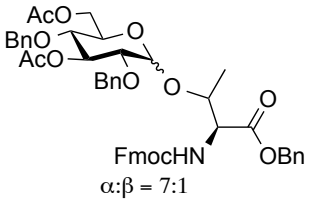


3-azidopropyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-D-glucopyranosyl-(1→6)-4-*O*-benzyl-2,3-*O*-dibenzoyl-β-D-galacopyranoside (7b). R_f = 0.32 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 – 7.08 (m, 25H, Ar*H*), 5.85 – 5.67 (m, 1H, H-2^{I}), 5.56 (t, J = 9.5 Hz, 1H, H-3^{II}), 5.35 (dd, J = 10.5, 3.0 Hz, 1H, H-3^{I}), 4.76 (d, J = 3.5 Hz, 1H, H-1^{II}), 4.64 (d, J = 8.0 Hz, 1H, H-1^{I}), 4.61 – 4.40 (m, 6H, 3 × CH_2Ph), 4.40 – 4.24 (m, 3H, H-6$^{I}_{a,b}$), 4.12 (dd, J = 8.1, 3.0 Hz, 1H, H-4^{I}), 4.02 (ddd, J = 10.2, 4.4, 2.3 Hz, 1H, H-5^{I}), 3.97 – 3.85 (m, 4H, H-5^{II}, H-6$^{II}_{a}$, CH_2^{Linker}), 3.61 – 3.37 (m, 3H, H-6$^{II}_{b}$, H-4^{II}, H-2^{II}), 3.22 – 3.06 (m, 2H, CH_2^{Linker}), 2.05 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.78 – 1.49 (m, 2H, CH_2^{Linker}); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 101.36 (C-1^{I}), 96.52 (C-1^{II}), 77.27 (C-2^{II}), 75.98 (C-4^{II}), 74.35 (C-3^{I}), 74.54 (CH_2Ph), 74.37 (C-3^{II}), 74.32 (CH_2Ph), 74.11 (C-4^{I}), 73.34 (C-5^{II}), 72.97 (CH_2Ph), 70.05 (C-2^{I}), 68.62 (C-5^{I}), 67.58 (CH_2^{Linker}), 66.60 (C-6^{II}), 62.82 (C-6^{I}), 47.87 (CH_2^{Linker}), 28.85 (CH_2^{Linker}); HR MALDI-TOF MS: m/z: calcd for $C_{54}H_{57}N_3O_{15}$ $[M+Na]^+$: 1010.3687; found: 1010.3745.



α:β = 3:1

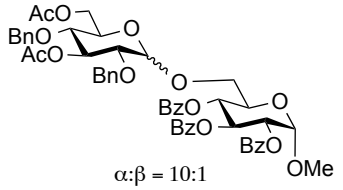
N^{α}-(9-Fluorenylmethyloxycarbonyl)-*O*-{3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-D-glucopyranosyl }-*L*-threonine benzyl ester (7c). R_f = 0.3 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.12 (m, 23H, Ar*H*), 6.04 (d, J = 8.8 Hz, 1H, N*H*), 5.53 (t, J = 9.6 Hz, 1H, H-3), 5.14 – 4.96 (m, 2H, *C*H$_2$Ph), 4.92 (d, J = 3.7 Hz, 1H, H-1), 4.66 – 4.46 (m, 3H, CH_2Ph, C*H*HPh), 4.45 – 4.14 (m, 8H, 2 × CH^{Thr}, CH_2^{Fmoc}, C*H*HPh, H-6$_{a,b}$, CH^{Fmoc}), 3.98 (dt, J = 10.0, 3.5 Hz, 1H, H-5), 3.46 (t, J = 9.7 Hz, 1H, H-4), 3.38 (dd, J = 10.1, 3.7 Hz, 1H, H-2), 2.05 (s, 3H, OAc), 1.96 (s, 3H, OAc), 1.32 (d, J = 6.3 Hz,



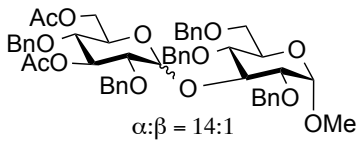
α:β = 7:1

3H, CH_3); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.48 (C-1), 76.92 (C-2), 76.18 (C-4), 76.05 (CH^{Thr}), 74.64 (CH_2Ph), 73.40 (C-3), 72.52 (CH_2Ph), 69.03 (C-5), 67.48 (CH_2^{Fmoc}), 67.48 (CH_2^{Fmoc}), 67.32 (CH_2Ph), 62.85 (C-6), 58.96 (CH^{Thr}), 47.09 (CH^{Fmoc}), 19.00 (CH_3); HR MALDI-TOF MS: m/z: calcd for $C_{50}H_{51}NO_{12}$ $[M+Na]^+$: 880.3309; found: 880.3468.

Methyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (7d). R_f = 0.23 (EtOAc/Hexanes, 1/2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.00 (m, 25H, Ar*H*), 6.15 (t, J = 9.7 Hz, 1H, H-3^I), 5.58 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.41 (t, J = 9.9 Hz, 1H, H-4^I), 5.27 – 5.13 (m, 2H, H-2^I, H-1^I), 4.71 (d, J = 3.2 Hz, 1H, H-1^{II}), 4.66 – 4.44 (m, 4H, 2 × CH_2Ph), 4.40 – 4.29 (m, 1H, H-5^I), 4.29 – 4.16 (m, 2H, H-6$^{II}_{a,b}$), 4.16 – 4.07 (m, 1H, H-5^{II}), 3.89 – 3.71 (m, 1H, H-6^I_a), 3.55 – 3.28 (m, 6H, H-6^I_b, H-4^{II}, H-2^{II}, OMe), 2.04 (s, 3H, OAc), 1.97 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 125 MHz, $CDCl_3$): δ 96.44 (C-1^I), 95.99 (C-1^{II}), 77.46 (C-2^{II}), 75.24 (C-4^{II}), 73.30 (CH_2Ph), 72.64 (C-3^{II}), 72.60 (CH_2Ph), 72.02 (C-2^I), 70.08 (C-3^I), 69.32 (C-4^I), 68.58 (C-5^I), 67.92 (C-5^{II}), 66.44 (C-6^I), 62.78 (C-6^{II}), 55.36 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{52}H_{52}O_{16}$ $[M+Na]^+$: 955.3153; found: 955.3228.

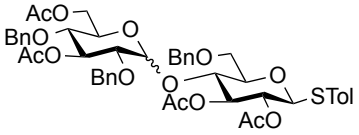


Methyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (7e). R_f = 0.39 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 6.93 (m, 25H, Ar*H*), 5.65 (t, J = 9.6 Hz, 1H, H-3^{II}), 5.57 (d, J = 3.6 Hz, 1H, H-1^{II}), 4.86 (d, J = 11.9 Hz, 1H, C*H*HPh), 4.73 – 4.61 (m, 2H,



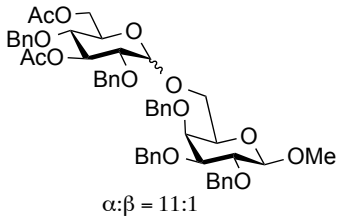
C*H*HPh, H-1^{I}), 4.61 – 4.37 (m, 8H, H-5^{II}, 3 × CH_2Ph, C*H*HPh), 4.31 (d, J = 12.1 Hz, 1H, C*H*HPh), 4.21 (t, J = 9.0 Hz, 1H, H-3^{I}), 4.17 (d, J = 12.2 Hz, 1H, H-6$^{II}_{a}$), 3.94 (dd, J = 12.2, 3.7 Hz, 1H, H-6$^{II}_{b}$), 3.80 – 3.69 (m, 2H, H-5^{I}, H-4^{I}), 3.63 (m, 2H, H-6$^{I}_{a,b}$), 3.56 (dd, J = 9.7, 3.6 Hz, 1H, H-2^{I}), 3.47 (t, J = 9.7 Hz, 1H, H-4^{II}), 3.43 (dd, J = 10.2, 3.6 Hz, 1H, H-2^{II}), 3.32 (s, 3H, OMe), 2.04 (s, 3H, OAc), 1.89 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 97.46 (C-1^{I}), 96.82 (C-1^{II}), 78.49 (C-4^{I}), 78.44 (C-2^{I}), 78.02 (C-2^{II}), 76.57 (C-3^{I}), 76.25 (C-4^{II}), 73.63 (*C*H$_2$Ph), 73.58 (C-3^{II}), 73.50 (*C*H$_2$Ph), 73.44 (*C*H$_2$Ph), 73.32 (*C*H$_2$Ph), 73.10 (*C*H$_2$Ph), 69.92 (C-5^{I}), 68.33 (C-6^{I}), 68.22 (C-5^{II}), 62.94 (C-6^{II}), 55.02 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{52}H_{58}O_{13}$ $[M+Na]^+$: 913.3775; found: 913.3860.

***p*-Methylphenyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-ß-D-glucopyranoside (7f).** R_f = 0.33 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 – 6.94 (m, 19H, Ar*H*), 5.43 – 5.24 (m, 2H, H-3^{II}, H-2^{I}), 5.06 (d, J = 3.5 Hz, 1H, H-1^{II}), 4.88 (t, J = 9.5 Hz, 1H, H-3^{I}), 4.67 – 4.29 (m, 7H, H-1I, 3 × CH_2Ph), 4.15 – 4.00 (m, 2H, H-6$^{II}_{a,b}$), 4.00 – 3.86 (m, 3H, H-4^{I}, H-5^{II}, H-6$^{I}_{a}$), 3.77 (d, J = 11.3 Hz, 1H, H-6$^{I}_{b}$), 3.53 (d, J = 9.8 Hz, 1H, H-5^{I}), 3.41 (t, J = 9.6 Hz, 1H, H-4^{II}), 3.32 (dd, J = 10.0, 3.4 Hz, 1H, H-2^{II}), 2.31 (s, 3H, Me), 2.07 (s, 3H, OAc), 1.98 (s, 1H, OAc), 1.92 (s, 3H, OAc), 1.91 (s, 1H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 96.52 (C-1^{II}), 85.43 (C-1^{I}), 79.03 (C-5^{I}), 77.52 (C-4^{II}), 77.34 (C-2^{II}), 74.98 (C-3^{I}), 74.00 (C-4^{I}), 73.91 （*C*H$_2$Ph), 73.83 （*C*H$_2$Ph), 72.93 (C-3^{II}), 72.69 （*C*H$_2$Ph), 70.58 (C-2^{I}), 69.69 (C-5^{II}), 68.31 (C-6^{I}), 62.87 (C-6^{II}) ; HR MALDI-TOF MS: m/z: calcd for $C_{48}H_{54}O_{14}S$ $[M+Na]^+$: 909.3132; found: 909.3185.



α:β = 15:1

Methyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-galacopyranoside (7g). R_f = 0.41 (EtOAc/Hexanes, 1/2, v/v); α-anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 6.95 (m, 25H, Ar*H*), 5.58 (t, J = 9.5 Hz, 1H, H-3^{II}), 4.98 – 4.83 (m, 2H, CH*H*Ph, CH*H*Ph), 4.82 – 4.65 (m, 4H, H-1^{II}, 3 × C*H*HPh), 4.64 – 4.46 (m, 5H, C*H*HPh, 2 × C*H*$_2$Ph), 4.34 – 4.23 (m, 2H, H-6$^{II}_{a,b}$, H-1^I), 3.98 (dt, J = 10.0, 3.1 Hz, 1H, H-5^{II}), 3.88 (d, J = 2.3 Hz, 1H, H-4^I), 3.86 – 3.72 (m, 1H, H-6^I_a, H-2^I), 3.60 (t, J = 6.1 Hz, 1H, H-5^I), 3.59 – 3.39 (m, 7H, OMe, H-6^I_b, H-4^{II}, H-2^{II}, H-3^I), 2.05 (s, 3H, OAc), 1.99 (s, 3H, OAc); ^{13}C NMR (selected HSQCAD, 150 MHz, $CDCl_3$): δ 104.93 (C-1^I), 96.52 (C-1^{II}), 82.00 (C-3^I), 79.49 (C-2^I), 77.56 (C-2^{II}), 76.26 (C-4^{II}), 75.10 (*C*H$_2$Ph), 74.35 (*C*H$_2$Ph), 74.28 (*C*H$_2$Ph), 73.73 (C-4^I), 73.54 (C-3^{II}), 73.27 (*C*H$_2$Ph), 73.10 (*C*H$_2$Ph), 72.86 (C-5^I), 68.59 (C-5^{II}), 68.43 (C-6^I), 62.79 (C-6^{II}), 57.13 (OMe); HR MALDI-TOF MS: m/z: calcd for $C_{52}H_{58}O_{13}$ $[M+Na]^+$: 913.3775; found: 913.3837.



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CHAPTER 4

FACILE SYNTHESIS OF CARBOHYDRATE EPITOPES DERIVED FROM α-DYSTROGLYCAN AND THE ASSEMBLIES OF GLYCOCONJUGATE VACCINES[†]

[†] Tao Fang and Geert-Jan Boons*.
To be submitted to ChemBioChem.

ABSTRACT

α-Dystroglycan (α-DG), a heavily glycosylated extracellular subunit of the dystroglycan complex, is an important receptor for the binding of extracellular ligands. Mutations in glycosyltransferases that mannosylate α-DG result in loss of laminin binding and muscular dystrophy. In invasive carcinomas, alterations in the glycosylation of α-DG impair epithelial cell-basement membrane interactions, leading to increased cell migration. Although it has been realized that the glycans of DG are important, convenient reagents such as monoclonal antibodies for profiling the glycosylation status of DG are not available. In this project, SiaAα(2-3)Galβ(1-4)GlcNAcβ(1-2)Manα-threonine and its fragments were synthesized using the cassette strategy, and 4,5-oxazolidinone was selected for the protection of sialic acid, which gave complete anomeric stereocontrol during sialylation. The resulting glycosylated amino acids were either conjugated into a fully synthetic tripartite vaccine construct or with various carrier proteins for eliciting specific antibodies. Immunization of mice with these immunogens produced abundant antibodies against the α-DG–derived carbohydrate epitopes.

