CHIRAL AUXILIARIES FOR 1,2-*CIS* STEREOSELECTIVE GLYCOSYLATIONS

by

JIN PARK

(Under the direction of Geert-Jan Boons)

ABSTRACT

A novel strategy for the stereoselective introduction of 1,2-*cis*-glycosides is described here. The new glycosylation approach is based on neighboring group participation of a (*S*)-(phenylthiomethyl)benzyl chiral auxiliary at the C-2 of a glycosyl donor which can form a quasi-stable anomeric sulfonium ion. The formation of *trans*-decalin is expected due to steric and electronic factors. Displacement of the equatorial anomeric sulfonium ion by glycosyl acceptors leads to the stereoselective formation of α-glycosides. NMR experiments were employed to show convincingly the presence of the β-linked sulfonium ion intermediate. This methodology has been applied to the synthesis of Galili trisaccharide, an epitope that can trigger acute rejections in xeno-transplantations. To explore the possibility of the remote participation of the chiral auxiliary, a series of 2-deoxy glycosyl donors containing a chiral auxiliary at C-6 were synthesized. This methodology proved to be very useful for the synthesis of 2-deoxy glycosides for α-selective glycosylations.

In situ formation of sulfonium ions by addition of thioethers to the reaction mixture was also investigated. We have observed that glycosylations of 2-azido-2-deoxy-glucosyl donors performed in the presence of a thioether such as PhSEt provide glycosides with excellent α-selectivity. Traditional glycosylations with trichloroacetimidates give products within a short period of time. However, the addition of PhSEt led to a different reaction profile. The

glycosylation products were formed over a period of several hours. Thus it is reasonable to assume that the intermediate sulfonium-ion had been formed. NMR and computational studies have indicated that steric factors determine the selective formation of the β-anomeric sulfonium ion.

INDEX WORDS: Chiral auxiliary, Carbohydrate, Glycosylation, Sulfonium ion.

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DEDICATION

To my parents, my wife Suyeon and my family for their unconditional love and prayers

To God in his unwavering love

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LIST OF ABBREVIATIONS

Å ……..Ångström

Ac ……Acetyl

Ac_2O……...Acetic anhydride

AcOH…….. Acetic acid

All……..……..……...Allyl

AgOTf..... Silver triflate

AIBN.....2,2′-Azobis(2-methylpropionitrile)

Bn……..……...……...……Benzyl

BF_3•OEt_2……..……Borontrifluoride diethyletherate

BSP ..... 1-Benzenesulfinyl piperidine

Bu_4NBr……Tetrabutyl ammonium bromide

Bz……..……..……...Benzoyl

CSA……..……Camphor-2-sulphonic acid

COSY…….....Correlation homonuclear spectroscopy

DAST..... (Diethylamino)sulfur trifluoride

DBU……..…1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM……...Methylene chloride

DDQ ……2,3-Dicyano-5,6-dichloro quinone

DMAP…… *N,N*-Dimethylaminopyridine

DMF……*N,N*-Dimethylformamide

DMTST….....Dimethyl(methylthio)sulfoniumtriflate

DTBMP….....2,6-Di-*tert*-butyl-4-methylpyridine

eq……..Equivalent

Et……Ethyl

EtOH……Ethanol

Et_2O……Diethyl ether

Fuc……Fucoside

Gal……Galactoside

Glc……Glucoside

h……Hour

Hz……Hertz

HMBC……Heteronuclear multiple bond correlation

HSQC……Heteronuclear single quantum coherence

IAD ..... Intramolecular aglycon delivery

IDCP……Iodonium dicollidine perchlorate

m……Multiplet

m/z……Mass to charge ratio

Man……Mannoside

MALDI-TOF……Mass assisted laser desorption ionization time of flight

Me……Methyl

MeOH……Methanol

MeCN..... Acetonitrile

MeOTf.....Methyl triflate

$MgSO_4$……..... Magnesium sulfate

Min……Minute

mM……Millimolar

mmol……Millimole

MS……Molecular sieves

Ms……Methanesulfonyl

NBS……*N*-Bromosuccinimide

NIS……..*N*-Iodosuccinimide

NMR……Nuclear magnetic resonance

NOESY…… Nuclear overhauser enhancement spectroscopy

NPth……...*N*-Phthalimido

Naph……2-Naphthalenemethanol

Pd/C……...Palladium on charcoal

Ph……Phenyl

q……Quartet

Rf……Retention factor

RT……...Room temperature

s……...Singlet

SEt……Thioethyl

t……Triplet

TBAF……...Tetrabutylammonium fluoride

TBDMS……...*tert*-Butyl dimethylsilyl

TBDPS……*tert*-Butyldiphenylsilyl

TFA……Trifluoroacetic acid

Tf……Trifluoromethanesulfonyl

TfOH……Trifluoromethanesulfonic acid

THF……Tetrahydrofuran

TLC……Thin layer chromatography

TMSOTf……Trimethylsilyl trifluoromethanesulfonate

TOCSY…… Total correlation spectroscopy experiment

Ts……*p*-Toluenesulfonyl

CHAPTER I

INTRODUCTION AND LITERATURE REVIEW

Carbohydrates in biological systems

Polysaccharides and glycoconjugates play important roles in a range of biological processes such as development of immunity, fertilization, viral replication, cell growth, cell trafficking, cell-cell adhesion and communication, blood anticoagulation and inflammation.[1-3] Protein structure and function are modulated by post-translational modification by glycosylation.[4-8] Errors in these glycosylation patterns may result in serious outcomes which are seen by the growing number of human health related disorders such as so-called Congenital Disorder of Glycosylation (CDG).[9] Furthermore, interactions between carbohydrates and proteins are involved in pathogen attachment, invasion and replication and inflammatory responses.

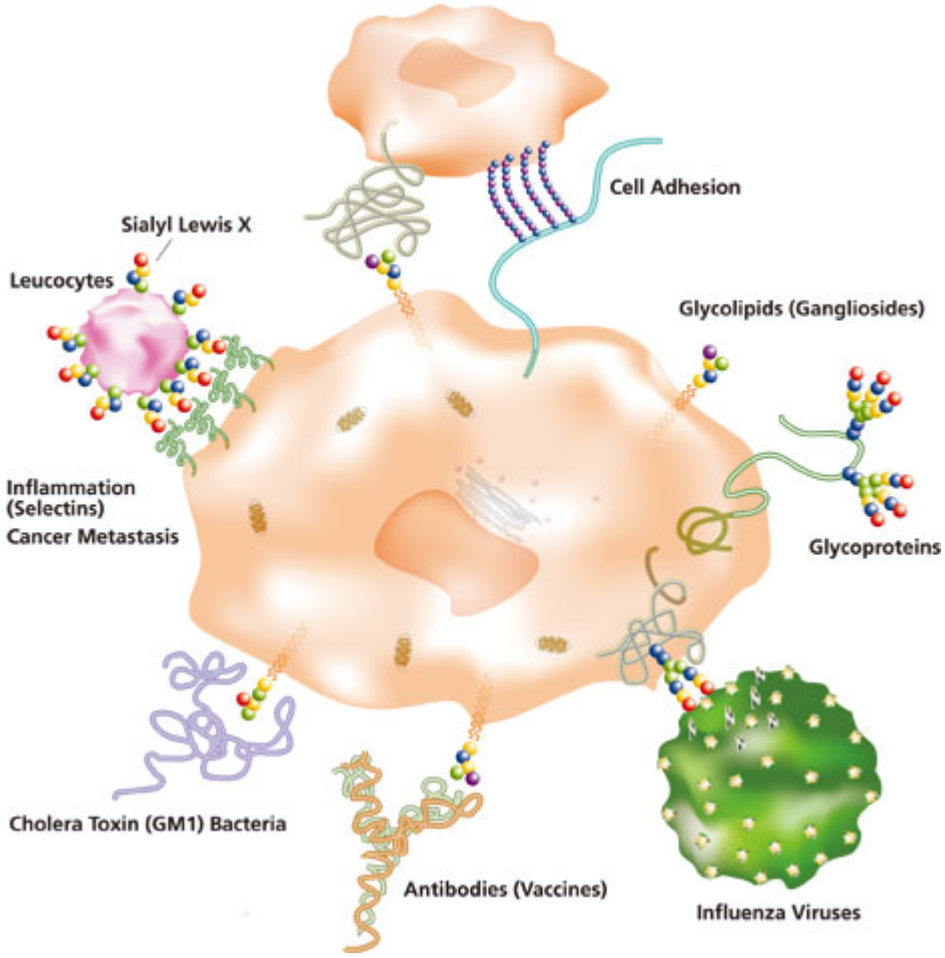
Traditionally, analyzing carbohydrate-protein and carbohydrate-lipid interactions has been quite challenging for several reasons. First, obtaining carbohydrates in pure homogeneous forms is extremely difficult. Secondly, there are no dependable techniques to study and confirm these carbohydrate-biomolecular interactions. Current techniques such as Isothermal Calorimetry (ITC), Surface Plasmon Resonance (SPR), and mass spectrometry are used, but these are too labor intensive and require large amounts of carbohydrate sample. Microarray technology can overcome many of these challenges. In general, sugars are attached to a microarray chip in large numbers with the help of an artificial linker. Microarray screening is a very sensitive high throughput method to measure binding events. One of the best resources for glycan array screening is the Consortium for Functional Glycomics (CFG). The CFG has

developed one of the largest glycan arrays in the world and has provided routine screening to many investigators.[10-12]

Carbohydrate-based vaccines

Healthy cells can be differentiated from cancerous cells with the help of carbohydrates they express. For instance, during the development and progression of a tumor, cell-surface carbohydrates change dramatically, which may lead to metastasis. These modified carbohydrates on the surface of the tumor cells can be used for targeting therapeutics towards tumor cells. Also, potent semi-synthetic cancer vaccination strategies have been designed and developed which are based on mimicking the carbohydrate signatures found on tumor cells. The carbohydrates present on cell surfaces have been used as synthetic polysaccharide epitopes and these have been exploited for new strategies for vaccine development.[13] Efforts are taken to develop vaccines for infectious diseases such as *Haemophilus influenza* tybe b, HIV*, Plasmodium falciparum, Vibrio chlorella, Cryptococcus neoformans, Bacillus anthrasis and Candida albicans*.[14-17] Natural polysaccharides have been employed for vaccine development, but they often lose important immune-dominant features during chemical manipulations and can also contain toxic compounds which may be difficult to remove.[14] Organic chemistry provides a key technology for obtaining these carbohydrates, which possess undisputable structural integrity in large quantities and can be conjugated to proteins in a controlled fashion by artificial linkers.

Chemical syntheses of complex oligosaccharide structures have become an essential component of glycobiology. Diversity and complexity in the molecular architecture of complex oligosaccharides offers various appealing synthetic challenges. The continued improvements in synthetic methodology have equipped organic chemists with more sophisticated tools including one-pot syntheses and automated synthesis.[18]



This image has been taken from tansaku.otsukac.co.jp/en/oligo02.html

Figure 1.1. The various functions and processes involving oligosaccharide interactions

Carbohydrates can be classified according to relative stereochemistry. The configuration determined by the anomeric position is most commonly referred to as α- and β- or 1,2-*cis* and 1,2-*trans* glycosides. The α- and β- configuration depends on the stereochemical relationship between the anomeric center and the configuration of the most distant stereogenic center. If the hydroxyl groups bound to this center point in the same direction (*cis*), this anomer is called an α-anomer, when they are pointing in opposite directions (*trans*), it is named the β–anomer. 1,2-*Cis* glycosides (such as D-glucose, D-galactose, L-fucose, D-xylose which are α-configured and D-mannose, L-arabinose which are β-configured) and their 1,2-*trans* counterparts (such as D-glucose, D-galactose which are β-configured and D-mannose which is α-configured) are equally

important components of natural products. Some other types of glycosides, in particular 2-deoxy-glycosides and sialosides, cannot be defined 1,2-*cis* or 1,2-*trans* derivatives, yet are important targets because of their common occurrence as components of many classes of natural glyco-structures (**Figure 1.2**).

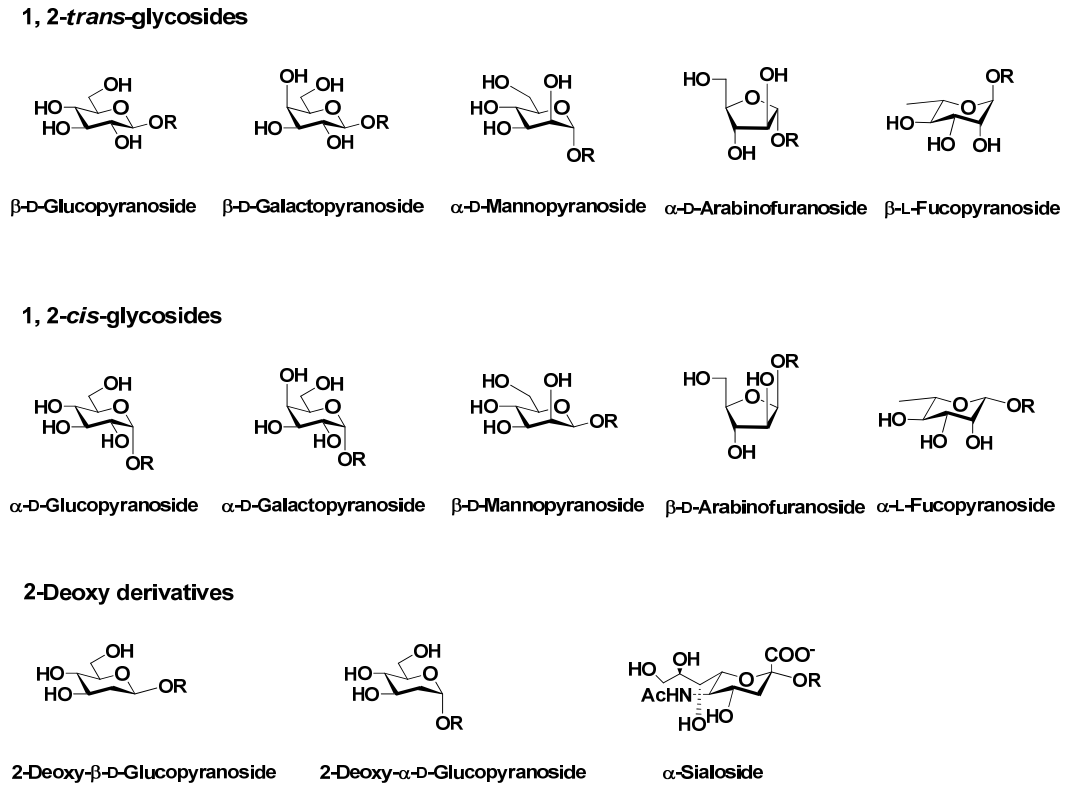
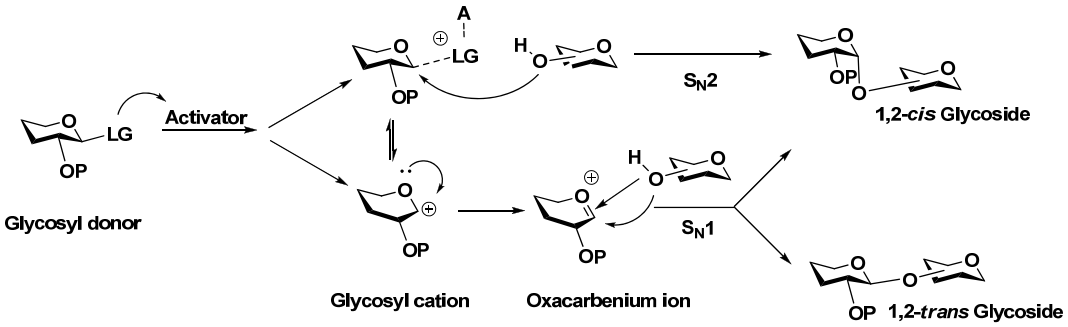


Figure 1.2. General nomenclatures of carbohydrates

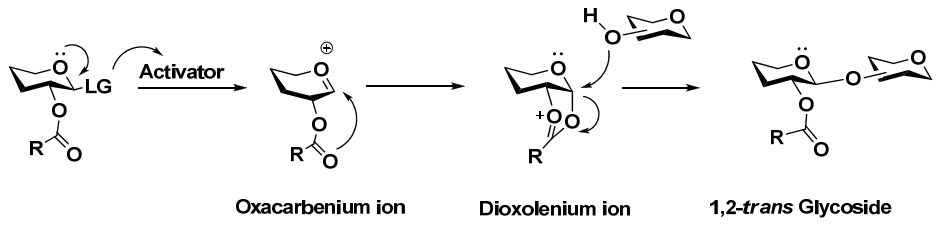
1.1 General aspects of glycosylation

The development of synthetic procedures for the stereoselective introduction of glycosidic linkages is a main challenge in oligosaccharide synthesis. Since Koenigs and Knörr described the first stereoselective glycosylation, numerous methods for the synthesis of glycosidic linkages have been reported.[19-21] The efficient chemical construction of a glycosidic bond by organic synthesis entails the regio- and stereoselective condensation of two polyfunctional reaction partners ideally affording a single product. A typical glycosylation reaction starts with the activation of an anomeric substituent (leaving group, **LG**) of a glycosyl donor by an appropriate activator (**A**). The bond between the anomeric carbon atom and leaving group is partially or completely broken, affording an electrophilic glycosyl intermediate which undergoes nucleophilic attack by a hydroxyl group of an acceptor (**ROH**) to afford a glycosidic bond (**Scheme 1.1**).[22] Even though the α-product is thermodynamically favored because of the so-called anomeric effect,[23] the outcome of a glycosylation reaction in terms of yield and stereochemistry is difficult to predict because of its dependence on other factors such as the reactivity of the anomeric leaving group, the activator system, the reaction conditions (*e.g.* temperature, solvent, etc.), the protecting groups, and the structure of both the glycosyl donor and acceptor.[24,25] The glycosylation reactions often give a mixture of the two possible anomers. The separation of these two isomers can be quite cumbersome. *In vivo*, the stereochemical purity of glycosylation products is not an issue as glycosyl transferases are responsible for giving rise to stereoselective glycosides. Thus, chemical *O*-glycosylation with complete stereoselectivity remains the principle challenge in complex oligosaccharide synthesis.



Scheme 1.1. General glycosylation reaction mechanism

The stereoselective synthesis of 1,2-*trans* glycosides can be achieved by neighboring group participation. As shown in **scheme 1.2**, promoter-assisted departure of a leaving group from a glycosyl donor results in the formation of an oxacarbenium ion. After activation of the glycosyl donor, the oxacarbenium intermediate is intramolecularly trapped by C-2 acyl group such as *O*-acetyl (Ac) and *O*-benzoyl (Bz)[20] to give a dioxolenium ion. This intermediate can undergo an S_N2-like attack leading to 1,2-*trans* glycosides. Indeed, a variety of glycosyl donors give excellent 1,2-*trans* stereoselectivity in almost quantitative yields.



Scheme 1.2. Neighboring group participation by C-2 ester leading to 1,2-*trans* glycosides

Hence, neighboring group participation by C-2 esters is very reliable and is extensively used to synthesize 1,2-*trans* glycosides. General strategies for 1,2-*cis* glycosylation depend on use of a non-participating functionality at C-2 position such as alkyl ethers. The most commonly applied nonparticipating groups are benzyl ethers and azide (N_3) for 2-amino-2-deoxy sugars. However, it must be noted that the use of such a functionality does not guarantee the stereoselective formation of 1,2-*cis* glycosidic linkages.

1.2 Methods to control 1,2-*cis* stereoselectivity

1.2.1 Anomeric effect

The anomeric effect, which originally was defined as the preference of an electronegative substituent at the anomeric position of a carbohydrate to be axially rather than equatorially oriented, is now understood to be the result of stereoelectronic interactions. The anomeric effect is of a different magnitude in every case. It is strongly influenced by the substituent at C-2. When this substituent is equatorial, as in glucose and galactose, the anomeric effect is weakened, and is enhanced in the case of an axial C-2 substituent as in mannose. An aqueous solution of D-glucose, for example, contains the α- and β-form in a ratio of 36:64 whereas for mannose it is 69:31. A more electronegative substituent at the anomeric position changes the observed ratio to even a greater extent. The unusual preference of sterically unfavored axial position over the equatorial position at the anomeric center has been termed the anomeric effect by R. Lemieux (**Figure 1.3**).[26]

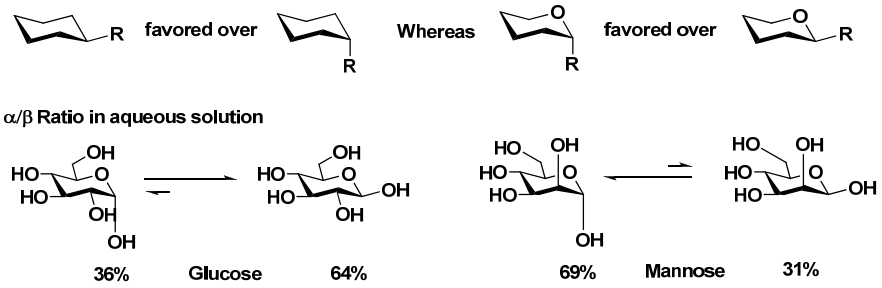


Figure 1.3. Anomeric effect

The anomeric effect can be explained by several models, but there are two most widely accepted explanations, namely orbital stabilization[27] and dipole destabilization.[28] The orbital stabilization theory is based on cyclic acetal systems preferring their substituents to display a gauche arrangement around two contiguous C-X bonds (where X = electronegative element). For carbohydrate systems, one of the C-X bonds is a C-O bond. When the two bonds display the gauche arrangement, the lone pair electrons on the oxygen atom within the ring is displaced

antiperiplanar to the substituent C-X bond. This arrangement is stereoelectronically favored, as donation of the lone pair electrons on the ring oxygen into a vacant σ*orbital of the adjacent heteroatom can occur.[27] The other model is based on the intramolecular electrostatic interactions of two dipoles of the anomeric center. One of the two dipoles arises from the lone pair electrons of the endocyclic carbohydrate ring oxygen. The other dipole points are along the polarized bond between the anomeric carbon atom and its bound atom. Anomeric configurations in which the two dipoles are anti parallel are favored over the diastereomers where the anomeric configuration leads to partial intramolecular addition and thus repulsion of two dipoles (**Figure 1.4**). [28]

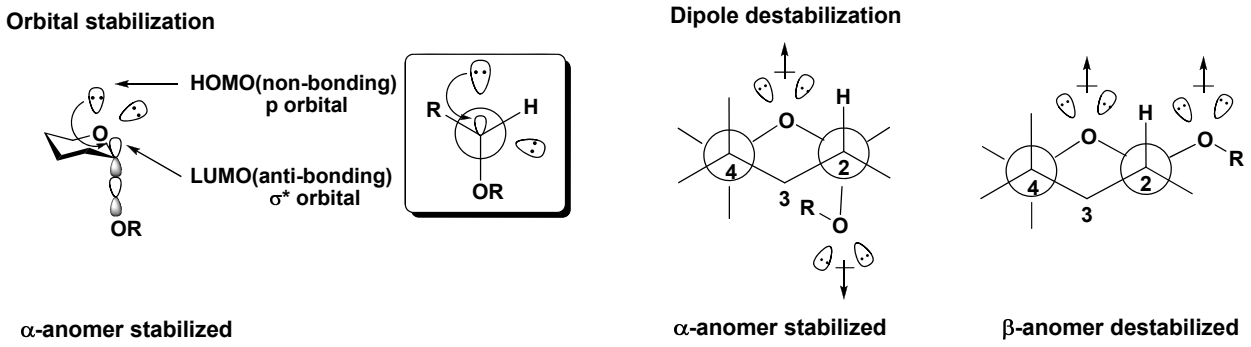


Figure 1.4. Two most widely accepted explanations of the anomeric effect

Despite the favorable influence of the anomeric effect on the formation of 1,2-*cis* linkages in the gluco-series (equatorial C-2 substituent), the degree of selectivity as obtained for the introduction of 1,2-*trans* glycosides by neighboring group participation is seldom attained. The construction of 1,2-*cis*-linkages with donors bearing an axial C-2 substituent, as in β-D-mannosides and β-L-rhamnosides, is even more daunting for the following reasons. First, equatorial attack of the acceptor suffers from unfavorable steric interactions with the axial C-2 substituent. Secondly, 1,2-*cis*-product formation does not benefit from stabilization by the anomeric effect. Thirdly, there is an additional α-favoring interaction, the so-called Δ effect (**Figure 1.5**). [29,30]

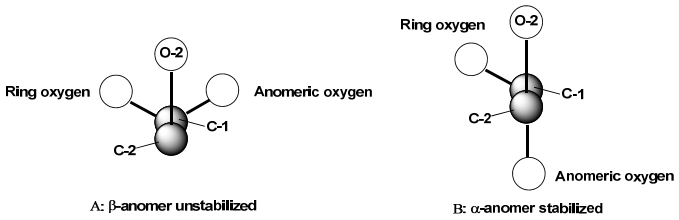
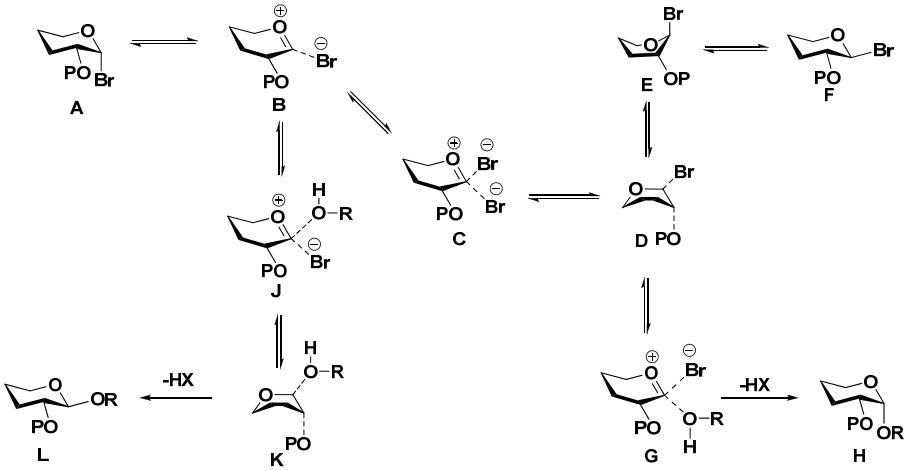


Figure 1.5. The Δ effect: In A, three atoms are in close proximity resulting in conformational instability. In B, Less stereo-electronic repulsion more stable.

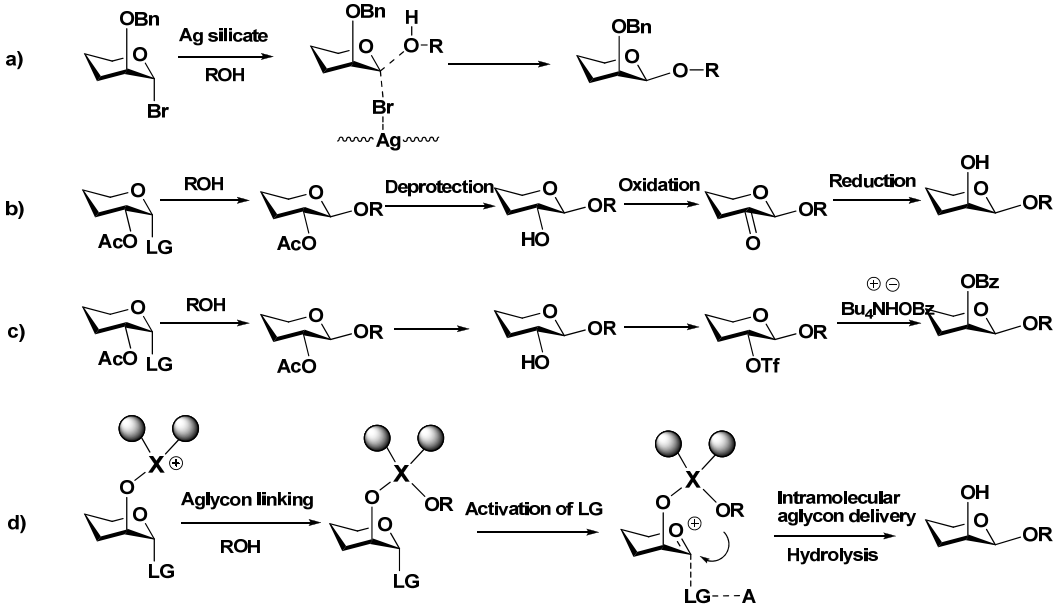
In-situ anomerization described by Lemieux and co-workers was the first reported method for the synthesis of 1,2-*cis* glycosides. In this approach, a rapid equilibrium needs to be established between a thermodynamically stable α-halide (**A**) and the more reactive β-halide (**F**) (*via* **B**-**C**-**D**-**E**) by for example, the addition of the tetra-butyl ammonium bromide (Bu_4NBr). Since the energy barrier of nucleophilic substitution of the β-halide (**F**) with the alcohol leading to the *cis*-glycoside (**H**) (*via* **E**-**D**-**G**) is lower than that of the corresponding reaction of the α-halide (**A**) to the *trans*-glycoside (**L**) (*via* **B**-**J**-**K**). The formation of 1,2-*cis* glycosides is faster than that of 1,2-*trans* glycosides. If the difference in the energy barrier is sufficient, it would be possible to direct the reaction of 1,2-cis glycosides stereoselectively. While the reaction has proven useful in several cases, it requires reactive glycosyl donors and acceptors as well as long reaction times (**Scheme 1.3**).[31]



Scheme 1.3. Proposed mechanism of *in-situ* anomerization

1.2.2 Protecting groups

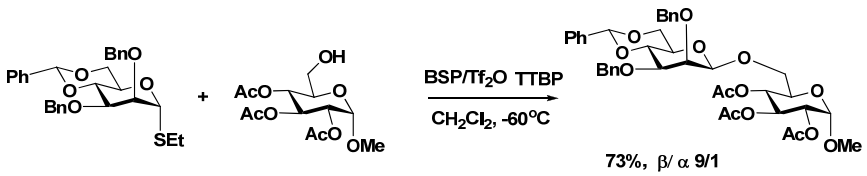
Protecting groups have a major influence on the stereochemistry and reactivity of glycosyl donors and acceptors. The challenge to construct 1,2-*cis* bonds in mannopyranosides has resulted in the development of several methodologies, including insoluble silver salt to promote S_N2 displacements of α-mannosyl bromides (**Scheme 1.4a**). [32] Indirect methods are based on manipulation at C-2 (direct oxidation→reduction (**Scheme 1.4b**)[33-35] for conversion of β-glucosyl inversion (**Scheme 1.4c**))[36-39] or tethering of the aglycon to the glycosyl donor prior to the actual coupling (**Scheme 1.4d**).[40-46]



Scheme 1.4. Methods for 1,2-*cis* mannosylations

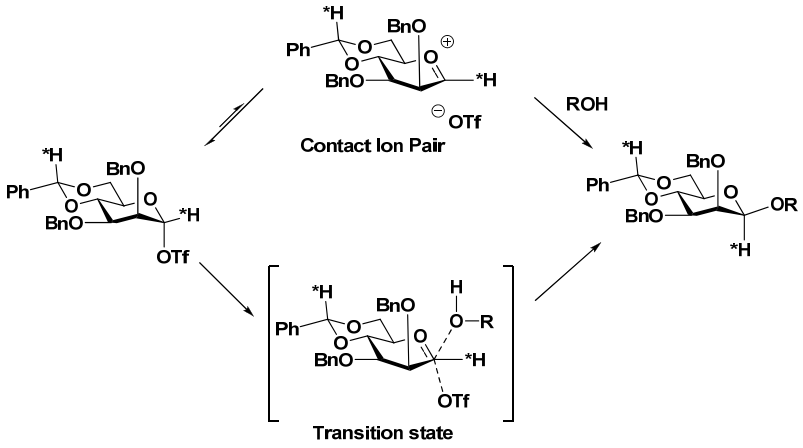
As mentioned above, the α-mannosidic linkage is strongly favored because of the concomitant occurrence of both the α-directing anomeric effect and repulsion between the axial C-2 substituent and the approaching nucleophile. Crich and co-workers demonstrated that a 4,6-*O*-benzylidene protecting group restricts the conformation of mannosyl donors, which upon activation reacted with acceptors to give the corresponding mannosides in a highly β-selective fashion.[47,48] The reaction involves a two-step, one-pot activation coupling sequence in which first thioglycosyl donor was treated with 1-benzenesulfinyl piperidine (BSP) and

trifluoromethansulfonic anhydride (Tf_2O) at -60 ^oC in DCM in the presence of acid scavenger TTBP, followed by the addition of a glycosyl acceptor (**Scheme 1.5**). [49]



Scheme 1.5. Stereoselective glycosylation of benzylidene constrained donors

The 4,6-*O*-benzylidene acetal was found to be indispensable for high β-selectivity. Crich and Sun suggested that under pre-activation conditions, the oxacarbenium ion is trapped by a triflate anion which would lead to the formation of the more stable α-triflate. A mechanistic study of the reaction by low temperature NMR analysis[50] (^1H, ^{13}C and ^{19}F) strongly suggests the presence of the α-anomeric triflate which is stabilized by the torsionally disarming benzylidene function. The axial triflate is thought to undergo S_N2-type displacement upon addition of a glycosyl acceptor, leading to the formation of a β-mannoside. On the basis of α-deuterium kinetic isotope effects of 4,6-*O*-benzylidene directed β-mannosylation, Crich and Chandrasekera concluded that displacement of the anomeric triflate by the glycosyl acceptor proceeds with the development of substantial oxacarbenium ion character (**Scheme 1.6**).[51]

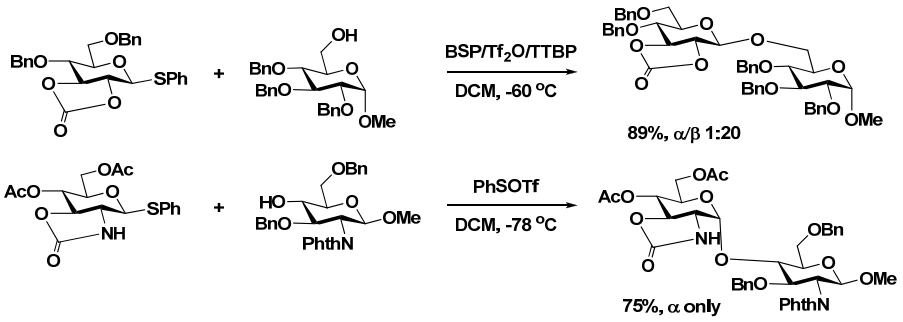


Scheme 1.6. The proposed mechanism of α-deuterium kinetic isotope effects[51]

In earlier work, Fraser Reid found that cyclic acetals fused with *n*-pentenyl glycoside donors could deactivate glycosyl donors by imposing a torsionally disarming effect. Bols and co-workers reported a very comprehensive study to dissect the electronic and torsional effects imposed by 4,6-*O*-acetals. Indeed, Bols established the presence of torsional disarmament of the donor. In addition to the torsional effect, the electronic influence of the 4,6-*O*-acetal was investigated and found to be significant. The *O*-6 can adopt three staggered conformations when no 4,6-*O*-acetal is present: *tg*, *gt* and *gg*. A 4,6-*O*-acetal forces the *O*-6 substituent to adopt the *tg* conformation, which places its dipole roughly anti parallel to the electron deficient center which is formed in the transition state, therefore destabilizing it. In the *gg* and *gt* conformation, the dipoles are more or less perpendicular to the developing positive charge and thus less destabilizing. This electronical disarming effect was found to be roughly equal to the torsional disarming effect of a 4,6-*O*-acetal (**Figure 1.6**).[52,53]

Figure 1.6. Three staggered conformations

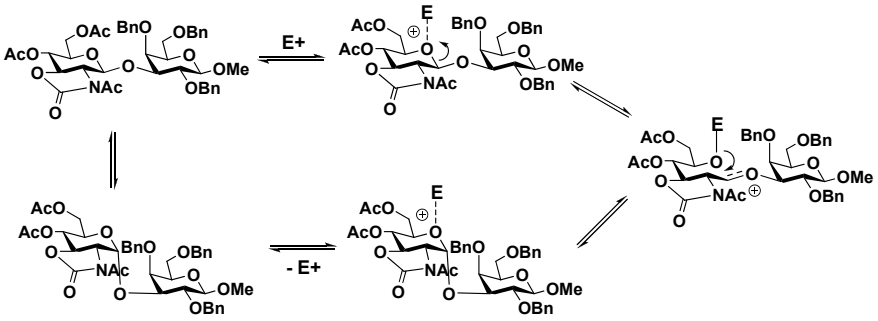
The stereodirecting effect of the benzylidene group inspired a reinvestigation of carbonates and oxazolidinone groups with regards to their influence on anomeric selectivity. Thioglycosides protected with 2,3-cyclic carbonates showed β-selectivities and enabled the synthesis of β-glucosides without recourse to neighboring group participation. The oxazolidinone group has attracted much attention as a stereodirecting group in glycosylations. Many natural products and biologically significant glycoconjugates contain *N*-substituted 2-amino-2-deoxy-D-glycopyranoside residues. While there are a number of strategies to obtain β-linked 2-amino-D-glycopyranosides[54,55] (found in hyaluronate and dermatan sulfate GAGs), the formation of α-linked 2-amino-D-glucopyranosides (found in heparin and heparin sulfate (HS)GAGs) relies almost exclusively on employing 2-azido-glycosyl donors. In general, glycosylations of the 2-azido donors afford α/β mixtures of coupled product, although the α-anomer usually predominates. Kerns and co-workers demonstrated that 2,3-*O*-oxazolidinone protected thioglycosides were highly efficient substrates for the synthesis of α-linked 2-amino-2-deoxy-glucopyranosides (**Scheme 1.7**). [56]



Scheme 1.7. Stereoselective glycosylation of carbonate and oxazolidinone constrained groups

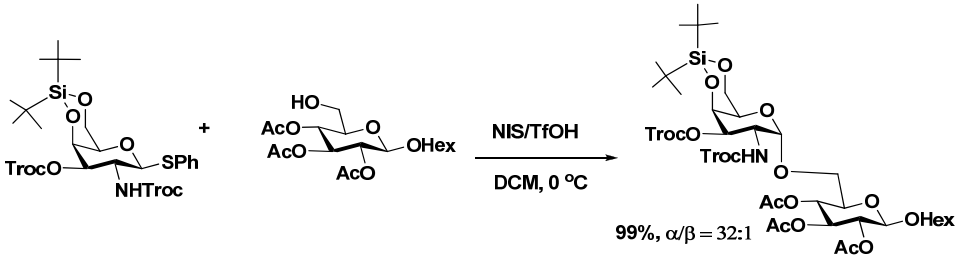
Oscarson and co-workers suggested that these results were due to an efficient anomerization of the initially formed β-glycoside when more acidic conditions were used. NMR-monitored glycosylation reactions show that the β-glycoside is initially formed and anomerized by an intramolecular reaction involving an endocyclic C-O bond cleavage, to give mainly or exclusively an α-glucoside under longer reaction times and more acidic conditions. Both of the

N-acetyl and oxazolidinone group as well as AgOTf were found to be important for an effective anomerization (**Scheme 1.8**).[57]



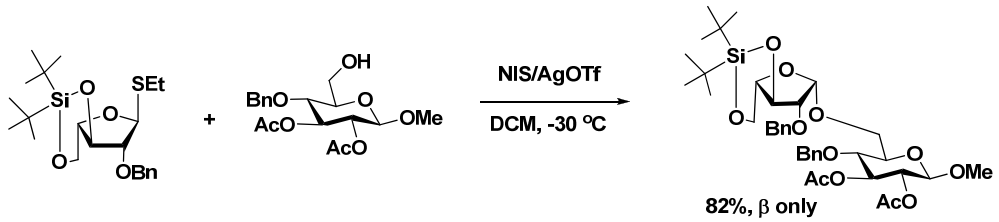
Scheme 1.8. proposed mechanism for the anomerization reaction[57]

Cyclic bifunctional silyl groups have also been used as protecting groups. An interesting example is the di-*tert*-butylsilylene (DTBS) group. It has attracted much attention owing to its strong stereodirecting effect on glycosylation reactions. Glycosylations with galactosyl donors protected with a 4,6-*O*-DTBS group gave the corresponding α-galactosides with very high selectivities. High α-selectivities were even observed in the presence of a C-2 neighboring participating groups, which indicates that the DTBS group has a very strong effect. It has been rationalized that the bulky DTBS group blocks the β-face of galactoside, leading the nucleophile to approach from the α-face (**Scheme 1.9**).[58]



Scheme 1.9. DTBS directed α-galactosylation[58]

The DTBS group was also used to control the anomeric configuration in the formation of L-arabinofuranosides. A new practical approach for the stereoselective introduction of β-L-arabinofuranosides has been demonstrated by Boons and coworkers (**Scheme 1.10**). [59]



Scheme 1.10. Stereoselective glycosylation of silyl constrained donors[59]

In this approach, the arabinosyl donor has a 3,5-*O*-(di-*tert*-butylsilane)-protecting group, which can lock the oxacarbenium ion in the E_3 conformer. As a result, oxacarbenium ions of L-arabinofuranosides can adopt two possible low energy conformations in which C-3 is either above (^3E) or below the plane (E_3) of C-4,O (endo), C-1 and C-2. Analysis of the Newman projection of ^3E conformer indicated that nucleophilic attack from the β-face is disfavored due to siginificant steric interactions from an eclipsed C-2 substituent. On the other hand, an approach from the α-face is preferred, because it will encounter only staggered substituents. In contrast, nucleophilic attack from the α-face of the E_3 conformer is predicted to be disfavored because it will experience an eclipsed H-2. In this case, an approach from the β-face is more favorable because it will encounter only staggered constituents (**Figure 1.7**).[59]

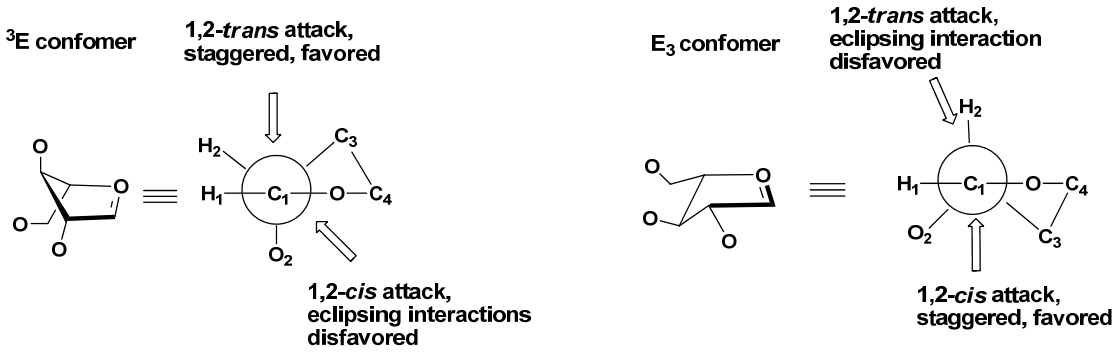


Figure 1.7. Two low energy conformations ^3E and E_3 of oxacarbenium ions of L-arbinose

1.2.3 Glycosyl donors

Considerable effort has been devoted to the development of synthetic methodologies towards the construction of complex oligosaccharides. A variety of new anomeric leaving groups such as thioglycosides,[60] glycosyl trichloroacetimidates,[61] glycosyl halides,[62] glycosyl sulfoxides[63] and *n*-pentenyl glycosides[64] have been used as glycosyl donors for the synthesis of various important oligosaccharides. These set of donors can be prepared under mild conditions and are sufficiently robust for purification and storage for a considerable period of time. Additionally, glycosylations can be carried out under mild reaction conditions. All these favorable features permit the construction of complex oligosaccharides by highly convergent strategies. Regardless of all these important advances, complex oligosaccharide synthesis still remains a major challenge. The fact remains that no general reaction conditions exist for carbohydrate synthesis (**Figure 1.8**).