INTRODUCTION

α-Dystroglycan (α-DG), a heavily glycosylated glycoprotein with more than 50% weight of carbohydrate,[1] is the extracellular component of the dystrophin-glycoprotein complex and the key mediator for maintaining the linkage between the extracellular matrix (ECM) and the internal actin-cytoskeletal machinery. α-DG is non-covalently bound to the intracellular component β-DG, which binds to the cytoskeleton adapter protein dystrophin.[2] Both α- and β-DG are encoded from a single gene but post-transcriptionally

divided into two subunits. Dystroglycans have been prominently found on the cell membranes of skeletal muscle, nerve, and brain. Thus, defects of dystrolgycans are closely related to the neuromuscular diseases. Emerging evidence has suggested that *O*-glycan modifications of the central mucin-like region of α-DG play crucial roles in these pathology processes. For example, defects of α-DG *O*-glycan impair muscle fiber integrity and neuronal migration, resulting in congenital muscular dystrophy (CMD).[3] α-DG also functions as the receptor for viral and bacterial invasions, such as arena viruses and *Mycobacterium Leprae*, while β-DG is not essential for virus binding and entry.[4] Perturbations in α-DG processing also impact the affinity of a cell to its basal laminin, which can play a role in cancer metastasis.[5]

Unfortunately, it has been difficult to identify the causative genes due to the fact that these disorders are not caused by gene mutations of dystroglycan itself but rather by posttranscriptional glycosylations of proteins. The glycosylations of α-DG are diverse, including not only the common *N*-glycans and mucin-associated *O*-glycans but also unique *O*-Man initiated glycans. *O*-mannosylation site mapping found its underlying amino acid sequence is conserved across vertebrates, reinforcing its significance.[6]

The biosynthesis of α-dystroglycans involves multiple defined and putative enzymes.[7,8] Mutation of one or more of the glycotransferases results in complex disease-related glycosylation patterns. Protein *O*-mannosyl-transferase 1 and 2 (POMT1 and POMT2), which are localized in the endoplasmic reticulum, initiate the attachment of a mannosyl residue to Ser/Thr by employing dolichol-phosphate-activated mannose (Dol-P-Man) as the glycosyl donor. Malfunctions of these two enzymes demolish the minimal functional structure of *O*-Man glycan, and are therefore generally fatal, with no survival

of affected individuals beyond embryonic stage. It is only after the *O*-mannosylated glycoprotein undergoes translocation to the Golgi apparatus that it can be elongated by protein *O*-linked mannose *N*-acetylglucosaminyltransferase 1 (POMGnT1), which attaches to a β(1,2)-linked GlcNAc residue. The GlcNAc-β(1,2)-Man disaccharide can be further extended by glycosyltransferases, giving tetrasaccharide NeuAcα(2-3)-Galβ(1-4)-GlcNAc(β1-2)-Manα1-Ser/Thr **1** and its derivatives (e.g. asialo and fucosides α1,3-linked to GlcNAc).

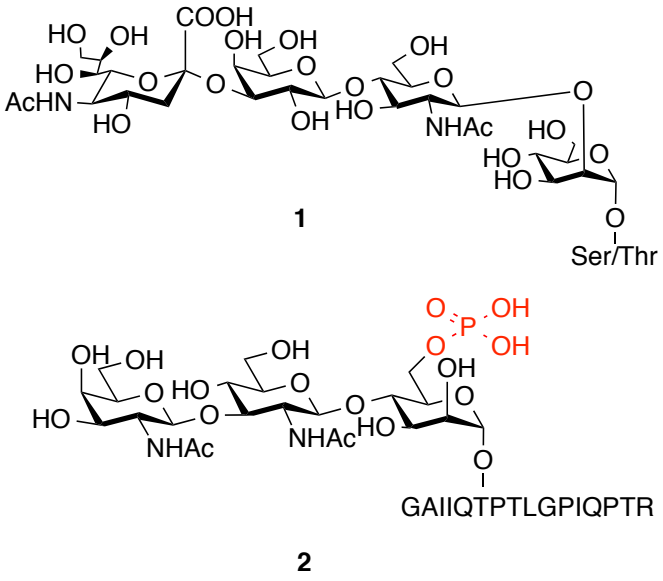


Figure 4.1: Dystroglycan related structures.

Recently, a unique 6-phosphomannose structure with **2** GlcNAc(β1-4) instead of GlcNAc(β1-2) elongation was discovered,[9,10] which was further shown to be extended by LARGE with a GlcUA-α(1,3)-Xyl disaccharide repeating unit through phosphodiester linkage.[11] The extension to different lengths serves as a tunable ECM protein scaffold

with a clear correlation between glycosylation status and phenotype.[12] This finding apparently raises several questions regarding the biosynthesis and functional identities of **1** and **2**. No enzyme has been identified for the GlcNAc(β1-4) extension of dystroglycan, but such an enzyme would have to be spatially separated from POMGnT 1 and encounter the substrate at an earlier stage to avoid diverting from the functional structure. If **2** is the functional structure, but not an artifact due to overexpression of a recombinant α-DG fragment in HEK293 cells, the abundant expression of **1** on α-DG and the role of POMGnT1 will be puzzling, becayse absence of POMGnT1 clearly leads to dystroglycanopathy.

Although the structural and biological implications of *O*-Man glycans have been described in great detail, no convenient reagents or methods are available for quick detection of *O*-Man initiated structures. Conventional methods require tedious enrichment, digestion, and complicated LC/MS analysis in order to distinguish α-DG and its related structures.[13] To accelerate this process, carbohydrate-specific antibodies are potentially useful tools for distinguishing these complex patterns due to their high specificity. It is traditionally challenging to prepare these antibodies for two reasons. The T-cell independence of carbohydrate renders low immunogenicity, and the conjugation of additional carrier proteins may suppress the carbohydrate-specific immune response. Meanwhile, the preparation of related carbohydrate epitopes in a scalable and structurally defined manner is also a prerequisite for the success of eliciting specific immune responses.

We anticipate to overcoming these challenges by employing chemical synthesis of a library of different glycans derived from α-DG. This provides an opportunity for

systematic testing and comparison of different carbohydrate vaccine platforms, and eventually generated carbohydrate and stage-specific antibodies for detecting α-DG glycosylation status. To this end, we report the stereocontrolled assembly of the most abundant α-dystroglycan tetrasaccharide NeuAcα(2-3)-Galβ(1-4)-GlcNAc(β1-2)-Manα1-Thr as its glycosylated amino acid fragment. The synthesis employed the cassette strategy in which Manα1-Thr was first synthesized with the C-2 orthogonal participating group and conveniently converted to the glycosyl acceptor for coupling with GlcNAc or NeuAcα(2-3)-Galβ(1-4)-GlcNAc derived donors, resulting in a library of three *O*-Man initiated structures. Further incorporation of the library into a tripartite vaccine construct previously developed in our lab[14,15] resulted in multiple immugens. Immunization of mice obtained abundant antibodies against synthetic α-DG epitopes. The parent tetrasaccharide was further deprotected, modified with a merceptan-containing linker, and conjugated to carrier proteins like CRM_{197}, BSA, and cationized BSA. The immunization and antibody screen are currently ongoing.

RESULT AND DISCUSSION

Generally, glycopeptides are chemically synthesized by a strategy in which preformed glycosylated amino acids are used in stepwise solid phase peptide synthesis (SPPS).[16] This approach requires, however, special care in the selection of protecting groups because *O*-glycosidic bonds can be hydrolyzed under acid conditions or undergo β-elimination upon treatment with moderately strong bases.[17] It has been established that these problems can be circumvented by the use of acetyl esters for hydroxyl protection combined with N^{α}-9-fluorenylmethyloxycarbonyl (Fmoc) protected amino acids. The

convenience with which multiple *O*-Man glycosylated amino acids can be conveniently generated is desirable. To this end, the cassette strategy proved to be advantageous. In this strategy, an orthogonally protected mannosyl donor bearing a C-2 participating group was first coupled with the side chain of threonine to ensure the formation of α-mannosyl linkage. Then the C-2 protecting group was removed and further used as a common acceptor for glycosylations with various donors.[18] Synthetically, the establishment of the α-sialyl linkage was also challenging duo to the C-3 deoxy nature of sialic acid, in which the formation of the anomeric mixture and donor glycal are two factors that affect the efficient assembly of sialic acid containing oliogosaccharide.[19]

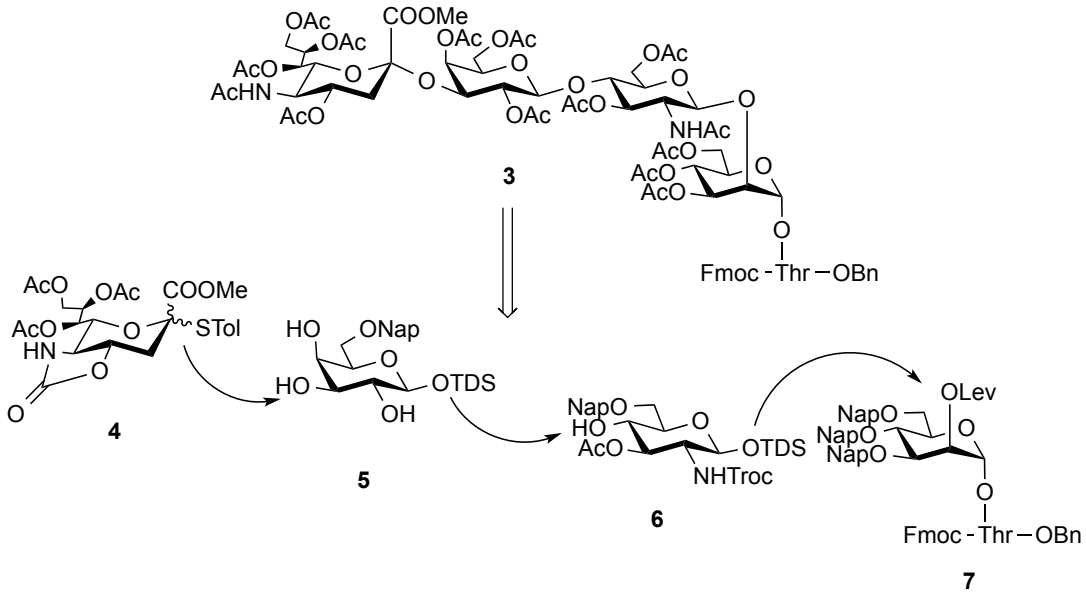


Figure 4.2: Retrosynthetic analysis.

Based on these considerations, we envisaged that target **3** could be readily accessed using building blocks **4** to **7**. As analyzed in Figure 4.2, properly functionalized sialyl

donors **4** were screened for stereoselective glycosylations with galactosyl acceptor **5**. Due to the steric and electronic deactivation of the C-4 and C-2 hydroxyls of **5**, a regioselective glycosylation was also proposed. After the sialylation, free hydroxyls were blocked and the anomeric center was further activated, preparing it for glycosylation with **6** to yield the trisaccharide. Deprotection of the levulinyl group of **7** using hydrazine acetate was orthogonal to the benzyl ester and Fmoc carbamate, thus converting **7** into a common mannosyl acceptor ready for coupling with either the aforementioned trisaccharide or other donors.

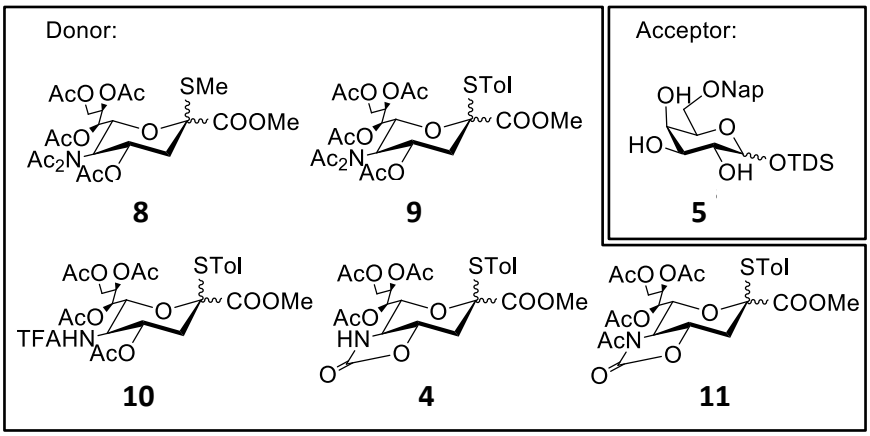
We first tested different protecting and leaving groups for optimizing the sialylations (Table 4.1). The *N*-acetoamido group of sialic acid possesses partial basicity, which complicates the activation process with acidic promoters. We had found that blocking the *N*-acetoamido group via diacetyl substitution could benefit the α-selectivity and yield of sialylation.[20] Similarly, by employing other stronger electron-withdrawing groups like *N*-TFA[21] or *N*-Troc[22] as amino protecting group, improved α-selectivity was also reported. Thus, sialyl donors **8**, **9**, and **10** were prepared accordingly and tested in regio- and stereoselective sialylations with acceptor **5**. It was found that donor **8**, bearing a methylmercepto leaving group could be quickly activated in the presence of 3 equivalent NIS and 0.6 equivalent TfOH with 35% yield. No regiomer or stereoisomer were observed, but a significant amount of donor glycals were formed due to elimination. Further manipulation of solvent combination, temperature and promoter ratio gave 45% as the best yield obtained. Surprisingly, no activation was observed after changing the leaving group from SMe to STol to give donor **9**, a donor deactivated by multiple acetated protecting groups and especially the anomeric carbonyl group. Activation of

TFA donor **10** was successful, but it was too reactive to fine tune the regio- and stereoselectivity such that a complex mixture of regiomers and stereoisomers were obtained.

Table 4.1: Screen donors for α-sialylation[a]

Donor	Acceptor	NIS (eq.)	TfOH (eq.)	Solvent	Temp. (°C)	Time (h)	Yield (%)
8	**5**	3	0.6	MeCN	-40	1	35
8	**5**	3	1.2	MeCN/THF=1/1	-25->r.t.	1	45
8	**5**	3	1.2	MeCN/THF=1/1	-40->r.t.	1	33
8	**5**	3	1.2	MeCN/THF=1/1	0	1	24
9	**5**	3	1.2	MeCN/THF=1/1	-25->r.t.	1	-[b]
10	**5**	2	0.2	MeCN	-25->r.t.	1	-[c]
4	**5**	2	0.2	MeCN	-35	1	60
11	**5**	2	0.2	DCM/MeCN=2/1	-70	0.5	43[c]
11	**5**	2	0.2	DCM/MeCN=2/1	-40	0.5	40[c]

[a] all reactions employed 1.5 eq. donor and 1 eq. acceptor; [b]no donor activation was observed; [c] complex mixture of regiomer/stereomer.



The application of 4,5-*O,N*-oxazolidinone as a new protecting group for sialic acid donora has attracted great interest since its discovery by Takahashi and co-workers.[23] It provides several advantages, including placing favorable dipole moment in the mean

plane of pyranose ring for the α-sialoside formation[24] and, more importantly, the cyclic oxazolidinone fixes the sialic acid in a chair conformation that strongly disfavors the formation of glycal, which has a flattened half-chair conformation. Indeed, sialylation with donor **4** provided 60% yield and was the only disaccharide that formed glycal. Further acetylation of the oxazolidinone gave donor **11**, but no significant improvement in sialylation was observed.

Table 4.2: Optimization of α-sialylation conditions between **4** and **5**.