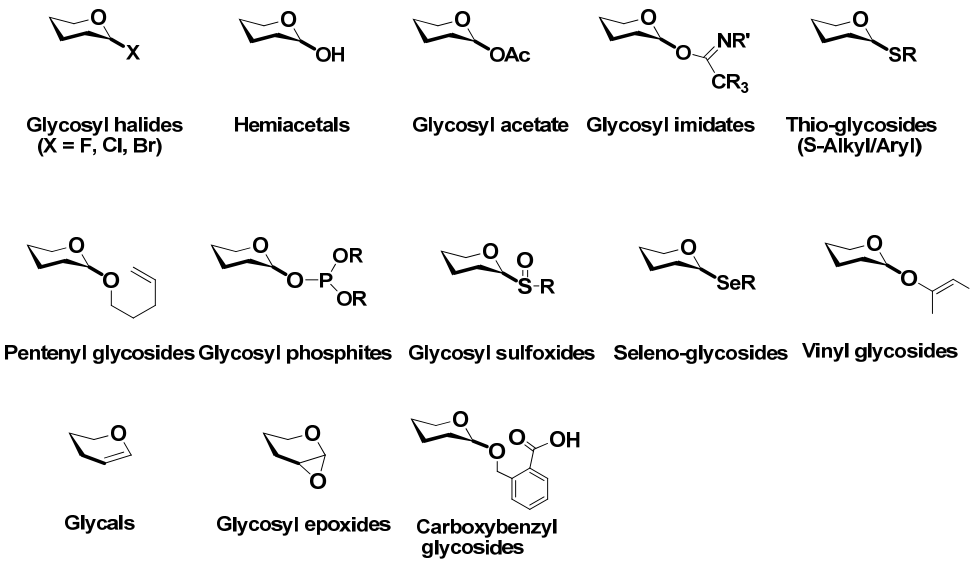
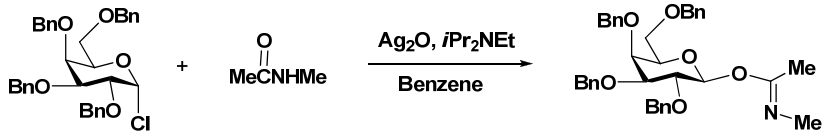


Figure 1.8. Glycosyl donors with different leaving groups

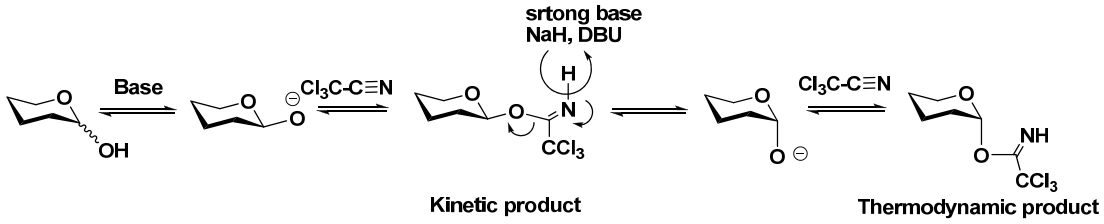
Imidate donors

Glycosyl acetimidates were introduced by Sinaÿ and coworkers as an alternative to the classic Koenigs-Knörr approach for the synthesis of 1,2-*cis* glycosides. They are prepared by the reaction of perbenzylated glycosyl chlorides with *N*-methylacetamide (**Scheme 1.11**). [65]



Scheme 1.11. Synthesis of glycosyl acetimidates

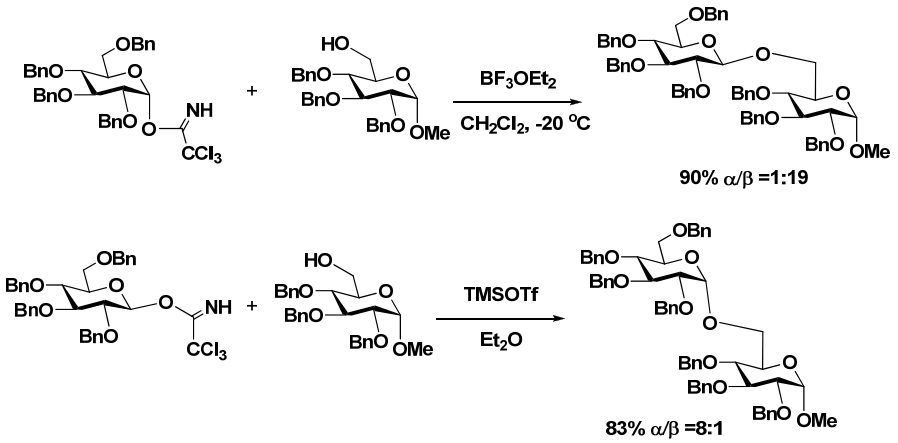
The original imidate methodology was further developed by Schmidt, who discovered that trichloroacetimidates are more potent glycosyl donors. The trichloroacetonitrile readily adds to the hydroxyl of lactols under basic conditions. In the presence of a weak base, such as potassium carbonate, the β-trichloroacetimidate can be isolated as the kinetic product, whereas the use of a strong base, such as sodium hydride or DBU, results in the formation of thermodynamically more stable α-trichloroacetimidates (**Scheme 1.12**). [66-68]



Scheme 1.12. Formation of glycosyl trichloroacetimidates

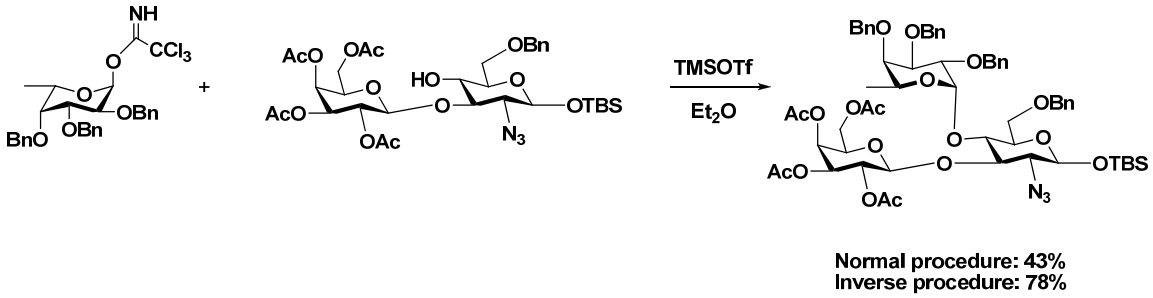
The general significance of *O*-glycosyl trichloroacetimidates lies in their ability to act as potent glycosyl donors under relatively mild acid catalysis. Initially, Lewis acids, such as *p*-TsOH and BF_3OEt_2 were used as activators, however, TMSOTf is currently the most frequently employed activator. Glycosylations with these activators take place at low temperatures under mild conditions. The use of BF_3OEt_2 favors the formation of the reaction product with inversion of configuration. Moreover, the use of TMSOTf in diethyl ether preferentially affords 1,2-*cis* glycosides. Thus BF_3OEt_2 promoted reaction of the α-trichloroacetimidate with glycosyl acceptor

afforded the disaccharide with high β-selectivity, whereas reaction of the β-imidate, assisted by TMSOTf, resulted in the formation of the α-glycosides as the major product (**Scheme 1.13**).[66]



Scheme 1.13. Stereoselective glycosylations of glycosyl trichloroacetimidates

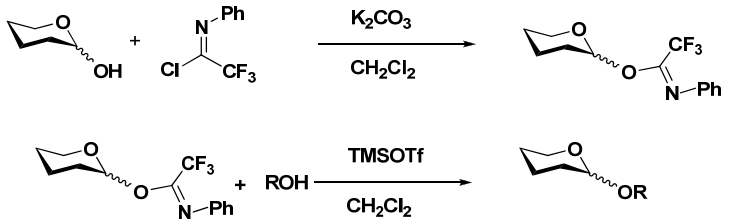
Highly reactive glycosyl trichloroacetimidates can also lead to side reactions or even decomposition of the donor before reaction with a glycosyl acceptor. When the glycosyl acceptor is very unreactive, the donor may rearrange to the corresponding glycosyl trichloroactetamide. To improve yields and stereocontrol, a so-called inverse glycosylation procedure is often used, where the glycosyl acceptor and an activator are dissolved together first and then the glycosyl donor is added. This method often leads to improved yields (**Scheme 1.14**). [69]



Scheme 1.14. The normal and the inverse procedure of glycosyl trichloroacetimidates

Recently, glycosyl trifluoroacetimidates have been introduced as glycosyl donors. These compounds are prepared by reaction of the hemiacetal with *N*-substituted trifluoroacetimidoyl

halides providing anomeric mixtures of imidates. The glycosylations with glycosyl trifluoroacetimidates are promoted by the same reagents used for trichloroacetimidates. The most important feature of the *N*-phenyl trifluoroacetimidate is that it is less prone to rearrange to the trifluoroacetamide (**Scheme 1.15**).[70]

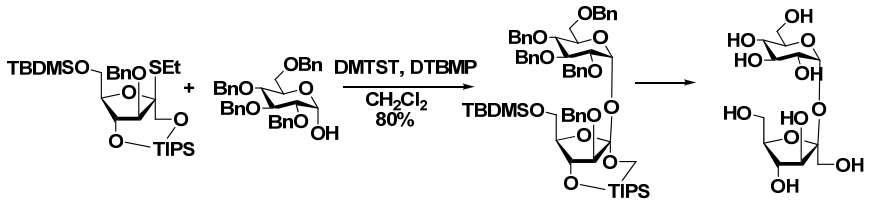


Scheme 1.15. Synthesis of and glycosylation with glycosyl *N*-phenyl trifluoroacetimidate

Thioglycosides

Thioglycosides show a remarkable stability and also tolerate very diverse chemical manipulations leaving the thioglycoside functionality intact. Moreover, they are inert under several glycosylation conditions and therefore thioglycosides can serve as glycosyl acceptors in the assembly of oligosaccharide building blocks. These oligosaccharide blocks can be directly used as glycosyl donors in the next step. Furthermore, thioglycosides are readily transformed into other types of glycosyl donors. Thioglycosides are activated selectively by the use of thiophilic reagents. Initial attempts for the activation of thioglycosides used heavy metal salts such as $HgSO_4$, $Hg(OAc)_2$, $HgCl_2$ and PhOTf.[71-73] These promoters gave only modest yields and stereoselectivity. Heavy metal salt promoters like $Hg(NO_3)_2$, $Cu(OTf)_2$ and AgOTf were employed in the synthesis of complex natural products such as erythromycin and avermectin oligosaccharides.[74-76] In the mid-1980s, highly powerful activation methods based on the alkylation of the thioglycoside sulfur by MeOTf were introduced by Lönn and coworkers. [77-79] Alkylation with much milder reagent MeI afforded 1,2-*cis* glycosides with good stereoselectivities. Another concept of the activation of thioglycosides was introduced in the synthesis of α-neuraminic acid linkages with high stereoselectivity by employing dimethyl(methylthio)sulfonium

triflate (DMTST)[80,81] and the corresponding tetrafluoroborate (DMTSF),[82] which are powerful methylsulfenylating agents. In this synthesis, the glucosyl acceptor was coupled with the fructofuranose thioglycoside, which has the β-directing silyl protecting group, using DMTST to afford disaccharide. After deprotection, sucrose was obtained in a quantitative yield (**Scheme 1.16**). [81]



Scheme 1.16. DMTST promoted glycosylation in the synthesis of sucrose

More recently, powerful thiophilic reagents such as *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT), 1-benzenesulfinyl piperidine (BSP)[83] and diphenyl sulfoxide[84] all in combination with triflic anhydride, were introduced. For example, the combination system of BSP and Tf_2O proved very useful for the synthesis of the Salmonella type E1 core trisaccharide.[85] Ph_2SO and Tf_2O has been employed successfully for the synthesis of sialic acid glycosides and hyaluronic acid oligomers.[86] Another efficient system was introduced for the activation of thioglycosides, namely Me_2S_2/Tf_2O. An important feature of these sulfinyl systems is the ability to preactivate thioglycosides at low temperature. Hanessian and coworker demonstrated halonium ions (*N*-bromosuccinimide, NBS)[87] as another type of electrophile in activation of thioglycosides. To increase yields and stereoselectivity, NBS is frequently used together with different additives such as TfOH, Ph_2IOTf, Bu_4NOTf, Bu_4NClO_4 and TMSOTf. Iodonium dicollidine perchlorate (IDCP)[88] was introduced as an iodonium ion source. The use of a stoichiometric amount or an excess of *N*-iodosuccinimide (NIS)[89] in the presence of catalytic amount of triflic acid was demonstrated by van Boom and coworkers to be a powerful activating system for thioglycosides. Different Lewis acids such as TMSOTf, TESOTf, AgOTf and BF_3OEt_2 can be used to promote glycosylations instead of triflic acid (**Figure 1.9**).

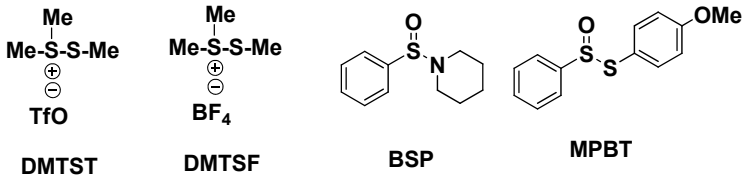
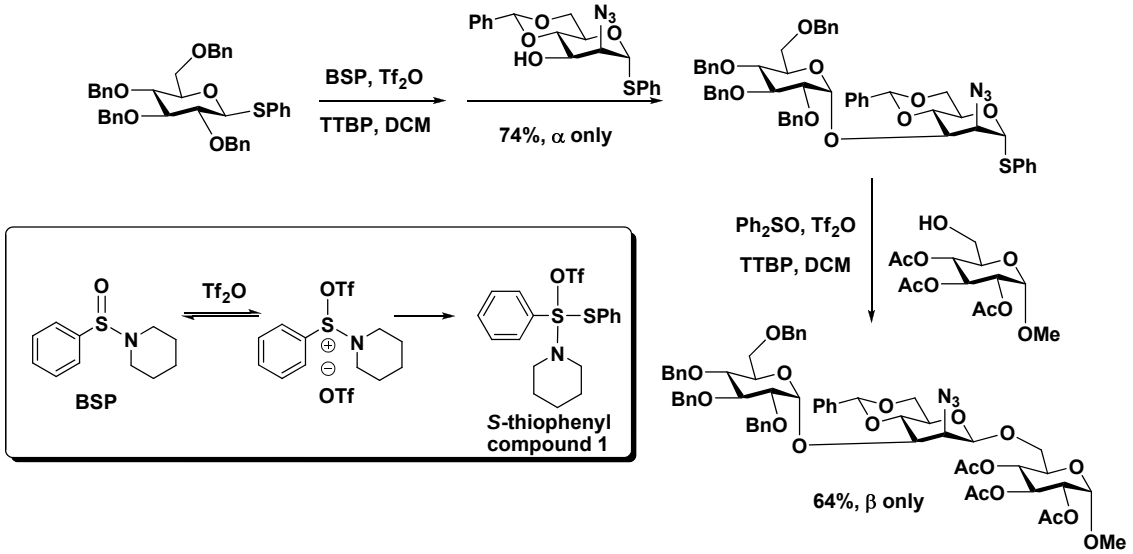


Figure 1.9. Structures of activators for thioglycosides

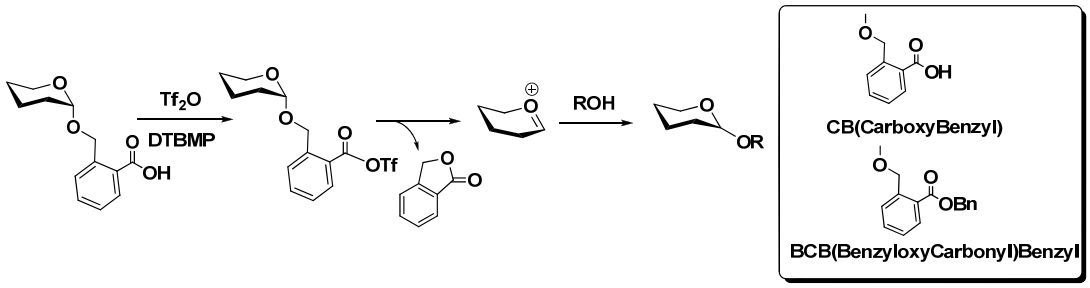
Van der Marel and coworkers have reported a chemo- and stereoselective condensation sequence in which both armed and disarmed thiodonors can be chemoselectively and stereoselectively condensed in the first glycosylation step by using the difference in reactivity of the BSP/Tf_2O and Ph_2SO/Tf_2O activating agents. The armed thiogalactosyl donor can be activated by BSP/Tf_2O and condensed with disarmed thiomannoazide acceptor to form 1,2-*cis* linked dissacharide. Unfortunately, the transiently formed *S*-thiophenyl species **1** lead the hydrolysis of the disaccharide during aqueous workup. The addition of triethyl phosphite can however, avoid this problematic hydrolysis and lead to the isolation of the desired α-linked disaccharide in a 74% yield. The condensation with glucosyl acceptor by using Ph_2SO/Tf_2O gave a trisaccharide with excellent stereoselectivity in a 64% yield (**Scheme 1.17**). [84]



Scheme 1.17. Chemo- and stereoselective glycosylations using thioglycosides

Carboxybenzyl glycosides

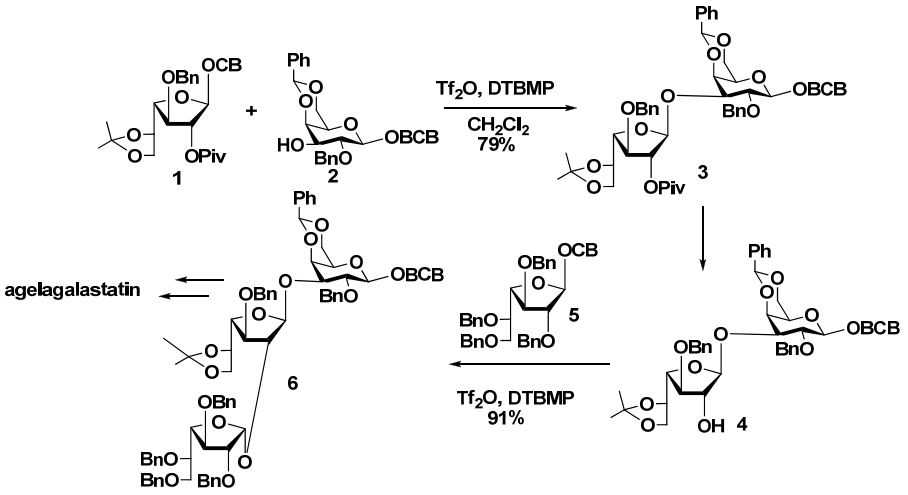
In 2001, Kim and coworkers reported a new type of glycosyl donor, 2-carboxybenzyl glycosides (CB), which undergo glycosylation with high stereoselectivity in high yield. 2-Carboxybenzyl glycosides are prepared in the form of their benzyl esters. The free carboxylic acids react in the presence of Tf_2O and DTBMP as a base to give stereoselective disaccharides in good yields with the formation of the stable phthalide lactone as a by-product (**Scheme 1.18**).[90]



Scheme 1.18. Proposed mechanism for the activation of CB glycosides

CB glycosides have been shown to be highly efficient for the stereoselective introduction of β-mannosides. By employing a (benzyloxycarbonyl)benzyl (BCB) protected acceptor and an active CB donor a selective activation could be achieved. The utility of CB donors has also been demonstrated in the construction of β-galatofuranosides. The stereospecific construction of 1,2-*cis* α-galactofuranosyl and α-galactopyranosyl linkages has been one of the challenges of glycoside chemistry. The CB glycoside method permitted a completely α-stereoselective galactofuranosylation. Glycosylation of BCB galactosyl acceptor **2** with CB furanosyl donor **1** was carried out to give β-disaccharide by employing neighboring participating group at C-2 of furanosyl donor **1**. Removal of the *O*-pivaloyl group from disaccharide **3** afforded disaccharide glycosyl acceptor **4**. Then, the crucial α-galactofuranosylation of the acceptor **4** with the donor **5** was successfully executed to give the desired α-galactofuranosyl trisaccharide **6**. The BCB

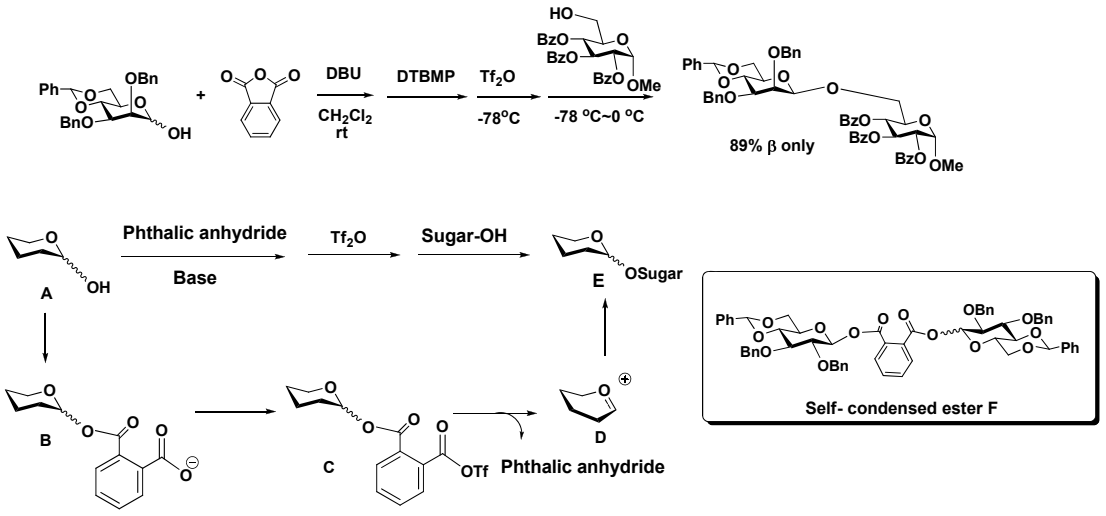
trisaccharide **6** was converted into CB trisaccharide for the further reactions for the synthesis of Agelagalacstatin (**Scheme 1.19**).[91]



Scheme 1.19. Stereoselective synthesis of Agelagalacstatin with CB glycosides as donors

More recently, an one-pot direct glycosylation method starting from an anomeric hydroxy as glycosyl donors employing phthalic anhydride and triflic anhydride as activating system has been described for stereoselective β-mannosylations (**Scheme 1.20**).[92] Anomeric hydroxy sugar **A** was treated with phthalic anhydride in the presence of a base such as DBU to generate glycosyl phthalate anion **B**. Addition of Tf_2O led to the formation of **B** which cyclizes the resulting triflate **C** and affords oxacarbenium ion **D**. Subsequent reaction of **D** with a glycosyl acceptor provides glycoside **E**. During the glycosylation of the anomeric hydroxyl with the glycosyl acceptor by the same procedure used for the β-mannosylation, unexpected self-condensed ester **F** was formed. Probably, the undesired ester **F** resulted from the reaction between the oxacarbenium **D** and phthalate anion **B**. Unlikely in the mannosylations mentioned above, the conversion of the carboxylate **B** into triflate **C** was slower than the conversion of the triflate **C** into the oxacarbenium ion **D** so that a substantial amount of **B** remained even after formation of the oxacarbenium ion **D**. Self-condensed ester **F** can be reduced by employing modified conditions. When the carboxylate anion **B** was protonated by TfOH, the oxacarbenium ion **D**

preferentially reacted with the glycosyl acceptor over the less nucleophilic carboxylic acid. Actually, self-condensed ester **F** was reduced under the modified condition (**Scheme 1.20**).[92]

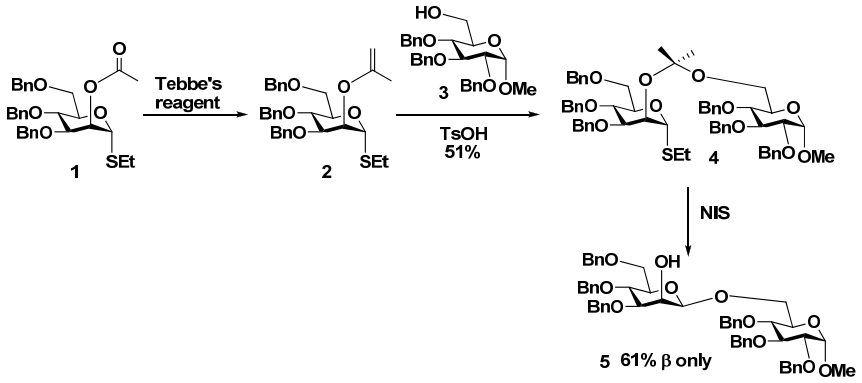


Scheme 1.20.

1.2.4 Intramolecular aglycon delivery

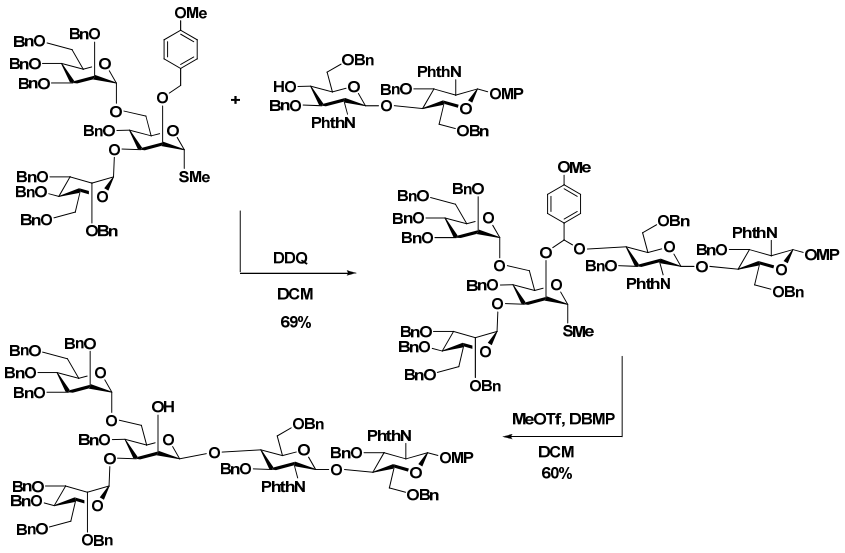
The intramolecular aglycon delivery method was developed to improve stereocontrol and yields in difficult glycosylations such as β-mannosylations. [93] The donor is connected to the acceptor by a spacer pior to the glycosylation events. The tether can be used to prearrange the donor and acceptor in such a way that it can direct the stereochemical outcome of the ensuing glycosylation event. Tethering at non reactive centers has been successfully implemented although the installation and removal of the tether involves additional steps. Anomeric tethers have been successfully implemented; however the anomeric selectivity is difficult to control since this type of tether needs to be broken in order for the glycosylation to take place. This leads to competition of intra- and intermolecular reaction pathways usually resulting in a loss of stereoselectivity. The most reliable and useful intramolecular aglycon delivery methodologies employ a tether between the *O*-2 of the glycosyl donor and the 2-, 3-, 4-, or 6-OH of the acceptor. Different types of tethers capable of stabilizing a positive charge have been explored

such as the silicon-tether which can be installed using dichlorodimethylsilane. Furthermore, acetals are attractive tethers and the isopropylidene mixed acetal can be readily obtained under mildly acidic conditions from an isopropenyl functionalized sugar and a glycosyl acceptor. The isopropenyl functionality is obtained from the acetyl precursor upon treatment with Tebbe's reagent. The 2-*O*-acetyl thioglycoside **1** was transformed into the isopropenyl ether **2** using tebbe's reagent. Acid- catalyzed addition of glycosyl acceptor **3** afforded tethered derivative **4**. Glycosylation by activation of the thioglycoside with NIS gave the β-mannoside **5** with excellent stereoselectivity (**Scheme 1.21**).[94]



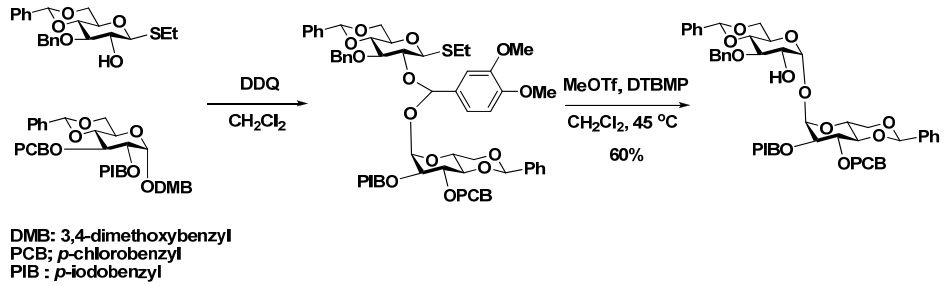
Scheme 1.21. 1,2-*cis* glycoside synthesis using Intramolecular Aglycon Delivery

Another approach to mixed acetal formation exploits the oxidation of an electron-rich aryl ether in the presence of an alcohol acceptor. The mixed acetal is usually prepared by DDQ oxidation of an glycosyl donor carrying an 2-naphtylmethyl, 4-methoxybenzyl or 3,4-dimethoxybenzyl ether at C-2 under dry conditions in the presence of an acceptor alcohol. Ogawa and coworkers illustrated that the trisaccharide donor with a 4-methoxybenzyl ether function at *O*-2, and the chitobiose acceptor were tethered using DDQ. The resulting mixed acetal was activated with MeOTf as a promoter to produce exclusively the β-mannosidically linked pentasaccharide. The unprotected 4-methoxyphenyl glycoside of the core pentasaccharide was obtained after deprotections (**Scheme 1.22**). [95]



Scheme 1.22. Intramolecular aglycon delivery method for stereoselective glycosylation

The position of the substituted aryl ether can also be switched from the acceptor to the donor, and this approach is referred to as inverse tethering, which may lead to improved yields of the mixed acetal. Upon activation of the glycosyl donor, the mixed aryl acetal ensures the acceptor oxygen to be delivered from the same face as the 2-*O* substituent (1,2-*cis*) on the glycosyl donor since it forms a five membered ring in the proposed transition state. Usually, the product disaccharide is formed with a free 2-OH′ which can directly serve as a glycosyl acceptor. Bertozzi and coworkers demonstrated the inverse tethering type of intramolecular aglycon delivery in the synthesis of the α,α-trehaloses core such as Sulfolipid-1. A glucosyl acceptor carrying an α-anomeric 3,4-dimethoxybenzyl (DMB) ether, which was obtained using altered Gervay-Hague glycosylation conditions with DMB-OH, upon oxidation with DDQ in the presence of a thioglycoside donor afforded the mixed acetal (inverse tethering). Ensuing glycosylation using MeOTf as promoter afforded only the α,α- trehalose product in good yield (**Scheme 1.23**).[96]



Scheme 1.23. Construction of the trehalose core

1.3 Outline of thesis

The research described in this thesis is aimed at the stereoselective introduction of 1,2-*cis*-glycosides by the application of the chiral auxiliary. **In chapter II**, we have demonstrated a new strategy for stereoselective induction of 1,2-*cis*-glycosides by employing a (*S*)-(phenylthiomethyl)benzyl chiral auxiliary at the C-2 position of glycosyl donors. The C-2 chiral auxiliary can stabilize the oxacarbenium ion intermediate of the glycosyl donor by formation of a quasi-stable anomeric sulfonium ion. The equatorial anomeric sulfonium ion can be displaced by the glycosyl acceptor leading to formation of α-glycosides. **In chapter III**, we have introduced PhSEt externally as an additive to generate a similar sulfonium ion intermediate. Glycosylations of 2-azido-2-deoxy-glucosyl donors carried out in presence of a thioether provide α-glycosides stereoselectively. NMR and computational studies have indicated that steric factors determine the selective formation of the β-anomeric sulfonium ion.

In chapter IV, we have extended the usage of the chiral auxiliary to 2-deoxy-glycosides. Since 2-deoxy glycosides have no C-2 functionality, we decided to introduce the auxiliary at the C-6 position instead, to explore its remote participation during the glycosylation reactions. Results demonstrated that the α-glycosides could be formed in efficient yields.

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CHAPTER II

A GENERAL STRATEGY FOR STEREOSELECTIVE GLYCOSYLATIONS

2.1 ABSTRACT

It is shown here that neighboring group participation by a chiral auxiliary such as a (*S*)-(phenylthiomethyl)benzyl moiety at the C-2 of a glycosyl donor can perform to give a quasi-stable anomeric sulfonium ion. The formation of β-sulfonium ion is expected due to steric and electronic factors as a *trans*-decalin. Displacement of the sulfonium ion by glycosyl acceptors leads to the stereoselective formation of α-glycosides. NMR analysis (TOCSY, HSQC and HMBC) showed convincingly the presence of the β-linked sulfonium ion intermediate. The (*S*)-(phenylthiomethyl)benzyl moiety could be introduced and removed under mild reaction conditions by exploiting the high reactivity of an episulfonium ion intermediate. The combination of the new methodology with traditional neighboring group participation by esters to introduce β-glycosides makes it possible to synthesize a wide variety of oligosaccharides by routine procedures. This methodology has been applied by the synthesis of the Galili trisaccharide, an epitope that can trigger acute rejections in xeno-transplantations.

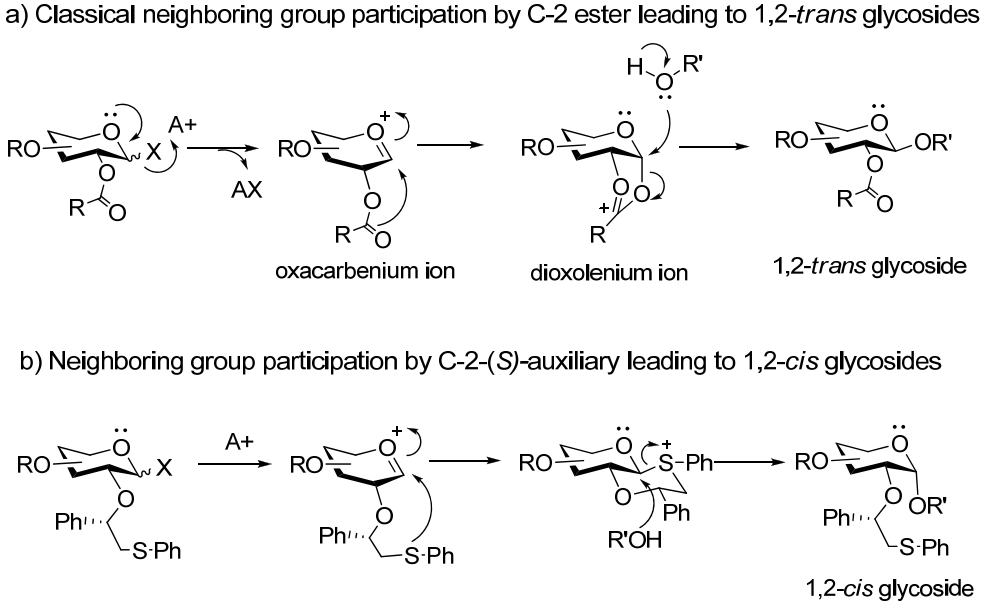
2.2 INTRODUCTION

Glycoconjugates have unique roles to play within living systems and actively control a whole range of biological processes impacting eukaryotic biology and disease.[1-3] Examples of such processes include fertilization, embryogenesis, neuronal development, hormone activities, the proliferation of cells, and their organization into specific tissues. During the development and progression of a tumor, remarkable changes in the cell-surface carbohydrates occur, which may

lead to metastasis. Furthermore, carbohydrates are capable of inducing a protective antibody response, which is a major contributor to the survival of the organism during infection. The development of routine procedures for the chemical synthesis of oligonucleotide fragments (DNA and RNA) and peptides has altered the face of modern biology. Oligosaccharides have also been found to control the development and defense mechanisms of plants. Although many advances have been made in the synthesis of complex carbohydrates,[4-6] there is still no general method for the preparation of complex carbohydrates of biological importance. A major obstacle to advances in glycobiology is the lack of pure and structurally well-defined carbohydrates and glycoconjugates. These compounds are often found in low concentrations and in microheterogeneous forms, which greatly complicates their isolation and characterization.

The chemical synthesis of complex carbohydrates involves the coupling of a fully protected glycosyl donor bearing a leaving group at its anomeric center, with a suitably protected glycosyl acceptor that contains often only one free hydroxyl group.[7] In many cases, these reactions lead to a mixture of two stereoisomers that differ in the configuration of the anomeric center. The most reliable method for stereoselective glycosylations is based on the neighboring group participation by a 2-*O*-acyl functionality (**Scheme 2.1a**).[4] In these reactions, a promoter activates an anomeric leaving group resulting in its departure and the formation of an oxocarbenium ion. Subsequent, neighboring group participation of the 2-*O*-acyl protecting group will give a more stable acetoxonium ion. An alcohol can attack the anomeric center of the acetoxonium ion from only one face providing a 1,2-*trans*-glycoside. Thus, in the case of glucosyl-type donors, β-linked products will be formed while mannosides will give α-glycosides. The introduction of 1,2-*cis*-glycosidic linkages, such as α-glucosides and α-galactosides, requires glycosyl donors with a nonassisting functionality at C-2. Invariably, the use of these glycosyl donors leads to the formation of mixtures of anomers.[5] Separation of these anomers requires time-consuming purification protocols resulting in loss of material. It also limits the use of one-pot multistep glycosylations[6,8] and automated polymer-supported synthesis[9-11] to

oligosaccharides that only contain 1,2-*trans*-glycosides. Thus, the stereoselective formation of 1,2-*cis*-glycosides is the principal challenge of complex oligosaccharide synthesis.