Entry	NIS(eq.)	TfOH(eq.)	Solvent (v/v)	Temp.(°C)	Yield(%)
1	1.2	0.2	MeCN	-35	-[b]
2	2	0.2	DCM	-20	-[c]
4	2	0.2	DCM/THF=2/1	-60->r.t.	-[b]
5	2	0.2	DCM/MeCN=2/1	-70->-60	84[d]
6	2	0.2	DCM/MeCN=1/1	-70->-60	81[d]
7	2	0.2	Et_2O	-65	<10[e]

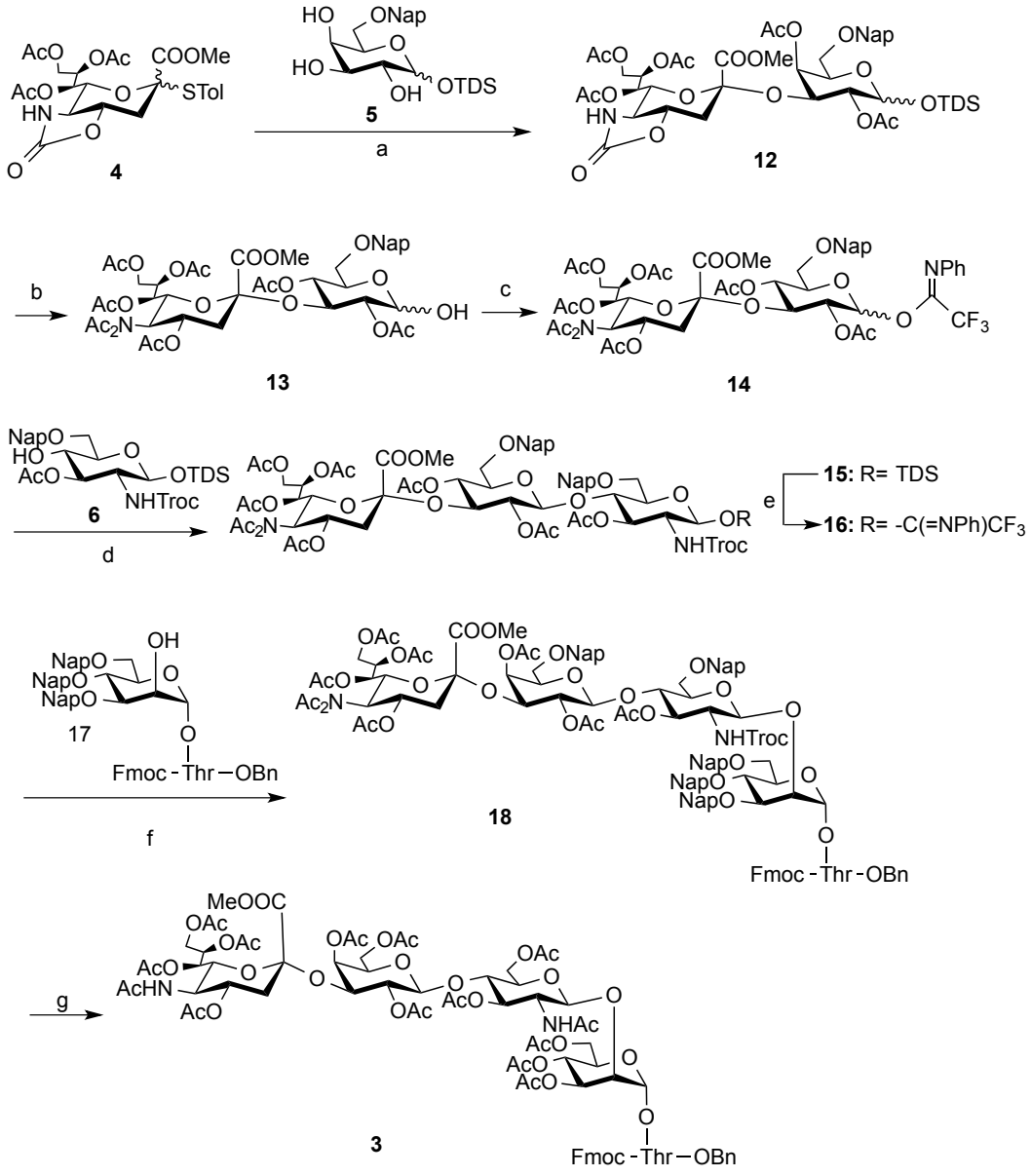
[a] all reactions employed 1.5 eq. donor, 1 eq. acceptor and reaction time was 1 h unless mentioned; [b] very slow activation; [c] mixture of regiomer and disialylated compound; [d] reaction completed in 20 min, α only; [e] compound precipitated out.

Encouraged by the success of the 4,5-*O,N*-oxazolidilone equipped donor, we fine-tuned the reaction conditions. It was observed that solvent effect is critical to donor activation. In neat acetonitrile, **4** was activated very slowly, but it was quickly activated and lost its selectivity in neat DCM. Changing to other participating solvents, such as THF and Et_2O, did not provide any benefit. Therefore, a mixture of DCM and MeCN was

chosen to balance activation and selectivity. Finally, a delightful yield of 84% was obtained with a 2:1 DCM : MeCN mixture.

Having circumvented the limiting step, the assembly of target tetrasaccharide **3** became more straightforward (Scheme 4.1). Although oxazolidinone performed well as a protecting group during sialylation, its deprotection requires strong basic condition that is not tolerated by *O*-linked glycopeptide in the final stages. Therefore, oxazolidinone was deprotected immediately after glycosylation. Free hydroxyls of disaccharide were first blocked with acetates to give **12**. Then the oxazolidinone was further acetylated with AcCl, converting it into *N*-acetyl-5-*N*,4-*O*-carbonyl to facilitate the deprotection of amide.[25] Due to the strain of oxazolidinone, it was removed together with other acetates under Zemplén condition, leading directly to the *N*-acetylated target, which was followed by global reacetylation and the removal of anomeric TDS to give **13**. Anomeric activation by conversion to imidate using trifluorochloroformate in the presence of DBU generated donor **14**. Glycosylation with acceptor **6** delivered trisaccharide **15** in 73% yield. It was conveniently converted to donor **16** by repeating the desilylation and anomeric imidate activation. Finally, the glycosylation between **16** and **17** resulted in the fully protected target **18**. In the final deprotection steps, amino diacetate was deprotected by hydrazine acetate followed by a DDQ treatment to remove Nap. However, a substantial amount of side product was detected and identified as naphtylidene protected compound. This was rationalized as due to the biphasic condition used for Nap deprotection, in which the proton donor may not be readily available, resulting in the formation of naphylidene under oxidative conditions. Fortunately, this side product was converted back into the desired compound by a quick treatment with 10% TFA in DCM. In the last step, the Troc

group was reductively removed and amine was capped with acetate to give final compound **3**, which can be used for SPPS.



Scheme 4.1: The assembly of DG-tetrasaccharide **3**. a) i. NIS, TfOH, -60 ^{o}C, 30 min, 84%, a only; ii. Ac_2O, Py; b) i. AcCl, DIPEA, DCM, r.t., 3 h, 91%; ii. NaOMe, MeOH; iii. Ac_2O, Py; iv. AcCl, DIPEA, DCM; v. TBAF, AcOH, THF, 78%; c) $CF_3C(=NPh)Cl$, DBU; d) DCM, TfOH, -25 ^{o}C, 73%; e) i. HF/Py, THF; ii. $CF_3C(=NPh)Cl$, DBU, 96% 2

steps; f) DCM, TfOH, -40 ^{o}C, 53%; g) i. H_2NNH_2-HOAc, Tol, EtOH, ii. DDQ, DCM, H_2O, then 10% TFA in DCM, iii. Ac_2O, Py, iv. Zn, $CuSO_4$-Ac_2O-AcOH.

With **3** on hand, focus then turned to the assembly of the tripartite vaccine shown in Fig 4.3a. We have previous synthesized similar constructs with MUC1 derived B-epitope bearing the Tn antigen as anticancer vaccines,[26] but without the experience of α-DG derived B-epitope. The choice of sequences connecting the tripartite components could affect the subsequent processing and presentation upon internalization of the vaccine construct by antigen processing cells. Synthetically, we also lack the experience of dealing with bigger carbohydrate epitopes. Therefore, truncated α-DG structures **19** and **20** were first tested for synthetic feasibility and immune response.

On Rink amide resins, the first two amino acids valine and alanine were coupled subsequently followed by the manual coupling of glycosylated amino acid building blocks **19** or **20** at lower equivalent. The C-terminal benzyl ester was removed by selective hydrogenolysis with Pd/C poisoned by pyridine just prior to coupling. The resins were then tested for coupling efficiency by Kaiser test and capped with acetate before be returned to the solid phase peptide synthesizer. After finishing the rest of the B- and helper T-epitope, the carbohydrate epitope was deacetylated on resin by a treatment of 80% hydrazine in methanol followed by peptide side chain deprotection and cleavage from the resin using a cocktail of reagents. Finally, the native chemical ligation between the glycopeptide just synthesized with cysteine at the *N*-terminal and the thioester of glycolipopeptide Pam_3CysSK_4 gave the vaccine constructs **21** and **22**, which were further formulated as liposomes before immunization.

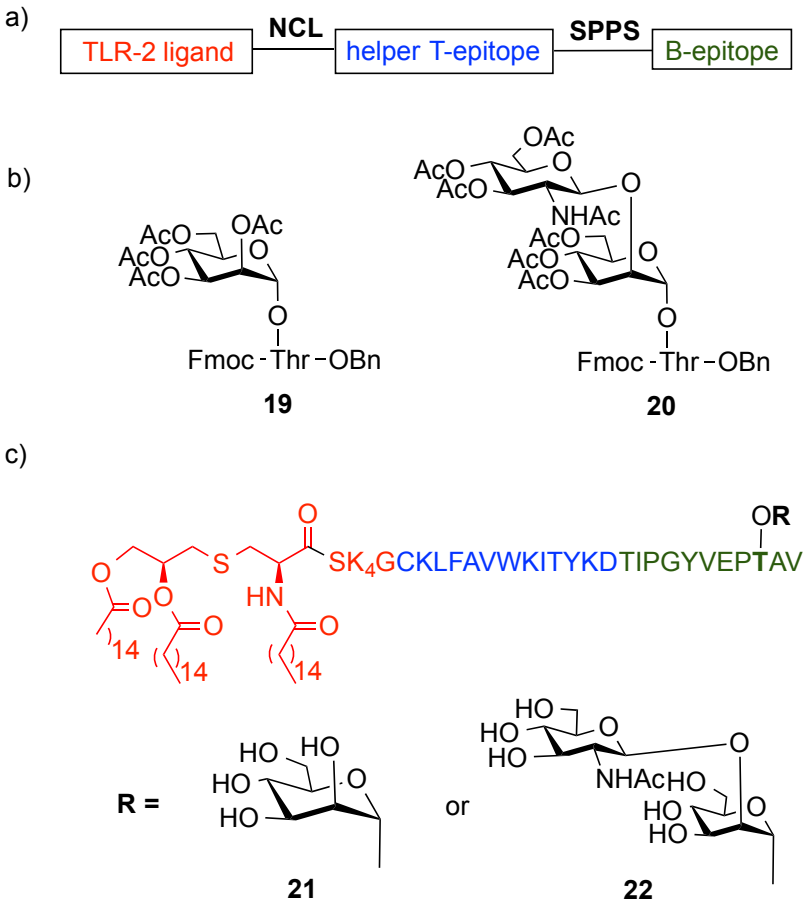
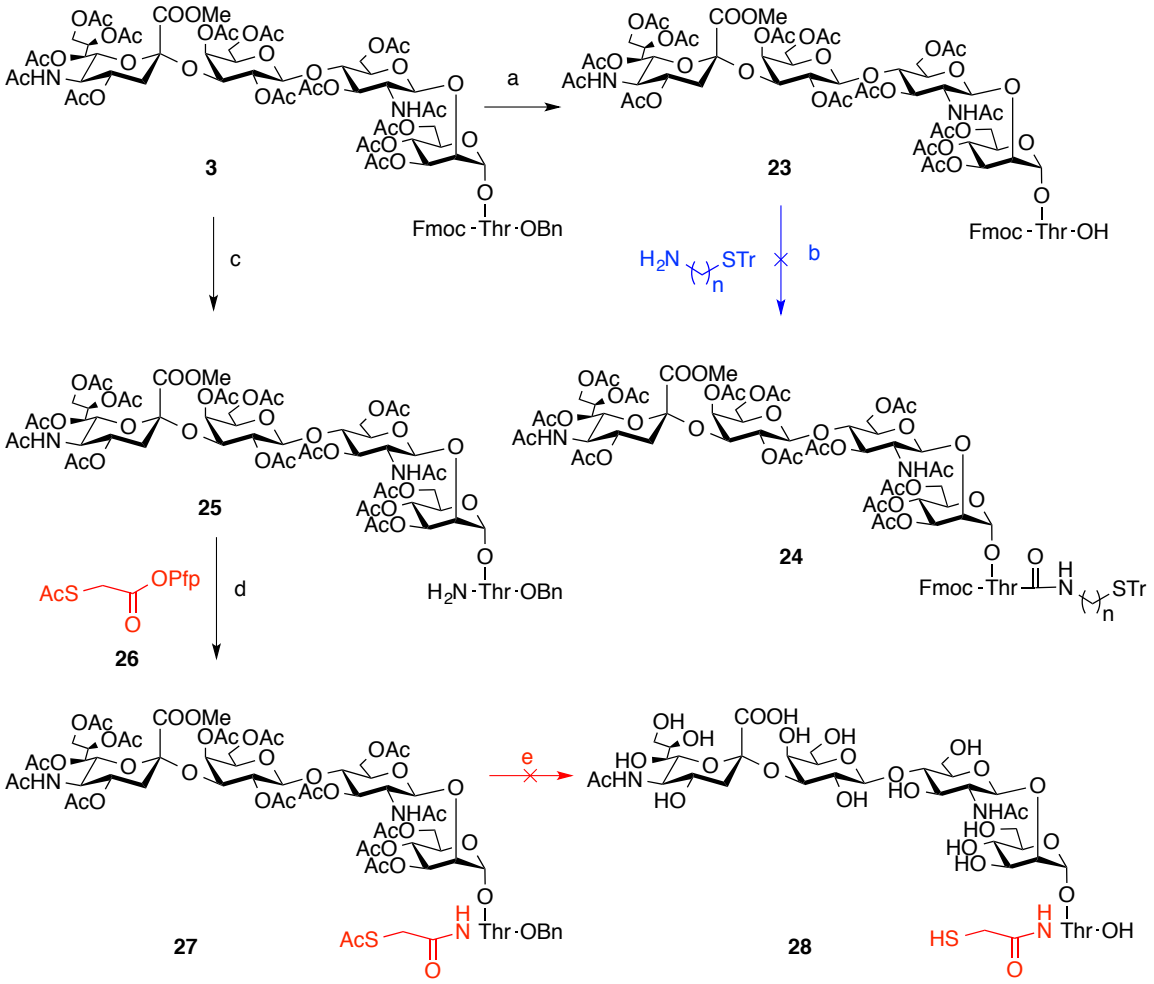


Figure 4.3: Assembly of tripartite vaccines with structures derived from dystroglycan.

Based on the results of immunization with fully synthetic tripartite vaccines, we became interested in comparing the immunogenicity of semi-synthetic carbohydrate vaccines conjugated with carrier proteins like CRM_{197} and cationized BSA (cBSA). CRM_{197}, a nontoxic single mutant of diphtheria toxin,[27] has been shown to enhance the immunogenicity when coupled with polysaccharide in conjugate vaccines,[28] and it is currently used as a carrier in Prevnar, Pfizer's pneumococcal disease vaccine. cBSA is modified from native BSA by blocking carboxylic acid through amide coupling with ethylenediamine. The availability of excessive amine functionality on the surface of

cBSA provides more conjugation sites, thus enhancing the cluster effect by multivalent presentation. Meanwhile, the positively charged cBSA, compared to native BSA, shows improved pharmacokinetics and preferentially interacts with the negatively charged membranes of antigen processing cells.[29,30]

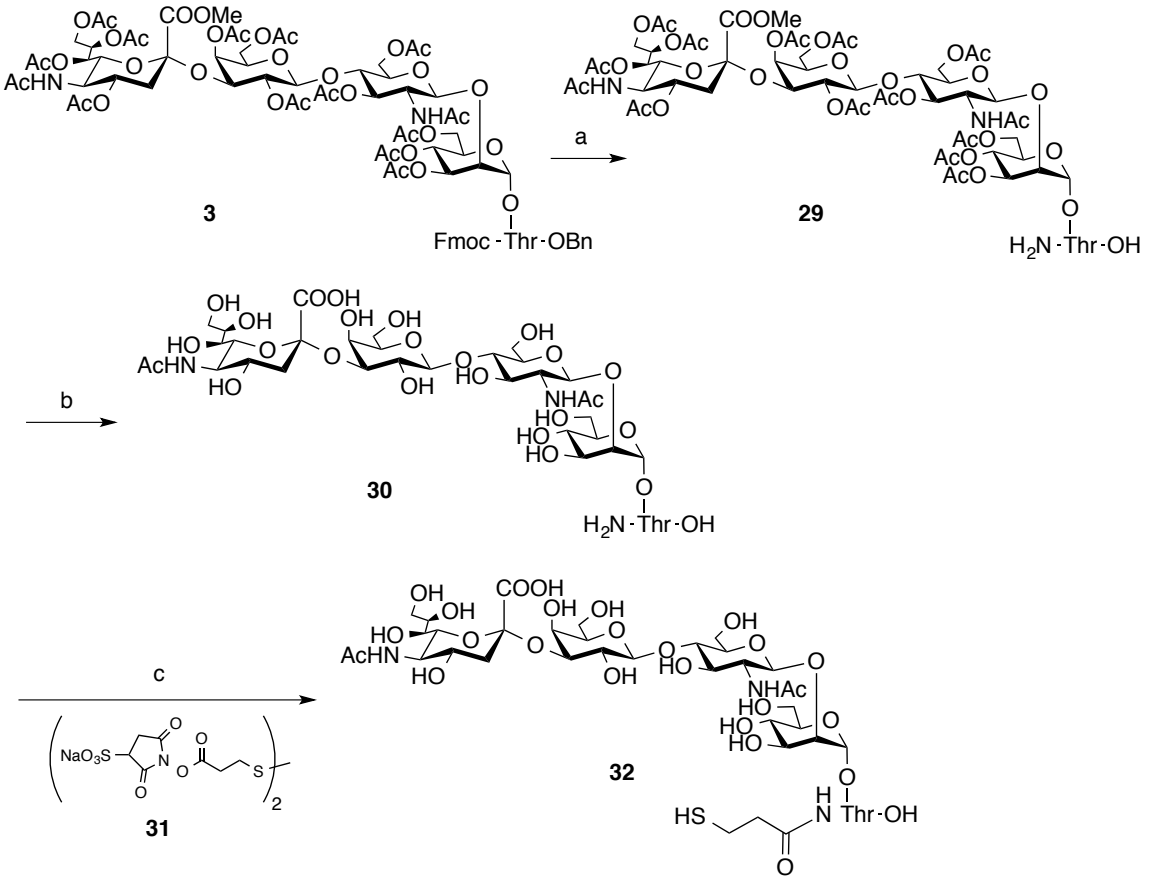
The effectiveness of Thiol-Michael addition reactions in bioconjugation and the relative ease of introducing reactive patterns to both the carrier protein and the synthetic carbohydrate prompted us to modifying the synthetic tetrasaccharide with a mercepto-containing linker. Intuitively, the mercepto-containing linker can be installed through amide coupling reactions with either the *N*- or *C*- terminal of threonine (Scheme 4.2). However, neither coupling could provide the final product due to different reasons. Amide coupling by activation of the C-terminal of **23** with HATU resulted in complete β-elimination of the synthetic tetrasaccharide. Coupling with *S*-acetylthioglycolic acid pentafluorophenyl ester **26** at the *N*-terminal provided the desired product **27** with minor β-elimination, but, the global deacetylation proved to be problematic in that one of the acetates of **28** could not be removed at suitable basicity without significant β-elimination.



Scheme 4.2: Initial deprotection and linker strategy for synthesizing conjugatable DG-tetrasaccharide. Reagents and conditions: a) Pd/C, H_2, iPrOH/Py; b) HATU, DIPEA, DMF; c) 20% piperdine, DMF; d) DIPEA, DMF; e) NaOH, pH = 11.

Learning from these failures, we decided to first fully deblock the tetrasaccharide based on our experience that fully deprotected glycopeptides are generally less prone to β-elimination than blocked ones. Indeed, after removing the benzyl ester and Fmoc carbamate by hydrogenation and piperidine treatment, the partially blocked tetrasaccharide **29** was deacetylated by hydrolysis with an aqueous sodium hydroxide

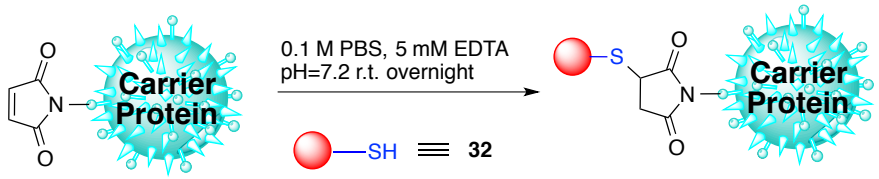
solution. The pH value of the solution was monitored and maintained between pH 11 and 12 until complete deacetylation was achieved. Though the final acetate was still sluggish to remove, complete deacetylation could be achieved after 4 to 7 days, and this method proved to be scalable.



Scheme 4.3: Final deprotection and linker strategy for synthesizing conjugatable DG-tetrasaccharide a) i. 20% piperidine/DMF; ii. Pd/C, H_2, MeOH; b) aq. NaOH, pH=11~12, 7 days; c) i. H_2O, then maintain pH=7~8 with 0.1 M NaOH, 2h; ii. DTT, PBS, pH=7.4, 40^oC, 1h.

With a good quantity of **30** on hand, amide coupling with sulfo-SMCC **31** proceeded smoothly in water at neutral to slightly basic pH. After removal of the excessive sulfo-SMCC by P-2 bio-gel, the disulfide linkage was reductively cleaved by DTT treatment, and further purification by size exclusion column gave final compound **32** ready for conjugation.

Table 4.3: Synthesis of glycoconjugates by Thiol-Michael addition and analytic data.



Entry	Carrier Protein	Maleimide loading	Equivalent of **32**	Loading (**32**/protein)	Protein concentration
1	BSA	17	30	11	1.91 mg/ml
2	cBSA	4	120	0.94	2.3 mg/ml
3	CRM_{197}	22	30	5.5	1.65 mg/ml

Both maleimide-modified BSA and cBSA are commercially available, while maleimide-activated CRM_{197} needs to be prepared manually. CRM_{197} was treated with excessive DTSSP in a 0.1 M PBS buffer at pH = 7.2 for 2 hours. MALDI-TOF analysis of the reaction mixture indicated a satisfactory maleimide modification ratio on the surface of CRM_{197}, where 22 free amines were modified with maleimide. After purification by spin filtration, maleimide modified carrier proteins were used directly for

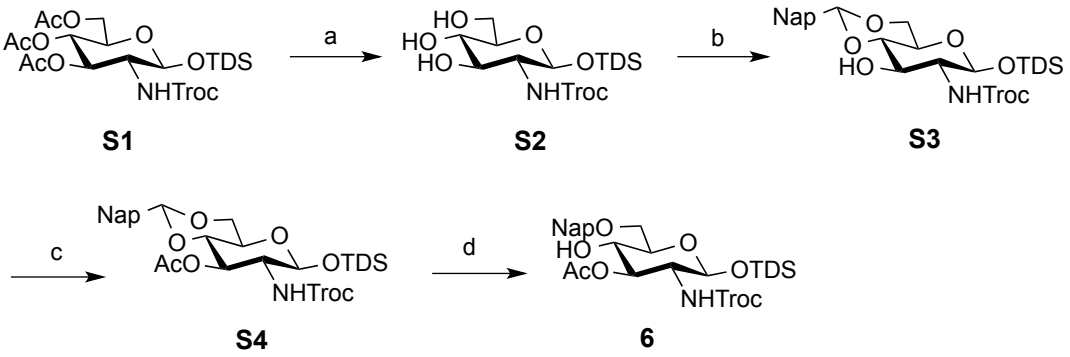
bioconjugation with **32**, which was briefly incubated with agarose supported TCEP in case of disulfide bond reformation. The reaction mixtures were left over night at room temperature before purification by spin filtration again. The efficiency of conjugation was conveniently analyzed by comparing the difference between molecular weight before and after reaction using MALDI-TOF. Protein concentration was tested using the Bradford assay. Similar procedures were repeated for maleimide activated BSA and cBSA and the analytic results are shown in Table 4.3. The obtained glycoconjugate vaccines are currently being tested by immunization of mice.

CONCLUSIONS

We developed a stereoselective and scalable route for synthesizing α-DG related carbohydrate epitopes. A small library was constructed by the cassette strategy. By thorought studies of the protecting groups, leaving groups and solvent effects, the synthetically challenging α-sialoside linkage in the parent tetrasaccharide was contained in good yield and exclusive α-selectivity. These synthetic epitopes bearing amino acid at their reducing ends functioned as valuable building blocks for the assembly of the fully synthetic tripartite vaccines through SPPS and native chemical ligation. Two vaccine constructs were obtained and immunized on mice. We also prepared semi-synthetic glycoconjugate vaccines with various carrier proteins and they will be immunized on mice for comparision of the immune response. These vaccine constructs provided access to glycosylation stage specific antibodies for α-DG.

EXPERIMENTAL SECTION

Reagents and general procedures. Reagents were obtained from commercial sources and used as purchase. Dichloromethane (DCM) was freshly distilled using standard procedures. Other organic solvents were purchased anhydrous and used without further purification. Unless otherwise noted, all reactions were carried out at room temperature in oven-dried glassware with magnetic stirring. Molecular sieves were flame dried under high vacuum prior to use. Organic solutions were concentrated under diminished pressure with bath temperatures < 40^{o} C. Flash column chromatography was carried out on silica gel G60 (Silicycle, 60-200 μm, 60 Å). Thin-layer chromatography (TLC) was carried out on Silica gel 60 F_{254} (EMD Chemicals Inc.) with detection by UV absorption (254 nm) 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 $(NH_4)_6Mo_7O_{24}.H_2O$ (25 g/L) in 10% sulfuric acid in ethanol followed by charring at ~150^{o} C. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-300 (300/75 MHz), a Varian Inova-500 (500/125 MHz) and a Varian Inova-600 (600/150 MHz) spectrometer equipped with sun workstations. Multiplicities are quoted as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), or multiplet (m). Spectra were assigned using COSY, DEPT and HSQC experiments. Signals marked with a superscript Roman numeral I were the reducing end, whereas II and III were the second sugar from the reducing end and the non-reducing end, respectively. All chemical shifts are quoted on the δ-scale in parts per million (ppm). Residual solvent signals were used as an internal reference.



Scheme S4.1: Synthesis of GlcNAc building block **6**. Reagents and conditions: a) Guanidine HCl, NaOMe, DCM, 10 min, 79%; b) $NapCH(OMe)_2$, CSA, DMF, 60 ^oC, reduced pressure, 63%; c) Ac_2O, Py; d) Et_3SiH, TfOH, DCM, - 78 ^oC, 79%.

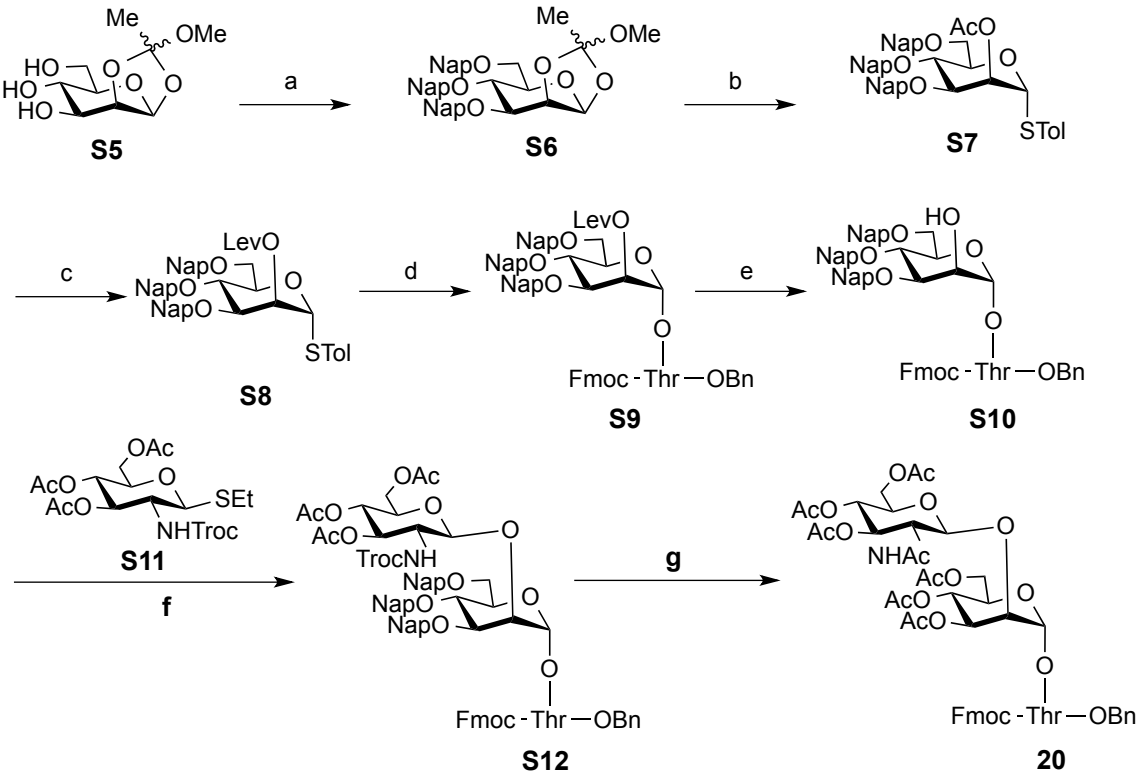
S1 was prepared according to reported procedures.[9]

S1 (2.0 g, 3.2 mmol) was dissolved in MeOH (20 ml) followed by the addition of guanidine-HCl (0.48 g, 5 mmol). To the solution, freshly prepare NaOMe (~50 mg) in MeOH was added, and the reaction mixture was stirred at room temperature for 10 min. After the completion of reaction as indicated by TCL, Dowex-50W was added and the pH was adjusted to neutral. The resin was removed by filtration and the filtrate was concentrated *in vacuo* to obtain crude product, which was passed through a silica column to obtain **S2** (1.26 g, 2.54 mmol, 79%).

After drying under high vacuum over night, **S2** (1.26 g, 2.54 mmol) was redissolved in dry DMF (8 ml) and naphthalenealdehyde dimethyl acetal (1.03 g, 5.1 mmol), camphorsulfonic acid (0.012g) was added, the reaction mixture was stirred at 60 ^oC under house vacuum for 2 h, then quenched with triethylamine. The solvent was removed *in vacuo* again and redissolved in a mixture of pyridine and acetic anhydride (6 ml, 1/1, v/v).

The solution was stirred at room temperature for 4 h and all the solvent was removed *in vacuo* to yield concentrated yellow liquid, which was directly purified by silica column to obtain **S4** (1.0 g, 1.59 mmol, 63%).