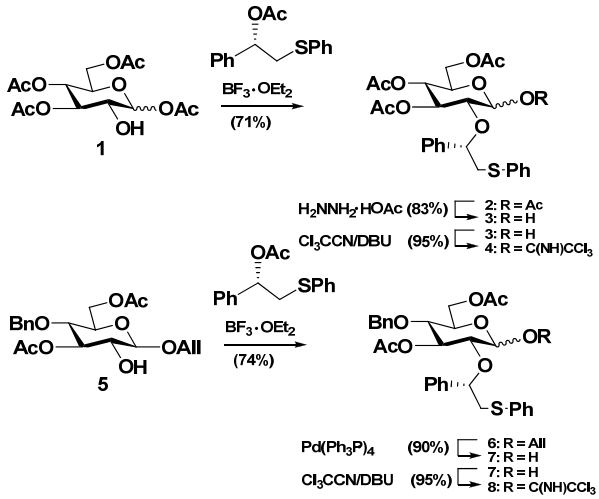


Scheme 2.1. Conventional and new approaches for stereoselective glycosylation

We describe here a novel strategy for the stereoselective introduction of 1,2-*cis*-glycosides, which in combination with conventional methods using neighboring group participation by C-2 esters[5] will allow the routine preparation of a wide variety of complex oligosaccharides. The new glycosylation approach is based on neighboring group participation of a (*S*)-(phenylthiomethyl)benzyl moiety at C-2 of a glycosyl donor (**Scheme 2.1b**). Upon formation of an oxacarbenium ion, the nucleophilic phenylsulfanyl moiety of the C-2 functionality will participate, leading to the formation of an intermediate sulfonium ion as either *trans*- or *cis*-decalin. The formation of the *trans*-decalin is expected due to the absence of unfavorable gauche interactions. In addition, the *cis*-decalin system will place the phenyl substituent in an axial position inducing further unfavorable steric interactions.[12] Displacement of the equatorial anomeric sulfonium ion by a sugar alcohol will then lead to the formation of a 1,2-*cis*-glycoside.

2.3 RESULT AND DISCUSSION

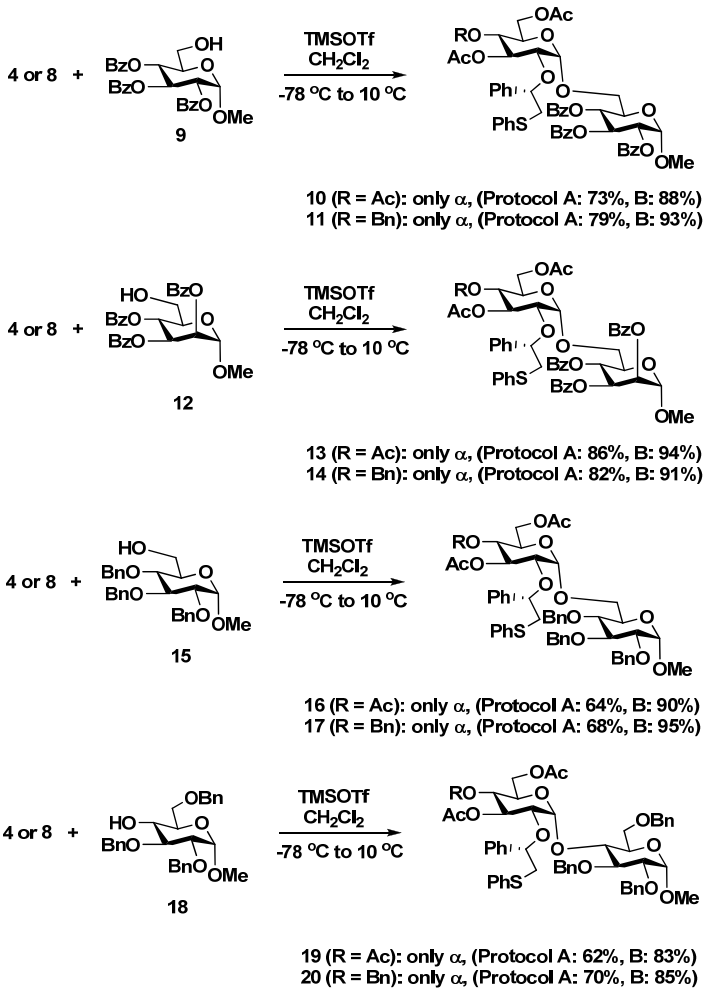
The (*S*)-(phenylthiomethyl)benzyl moiety could easily be installed by reaction with a sugar alcohol, such as **1**[13] and **5**,[14] with acetic acid (*S*)-(phenylthiomethyl)benzyl ester in the presence of $BF_3{\cdot}OEt_2$.[15] This reaction proceeds by a $BF_3{\cdot}OEt_2$-promoted departure of 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. Detailed NMR analysis of products **2** and **6** revealed that no other regio- or stereoisomers had been formed. Compounds **2** and **6** could be converted into glycosyl donors **4** and **8** by either removal of the anomeric acetyl ester or allyl ether followed by conversion of the hemiacetals into anomeric trichloroacetimidate using standard reaction conditions (**Scheme 2.2**).[16]



Scheme 2.2. Preparation of glycosyl donors **4** and **8**

With glycosyl donors **4** and **8** at hand, attention was focused on the glycosylation of a range of different glycosyl acceptors (**Scheme 2.3**). Thus, coupling of **4** or **8** with glycosyl acceptor **9** using a catalytic amount of TMSOTf in dichloromethane at −78 °C followed by gradual warming to 10 °C gave, after a reaction time of 3 h, disaccharides **10** and **11** as only the α-glycosides in good yields (**protocol A**). To demonstrate the generality of the approach,

glycosyl acceptors **12**, **15**, and **18** were also coupled with **4** and **8** and as can be seen in **Scheme 2.3**; in each case, only the expected α-anomer was isolated.

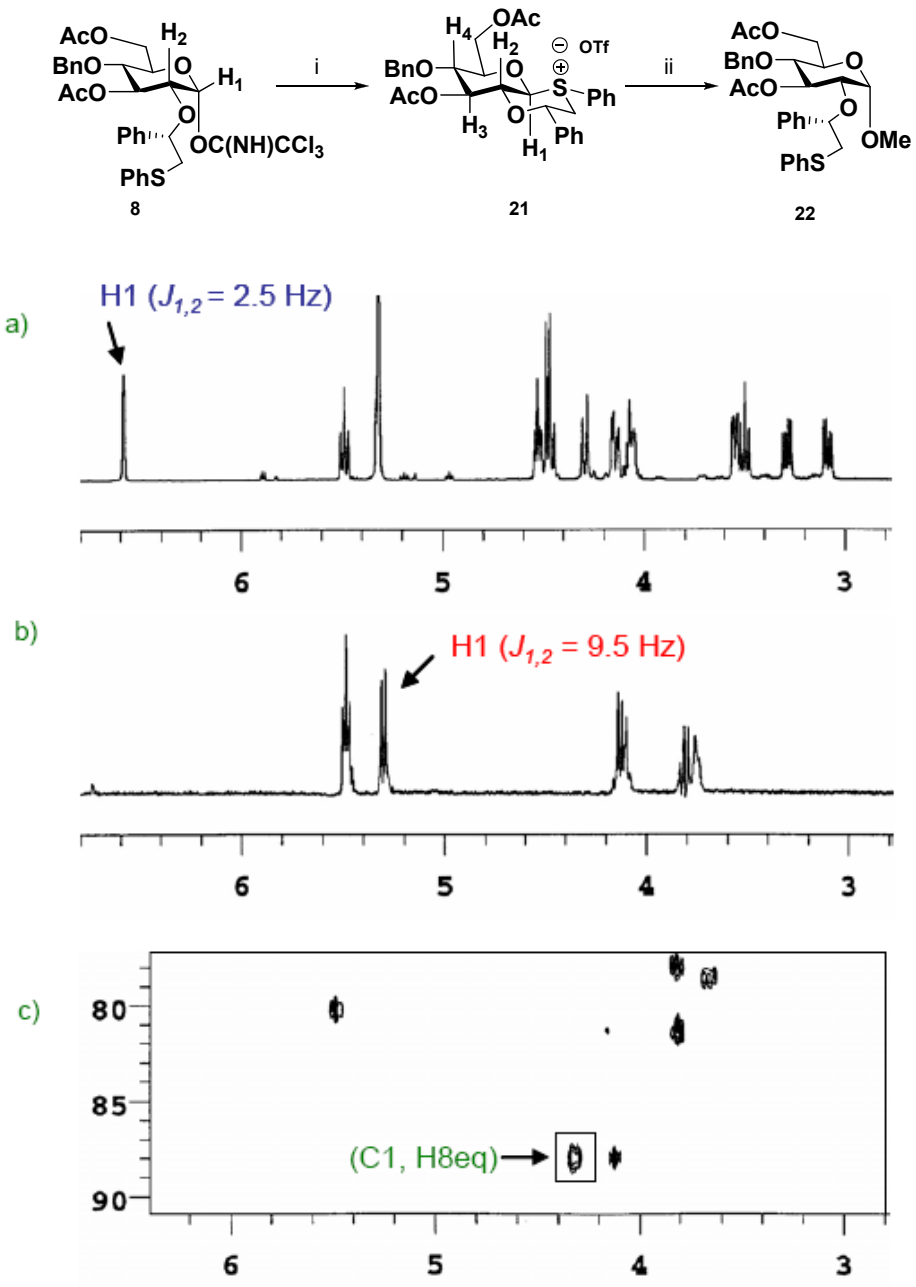


Scheme 2.3. Stereoselective glycosylations with glycosyl donors **4** and **8**

TLC analysis of the reaction mixture indicated that the glycosyl donor had been consumed within 10 min after adding TMSOTf. The glycoside products were, however, formed over a period of 3 h indicating the presence of a quasi-stable intermediate anomeric sulfonium ion. Furthermore, it was observed that some degradation had occurred probably due to the acidic nature of the reaction conditions. To address the latter problem, the glycosylations were performed by an alternative protocol (**Scheme 2.3**, **protocol B**) whereby the glycosyl donor was first activated with TMSOTf followed by the addition of the acceptor in the presence of the base

2,6-di-*tert*-butyl-4-methylpyridine. As expected, under these conditions no degradation was observed and, in each case, the disaccharides were isolated in improved and near quantitative yield.

The fact that the glycosylations lead to the formation of exclusively α-anomers provides strong support that the reactions proceed through an equatorially substituted anomeric sulfonium ion. To confirm the presence of this intermediate, glycosyl donor **8** in CD_2Cl_2 at −50 °C was treated with 1 equiv of TMSOTf, and after the temperature was raised to −20 °C, ^{1}H, ^{1}H-TOCSY, HSQC, and HMBC NMR spectra were recorded. The collected data showed the formation of a single new compound, which was unambiguously identified as the sulfonium ion **21** (**Scheme 2.4**). Upon activation, the anomeric proton of **8** (δ 6.58, d, $J_{1,2}$ = 2.5 Hz) shifted upfield (δ 5.30, d, $J_{1,2}$ = 9.5 Hz) and its large vicinal coupling constant established an equatorial orientation of the anomeric substituent. The coupling constants of the other saccharide protons showed that no conformational distortion of the saccharide ring had occurred. The HMBC spectrum, which allows the determination of three-bond proton−carbon couplings, showed a correlation between C-1 and H8eq, proving that the *trans*-decalin system of **21** had been formed. Treatment of **21** with methanol resulted in the clean formation of the α-methyl glycoside **22**, demonstrating that the glycosylation proceeds by inversion of configuration of the anomeric center.

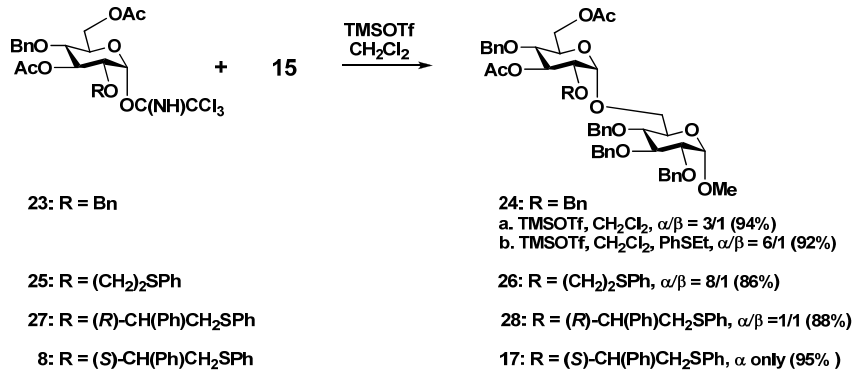


Scheme 2.4. [a]

[a] Key: (i) TMSOTf, CD_2Cl_2, −50 to 0 °C; (ii) MeOH, −20 to 0 °C. (a) ^{1}H NMR spectrum of glycosyl donor **8**. (b) ^{1}H TOCSY 1D spectrum on irradiation of H4 of sulfonium ion **21**. (c) HMBC spectrum of sulfonium ion **21**.

Next, a number of experiments were performed to establish which features of the (*S*)-(phenylthiomethyl)benzyl moiety are important for controlling the α-anomeric selectivity. In this respect, a reaction of an intermediate oxocarbenium ion with an externally delivered sulfide may also lead to the formation of an equatorially substituted sulfonium ion, which may be displaced by a sugar alcohol to give an α-glycoside. Furthermore, the chiral center of the (*S*)-(phenylthiomethyl)benzyl moiety may not be essential for achieving absolute α-anomeric selectivity. It may well be possible that *trans*- vs *cis*-decalin formation in combination with stereoelectronic effects is sufficient to induce the formation of a β-substituted sulfonium ion reacting to an α-glycoside. To investigate these issues, trichloroacetimidates **23**, **25**, and **27** were coupled with **15** using TMSOTf as a promoter and the results were compared with a similar coupling with glycosyl donor **8** (**Scheme 2.5**). A standard glycosylation of trichloroacetimidate **23**, which has a C-2 benzyl ether, gave the disaccharide **24** as a 3/1 mixture of α/β anomers. When the glycosylation was performed in the presence of ethyl phenyl sulfide (5 equiv), only a marginal increase in α-anomeric selectivity (α/β = 6/1) was observed. With the establishment that intramolecular delivery of the phenylsulfanyl moiety is important for obtaining absolute α-anomeric selectivity, glycosylations were performed with glycosyl donors **25** and **27**, which have modified C-2 functionalities. In the case of **25**, the C-2 functionality lacks the (1*S*)- phenyl moiety whereas, in the glycosyl donor **27**, it has an opposite (1*R*)-stereochemistry. In the latter case, the formation of a β-substituted sulfonium ion will place the (1*R*)-phenyl substituent in an axial orientation inducing unfavorable steric interactions. In the alternative α-substituted sulfonium ion (*cis*-decalin), the (1*R*)-phenyl group will adopt an equatorial orientation; however, this intermediate will experience unfavorable gauche interactions. Displacement of the α-sulfonium ion would lead to the formation of β-glycoside. Thus, a standard glycosylation with glycosyl donor **25** gave the disaccharide **26** as a 8/1 mixture of α/β anomers. A similar glycosylation with **27** resulted in the formation of **28** as an anomeric mixture (α/β = 1/1). These results indicate that a combination of an equatorially oriented (1*S*)-

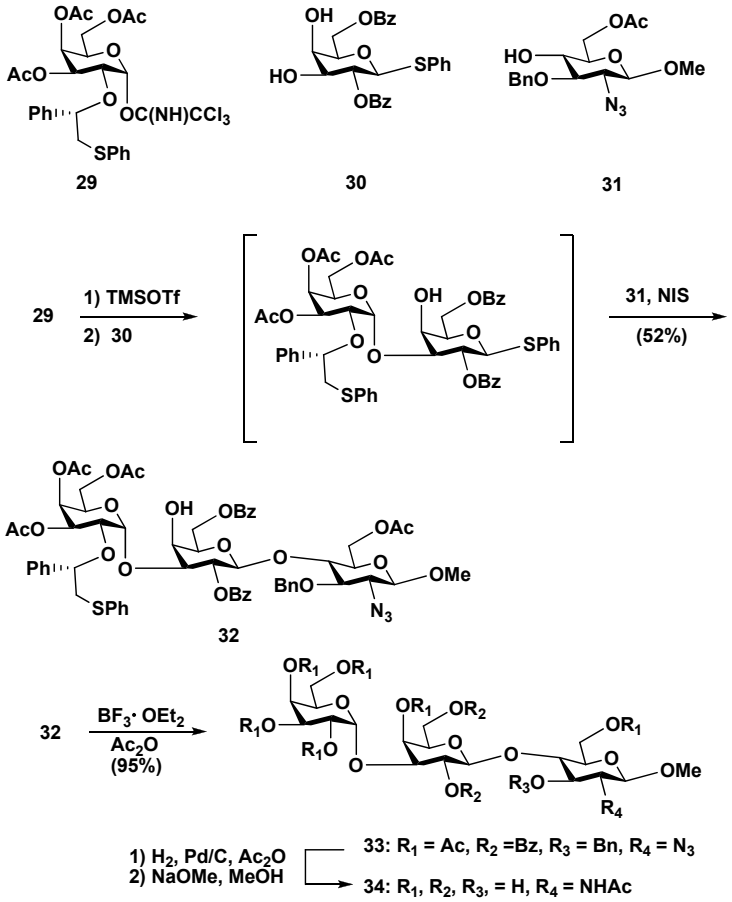
phenyl substituent and *trans*-decalin formation are important features for controlling the α-anomeric selectivity.



Scheme 2.5. Glycosylations with Glycosyl Donors **23**, **25**, **27**, and **8**

The new glycosylation protocol described here in combination with traditional neighboring group participation by esters should allow the installment of α- as well as β-glycosides. To demonstrate the combined use of these methodologies trisaccharide **34**,[17-24] which has been identified as an epitope that can trigger acute rejections in xeno-transplantations,[25,26] was prepared. It was anticipated that this compound could be assembled from the monomeric building blocks **29**, **30**, and **31** using a one-pot two-step glycosylation sequence. Galactosyl donor **29**, which possesses a (*S*)-(phenylthiomethyl)benzyl functionality at C-2, will direct the formation of an α-galactoside, whereas the C-2 benzoyl of **30** will induce the formation of a β-galactoside. The novel galactosyl donor **29** could be prepared in a good overall yield starting from 1,3,4,6-tetra-*O*-acetyl-α-d-galactose[27] using a sequence of reactions similar to that used for the synthesis of compound **4** (**Scheme 2.6**). Glycosyl donor **29** was treated with TMSOTf to form an intermediate anomeric sulfonium ion, which was reacted with glycosyl acceptor **30** for 4 h at 0 °C. Next, methyl glycoside **31** and NIS were added to the reaction mixture, and within 2 h, trisaccharide **32** was formed. This compound was isolated in a yield of 52% as a single anomer with expected anomeric configuration. Interestingly, the NIS/TMSOTf

promoter system does not affect the (*S*)-(phenylthiomethyl)benzyl group. Furthermore, preactivation of **29** was required to achieve a high yield.



Scheme 2.6. Preparation of Glycosyl Donor **29**, One-Pot Two-Step Synthesis of Trisaccharide **32**, and Deprotection

Finally, we explored reaction conditions for the removal of the (*S*)-(phenylthiomethyl)benzyl group. It was anticipated that this functionality could be converted into an acetyl ester by treatment with $BF_3{\cdot}OEt_2$ in acetic anhydride. In this reaction, an acetoxonium ion, generated from a reaction of $BF_3{\cdot}OEt_2$ with acetic anhydride, will react with oxygen of the (*S*)-(phenylthiomethyl)benzyl moiety. An intramolecular nucleophilic substitution of sulfur of the resulting intermediate should lead to the formation of an episulfonium ion and acetyl ester. Nucleophilic attack of acetic acid at the benzylic position of the episulfonium ion should regenerate acetic acid (*S*)-(phenylthiomethyl)benzyl ester. Indeed, treatment of **32** with

$BF_3 \cdot OEt_2$ in acetic anhydride gave, after a reaction time of 30 min, a quantitative yield of C-2" acetate **33** and full recovery of acetic acid (*S*)-(phenylthiomethyl)benzyl ester. The latter compound could be reused for the installment of an (*S*)-(phenylthiomethyl)benzyl moiety. Compound **33** could be further deprotected under standard conditions to give the target compound **34**.

2.4 CONCLUSION

It has been shown that a (*S*)-(phenylthiomethyl)benzyl moiety at C-2 of a glycosyl donor can direct the formation of α-gluco and α-galactosides. These glycosyl donors react through a new reaction mechanism whereby the phenylsulfanyl moiety of the C-2 functionality performs neighboring group participation to give a quasi-stable anomeric sulfonium ion. Due to steric and electronic effects, the sulfonium ion is only formed as a *trans*-decalin. Displacement of the sulfonium ion by a sugar hydroxyl leads exclusively to the formation of an α-glycoside. The formation of an intermediate cyclic β-linked sulfonium ion was convincingly demonstrated by NMR experiments. This (*S*)-(phenylthiomethyl)benzyl moiety can be introduced and removed under mild reaction conditions by exploiting the high reactivity of an episulfonium ion. It is to be expected that the new methodology can be expanded to include the synthesis of 1,2-*cis*-amino sugars. A combined use of a new approach to introduce α-glycosides and traditional neighboring group participation by C-2 esters to give β-glycosides provides a general strategy for the synthesis of a wide variety of oligosaccharides.