S4 (0.1 g, 0.15 mmol) was dissolved in anhydrous DCM (3 ml) followed by the addition of activated MS 4 Å. After stirring under Ar atmosphere at room temperature for 30 min, the temperature of the reaction mixture was lowered to -78 ^{o}C, then Et_3SiH (0.047 ml, 0.295 mmol), TfOH (0.026 ml, 0.295 mmol) were added subsequently. The reaction was stirred at this temperature before quenched by the addition of MeOH (0.5 ml) and pyridine (0.5 ml). The reaction mixture was filtered and the filtrate was concentrated and separated by silica gel to give **6** (0.079g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 6.89 (m, 7H, ArH), 5.00 (d, J = 9.2 Hz, 1H, NH), 4.90 (t, J = 9.0 Hz, 1H, H-3), 4.72 – 4.52 (m, 4H, H-1, NapC*H*H, CH_2^{Troc}), 4.44 (d, J = 12.0 Hz, 1H, NapCH*H*), 3.76 – 3.30 (m, 5H, H-2, H-4, H-5, H-$6_{a,b}$), 2.90 (bs, 1H, OH), 1.96 (s, 3H, OAc), 1.53 – 1.42 (m, 1H, C*H*^{TDS}), 1.00 – 0.47 (m, 12H, CH_3 × 4), 0.22 (d, J = 13.0 Hz, 6H, CH_3 × 2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.31, 157.60, 138.53, 136.63, 136.45, 131.73, 131.29, 131.12, 129.93, 129.61, 129.42, 128.97, 99.72, 98.82, 80.86, 80.44, 80.01, 78.51, 78.00, 77.59, 77.33, 74.40, 73.88, 61.31, 37.38, 28.22, 24.36, 23.40, 23.36, 21.92, 21.90, 1.58, 0.00.



Scheme S4.2: Synthesis of mannose acceptor **S10** and disaccharide glycosylated amino acid **20.** Reagents and conditions: a) NapBr, NaH, DMF, 92%; b) $HgBr_2$, TolSH, 60 ^oC, 83%; c) i. NaOMe, MeOH; ii. Levlinic acid, DCC, DMAP, DCM, 68%; d) Fmoc-Thr-OBn. NIS, TMSOTf, 0 ^oC, 1h, 86%; e) H_2NNH_2-HOAc, DCM/MeOH=4/1, 97%; f) NIS, TMSOTf, 83%; g) i. Zn, AcOH, Ac_2O,THF, sat. $CuSO_4$; ii. DDQ, DCM/H_2O; iii. Ac_2O, Py, 55% 3 steps.

S5 was prepared according to reported procedures.[31]

S5 (8.8 g, 24.3 mmol) was dissolved in anhydrous DMF and cooled to 0 ^oC before the addition of NapBr (29.7 g, 0.13 mol) and NaH (4 g, 0.16 mol). The reaction was left overnight before poured into water. The mixture was extracted by ethyl acetate (100 ml ×

3). The organic layer was combined and the solvent was removed *in vacuo* and the crude was purified by silica gel column to give **S6** (22.3 g, 92%).

S6 (0.52 g, 0.8 mmol) was redissolved in dry MeCN followed by the addition of TolSH (0.20 g, 1.6 mmol) and $HgBr_2$ (0.029 g, 0.08 mmol), the reaction temperature was raised to 60 ^oC and kept for overnight. After completion of the reaction, the reaction mixture was diluted with DCM and washed with aq. $NaHCO_3$. The organic layer was combined, concentrated and purified by silica gel column to give **S7** （0.5 g, 83 %).

S7 (0.5 g, 0.67 mmol) was dissolved in anhydrous MeOH followed by the addition of catalytic amount of NaOMe. After stiring for 1 h, the reaction was quenched with Dowex 50W and filtrated, the filtrate was concentrated and dried under vacuum and redissolved in DCM. Levulinic acid (0.85 ml, 5.36 mmol), DCC (1.7 g, 5.36 mmol), and DMAP (0.02 g) were added and the reaction was stirred over night. After completion of the reaction, silica gel (2 g) was added and the mixture was dried. The silica powder loaded with crude compound was transferred to the column and purified to give **S8** (0.36 g, 68 %).

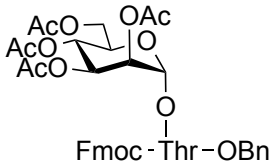
S8 (0.24 g, 0.30 mmol) was premixed with acceptor Fmoc-Thr-OBn (0.11 g, 0.25 mmol) followed by the addition of DCM (4 ml), NIS (0.084 g, 0.45 mmol), activated MS 4 Å. After stirring under Ar atmosphere for 30 min, TMSOTf (0.011 ml, 0.06 mmol) was added at 0 ^oC and the reaction was stirred at this temperature for 2 h. After quenching with pyridine, the mixture was filtered and washed with sat. $Na_2S_2O_3$ and aq. $NaHCO_3$, the organic layer was collected, concentrated and purified by silica column to give **S9** (0.29 g, 86 %). Finally, **S9** (0.55 g, 0.50 mmol) was dissolved in DCM (10 ml), MeOH (2.5 ml), H_2NNH_2-HOAc (0.18 g, 2 mmol) was added and the reaction was stirred at 50

^{o}C for 1 h before washed with aq. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was combined and dried *in vacuo* followed by the purification on silica column to give **S10** (0.48 g, 97 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 6.87 (m, 44H, ArH), 5.31 (d, *J* = 9.8 Hz, 1H, NH), 5.15 – 4.95 (m, 2H, NapCH_2), 4.89 (d, *J* = 10.9 Hz, 1H, NapCH*H*), 4.81 – 4.64 (m, 5H, NapCH_2, H-1, CH, NapCH*H*), 4.55 (t, *J* = 11.0 Hz, 3H,), 4.42 – 4.22 (m, 4H), 4.15 (t, *J* = 7.1 Hz, 1H), 3.90 – 3.54 (m, 7H), 1.22 (d, *J* = 6.4 Hz, 3H, CH_3^{Thr}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.50, 156.82, 144.09, 143.92, 141.52, 135.77, 135.74, 135.47, 135.30, 133.51, 133.45, 133.41, 133.30, 133.23, 133.15, 129.03, 129.01, 128.94, 128.61, 128.41, 128.29, 128.20, 128.12, 127.95, 127.82, 127.35, 127.33, 126.92, 126.89, 126.77, 126.48, 126.33, 126.31, 126.18, 126.09, 126.05, 126.02, 125.33, 120.22, 101.47, 80.07, 77.69, 77.27, 76.84, 75.53, 74.44, 73.85, 72.23, 71.90, 68.99, 68.41, 67.73, 67.54, 59.17, 47.41, 18.62.

Donor **S11** (23 mg, 0.044 mmol) and acceptor **S10** (30 mg, 0.030 mmol) were premixed and dried under high vacuum over night, then anhydrous DCM (2 ml), activated MS 4 Å were added and stirred under Ar atmosphere for 30 min. After cooling to -25 ^{o}C, NIS (15 mg, 0.067 mmol), TMSOTf (2 μl, 9 μmol) were added subsequently and the reaction was stirred at this temperature for 2 h before quenching with pyridine. The mixture was then filtered and washed with sat. $Na_2S_2O_3$ and aq. $NaHCO_3$, the organic layer was collected, concentrated and purified by silica column to give **S12** (36 mg, 83%). **S12** (100 mg, 0.07 mmol) was dissolved in a mixture of solvents THF/Ac_2O/AcOH=3/2/1 (2.2 ml) followed by the addition of zinc powder (50 mg) and sat. $CuSO_4$ (0.09 ml). The reaction was stirred for 1 h at room temperature until the completion of reaction, the reaction mixture was filtered and the filtrated was

concentrated and passed through a short silica column. The resulting compound was redissolved in DCM/H_2O=10/1 (4 ml), and DDQ (95 mg, 0.42 mml) was added. The reaction was stirred with protection from light. After the completion of reaction, the reaction was diluted by DCM and poured into aq. $NaHCO_3$ and washed (aq. $NaHCO_3$ × 3). The organic layer was collected and concentrated. Pyridine (1 ml) and acetic anhydride (1ml) were added to the crude and the reaction was stirred over night. The solvent was then removed *in vacuo* and the resulting crude was purified by silica column to give **20** (0.039 g, 55 %, 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 6.96 (m, 13H, ArH), 5.60 (d, J = 9.6 Hz, 1H, NH), 5.49 (d, J = 7.7 Hz, 1H, NH), 5.34 (t, J = 9.9 Hz, 1H, H-3^{II}), 5.23 (s, 2H, $PhCH_2$), 5.13 (t, J = 9.8 Hz, 1H, H-4^{I}), 4.98 (dd, J = 9.6, 3.4 Hz, 1H, H-3^{I}), 4.90 (t, J = 9.6 Hz, 1H, H-4^{II}), 4.77 – 4.61 (m, 2H, H-1^{I}, H-1^{II}), 4.44 (d, J = 9.6 Hz, 1H, CH^{Thr}), 4.42 – 4.26 (m, 3H, CH_2^{Fmoc}, CHThr), 4.25 – 4.06 (m, 3H, CH^{Fmoc}, H-6$_a^{I}$, H-6$_a$II), 4.06 – 3.75 (m, 4H, H-6$_b^{I}$, H-6$_b$II H-2I, H-5I), 3.55 – 3.32 (m, 2H, H-2^{II}, H-5^{II}), 2.06 – 1.89 (m, 21H, OAc × 7), 1.24 (d, J = 6.5 Hz, 3H, Me^{Thr}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.05, 170.02, 169.62, 169.57, 169.22, 168.53, 155.43, 142.79, 142.58, 140.24, 134.63, 134.59, 134.50, 134.47, 134.08, 132.24, 132.17, 132.15, 132.02, 131.92, 131.90, 127.99, 127.77, 127.63, 127.54, 127.18, 127.14, 127.06, 126.91, 126.88, 126.77, 126.71, 126.64, 126.57, 126.08, 125.98, 125.57, 125.31, 125.25, 125.21, 125.11, 125.06, 124.97, 124.90, 124.82, 124.55, 124.04, 118.97, 97.82, 97.18, 76.66, 76.44, 76.01, 75.59, 75.19, 73.77, 73.53, 72.96, 72.33, 71.18, 70.80, 70.53, 70.30, 68.35, 68.07, 66.32, 66.26, 61.33, 57.63, 54.92, 46.12, 22.18, 19.65, 19.62, 19.57, 17.33.

2,3,4,6-tetra-acetyl thiomannoside were premixed and dried under high vacuum over night, then anhydrous DCM (2 ml), activated MS 4 Å were added and stirred under Ar



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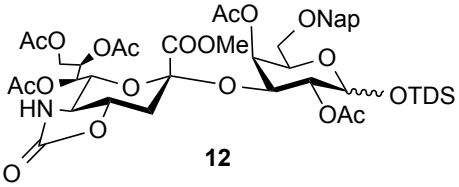
atmosphere for 30 min. After cooling to -25 ^{o}C, NIS (15 mg, 0.067 mmol), TMSOTf (2 µl, 9 µmol) were added subsequently and the reaction was stirred at this temperature for 2 h before quenching with pyridine. The mixture was then filtered and washed with sat. $Na_2S_2O_3$ and aq. $NaHCO_3$, the organic layer was collected, concentrated and purified by silica column to give **19** (36 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.06 (m, 13H, ArH), 5.59 (d, J = 9.6 Hz, 1H, NH), 5.37 – 5.14 (m, 4H, H-3, H-4, CH_2Ph), 5.08 (s, 1H, H-2), 4.86 (s, 1H, H-1), 4.53 (dd, J = 9.7, 2.5 Hz, 1H, CH^{Thr}), 4.49 – 4.32 (m, 3H, CH^{Thr}, CH_2^{Fmoc}), 4.33 – 4.18 (m, 2H, H-6_a, CH^{Fmoc}), 4.17 – 4.07 (m, 1H, H-6_b), 4.09 – 3.98 (m, 1H, H-5), 2.23 – 1.96 (m, 12H, OAc × 4), 1.33 (d, J = 6.4 Hz, 3H, Me^{Thr}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.76, 170.07, 169.94, 156.88, 144.11, 143.95, 141.52, 135.26, 128.87, 128.82, 128.76, 127.96, 127.37, 127.35, 125.46, 120.21, 120.20, 99.03, 77.77, 77.69, 77.26, 76.84, 69.93, 69.31, 68.91, 68.06, 67.78, 66.56, 62.77, 58.94, 47.36, 21.11, 20.93, 20.91, 18.21.



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Donor **4** (158 mg, 0.30 mmol) was premixed with acceptor **5** (118 mg, 0.25 mmol) and dried under high vacuum over night before dissolved in a mixture of DCM and MeCN (2/1, v/v) followed by the addition of activated MS 4 Å and NIS (136 mg, 0.60 mmol). After stirring under Ar atmosphere at room temperature for 30min, the reaction mixture was cooled to -78 ^{o}C and TfOH (11 µl) was added. The reaction temperature was allowed to rise to -60 ^{o}C gradually in 20 min and TLC indicated the complete disappearance of donor. The reaction was then quenched by the addition of

Et_3N, diluted by DCM, filtered and the filtrate was washed with $Na_2S_2O_3$ and $NaHCO_3$. Pyridine (1 ml) and acetic anhydride (1ml) were added to the crude and the reaction was stirred over night. The solvent was then removed *in vacuo* and the resulting crude was purified by silica column to give **12** as α/β mixture (193 mg, 84%). **12**-βTDS: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 6.89 (m, 7H, Ar*H*), 5.51 (dt, J = 10.0, 2.9 Hz, 1H, H-8^{II}), 5.07 (s, 1H, NH), 5.02 (dd, J = 9.9, 2.5 Hz, 1H, H-7^{II}), 4.92 – 4.75 (m, 2H, H-2^{I}, H-4^{I}), 4.68 (d, J = 7.6 Hz, 1H, H-1^{I}), 4.47 (q, J = 11.8 Hz, 2H, NapC*H*$_2$), 4.18 (dd, J = 10.2, 3.3 Hz, 1H, H-3^{I}), 4.13 (d, J = 2.8 Hz, 2H, H-9$_{a,b}^{II}$), 3.79 – 3.54 (m, 6H, H-6^{II}, H-4^{II}, H-5^{I}, OMe), 3.35 (qd, J = 9.9, 6.1 Hz, 2H, H-6$_{a,b}^{I}$), 2.93 – 2.61 (m, 2H, H-5^{II}, H-3$_a^{II}$), 2.06 – 1.80 (m, 15H, OAc × 5), 1.67 (dd, J = 13.0, 12.0 Hz, 1H, H-3$_b^{II}$), 1.53 – 1.41 (m, 1H, C*H*^{TDS}), 0.69 (d, J = 6.8 Hz, 12H, Me × 4), 0.02 (d, J = 4.0 Hz, 6H, Me × 2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.33, 173.73, 173.51, 173.29, 172.45, 170.80, 162.27, 138.69, 136.46, 136.19, 131.26, 131.04, 130.90, 129.52, 129.31, 129.09, 128.92, 101.85, 99.13, 80.68, 80.44, 80.25, 79.83, 76.78, 76.27, 75.48, 75.44, 74.93, 72.29, 71.67, 71.55, 69.90, 65.09, 60.94, 56.57, 39.83, 37.15, 28.09, 24.59, 24.29, 24.09, 24.07, 24.01, 23.88, 23.22, 23.15, 21.77, 21.72, 1.32, 0.00; **12**-αTDS: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.17 (m, 7H, ArH), 5.38 (dt, J = 9.9, 2.3 Hz, 1H, H-8II), 5.23 (d, J = 3.5 Hz, 1H, H-1I), 5.19 (s, 1H, NH), 5.07 (dd, J = 3.3, 1.1 Hz, 1H, H-4I), 4.94 (dd, J = 10.0, 1.8 Hz, 1H, H-7II), 4.86 (dd, J = 10.3, 3.6 Hz, 1H, H-2I), 4.52 (d, J = 12.0 Hz, 1H, NapC*H*H), 4.48 – 4.34 (m, 2H, NapCH*H*, H-3^{I}), 4.18 – 4.02 (m, 3H, H-9a,bII, H-5I), 3.92 – 3.79 (m, 1H, H-4II), 3.74 (dd, J = 9.8, 1.8 Hz, 1H, H-6II), 3.62 (s, 3H, OMe), 3.32 (d, J = 6.0 Hz, 2H, H-6a,bI), 2.80 (t, J = 10.4 Hz, 1H, H-5II), 2.69 (dd, J = 12.2, 3.6 Hz, 1H, H-3aII), 1.97 – 1.82 (m, 15H, OAc × 5), 1.82 – 1.67 (m, 1H, H-3bII), 1.52 – 1.38 (m, 1H, C*H*^{TDS}), 0.78 – 0.63 (m,

12H, Me × 4), 0.02 (d, J = 4.0 Hz, 6H, Me × 2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.72, 174.48, 173.57, 173.40, 172.04, 171.23, 162.80, 139.02, 136.80, 136.52, 131.59, 131.41, 131.23, 129.90, 129.61, 129.38, 129.30, 102.44, 95.106, 81.05, 80.63, 80.20, 77.04, 76.70, 73.44, 73.39, 72.32, 71.52, 70.57, 65.04, 61.70, 56.83, 40.05, 37.69, 28.71, 24.60, 24.47, 24.30, 24.22, 24.17, 23.77, 23. 56, 22.31, 22.14, 1.13, 0.00.

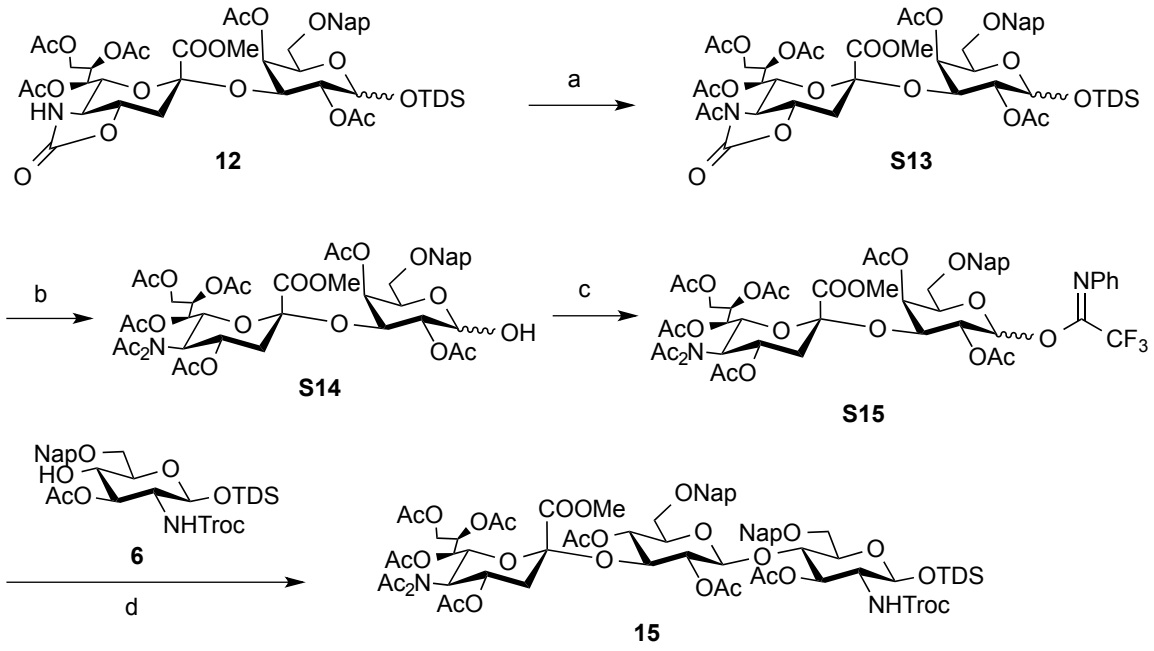


Figure S4.3: Deprotection of oxazolidinone and preparation of trisaccharide **15**. Reagents and conditions: a) AcCl, DIPEA, DCM, r.t. 3 h, 91%; b) i. NaOMe, MeOH; ii. Ac_2O, Py; iii. AcCl, DIPEA, DCM; iv. TBAF, AcOH, THF, 78%; c) $CF_3C(=NPh)Cl$, DBU; d) DCM, TfOH, -25 ^oC, 73%.

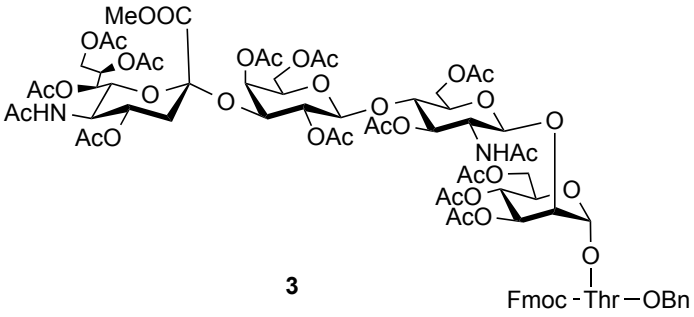
12 (30 mg, 0.031 mmol) was dissolved in DCM (1 ml), DIPEA (55 µl) and AcCl (18 µl) were added subsequently. After the completion of reaction, the reaction was diluted

with DCM, washed with aq. $NaHCO_3$ and organic layer was collected and concentrated. The resulting crude was passed through a short silica column to give **S13** (28.5 mg, 91%). **S13** (15 mg, 0.015 mmol) was dissolved in dry MeOH (0.3 ml) followed by the addition of catalytic amount of freshly prepared NaOMe solution in MeOH. After 60 min, the reaction was quenched by the addition of Dowex 50W resin and reaction solution was filtered. The filtrate was concentrated and redissolved in pyridine (1 ml) and acetic anhydride (1 ml). The mixture was stirred overnight before the removal of solvent *in vacuo*. The crude was treated again with DCM (1 ml), DIPEA (55 µl) and AcCl (18 µl). After the completion of reaction, the reaction was diluted with DCM, washed with aq. $NaHCO_3$ and organic layer was collected and concentrated. The resulting crude was dissolved in THF (1.5 ml) followed by the addition of TBAF (62 µl, 1 M in THF) at 0 ^oC. After 2 h, the reaction was poured into aq. $NaHCO_3$ solution and extracted with ethyl acetate, the organic layer was combined and concentrated. Purification by silica column gave **S14** (10 mg, 78%). **S14** (30 mg, 0.036 mmol) was dissolved in DCM (1 ml) followed by the addition of 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (37 mg, 0.18 mmol) and DBU (6 µl, 0.036 mmol) at room temperature. After 20 min, the reaction solution was briefly concentrated by airflow and loaded directly onto silica column to give **S15** (35 mg, 95 %).

Premix **S15** (110 mg, 0.10 mmol) and 6 (58 mg, 0.09 mmol) in dry DCM (2 ml). After stirring with activated MS 4 Å under Ar atmosphere for 30 min, the reaction mixture was cooled to -20 ^oC followed by the addition of TMSOTf (4 µl, 0.02 mmol). The reaction temperature was gradually raised to 0 ^oC in 2 h. After quenching with pyridine, the solvent was briefly concentrated by airflow and loaded directly onto silica column to give

15 (100 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.03 (m, 14H, Ar*H*), 5.56 – 5.30 (m, 2H, H-4^{III}, H-8^{III}), 5.13 – 4.91 (m, 4H, H-7^{III}, H-3^{I}, H-4^{II}), 4.86 (dd, J = 10.0, 7.8 Hz, 1H, H-2^{II}), 4.82 – 4.65 (m, 4H, H-1^{II}, NapC*H*H, CH_2^{Troc}), 4.64 – 4.41 (m, 6H, NapCH_2, H-1^{I}, H-6^{III}, H-3^{II}, NapCH*H*), 4.28 (dd, J = 12.5, 3.0 Hz, 1H, H-9_a^{III}), 4.20 (t, J = 10.2 Hz, 1H, H-5^{III}), 3.98 – 3.85 (m, 2H, H-4^{I}, H-9_b^{III}), 3.83 (s, 3H, OMe), 3.78 (t, J = 6.5 Hz, 1H, H-5^{II}), 3.72 (s, 2H, H-$6_{a,b}^{I}$), 3.63 (q, J = 9.7 Hz, 1H, H-2^{I}), 3.50 (dt, J = 9.5, 3.5 Hz, 1H, H-5^{I}), 3.47 – 3.38 (m, 1H, H-6_a^{II}), 3.39 – 3.26 (m, 1H, H-6_b^{II}), 2.59 (dd, J = 12.7, 5.3 Hz, 1H, H-3_a^{III}), 2.33 – 1.73 (m, 27H, OAc × 9), 1.60 – 1.42 (m, 2H, H-3_b^{III}, C*H*^{Troc}), 0.89 – 0.66 (m, 12H, Me × 4), 0.09 (d, J = 30.9 Hz, 6H, Me× 2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.44, 176.99, 174.08, 173.89, 173.87, 173.55, 173.30, 173.20, 173.10, 171.21, 157.62, 139.45, 138.69, 136.67, 136.63, 136.39, 136.32, 131.51, 131.42, 131.30, 131.25, 131.12, 131.07, 129.80, 129.52, 129.48, 129.43, 129.29, 129.17, 129.11, 129.07, 128.99, 104.02, 100.19, 99.91, 80.85, 80.63, 80.43, 80.00, 78.75, 78.43, 77.99, 77.13, 76.80, 75.26, 75.08, 74.27, 72.86, 72.00, 71.18, 71.04, 70.57, 70.41, 65.65, 61.67, 59.41, 56.60, 41.82, 37.40, 31.51, 30.12, 28.23, 24.90, 24.53, 24.34, 24.14, 24.10, 23.41, 23.38, 21.93, 1.62, 0.03.

15 (95 mg, 0.076 mmol) was dissolved in THF (2ml) followed by the addition of HF in pyridine solution (0.2 ml) at 0 ^{o}C. The reaction was stirred then without regulation of temperature for 16 h and diluted with DCM before poured into aq. $NaHCO_3$. The solution was extracted with DCM and the organic layer was combined and



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concentrated in vacuo. Purification by a short silica column to hemiacetal (83 mg, 0.075 mmol), which was dried and dissolved in DCM (1 ml) followed by the addition of 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (59 mg, 0.29 mmol) and DBU (9 µl, 0.058 mmol) at room temperature. After 20 min, the reaction solution was briefly concentrated by airflow and loaded directly onto silica column to give **16** (94 mg, 96 %) for direct use without further characterization.

Donor **16** (93 mg, 0.075 mmol) and acceptor **17** (150 mg, 0.15 mmol) was premixed and dried followed by the addition of DCM (2ml) and activated MS 4 Å. After stirring under Ar atmosphere for 30 min, the reaction mixture was cooled to -40 ^{o}C followed by the addition of TMSOTf (3 µl, 0.015 mmol). After 1 h, the reaction was quenched with pyridine, the solvent was briefly concentrated by airflow and loaded directly onto silica column to give **18** (87 mg, 53%). The resulting product was deprotected by the treatment of DDQ (2 eq. per Nap) in a mixture of H_2O : DCM=1 : 10 (v/v). After completion of the reaction, reaction mixture was diluted with DCM and washed with aq. $NaHCO_3$, the organic phase was collected and concentrated *in vacuo*. The residue was redissolved in 10% TFA in DCM in order to remove the napthelidene formed during previous step. After 30 min, the reaction mixture was poured into aq. $NaHCO_3$ and extracted with DCM, the organic phase was collected and concentrated *in vacuo*. The residue was redissolved in a mixture of pyridine: Ac_2O = 1 : 1 (v/v). After stirring for 16 h, the solvent was removed *in vacuo* and the residue was purified by silica gel column. The corresponding fractions were collected and concentrated. The compound was then redissolved in a mixture of Ac_2O-AcOH followed by the addition of Zinc powder and sat. $CuSO_4$. After 30 min, the reaction mixture was filtered and the filtrate was concentrated and purified by silica gel

column to give **3**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 7.15 (m, 13H, Ar*H)*, 5.60 (dd, J = 9.3, 2.7 Hz, 1H, NH^{II}), 5.51 (ddt, J = 8.2, 5.8, 2.9 Hz, 1H, H-7^{IV}), 5.37 (dd, J = 9.2, 3.0 Hz, 1H, H-8^{IV}), 5.32 – 5.10 (m, 3H, CH_2Ph, H-7^{IV}), 5.13 – 4.96 (m, 2H, H-3^{I}, H-3^{II}), 4.99 – 4.73 (m, 5H, H-1^{I}, H-2^{III}, H-4^{III}, , H-4^{I}, H-4^{IV}), 4.62 (d, J = 8.0 Hz, 1H, H-1^{III}), 4.59 – 4.18 (m, 11H, H-3^{III}, H-1^{II}, H-2^{II}, CH^{Thr}, CH_2^{Fmoc}, H-9^{IV}_a, H-6_a, H-$6_{a,b}$, H-6^{II}_a), 4.19 – 3.72 (m, 15H, OMe, H-4^{II}, H-6^{II}_b, H-5^{IV}, H-2^{I}, H-5^{III}, H-5^{I}, H-6b, C*H*^{Thr}, C*H*^{Fmoc}, H-$6_{a,b}$, H-9^{IV}_b), 3.62 (dd, J = 10.9, 2.7 Hz, 1H, H-6^{IV}), 3.40 (ddd, J = 9.2, 5.6, 2.8 Hz, 1H, H-5^{II}), 2.56 (dd, J = 12.6, 4.6 Hz, 1H, H-3^{IV}_a), 2.32 – 1.75 (m, 42H, 14 × OAc), 1.65 (t, J = 12.4 Hz, 1H, H-3^{IV}_b), 1.28 (d, J = 6.4 Hz, 3H, CH_3^{Thr}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.37, 170.77, 170.71, 170.60, 170.55, 170.45, 170.37, 170.36, 170.29, 170.20, 170.14, 169.60, 169.56, 169.30, 167.91, 162.60, 156.52, 143.78, 143.62, 141.25, 135.13, 134.55, 129.50, 129.10, 128.84, 128.82, 128.71, 128.62, 128.35, 128.04, 127.81, 127.72, 127.08, 125.14, 122.73, 119.96, 100.91, 99.94, 98.76, 96.73, 77.46, 77.23, 77.03, 76.76, 76.61, 75.93, 74.52, 72.65, 72.48, 71.95, 71.23, 70.50, 69.88, 69.32, 67.70, 67.46, 67.31, 67.21, 66.89, 66.09, 62.69, 62.42, 62.20, 61.56, 58.56, 53.74, 53.09, 49.03, 47.10, 37.38, 29.65, 23.13, 23.10, 23.05, 21.49, 20.87, 20.82, 20.75, 20.71, 20.66, 20.60, 20.51, 17.99.

Formulation and General procedure for liposome preparation

Glycolipopeptide **21** and **22** were incorporated into phospholipid-based small unilamellar vesicles (SUVs) by hydration of a thin film of the synthetic compounds, egg phosphatidylcholine, phosphatidylglycerol, lipid A and cholesterol in a Hepes buffer (10 mM, pH 7.4) containing NaCl (145 mM) followed by extrusion through a 0.2-μm

Nucleo- pore polycarbonate membrane. Formulations and analysis results are shown in Table S4.1.

Table S4.1: Formulations and analysis results of liposomes prepared with **21** and **22**.