2.5 EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under a positive pressure of argon, unless otherwise noted. All chemicals were purchased from commercial suppliers and used without further purification, unless otherwise noted. Dichloromethane was distilled from calcium hydride under N_2. Toluene was distilled under nitrogen from molten sodium. *N,N*-Dimethylformamide (DMF) was distilled under nitrogen from barium oxide. Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh). Reactions were monitored by TLC on Kieselgel 60 F254 (EM Science) and the compounds were detected by examination under UV light and visualized by dipping the plates in a cerium sulfate-ammonium molybdate solution followed by heating. Organic solutions were concentrated by rotary evaporation below 40 ^{o}C under reduced pressure. Molecular sieves (3Å and 4Å), used for reactions, were crushed and activated *in vacuo* at 390 °C during 8 h in the first instance and then for 2-3 h at 390 °C directly prior to application. Optical rotations were measured with a 'Jasco P-1020' polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Inova 300 spectrometer and a Varian Inova 500 spectrometer equipped with Sun workstations. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Data are presented as follow: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = double of doublet, m = multiplet and/or multiple resonances), integration, coupling constant in Hertz (Hz). High-resolution mass spectra were run in a JMS SX/SX102A tandem mass spectrometer, equipped with FAB source. The matrix used was DHB and the internal standards ultramark 1621 and PEG.

Acetyl 3,4,6-Tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-glucopyranose (2). Boron trifluoride diethyl etherate (381 μL, 3.0 mmol) was added to a solution of acetyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranose (**1**) (697 mg, 2.0 mmol), acetic acid (1*S*)-phenyl-2-(phenylsulfanyl)ethyl ester (**39**) (817 mg, 3.0 mmol), and activated molecular sieves (4Å) in dichloromethane (10 mL) at 0 °C. After 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford **2** (796 mg, 71%): colorless syrup; R_f = 0.37 (ethyl acetate/hexane, 1/2); $[\alpha]^{20}_D$ = +124.6° (*c* = 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.17 (m, 10H, aromatic), 6.46 (d, 1H, *J* = 3.6 Hz, H-1), 5.39 (t, 1H, *J* = 9.6 Hz, H-3), 4.46 (t, 1H, *J* = 9.6 Hz, H-4), 4.46 (dd, 1H, *J* = 4.8, 8.1 Hz, H-7), 4.27−4.23 (m, 1H, H-6a), 4.08−3.98 (m, 2H, H-6b, H-5), 3.58 (dd, 1H, *J* = 3.6, 9.6 Hz, H-2), 3.22 (dd, 1H, *J* = 8.1, 13.8 Hz, H-8a), 3.04 (dd, 1H, *J* = 4.8, 13.8 Hz, H-8b), 2.18 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 1.82 (s, 3H, $COCH_3$); HR MALDI-TOF MS (*m*/*z*) calcd for $C_{28}H_{32}O_{10}S$ $[M + Na]^+$ 583.1614, found 583.1622.

3,4,6-Tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-glucopyranosyl Trichloroacetimidate (4). Hydrazinium acetate (144 mg, 1.56 mmol) was added to a solution of **2** (796 mg, 1.42 mmol) in DMF (10 mL) at room temperature. The reaction mixture was stirred overnight and then quenched with saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with ethyl acetate (20 mL × 2). The combined organic phase was washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford 3,4,6-tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-D-glucopyranose (**3**) (612 mg, 83%). Trichloroacetonitrile (1.18 mL, 11.8 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (71 μL, 0.47 mmol) were added to a solution of **3** (612 mg, 1.18 mmol, 1 equiv) in

dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then concentrated in vacuo. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford **4** (743 mg, 95%): R_f = 0.29 (ethyl acetate/hexane, 1/3); $[\alpha]^{20}_D$ = +50.0° (*c* = 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H, N*H*), 7.36−7.16 (m,10H, aromatic), 6.66 (d, 1H, *J* = 3.6 Hz, H-1), 5.44 (t, 1H, *J* = 9.6 Hz, H-3), 4.93 (t, 1H, *J* = 9.6 Hz, H-4), 4.53 (t, 1H, *J* = 6.3 Hz, H-7), 4.26−4.16 (m, 2H, H-5, H-6a), 4.06−4.03 (m, 1H, H-6b), 3.67 (dd, 1H, *J* = 3.6, 9.6 Hz, H-2), 3.21 (dd, 1H, *J* = 7.5, 13.8 Hz, H-8a), 3.06 (dd, 1H, *J* = 6.3, 13.8 Hz, H-8b), 2.02 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 1.76 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.53, 169.90, 169.68, 160.86, 139.68, 136.17, 129.34, 129.02, 128.56, 126.99, 126.19, 93.02, 81.34, 75.31, 71.22, 69.77, 67.99, 61.51, 41.50, 20.65, 20.59 (2); HR MALDI-TOF MS (*m*/*z*) calcd for $C_{28}H_{30}Cl_3NO_9S$ $[M + Na]^+$ 684.0604, found 684.0602.

Allyl 3,6-Di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-β-D-glucopyranoside (6). Boron trifluoride diethyl etherate (572 μL, 4.5 mmol) was added to a solution of allyl 3,6-di-*O*-acetyl-4-*O*-benzyl-β-D-glucopyranoside (**5**) (1.18 g, 3.0 mmol), acetic acid (1*S*)-phenyl-2-(phenylsulfanyl)ethyl ester (**39**) (1.23 g, 4.5 mmol), and activated molecular sieves (4 Å) in dichloromethane (10 mL) at 0 °C. After 10 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford **6** (1.35 g, 74%): colorless syrup; R_f = 0.30 (ethyl acetate/hexane, 1/3); $[\alpha]^{20}_D$ = +8.8° (*c* = 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.10 (m,15H, aromatic), 5.96−5.83 (m, 1H, OCH_2CHCH_2), 5.30−5.13 (m, 3H, H-3, OCH_2CHCH_2), 4.96 (t, 1H, *J* = 6.9 Hz, H-7), 4.43 (d, 1H, *J* = 8.4 Hz, H-1), 4.49−4.26 (m, 3H, H-6a, $OCHHCHCH_2$, $CHHPh$), 4.17−4.10 (m, 2H, H-6b, $OCHHCHCH_2$), 3.53−3.35 (m, 3H, H-4, H-5, H-8a), 3.23 (dd, 1H, *J* = 8.4, 9.6 Hz, H-2), 3.08 (dd, 1H, *J* = 6.9, 13.5 Hz, H-8b), 2.01 (s, 3H,

$COCH_3$), 1.76 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.58, 169.75, 140.32, 137.26, 136.89, 133.71, 128.78, 128.49, 128.347, 128.29, 128.01, 127.89, 127.69, 125.69, 118.15, 102.66, 81.41, 77.19, 76.24, 75.09, 74.42, 72.49, 70.73, 62.80, 40.38, 21.09, 20.81; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{34}H_{38}O_8S$ $[M + Na]^+$ 629.2185, found 629.2203.

3,6-Di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-glucopyranosyl Trichloroacetimidate (8). Tetrakis(triphenylphosphine)palladium (2.56 g, 2.22 mmol) was added to a solution of **6** (1.35 g, 2.22 mmol) in acetic acid (15 mL) at room temperature. The reaction mixture was stirred overnight and then diluted with dichloromethane (20 mL) and quenched with saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-D-glucopyranose (**7**) (1.13 g, 90%): R_f = 0.19 (ethyl acetate/hexane, 1/2). Trichloroacetonitrile (1.99 mL, 19.9 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (119 µL, 0.8 mmol) were added to a solution of **7** (1.13 g, 1.99 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then concentrated in vacuo. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford **8** (1.32 g, 93%): R_f = 0.45 (dichloromethane/acetone, 100/1); $[\alpha]^{20}_D$ = −0.03° (*c* = 6.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H, N*H*), 7.37−7.16 (m, 15H, aromatic), 6.62 (d, 1H, *J* = 3.6 Hz, H-1), 5.57 (t, 1H, *J* = 9.6 Hz, H-3), 4.52−4.42 (m, 1H, H-7), 4.50 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.44 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.29−4.17 (m, 2H, H-6a, H-6b), 4.13−4.08 (m, 1H, H-5), 3.55 (dd, 1H, *J* = 3.6, 9.6 Hz, H-2), 3.49 (t, 1H, *J* = 9.6 Hz, H-4), 3.25 (dd, 1H, *J* = 6.9, 13.5 Hz, H-8a), 3.05 (dd, 1H, *J* = 6.6, 13.5 Hz, H-8b), 2.00 (s, 3H, $COCH_3$), 1.81 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.44, 169.49, 161.08, 139.80, 137.07, 136,21, 129.35, 128.97, 128.54, 128.53, 128.13, 127.22, 126.11, 93.07, 80.86, 75.51, 75.47, 74.54, 72.70, 70.96, 62.33, 41.27, 20.95, 20.77; ^{13}C

NMR (75 MHz, $CDCl_3$) δ 170.44, 169.49, 161.08, 139.80, 137.07, 136,21, 129.35, 128.97, 128.54, 128.53, 128.13, 127.22, 126.11, 93.07, 80.86, 75.51, 75.47, 74.54, 72.70, 70.96, 62.33, 41.27, 20.95, 20.77; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{33}H_{34}Cl_3NO_8S$ $[M + Na]^+$ 732.0968, found 732.0957.

General Procedure for the Glycosylation Reaction Employing Glycosyl Donors 4 and 8.

Protocol A. A mixture of donor **4** or 8 (0.04 mmol), glycosyl acceptor (0.06 mmol), and activated molecular sieves (4 Å) in DCM (5 mL) was stirred for 10 min under an atmosphere of argon at room temperature. After the mixture was cooled to −78 °C, trimethylsilyl trifluoromethanesulfonate (2.2 µL, 0.012 mmol) was added. The reaction mixture was allowed to warm slowly to 10 °C. After the donor was consumed, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ (5 mL) and separated. The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane)

Protocol B. A mixture of donor **4** or 8 (0.04 mmol) and activated molecular sieves (4 Å) in DCM (5 mL) was stirred for 10 min under an atmosphere of argon at room temperature. After the mixture was cooled to −78 °C, trimethylsilyl trifluoromethanesulfonate (7.2 µL, 0.04 mmol) was added, and the reaction mixture was allowed to warm to 0 °C over a period of 40 min. After cooling of the reaction mixture to −78 °C, glycosyl acceptor (0.06 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (16 mg, 0.08 mmol) were added. The reaction mixture was allowed to warm slowly to room temperature and kept overnight at room temperature. After quenching with aqueous saturated $NaHCO_3$ (5 mL), the organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane)

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (10): $[\alpha]^{20}_{D}$ = +56.8° (*c* = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99−7.86 (m, 6H, aromatic), 7.53−7.08 (m, 19H, aromatic), 6.19 (t, 1H, *J* = 9.5 Hz, H-3), 5.45 (t, 1H, *J* = 10.0 Hz, H-3‘), 5.41 (t, 1H, *J* = 10.0 Hz, H-4), 5.26 (dd, 1H, *J* = 4.0, 9.5 Hz, H-2), 5.23 (d, 1H, *J* = 4.0 Hz, H-1), 5.07 (d, 1H, *J* = 3.0 Hz, H-1‘), 4.82 (t, 1H, *J* = 9.5 Hz, H-4‘), 4.43−4.37 (m, 2H, H-5, H-7‘), 4.24−4.16 (m, 2H, H-5‘, H-6a‘), 4.04−4.02 (m, 1H, H-6a), 3.93−3.89 (m, 1H, H-6b‘), 3.79−3.77 (m, 1H, H-6b), 3.54 (s, 3H, OCH_3), 3.48 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2‘), 3.24 (dd, 1H, *J* = 9.0, 14.0 Hz, H-8a‘), 3.06 (dd, 1H, *J* = 3.5, 14.0 Hz, H-8b‘), 2.06(s, 3H, $COCH_3$), 1.95 (s, 3H, $COCH_3$), 1.64 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.69, 170.02, 169.82, 165.87, 165.77, 165.56, 140.57, 136.40, 133.54, 133.366, 133.16, 133.09, 130.01, 129.96, 129.92, 129.67, 129.25, 129.09, 128.89, 128.80, 128.63, 128.58, 128.50, 128.43, 128.28, 126.54, 125.94, 96.68, 96.30, 82.20, 77.19, 72.26, 71.29, 70.47, 70.11, 68.71(2), 67.35, 67.10, 62.01, 55.61, 41.67, 20.76, 20.63, 20.56; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{54}H_{54}O_{17}S$ $[M + Na]^+$ 1029.2979, found 1029.2910.

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*-benzoyl-α-D-glucopyranoside (11): $[\alpha]^{20}_{D}$ = −14.6° (*c* = 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99−7.85 (m, 6H, aromatic), 7.52−7.09 (m, 24H, aromatic), 6.17 (t, 1H, *J* = 10.0 Hz, H-3), 5.54 (t, 1H, *J* = 9.0 Hz, H-3‘), 5.42 (t, 1H, *J* = 10.0 Hz, H-4), 5.26(dd, 1H, *J* = 4.0, 10.0 Hz, H-2), 5.19 (d, 1H, *J* = 4.0 Hz, H-1), 5.01 (d, 1H, *J* = 3.0 Hz, H-1‘), 4.48 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.43 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.38−4.36 (m, 2H, H-5, H-7‘), 4.27−4.10 (m, 3H, H-5‘, H-6a‘,H-6b‘), 3.89 (t, 1H, *J* = 10.0 Hz, H-6a), 3.75 (d, 1H, *J* = 10.0 Hz, H-6b), 3.51 (s, 3H, OCH_3), 3.38−3.34 (m, 2H, H-2‘, H-4‘), 3.26 (dd, 1H, *J* = 8.5, 14.0 Hz, H-8a‘), 3.03 (dd, 1H, *J* = 5.0, 14.0 Hz, H-8b‘), 2.04 (s, 3H, $COCH_3$), 1.70 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.66, 169.71, 165.81, 165.76, 165.57, 140.69, 137.53, 136.46, 133.46, 133.29, 133.04, 129.96, 129.93, 129.67, 129.28, 129.22, 129.14, 128.82, 128.59,

128.54, 128.46, 128.43, 128.39, 128.25, 128.08, 127.85, 127.06, 126.74, 125.85, 96.62, 96.19, 81.74, 77.22, 76.14, 73.81, 72.74, 72.23, 70.53, 69.93, 68.67, 68.34, 67.12, 62.87, 55.69, 41.43, 21.98, 20.88; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{59}H_{58}O_{16}S$ [M + Na]$^+$ 1077.3342, found 1077.3396.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-manopyranoside (13): $[\alpha]^{20}_D$ = −11.0 ° (*c* = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−7.81 (m, 6H, aromatic), 7.64−7.08 (m, 19H, aromatic), 5.91 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3), 5.81 (t, 1H, *J* = 10.0 Hz, H-4), 5.69 (m, 1H, H-2), 5.45 (t, 1H, *J* = 9.5 Hz, H-3‘), 5.06 (d, 1H, *J* = 3.50 Hz, H-1‘), 4.93 (s, 1H, H-1), 4.82 (t, 1H, *J* = 9.5 Hz, H-4‘), 4.41−4.37 (m, 2H, H-5, H-7‘), 4.22−4.19 (m, 1H, H-5‘), 4.13−4.10 (m, 1H, H-6a‘), 4.01−3.98 (m, 21H, H-6a, H-6b‘), 3.81−3.79 (m, 1H, H-6b), 3.57 (s, 3H, OCH_3), 3.47 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2‘), 3.23 (dd, 1H, *J* = 8.5, 14.0 Hz, H-8a‘), 2.94 (dd, 1H, *J* = 4.5, 14.0 Hz, H-8b‘), 1.96 (s, 3H, $COCH_3$), 1.92 (s, 3H, $COCH_3$), 1.69 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.61, 169.94, 169.81, 165.78, 165.55, 165.40, 129.97, 129.83, 129.72, 129.37, 129.13, 128.96, 128.91, 128.70, 128.61, 128.51, 128.36, 98.51, 96.37, 81.83, 77.22, 71.32, 70.68, 70.01, 69.76, 68.66, 67.58, 67.43, 67.23, 61.98, 55.52, 41.34, 20.64 (3); HR MALDI-TOF MS (*m*/*z*) calcd for $C_{54}H_{54}O_{17}S$ [M + Na]$^+$ 1029.2979, found 1029.2934.

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*-benzoyl-α-D-manopyranoside (14): $[\alpha]^{20}_D$ = −181.4° (*c* = 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−7.81 (m, 6H, aromatic), 7.63−7.08 (m, 24H, aromatic), 5.90 (dd, 1H, *J* = 3.0, 10.0 Hz, H-3), 5.80 (t, 1H, *J* = 10.0 Hz, H-4), 5.67 (s, 1H, H-1), 5.57 (t, 1H, *J* = 10.0 Hz, H-3‘), 5.04 (d, 1H, *J* = 3 Hz, H-1‘), 4.90 (s, 1H, H-2), 4.96 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.43 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.39−4.32 (m, 2H, H-5, H-7‘), 4.23−4.21 (m, 1H, H-6a‘), 4.14−4.09 (m, 2H, H-5‘, H-6b‘), 3.99−3.95 (m, 1H, H-6a), 3.78−3.76 (m, 1H, H-

6b), 3.54 (s, 3H, OCH_3), 3.39−3.34 (m, 2H, H-2‘, H-4‘), 3.25 (dd, 1H, 2.06, *J* = 8.0, 14.0 Hz, H-8a‘), 2.92 (dd, 1H, *J* = 5.0, 14.0 Hz, H-8b‘), 1.92 (s, 3H, $COCH_3$), 1.74 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.59, 169.65, 165.76, 165.56, 165.41, 140.59, 137.59, 136.44, 133.48, 133.45, 133.08, 129.99, 129.87, 129.73, 129.40, 129.18, 128.93, 128.69, 128.58, 128.51, 128.47, 128.43, 128.32, 128.26, 127.88, 127.84, 126.81, 125.85, 98.47, 96.22, 81.40, 77.23, 76.06, 73.78, 72.82, 70.67, 70.07, 69.72, 68.32, 67.47, 62.87, 55.59, 41.14, 21.04, 20.74; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{59}H_{58}O_{16}S$ $[M+Na]^+$ 1077.3342, found 1077.3392.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (16): ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.05 (m, 25H, aromatic), 5.36 (t, 1H, *J* = 9.5 Hz, H-3‘), 5.19 (d, 1H, *J* = 3.5 Hz, H-1‘), 4.97−4.90 (m, 2H, C*H*HPh), 4.84−4.79 (m, 2H, C*H*HPh, H-4‘), 4.73−4.69 (m, 2H, C*H*HPh), 4.61−4.56 (m, 2H, C*H*HPh, H-1), 4.49 (dd, 1H, *J* = 5.0, 8.0 Hz, H-7‘), 4.18−4.12 (m, 2H, H-4, H-6a‘), 4.06 (d, 1H, *J* = 11.0 Hz, H-6b‘), 4.01−3.95 (m, 3H, H-3, H-6a, H-6b), 3.60 (dd, 1H, *J* = 3.5, 9.5 Hz, H-2), 3.54−3.51 (m, 2H, H-5‘, H-5), 3.51 (dd, 1H, *J* = 3.5, 9.5 Hz, H-2‘), 3.42 (s, 3H, OCH_3), 3.25 (dd, 1H, *J* = 8.0, 14.0 Hz, H-8a‘), 3.07 (dd, 1H, *J* = 5.0, 14.0 Hz, H-8b‘), 1.99 (s, 3H, $COCH_3$), 1.94 (s, 3H, $COCH_3$), 1.65 (s, 3H, $COCH_3$); HR MALDI-TOF MS (*m*/*z*) calcd for $C_{54}H_{60}O_{14}S$ $[M + Na]^+$ 987.3601, found 987.3659.

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-α-D-glucopyranoside (17): $[\alpha]^{20}_D$ = −221.7° (*c* = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.07 (m, 30H, aromatic), 5.51 (t, 1H, *J* = 9.5 Hz, H-3‘), 5.14 (d, 1H, *J* = 3.0 Hz, H-1‘), 4.96 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.94 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.82 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.69 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.59 (d, 1H, *J* = 3.0 Hz, H-1), 4.58 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.47 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.48−4.41 (m, 1H, H-7‘), 4.40 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.20 (dd, 1H,

J = 2.0, 12.0 Hz, H-6a‘), 4.13 (dd, 1H, *J* = 4.0, 12.0 Hz, H-6b‘), 3,99 (t, 1H, *J* = 9.5 Hz, H-3), 3.92−3.91 (m, 1H, H-5‘), 3.85−3.83 (m, 1H, H-5), 3.80 (m, 2H, H-6a, H-6b), 3.64 (t, 1H, *J* = 9.5 Hz, H-4), 3.58 (dd, 1H, *J* = 3.0, 9.5 Hz, H-2), 3.40 (s, 3H, OCH_3), 3.38−3.34(m, 2H, H-2‘, H-4‘), 3.31(dd, 1H, *J* = 7.0, 13.5 Hz, H-8a‘), 3.05(dd, 1H, *J* = 5.0, 13.5 Hz, H-8b‘), 1.99 (s, 3H, $COCH_3$), 1.72 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.61, 169.66, 140.41, 138.88, 138.40, 138.22, 137.50, 136.53, 128.94, 128.75, 128.49, 128.45, 128.40, 128.34, 128.27, 128.06, 127.92, 127.76, 127.62, 127.49, 126.87, 125.85, 97.88, 96.60, 82.27, 80.93, 80.24, 78.02, 77.23, 76.12, 75.69, 75.03, 74.03, 73.27, 73.05, 70.18, 68.32, 66.37, 62.80, 55.26, 41.49, 20.91, 20.84; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{59}H_{64}O_{13}S$ $[M + Na]^+$ 1035.3965, found 1035.3988.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (19): $[\alpha]^{20}_D$ = +66.5° (*c* = 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−6.97 (m, 25H, aromatic), 5.71 (d, 1H, *J* = 3.5 Hz, H-1‘), 5.35 (t, 1H, *J* = 10.0 Hz, H-3‘), 5.07 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.96 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.78 (t, 1H, *J* = 10.0 Hz, H-4‘), 4.71 (d, 1H, *J* = 9.5 Hz, C*H*HPh), 4.63−4.54 (m, 3H, H-1, C*H*HPh), 4.35 (t, 1H, *J* = 7.0 Hz, H-7‘), 4.17 (t, 1H, *J* = 9.5 Hz, H-3), 4.10−3.93 (m, 4H, H-4, H-5, H-6a, H-5‘), 3.85−3.82 (m, 1H, H-6b), 3.76−3.74 (m, 1H, H-6b‘), 3.67−3.65 (m, 1H, H-6‘), 3.60 (dd, 1H, *J* = 3.5, 9.5 Hz, H-2), 3.38 (s, 3H, OCH_3), 3.34 (dd, 1H, *J* = 3.5, 10.0 Hz, H-2‘), 3.25 (dd, 1H, *J* = 7.0, 13.0 Hz, H-8a‘), 2.89 (dd, 1H, *J* = 7.0, 13.0 Hz, H-8b‘), 1.97 (s, 3H, $COCH_3$), 1.94 (s, 3H, $COCH_3$), 1.73 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.55, 170.04, 169.64, 140.08 139.31, 138.06, 137.97, 136.60, 128.87, 128.53, 128.54, 128.36, 128.28, 128.15, 127.92, 127.61, 127.36, 127.09, 126.87, 126.83, 125.68, 97.91, 94.97, 81.35, 81.28, 80.13, 77.22, 76.13, 74.23, 73.42, 73.29, 71.21, 69.66, 68.83, 68.69, 67.50, 61.92, 55.36, 40.83, 20.73, 20.65, 20.20; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{54}H_{60}O_{14}S$ $[M + Na]^+$ 987.3601, found 987.3666.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (20): $[\alpha]^{20}_{D}$ = −103.65° (*c* = 2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−6.98 (m, 30H, aromatic), 5.63 (d, 1H, *J* = 3.0 Hz, H-1‘), 5.45 (t, 1H, *J* = 10.0 Hz, H-3‘), 5.06 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.97 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.72 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.61 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.61(d, 1H, *J* = 3.0 Hz, H-1), 4.53 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.50 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.47 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.38 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.33 (t, 1H, *J* = 6.0 Hz, H-7‘), 4.14 (t, 1H, *J* = 9.0 Hz, H-3), 4.08−3.89 (m, 5H, H-6a‘, H-6b‘, H-5‘, H-5, H-6b), 3.71−3.69 (m, 1H, H-6a), 3.63−3.61 (m, 1H, H-4), 3.58 (dd, 1H, *J* = 3.0, 9.0 Hz, H-2), 3.37 (s, 3H, OCH_3), 3.34−3.29 (m, 2H, H-4‘, H-8b‘), 3.22 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2‘), 2.87 (dd, 1H, *J* = 6.0, 14.0 Hz, H-8a‘), 1.96 (s, 3H, $COCH_3$), 1.81 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.51, 169.67, 140.08 139.45, 138.12, 138.02, 137.60, 136.70, 128.81, 128.47, 128.43, 128.33, 128.25, 128.21, 128.16, 127.92, 127.41, 127.141, 127.06, 126.95, 125.56, 97.91, 94.95, 81.55, 80.90, 80.01, 77.22, 76.80, 76.11 (2), 74.36, 74.23, 73.27 (2), 72.87, 69.66, 68.74, 62.82, 55.28, 40.53, 21.04, 20.86; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{59}H_{64}O_{13}S$ $[M + Na]^+$ 1035.3965, found 1035.3979.

Procedure for Low-Temperature NMR Experiments. The ^{1}H NMR spectrum of **8** (14 mg, 0.02 mmol) in CD_2Cl_2 (0.5 mL) was recorded: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.67 (s, 1H, N*H*), 7.39−7.18 (m, 15H, aromatic), 6.58 (d, 1H, *J* = 3.0 Hz, H-1)**,** 5.48 (t, 1H, *J* = 10.0 Hz, H-3), 4.53 (t, 1H, *J* = 6.5 Hz, H-7), 4.49 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.46 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.30−4.08 (m, 1H, H-6a), 4.16−4.12 (m, 1H, H-6b), 4.09−4.05 (m, 1H, H-5), 3.55 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2), 3.51 (t, 1H, *J* = 10.0 Hz, H-4), 3.29 (dd, 1H, *J* = 7.0, 14.0 Hz, H-8a), 3.08 (dd, 1H, *J* = 7.0, 14.0 Hz, H-8b), 1.98 (s, 3H, $COCH_3$), 1.85 (s, 3H, $COCH_3$).

Trimethylsilyl trifluoromethanesulfonate (3.6 μL, 0.02 mmol) was added to the above solution at −50 °C. The reaction mixture was allowed to warm slowly to 0 °C. The NMR spectra of **21** (^{1}H, ^{1}H TOCSY 1D, HSQC, and HMBC) were recorded at −20 °C. **21**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ

7.89−7.87 (m, 2H, aromatic), 7.76−7.74 (m, 1H, aromatic), 7.65−7.62 (m, 2H, aromatic), 7.41−7.16 (m, 10H, aromatic), 5.48 (t, 1H, *J* = 9.5 Hz, H-3), 5.35 (d, 1H, *J* = 11.0 Hz, H-7), 5.30 (d, 1H, *J* = 9.5 Hz, H-1)**,** 4.56 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.50 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.32 (d, 1H, *J* = 11.0 Hz, H-8eq), 4.16−4.08 (m, 3H, H-2, H-6a, H-6b), 3.81 (t, 1H, *J* = 9.5 Hz, H-4), 3.77 (m, 1H, H-5), 3.66 (t, 1H, *J* = 11.0 Hz, H-8ax), 1.96 (s, 3H, $COCH_3$), 1.95 (s, 3H, $COCH_3$).

Methanol was added to the reaction mixture at the same temperature, and the ^{1}H NMR spectrum of **22** was recorded at 0 °C. **22**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.39−7.18 (m, 15H, aromatic), 5.47 (t, 1H, *J* = 9.0 Hz, H-3), 4.84 (d, 1H, *J* = 3.5 Hz, H-1), 4.44 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.39 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.39 (t, 1H, *J* = 5.5 Hz, H-7), 4.27−4.11 (m, 2H, H-6a, H-6b), 3.81−3.77 (m, 1H, H-5), 3.40 (s, 3H, OCH_3), 3.36−3.26 (m, 3H, H-2, H-4, H-8a), 3.10 (dd, 1H, *J* = 5.5, 14.0 Hz, H-8b), 1.96 (s, 3H, $COCH_3$), 1.72 (s, 3H, $COCH_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.18 (m, 15H, aromatic), 5.49 (t, 1H, *J* = 9.6 Hz, H-3), 4.94 (d, 1H, *J* = 3.6 Hz, H-1), 4.49 (d, 1H, *J* = 11.1 Hz, C*H*HPh), 4.42 (d, 1H, *J* = 11.1 Hz, C*H*HPh), 4.40 (t, 1H, *J* = 6.3 Hz, H-7), 4.25−4.22 (m, 2H, H-6a, H-6b), 3.92−3.86 (m, 1H, H-5), 3.44 (s, 3H, OCH_3), 3.41−3.30 (m, 3H, H-2, H-4, H-8a), 3.10 (dd, 1H, *J* = 4.8, 13.8 Hz, H-8b), 2.03 (s, 3H, $COCH_3$), 1.66 (s, 3H, $COCH_3$).

The ^{1}H NMR spectrum of **21** showed that the anomeric proton (H1) signal (δ 6.58, d, $J_{1,2}$ = 2.5 Hz, α-configuration) was shifted to upfield (δ 5.30, d, $J_{1,2}$ = 9.5 Hz, β-configuration). The change of anomeric configuration indicate that the α-imidate donor **8** was completely transformed to a new intermediate **21** after activation. H1, H7, H8eq, and H8ax signals of **21** were assigned from ^{1}H TOCSY 1D data irradiated on H4 and H7. The anomeric carbon signal (C1, δ 88.0) of **21** was assigned from HSQC data. The HMBC spectrum of **21** showed the three-bond coupling between C1 (δ 88.0) and H8eq (δ 4.32), which confirmed the presence of the C1−H8eq bond. So, the *trans*-decalin structure of the sulfonium ion **21** was proved directly from the low-temperature NMR experiments.

3,6-Di-*O*-acetyl-2,4-di-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate (23): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H, NH), 7.35−7.24 (m, 10H, aromatic), 6.47 (d, 1H, *J* = 3.5 Hz, H-1), 5.62 (t, 1H, *J* = 9.5 Hz, H-3), 4.68 (d, 1H, *J* = 12.0 Hz, CHHPh), 4.59 (d, 1H, *J* = 11.0 Hz, CHHPh), 4.55 (d, 1H, *J* = 12.0 Hz, CHHPh), 4.53 (d, 1H, *J* = 11.0 Hz, CHHPh), 4.31 (dd, 1H, *J* = 2.5, 12.5 Hz, H-6a), 4.24 (dd, 1H, *J* = 4.5, 12.5 Hz, H-6b), 4.14−4.09 (m, 1H, H-5), 3.66 (dd, 1H, *J* = 3.5, 9.5 Hz, H-2), 3.62 (t, 1H, *J* = 9.5 Hz, H-4), 2.03 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$).

Methyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-α/β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (24) (mixture as α/β = 3/1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (t, 1H, *J* = 9.5 Hz, H-3‘-α), 5.22 (t, 1H, *J* = 9.0 Hz, H-3‘-β), 4.96 (d, 1H, *J* = 3.0 Hz, H-1‘-α), 4.38 (d, 1H, *J* = 8.5 Hz, H-1‘-β), 3.36 (s, 3H, OCH_3-α), 3.34 (s, 3H, OCH_3-β), 2.01 (s, 3H, $COCH_3$-β), 2.00 (s, 3H, $COCH_3$-α), 1.97 (s, 3H, $COCH_3$-α), 1.86 (s, 3H, $COCH_3$-β).

3,6-Di-*O*-acetyl-4-*O*-benzyl-2-*O*-(2-(phenylsulfanyl)ethyl)-α-D-glucopyranosyl trichloroacetimidate (25): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H, N*H*), 7.38−7.17 (m,10H, aromatic), 6.51 (d, 1H, *J* = 3.6 Hz, H-1), 5.56 (t, 1H, *J* = 9.6 Hz, H-3), 4.60 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.54 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.34−4.21 (m, 2H, H-6a, H-6b), 4.14−4.09 (m, 1H, H-5), 3.86−3.49 (m, 4H, H-7a, H-7b, H-4, H-2), 3.08−2.99 (m, 2H, H-8a, H-8b), 2.04 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.49, 169.71, 161.24, 137.09, 135.76, 129.64, 129.46, 129.02, 128.60, 128.26, 128.22, 128.18, 128.07, 126.40, 126.32, 93.45, 77.84, 75.25, 74.55, 72.93, 71.19, 69.82, 62.38, 33.39, 21.11, 20.78.

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-(2-(phenylsulfanyl)ethyl)-α/β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (26) (mixture as α/β = 8/1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (t, 1H, *J* = 10.0 Hz, H-3‘-α), 5.17 (t, 1H, *J* = 9.5 Hz, H-3‘-β), 5.02 (d, 1H, *J* = 3.5 Hz, H-1‘-α), 4.31 (d, 1H, *J* = 7.5 Hz, H-1‘-β), 3.35 (s, 3H, OCH_3-α), 3.33 (s, 3H, OCH_3-β),

2.017 (s, 3H, $COCH_3$-α), 2.006 (s, 3H, $COCH_3$-β), 2.001 (s, 3H, $COCH_3$-β), 1.99 (s, 3H, $COCH_3$-α).

3,6-Di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*R*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-glucopyranosyl Trichloroacetimidate (27). Compound **27** was synthesized according to the procedure described for the synthesis of compound **8**: colorless syrup; R_f = 0.43 (dichloromethane/acetone = 100/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H, NH), 7.26−7.36 (m, 15H, aromatic), 5.79 (d, 1H, *J* = 4.0 Hz, H-1), 5.68 (t, 1H, *J* = 10.0 Hz, H-3), 4.60 (d, 1H, *J* = 11.0 Hz, CHHPh), 4.53 (d, 1H, *J* = 11.0 Hz, CHHPh), 4.50 (dd, 1H, *J* = 5.0, 8.0 Hz, H-7), 4.23−4.16 (m, 2H, H-6a, H-6b), 4.03−4.00 (m, 1H, H-5), 3.65 (dd, 1H, *J* = 4.0, 10.0 Hz, H-2), 3.60 (t, 1H, *J* = 10.0 Hz, H-4), 3.25 (dd, 1H, *J* = 8.0, 13.5 Hz, H-8a), 3.05 (dd, 1H, *J* = 5.0, 13.5 Hz, H-8b), 2.08 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$).

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(1*R*)-phenyl-2-(phenylsulfanyl)ethyl}-α/β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (28) (mixture as α/β **= 1/1):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (t, 1H, *J* = 10.0 Hz, H-3'-α), 5.28 (t, 1H, *J* = 9.0 Hz, H-3'-β), 4.24 (d, 1H, *J* = 6.5 Hz, H-1'-β), 4.23 (d, 1H, *J* = 3.5 Hz, H-1'-α), 2.04 (s, 3H, $COCH_3$-α), 2.00 (s, 3H, $COCH_3$-β), 1.98 (s, 3H, $COCH_3$-β), 1.95 (s, 3H, $COCH_3$-α).

Acetyl 3,4,6-Tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-galactopyranose (51). Boron trifluoride diethyl etherate (190 µL, 1.5 mmol) was added to a solution of acetyl 3,4,6-tri-*O*-acetyl-α-D-galactopyranose (348 mg, 1.0 mmol), acetic acid (1*S*)-phenyl-2-(phenylsulfanyl)ethyl ester (408 mg, 1.5 mmol), and activated molecular sieves (4 Å) in dichloromethane (5 mL) at 0 °C. After 20 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25%

ethyl acetate in hexane) to afford **51** (504 mg, 90%): colorless syrup; R_f = 0.37 (ethyl acetate/hexane, 1/2); $[\alpha]^{20}_D$ = −9.0° (*c* = 4.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.14 (m,10H, aromatic), 6.49 (d, 1H, *J* = 3.6 Hz, H-1), 5.37−5.36 (m, 1H, H-4), 5.24 (dd, 1H, *J* = 3.3, 10.2 Hz, H-3), 4.51 (dd, 1H, *J* = 4.8, 9.6 Hz, H-7), 4.27−4.23 (m, 1H, H-5), 4.03−3.96 (m, 2H, H-6b, H-6a), 3.83 (dd, 1H, *J* = 3.6, 10.2 Hz, H-2), 3.20 (dd, 1H, *J* = 9.6, 13.8 Hz, H-8a), 3.07 (dd, 1H, *J* = 4.8, 13.8 Hz, H-8b), 2.18 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$), 1.92 (s, 3H, $COCH_3$), 1.76 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.38, 169.98, 169.97, 169.42, 140.06, 136.39, 129.28, 128.99, 128.95, 128.92, 128.88, 128.68, 128.38, 126.85, 126.75, 126.16, 89.61, 81.24, 71.55, 68.84, 68.33, 67.67, 61.26, 41.77, 21.171, 20.65, 20.48, 20.43; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{28}H_{32}O_{10}S$ $[M + Na]^+$ 583.1614, found 583.1611.

3,4,6-Tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-galatopyranosyl Trichloroacetimidate (29). Hydrazinium acetate (91 mg, 0.99 mmol) was added to a solution of **51** (504 mg, 0.9 mmol) in DMF (5 mL) at room temperature. The reaction mixture was stirred overnight and then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (20 mL). The combined organic phases were washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford 3,4,6-tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-D-galactopyranose (**52**) (434 mg, 93%). Trichloroacetonitrile (0.84 mL, 8.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (50 µL, 0.33 mmol) were added to a solution of **52** (434 mg, 0.84 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then concentrated in vacuo. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford **29** (505 mg, 91%): R_f = 0.32 (ethyl acetate/hexane, 1/3); $[\alpha]^{20}_D$ = −56.37° (*c* = 3.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H, N*H*), 7.34−7.18 (m, 10H, aromatic), 6.70 (d, 1H, *J* = 3.3 Hz, H-1), 5.43−5.42 (m, 1H, H-4), 5.28 (dd, 1H, *J* = 3.3,

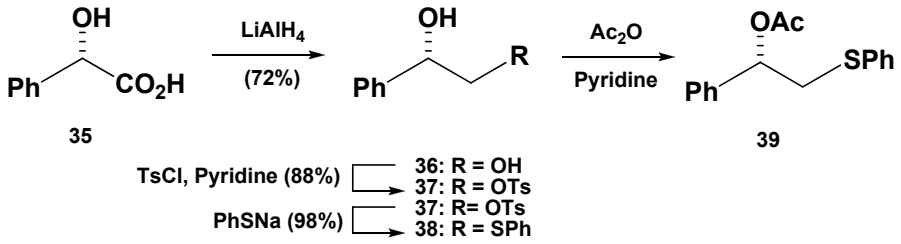
10.5 Hz, H-3), 4.57 (dd, 1H, *J* = 5.7, 7.8 Hz, H-7), 441−4.37 (m, 1H, H-5), 4.11−3.99 (m, 2H, H-6a, H-6b), 3.94 (dd, 1H, *J* = 3.3, 10.5 Hz, H-2), 3.21 (dd, 1H, *J* = 7.8, 13.8 Hz, H-8a), 3.11 (dd, 1H, *J* = 5.7, 13.8 Hz, H-8b), 1.99 (s, 3H, $COCH_3$), 1.96 (s, 3H, $COCH_3$), 1.69 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.33, 169.92, 169.84, 160.99, 140.26, 129.27, 129.02, 128.37, 128.25, 126.67, 126.14, 94.00, 81.41, 72.48, 69.10, 68.84, 67.71, 61.36, 41.86, 20.64, 20.45, 20.36; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{28}H_{30}Cl_3NO_9S$ $[M+Na]^+$ 684.0604, found 684.0612.