Batch	1	2	3
Phosphatidylcholine [mg(eq.)]	2.28 (12)	2.28 (12)	9.12 (24)
Phosphatidyl Glycerol [mg(eq.)]	0.96(5)	0.96(5)	3.84 (10)
Monophosphoryl Lipid A [mg(eq.)]	0.44(1)	0.44(1)	0.4 (0.5)
Cholesterol [mg(eq.)]	0.97(10)	0.97(10)	2 (10)
Vaccine **21** or **22** [mg(eq.)]	4.45(4)	4.45(4)	8.9 (4)
Buffer [ml]	0.5	0.5	2
Smallest Membrane Passed [µm]	0.1	0.1	0.2
Incorporation rate [%]	6.1	5.7	89.9
Sugar concentration [µg/ml]	3.3	3.1	24.7

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CHAPTER 5

CONCLUSIONS

We have demonstrated that 1,2-oxathiane ether is a versatile protecting group for preparing modular building blocks and a readily available precursor for *trans*-decalin sulfonium ions, which can reliably give high 1,2-*cis*-anomeric selectivities. In particular, 1,2-oxathiane ether is stable to commonly employed protecting groups manipulations, making it possible to install a variety of orthogonal protecting groups such as Lev ester, Fmoc and Alloc carbonates, and Nap ether. Furthermore, 1,2-oxathiane ether could easily be installed by a novel one-pot two-step procedure. It functions as a feasible protecting group for 1,2-diol facilitating the modification of the C-3, C-4 and C-6 alcohols. The resulting 1,2-oxathianes could be employed as glycosyl donors for highly selective 1,2-*cis*-glycosylation by oxidation to sulfoxides followed by the arylation with 1,3,5-trimethoxybenzene to give a bicyclic anomeric sulfonium ion. The attractiveness of the new building blocks has been demonstrated by the preparation of a biologically important branched α-glucan, which was assembled by a latent-active glycosylation strategy.

We have further illustrated the mechanistic itinerary of sulfonium ion mediated glycosylations. By designing structural mimics of donors with tunable participating ability, we confirmed that sulfonium ion mediated stereoselective glycosylations strongly rely on the participating ability of sulfur atom and the proper configuration of fused decalin system. DFT calculation revealed a low tendency toward configuration interconversion, which is supported by the clean formation of *trans*- or *cis*-sulfonium

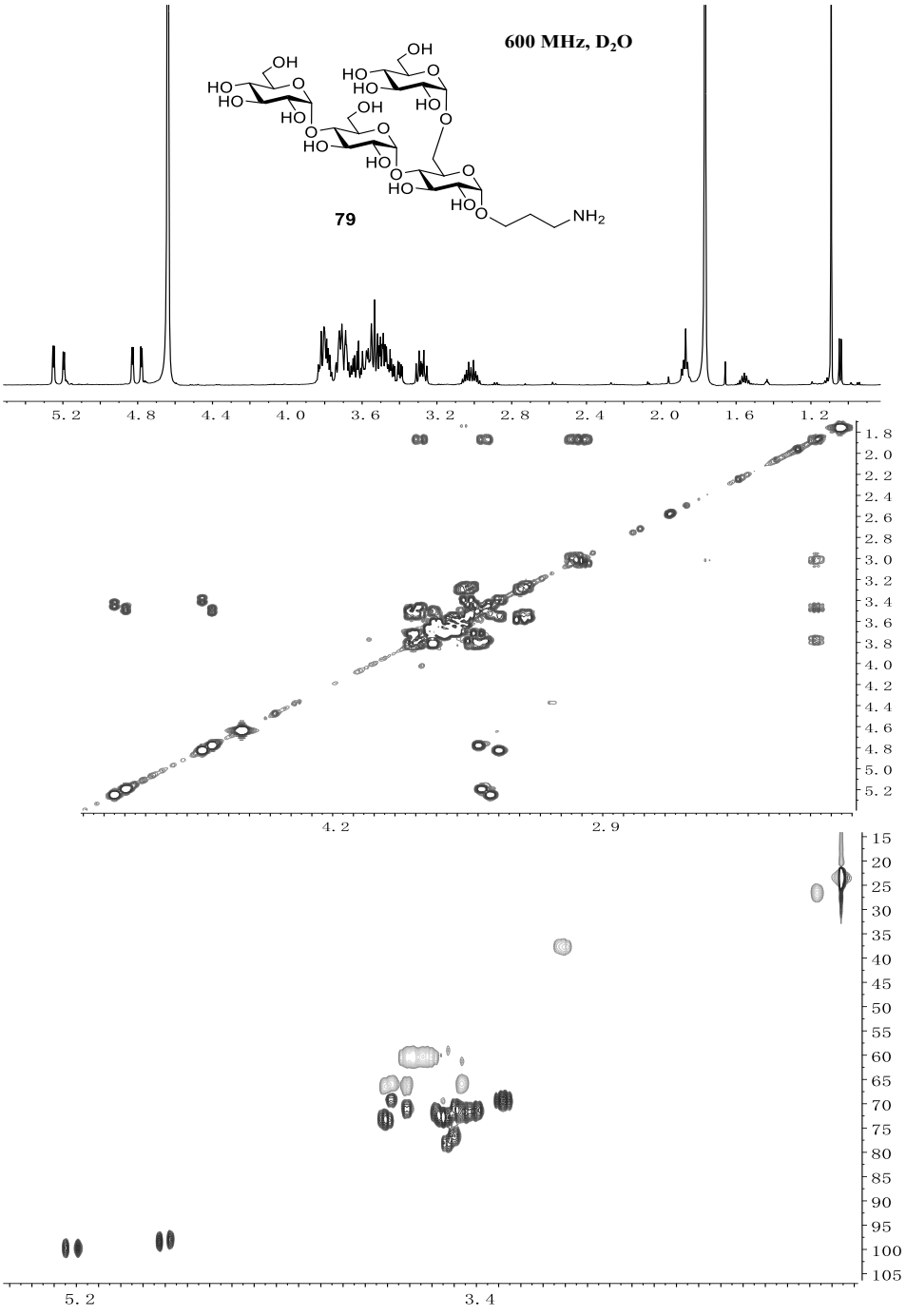
ions in NMR studies. Calculation also indicated a strong preference of S_N2-like mechanism for *trans*-decalin sulfonium ion with $\Delta\Delta G^{\neq}$ = -5.03 kcal/mol, while the *cis*-decalin sulfonium ion slightly prefers S_N1-like mechanism with $\Delta\Delta G^{\neq}$ = -0.55 kcal/mol. The tendency of *cis*-decalin sulfonium ion toward S_N1 reaction makes the two-conformer hypothesis a suitable model for the explanation of eroded but still preferred formation of α-product when *cis*-decalin sulfonium ions were employed for glycosylations.

Meanwhile, we developed a stereoselective and scalable route for synthesizing α-DG related carbohydrate epitopes. Glycosylation involving synthetically challenging α-sialoside linkage was optimized based on protecting group, leaving group, and solvent effects. Parent α-DG tetrasaccharide and its truncated derivatives were prepared in good yields and exclusive stereoselectivities. These synthetic epitopes bearing amino acids at their reducing ends functioned as valuable building blocks for the assembly of fully synthetic tripartite vaccines through SPPS and native chemical ligation. Two vaccine constructs were obtained and immunized on mice. We also prepared semi-synthetic glycoconjugate vaccines with various carrier proteins and they will be immunized on mice for comparision of the immune response with fully synthetic vaccine constructs. These vaccine constructs provided access to glycosylation stage specific antibodies for α-DG.

APPENDIX A

SUPPLEMENTARY DATA FOR CHAPTER 2

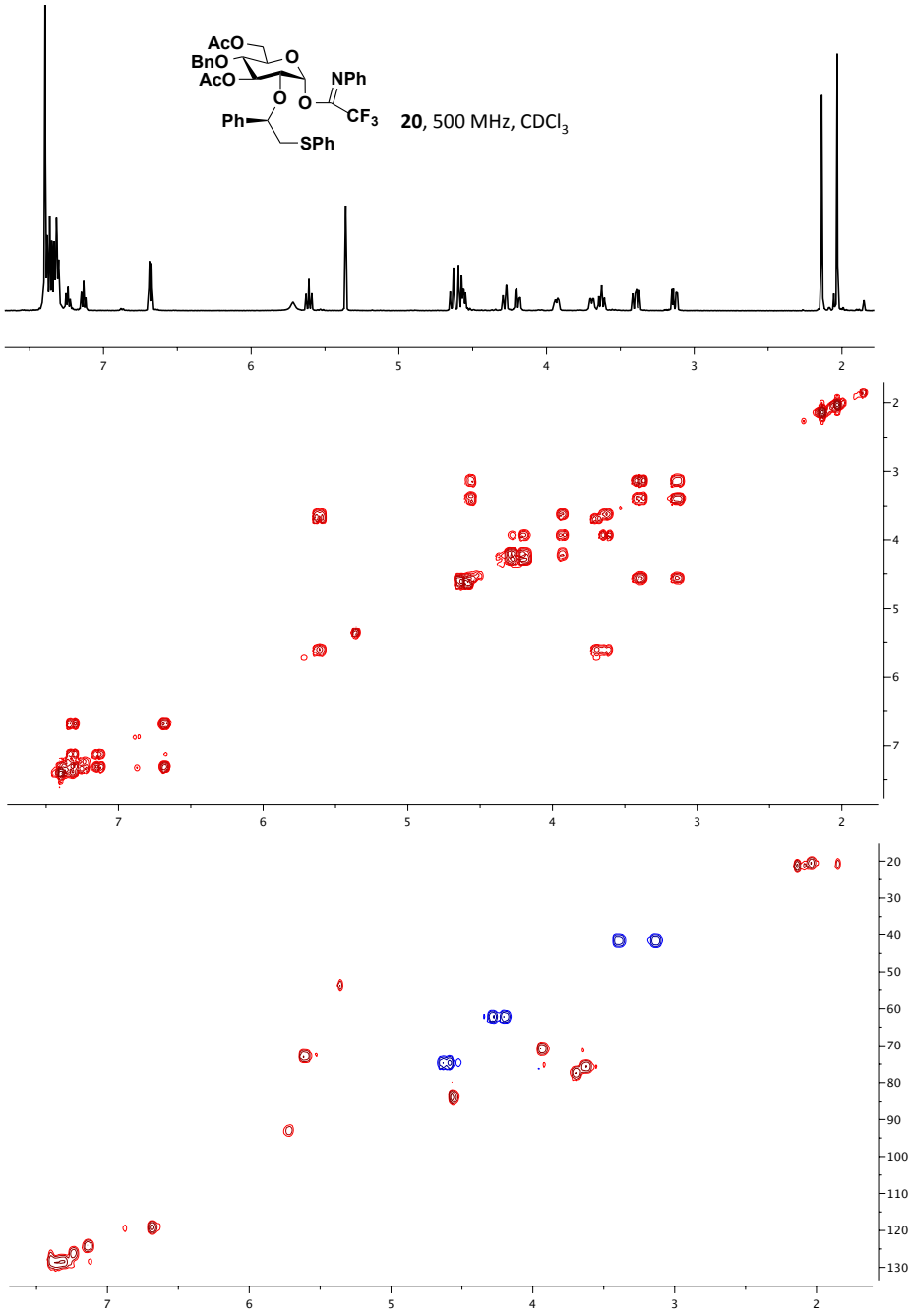
NMR data for synthetic α-glucan

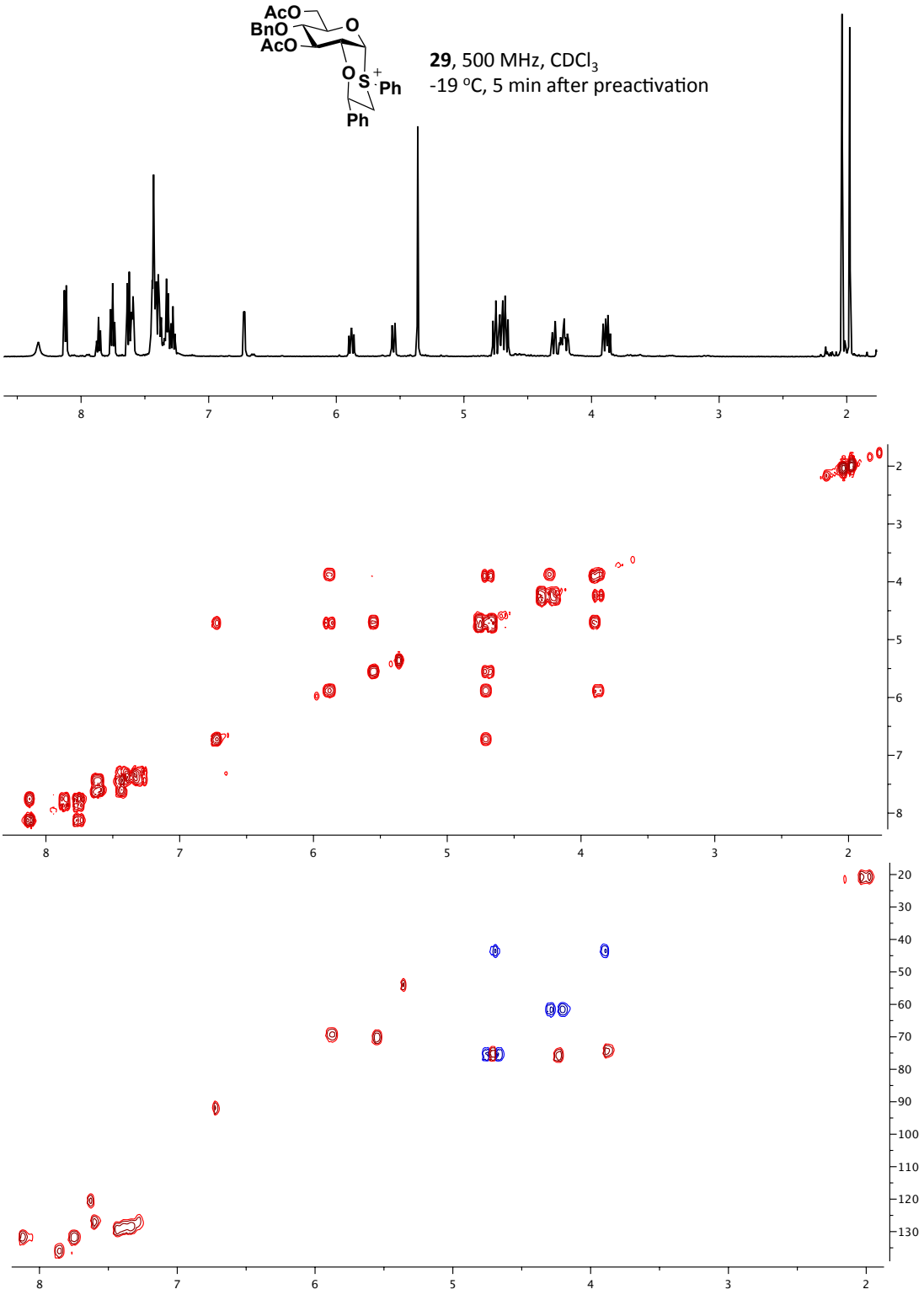


APPENDIX B

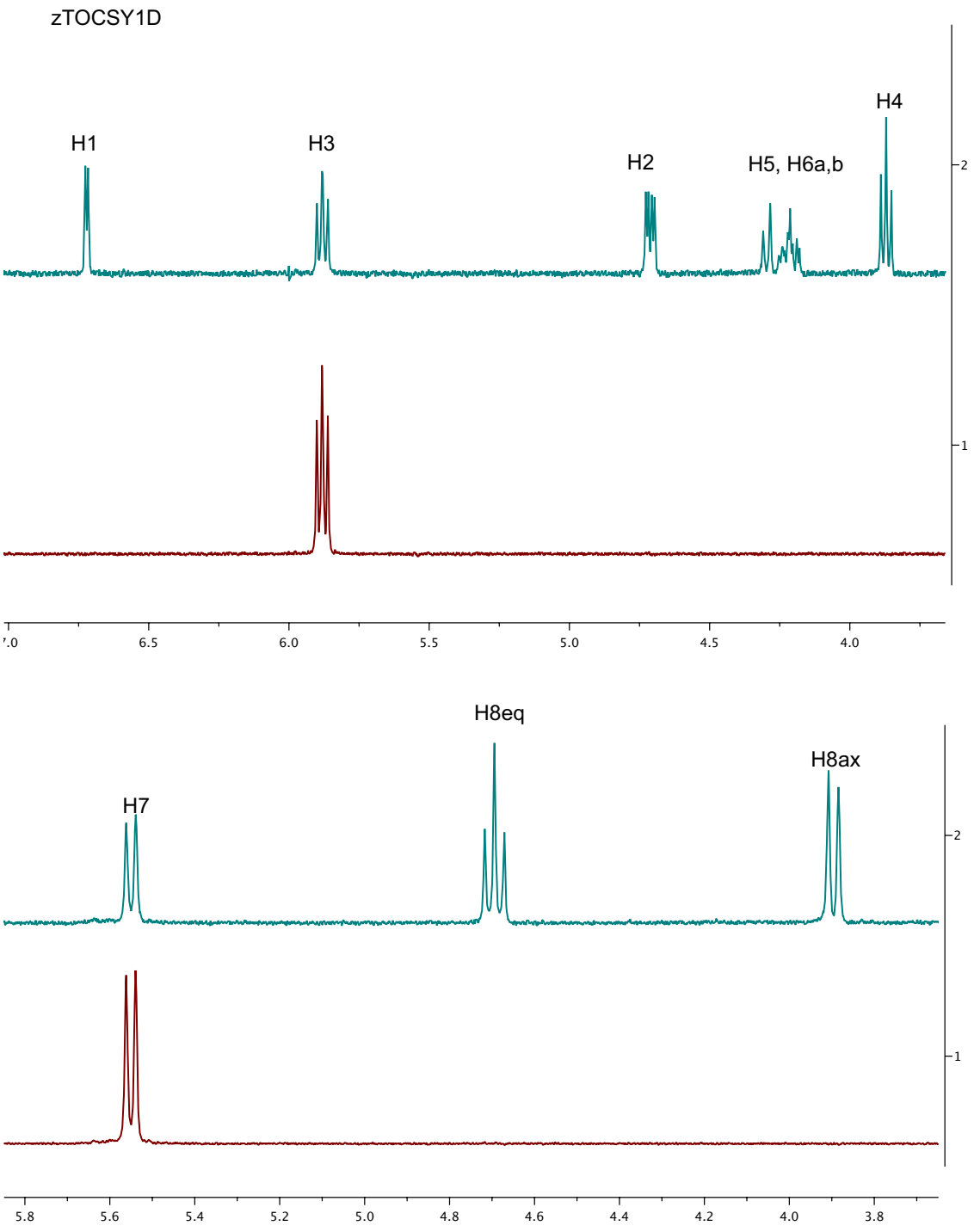
SUPPLEMENTARY DATA FOR CHAPTER 3

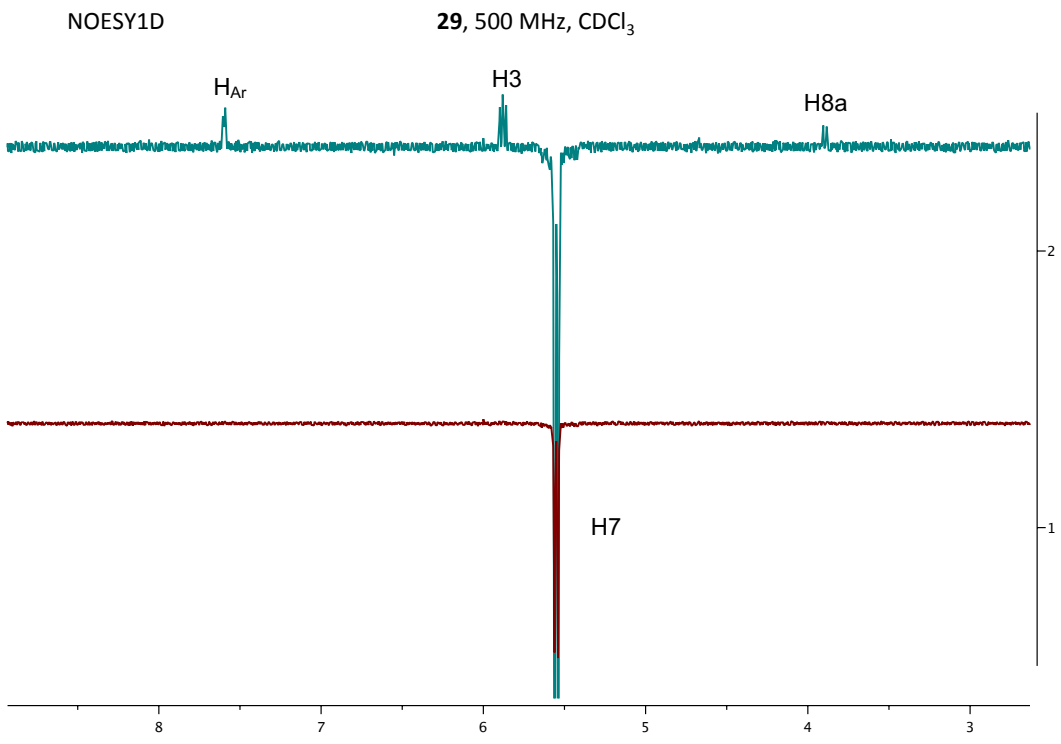
NMR data *cis*-decalin sulfonium ion




AcO
BnO
AcO
O
O
S
+
Ph
Ph
29, 500 MHz, CDCl3
-19 °C, 5 min after preactivation

29, 500 MHz, $CDCl_3$

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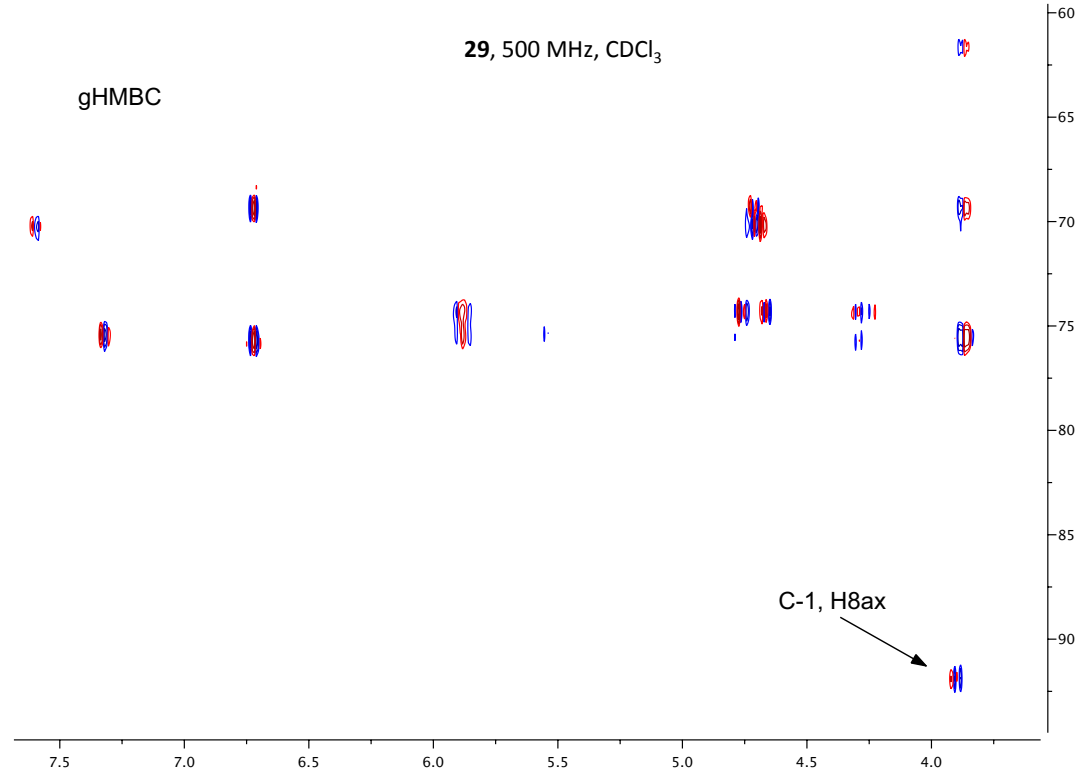
H3
H8a
H7
2
1
8
7
6
5
4
3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gHMBC
C-1, H8ax
60
65
70
75
80
85
90
7.5
7.0
6.5
6.0
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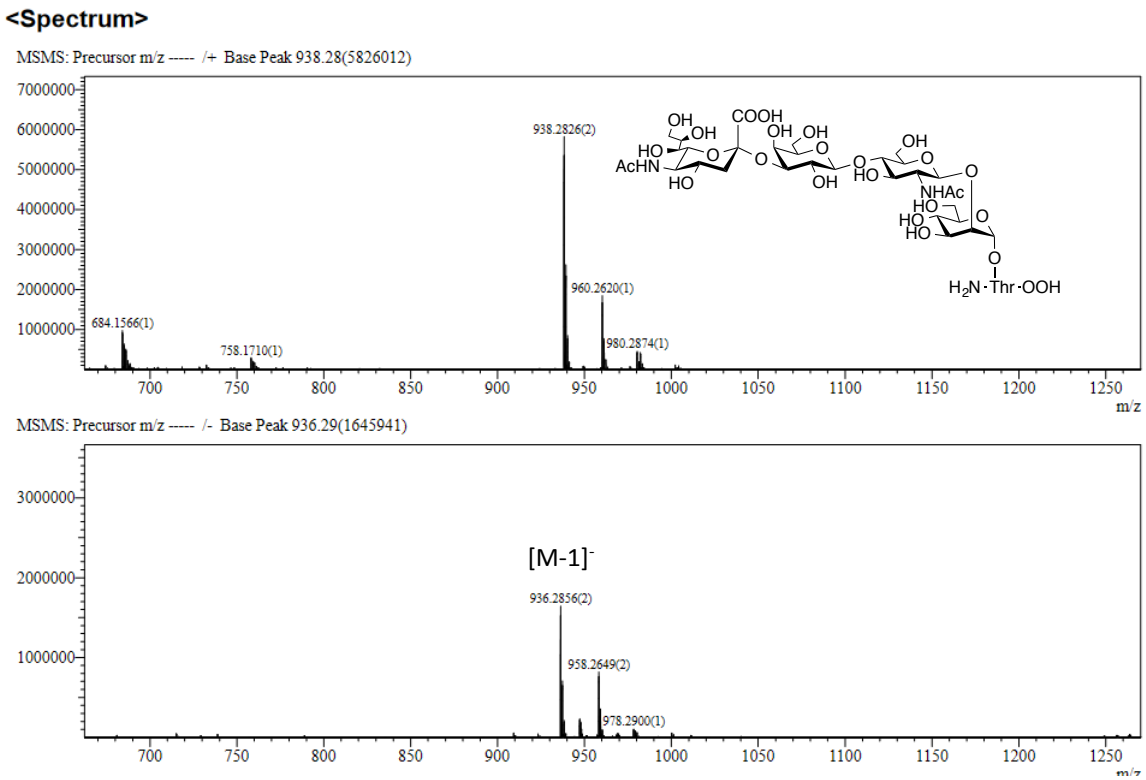
5.0
4.5
4.0

APPENDIX C

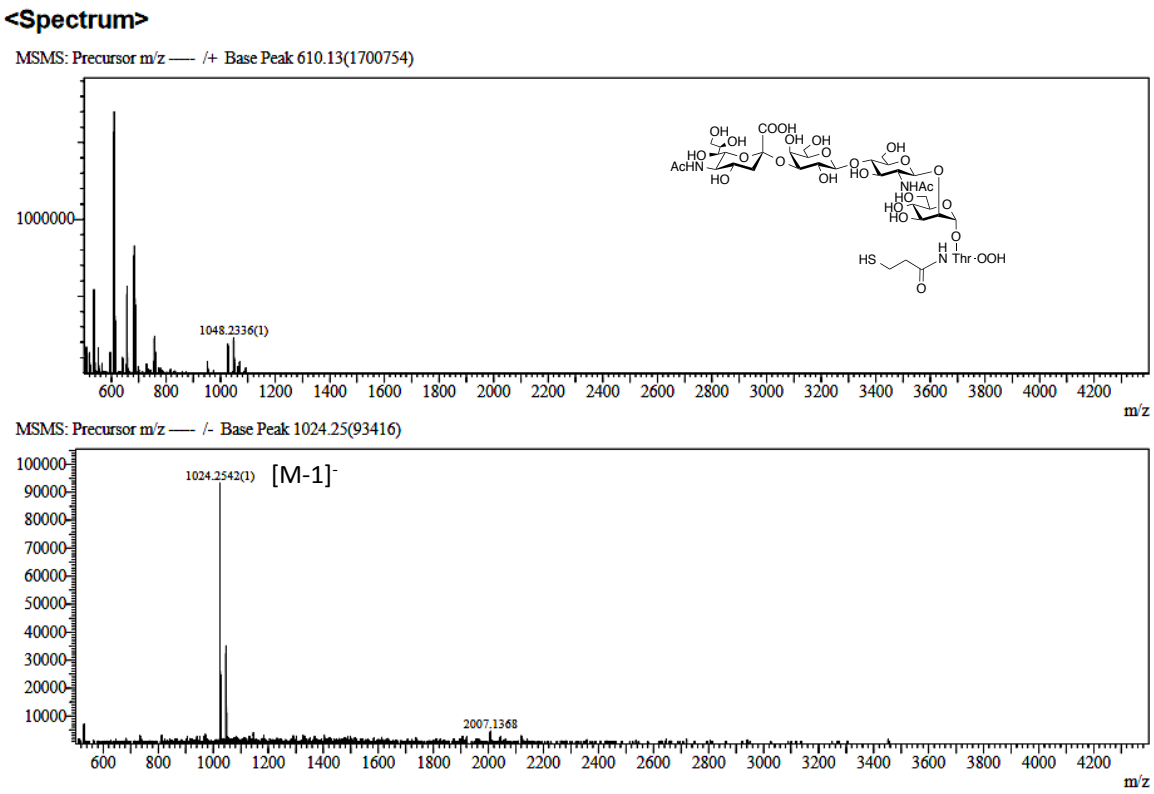
SUPPLEMENTARY DATA FOR CHAPTER 4

MS data for final tetrasacharride and conjugated proteins

i)



ii)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1000000
1048.2336(1)
600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600 2800 3000 3200 3400 3600 3800 4000 4200
m/z
MSMS: Precursor m/z ---- /- Base Peak 1024.25(93416)
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
1024.2542(1)
[M-1]-
2007.1368
600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600 2800 3000 3200 3400 3600 3800 4000 4200
m/z