Methyl 3,4,6-Tri-*O*-acetyl-2-*O*-{(1*S*)-phenyl-2-(phenylsulfanyl)ethyl}-α-D-galatopyranosyl-(1→3)-2,6-di-*O*-benzoyl-β-D-galatopyranosyl-(1→4)-6-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-azido-β-D-glucopyranoside (32). Trimethylsilyl trifluoromethanesulfonate (9.0 µL, 0.05 mmol) was added to a solution of **29** (66 mg, 0.1 mmol) and activated molecular sieves (4 Å) in DCM (10 mL) at 0 °C. After 5 min, phenyl 2,6-di-*O*-benzoyl-1-thio-β-D-galatopyranoside (30) (48 mg, 0.1 mmol) was added to the reaction mixture at the same temperature. After the temperature was raised gradually to room temperature over a period of 4 h, methyl 6-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-azido-β-D-glucopyranoside (**31**) (70.3 mg, 0.2 mmol) and *N*-iodosuccinimide (45.0 mg, 0.2 mmol) were added at −78 °C. The reaction mixture was allowed to warm gradually to room temperature over a period of 2 h and then quenched with aqueous saturated $NaHCO_3$ (10 mL). The organic phase was washed with aqueous solution of sodium thiosulfate (1 M, 10 mL) and then dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford the trisaccharide **32** (63 mg, 52%) as a colorless syrup: R_f = 0.32 (ethyl acetate/ hexane, 1/1); $[\alpha]^{20}_D$ = +19.5° (*c* = 0.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.13−7.97 (m, 4H, aromatic), 7.57−7.19 (m, 21H, aromatic), 5.61 (t, 1H, *J* = 9.0 Hz, H-2‘), 5.49 (d, 1H, *J* = 4.0 Hz, H-1‘ ‘), 5.11 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 5.08−5.06 (m, 1H, H-4‘ ‘), 5.05 (dd, 1H, *J* = 3.0, 10.0 Hz, H-3‘ ‘), 4.77 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.64 (d, 1H, *J* = 8.5 Hz, H-1‘), 4.54 (dd, 1H, *J* = 3.0, 10.0 Hz, H-7‘ ‘), 4.54−4.52 (m, 1H), 4.45 (dd, 1H, *J* = 7.0, 10.0 Hz), 4.33 (m, 1H, H-4‘), 4.21−4.18 (m, 1H), 4.04

(d, 1H, *J* = 7.5 Hz, H-1), 4.03−4.02 (m, 1H, H-3‘), 3.89−3.78 (m, 4H, H-2‘ ‘, H-4), 3.72−3.68 (m, 2H), 3.46 (s, 3H, OCH_3), 3.48−3.43 (m, 1H, H-3), 3.34−3.31 (m, 2H), 3.25 (t, 1H, *J* = 9.0 Hz, H-2), 3.20 (dd, 1H, *J* = 3.0, 10.0 Hz, H-8a‘ ‘), 3.01 (dd, 1H, *J* = 10.0, 14.0 Hz, H-8b‘ ‘), 1.93 (s, 3H, $COCH_3$), 1.92 (s, 3H, $COCH_3$), 1.77 (s, 3H, $COCH_3$), 1.19 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.60, 169.95, 169.75, 169.45, 166.24, 164.79, 141.20, 138.12, 135.43, 133.51, 133.08, 129.83, 129.78, 129.54, 129.34, 129.09, 128.73, 128.63, 128.42, 128.32, 128.19, 127.98, 127.65, 126.71, 125.32, 102.60, 100.93, 96.22, 84.42, 80.75, 78.94, 77.22, 77.02, 77.01, 75.46, 72.78, 72.18, 71.17, 69.73, 67.61, 66.77, 65.83, 65.57, 62.89, 62.19, 60.48, 57.18, 43.54, 20.69, 20.49, 19.65; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{62}H_{67}N_3O_{21}S$ $[M + Na]^+$ 1244.3884, found 1244.3809.

Methyl 2,3,4,6-Tetra-*O*-acetyl-α-D-galatopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galatopyranosyl-(1→4)-6-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-azido-β-D-glucopyranoside (33). To a solution of the trisaccharide **32** (63 mg, 0.051 mmol) in acetic anhydride (3 mL) was added boron trifluoride diethyl etherate (9.7 µL, 0.077 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 40 min and then quenched with aqueous saturated $NaHCO_3$ (10 mL). After dilution with DCM (10 mL), the reaction mixture was separated. The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford trisaccharide **33** (53 mg, 95%) as colorless syrup: R_f = 0.24 (ethyl acetate/hexane, 1/1); $[\alpha]^{20}_D$ = +41.8 ° (*c* = 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.12−7.97 (m, 4H, aromatic), 7.63−7.28 (m, 11H, aromatic), 5.57 (dd, 1H, *J* = 7.5, 9.0 Hz, H-2‘), 5.46 (d, 1H, *J* = 3.0 Hz, H-1‘ ‘), 5.21−5.19 (m, 2H, H-2‘ ‘, H-4‘ ‘), 5.05 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.99 (dd, 1H, *J* = 3.0, 10.0 Hz, H-3‘ ‘), 4.83 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.83−4.81 (m, 1H, H-4‘), 4.70 (d, 1H, *J* = 9.0 Hz, H-1‘), 4.28−4.11 (m, 4H), 4.06 (d, 1H, *J* = 7.5 Hz, H-1), 4.03 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3‘), 3.98 (t, 1H, *J* = 7.0 Hz), 3.86 (t, 1H, *J* = 7.0 Hz), 3.83−3.73 (m, 3H), 3.47 (s, 3H, OCH_3), 3.43 (t,

1H, *J* = 9.0 Hz), 3.40−3.27 (m, 2H), 2.16 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 1.93 (s, 3H, $COCH_3$), 1.87 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.44, 170.13(2), 169.95, 169.63, 169.40, 165.87, 164.69, 138.23, 133.88, 133.46, 129.89, 129.77, 129.29, 128.83, 128.65, 128.54, 128.24, 127.29, 127.60, 102.65, 100.92, 93.74, 80.81, 77.22, 76.77, 75.14, 73.67, 72.68, 70.94, 67.63, 66.88, 66.66, 66.47, 65.72, 64.78, 61.69, 61.30, 61.15, 57.22, 20.77, 20.73, 20.66, 20.62, 20.52, 20.49; HR MALDI-TOF MS (*m*/*z*) calcd for $C_{52}H_{59}N_3O_{23}$ $[M + Na]^+$ 1116.3436, found 1116.3418.



Scheme 2.7. Preparation of (*S*)-2-(Phenylthiomethyl)benzyl acetate **39**

(*S*)-Phenyl-1,2-ethanediol (36). To a solution of (*S*)-mandelic acid (10.0 g, 65.7 mmol) in diethyl ether (50 mL) was added slowly LiAlH4 (5.0 g, 131 mmol). After the reaction mixture was refluxed for 2 h, ethyl acetate (20 mL) was added slowly and then poured into ice water (100 mL). The organic phase was separated and dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by recrystallization (hexane/ethyl acetate) to afford **30** (6.54 g, 72%) as a white solid, *Rf* = 0.24 (ethyl acetate/hexane, 1/1); [α] $^{20}_D$ +60.5 (*c* 1.15, CHCl3); 1H NMR (500 MHz, $CDCl_3$) *δ* 7.37–7.26 (m, 5H, ArH), 4.82 (dd, 1H, *J* = 3.6, 8.1 Hz, C*H*OH), 3.76 (dd, 1H, *J* = 3.6, 11.4 Hz, C*H*HOH), 3.66 (dd, 1H, *J* = 8.1, 11.4 Hz, CH*H*OH), 2.42 (brs, 2H, OH). (Ref : Bradshaw, Jerald S. Jolley, Scott t.; Izatt, Reed M. *J. Org. Chem*. **1982**, *47*, 1229-1232.)

(*S*)-1-Phenyl-2-(tosyloxy)ethanol (37). To a solution of **36** (4.18 g, 30.3 mmol) in CH2Cl2 (60 mL) were sequentially added Bu2SnO (151 mg, 0.6 mmol), TsCl (5.77 g, 30.3 mmol) and Et3N

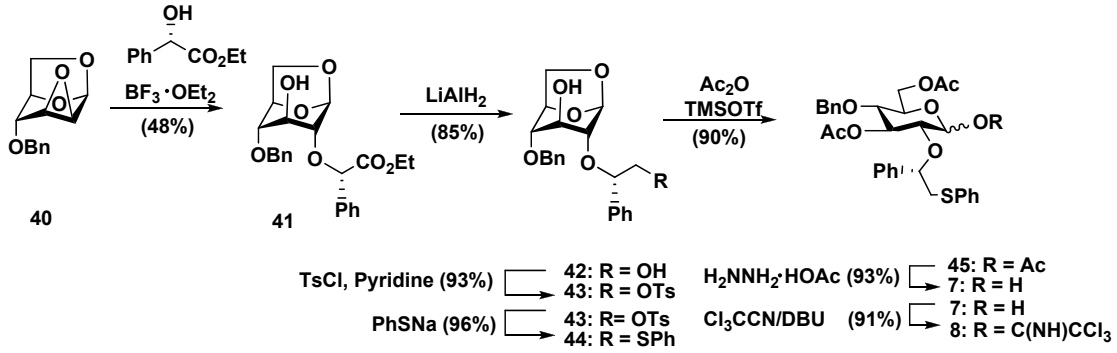
(4.2 mL, 30.3 mmol). After stirring at room temperature for 3 h, the reaction mixture was diluted with CH2Cl2 (60 mL) and washed with brine (40 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford **37** (7.81 g, 88%) as a colorless syrup, R_f = 0.69 (ethyl acetate/hexane, 1/1); [α] $^{20}_{D}$ +43.6 (*c* 1.12, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$) *δ* 7.70 (d, 2H, *J* = 8.4 Hz, ArH), 7.37–7.26 (m, 7H, ArH), 5.01-4.96 (m, 1H, C*H*OH), 4.16 (dd, 1H, *J* = 3.3, 10.5 Hz, C*H*HOTs), 4.05 (dd, 1H, *J* = 8.4, 10.5, Hz,, CH*H*OTs), 2.53 (d, 1H, *J* = 3.3 Hz, CHO*H*), 2.45 (s, 3H, CH_3). (Ref: Pandey, Rajesh Kumar; Fernandes, Rodney A.; Kumar, Pradeep. *Tetrahedron Lett*. **2002**, *43*, 4425-4426.)

(*S*)-1-Phenyl-2-(phenylthio)ethanol (38). To a solution of **37** (7.81 g, 26.7 mmol) in THF (40 mL) was added benzenethiol, sodium salt (90%, 5.11 g, 35.0 mmol). The reaction mixture was stirred at room temperature overnight, then concentrated *in vacuo*. The residue was dissolved with dichloromethane (50 mL) and washed with brine (50 mL).

The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford **38** (6.0 g, 98%) as a colorless syrup, R_f = 0.30 (ethyl acetate/hexane, 1/4); [α] $^{20}_{D}$ +21.0 (*c* 0.27, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$) *δ* 7.34-7.12 (m, 10H, ArH), 4.73 (dd, 1H, *J* = 2.1, 5.7 Hz, C*H*OH), 3.33 (dd, 1H, *J* = 2.1, 8.4 Hz, C*H*HSPh), 3.10 (dd, 1H, *J* = 5.7, 8.4 Hz, CH*H*SPh), 2.81 (s, 1H, OH). (Ref: Christoffers, Jens; Roessler, Ulrich. *Tetrahedron; Asymmetry*. **1999**, *10*, 1207-1215.)

(*S*)-(Phenylthiomethyl)benzyl acetate (39). To a solution of **38** (6.0 g, 26.0 mmol) in pyridine (30 mL) was added acetic anhydride (5.0 mL, 52.0 mmol). After stirring at 0 ^{o}C for 2 h, the reaction mixture was quenched with saturated sodium bicarbonate solution (50 mL) and then diluted with dichloromethane (50 mL). After separation, the organic phase was washed with

saturated sodium bicarbonate solution (50 mL × 3) and brine (50mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford **39** (5.82 g, 82%) as a colorless syrup, R_f = 0.47 (ethylacetate/hexane, 1/4); [α] $^{20}_{D}$ 20 +31.6 (*c* 1.52, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$) *δ* 7.39-7.20 (m, ArH), 5.89 (dd, 1H, *J* = 5.4, 8.1 Hz), 3.41 (dd, 1H, *J* = 8.1, 14.1 Hz*, CH*HSPh), 3.23 (dd, 1H, *J* = 5.4, 14.1 Hz, *C*H*H*SPh) 2.02 (s, 3H, $COCH_3$). (Ref: Bortolini, O.; Furia, F.; Licini, G.; Modena, G. *Phosphorus Sulfur*. **1988**, *37*, 171-174.)



Scheme 2.8. Preparation of glucosyl donor **8**

1,6-Anhydro-4-*O*-benzyl-2-*O*-(*S*)-(ethoxycarbonyl)benzyl-β-D-glucopyranose (41). Boron trifluoride diethyl etherate (543 µL, 4.27 mmol) was added dropwise to a solution of 1,6,2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranose (**40**) (5 g, 21.3 mmol), (*S*)-ethyl mandelate (11.5 g, 63.9 mmol) and activated molecular sieves (4Å) in toluene (20 mL) at room temperature. After 1h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and then diluted with ethyl acetate (30 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford **41** (4.23 g, 48%): colorless syrup, R_f = 0.34 (ethyl acetate/hexane, 1/1); [α] $^{20}_{D}$ = +40.3° (*c* = 1.0, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) *δ* 7.25-7.48 (m, 10H, aromatic), 5.54 (s, 1H, H-1), 5.22 (s, 1H, >C*H*Ph), 4.63 (d, 1H, *J* = 12.3 Hz, C*H*HPh), 4.61 (d, 1H, *J* =12.3 Hz, C*H*HPh), 4.54 (d, 1H, *J* = 5.4 Hz, H-5), 4.13-4.23 (m, 2H, $COOCH_2CH_3$), 3.88 (t, 1H, *J* = 4.8 Hz, H-3), 3.73 (d, 1H, *J* = 7.5 Hz, H-6a), 3.61 (dd, 1H, *J* = 5.4, 7.2 Hz, H-6b),

3.33 (d, 1H, *J* = 4.8, H-2), 3.29 (d, 1H, *J* = 5.1, H-4), 2.61 (b, 1H, OH), 1.21 (t, 3H, *J* = 7.2 Hz, $COOCH_2CH_3$); 13C NMR (75 MHz, $CDCl_3$) *δ* 171.07, 137.79, 136.01, 128.73, 128.59, 128.43, 127.78, 127.75, 127.50, 101.80, 80.49, 80.17, 80.02, 75.48, 71.80, 71.25, 66.85, 61.43, 14.01; HR MALDI-TOF MS: m/z: calcd for C23H26O7 [M+Na]+: 437.1577; found: 437.1532.

1,6-Anhydro-4-*O*-benzyl-2-*O*-{(*S*)-2-(hydroxymethyl)benzyl}-β-D-glucopyranose (42). To a solution of **41** (1.20 g, 2.90 mmol) in THF (35 mL) was added LiAlH4 (220 mg, 5.8 mmol). After the reaction mixture was refluxed for 4 h, diluted with ethyl acetate (20 mL) and then poured into ice water (10 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (67% ethyl acetate in hexane) to afford **42** (0.92g, 85%) as colorless syrup, R_f = 0.24 (ethyl acetate/hexane, 2/1); $[\alpha]_D^{20}$ = +28.36° (*c* = 5.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.35-7.27 (m, 10H, aromatic), 5.57 (s, 1H, H-1), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.60-4.58 (m, 1H, H-6a), 4.58 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.50 (d, 1H, *J* = 5.0 Hz, H-5), 3.79-3.77 (m, 2H, H-7, H-3), 3.71 (dd, 1H, *J* = 9.0, 12.0 Hz, H-8a), 3.62 (dd, 1H, *J* = 5.0, 5.5 Hz, H-4), 3.59 (dd, 1H, *J* = 3.5, 12.0 Hz, H-8b), 3.25-3.24 (m, 2H, H-2, H-6b); ^{13}C NMR (75 MHz, CDCl3) *δ* 138.22, 137.79, 128.63, 128.59, 128.52, 128.40, 127.92, 127.84, 127.08, 100.61, 82.60, 79.36, 78.27, 75.40, 71.72, 70.73, 67.08, 66.38; HR MALDI-TOF MS: m/z: calcd for C21H24O6 [M+Na]+: 395.1471; found: 395.1405.

1,6-Anhydro-4-*O*-benzyl-2-*O*-{(*S*)-2-(tosyloxymethyl)benzyl}-β-D-glucopyranose (43). To a solution of **42** (0.78 g, 2.09 mmol) in pyridine (10 mL) was added TsCl (0.44 g, 2.32 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with CH2Cl2 (20 mL) and washed with brine (40 mL). The organic phase was dried (MgSO4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (33% ethyl acetate in hexane) to afford **43** (1.02 g, 93%) as colorless syrup, *Rf* = 0.38 (ethyl acetate/hexane, 1/1); [α]20 D = -13.11° (*c* = 4.5, CHCl3); 1H NMR (500 MHz, CDCl3) *δ* 7.75 -

7.74 (m, 2H, aromatic), 7.34-7.28 (m, 12H, aromatic), 5.44 (s, 1H, H-1), 4.75 (dd, 1H, *J* = 5.0, 7.0 Hz ,H-7), 4.58 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.51 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.52-4.50 (m, 1H, H-4), 4.13-4.11 (m, 2H, H-8a,8b), 3.70-3.68 (d, 1H, *J* = 7.0 Hz, H- 6a), 3.63-3.60 (m, 1H, H-3), 3.62 (d,1H, *J* = 7.0 Hz, H-6b), 3.23 (d, 1H, *J* = 5.0 Hz, H-2), 3.19 (d, 1H, *J* = 5.0 Hz, H-5), 2.42 (s, 3H, CH3); 13C NMR (75 MHz, CDCl3) *δ* 144.89, 137.79, 136.94, 132.85, 129.88, 128.78, 128.77, 128.48, 127.93, 127.86, 127.78, 127.01, 101.31, 80.85, 80.20, 79.71, 75.50, 72.76, 71.73, 70.97, 66.78, 21.63; HR MALDI-TOF MS: m/z: calcd for C28H30O8S [M+Na]+: 549.1559; found: 549.1555.

1,6-Anhydro-4-*O*-benzyl-2-*O*-{(*S*)-2-(phenylthiomethyl)benzyl}-β-D-glucopyranose (44). To a solution of **43** (610 mg, 1.16 mmol) in THF (15 mL) was added benzenethiol, sodium salt (512 mg, 90%, 3.48 mmol). The reaction mixture was stirred at room temperature for 2 h, then concentrated *in vacuo*. The residue was dissolved with dichloromethane (10 mL) and washed with brine (10 mL). The organic phase was dried (MgSO4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford **44** (517 mg, 96%) as colorless syrup, *Rf* = 0.56 (ethyl acetate/hexane, 1/1); [α]20 D = -37.23° (*c* = 4.0, CHCl3); 1H NMR (500 MHz, CDCl3) *δ* 7.36-7.16 (m,15H, aromatic), 5.52 (s, 1H, H-1), 4.61 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.56 (dd, 1H, *J* = 5.0, 8.5 Hz, H-7), 4.53-4.50 (m, 1H, H-4), 4.52 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 3.69-3.65 (m, 2H, H-8a, H-5), 3.61-3.59 (m, 1H, H-8b), 3.58 (dd, 1H, *J* = 9.0, 14.0 Hz, H-3), 3.19-3.15 (m, 3H, H-2, H-6a, H-6b) ;13C NMR (75 MHz, CDCl3) *δ* 140.64, 137.89, 136.31, 129.40, 129.01, 128.72, 128.46, 128.44, 127.82, 127.78, 126.83, 101.42, 81.33, 80.79, 80.24, 75.64, 71.71, 71.12, 66.83, 41.74; HR MALDITOF MS: m/z: calcd for C27H28O5S [M+Na]+: 487.1555; found: 487.1540.

Acetyl 3,6-Di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(*S*)-2-(phenylthiomethyl)benzyl}-α-D-glucopyranose (45). Trimethylsilyl trifluoromethansulfonate (2.2 µL, 0.012 mmol) was added to

a solution of **44** (279 mg, 0.60 mmol) in acetic anhydride (10 mL) at -50 °C. The reaction mixture was allowed to warm to -20 °C and then quenched with saturated aqueous NaHCO3, then extracted with DCM (2 × 10 ml). The organic phase was washed with water (10 ml) and brine (10 ml) and dried (MgSO4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/ethyl acetate = 3/1) to afford **45** (329 mg, 90%) as colorless syrup, *Rf* = 0.51 (ethyl acetate/hexane, 1/2); [α]20 D = -54.3° (*c* = 2.0, CHCl3); 1H NMR (300 MHz, CDCl3) *δ* 7.379-7.16 (m,15H, aromatic), 6.41 (d, 1H, *J* = 3.3 Hz, H-1), 5.51 (t, 1H, *J* = 9.6 Hz, H-3), 4.50 (d, 1H, *J* = 10.8 Hz, C*H*HPh), 4.43 (d, 1H, *J* = 10.8 Hz, C*H*HPh), 4.46 (m, 1H, H-7), 4.23-4.22 (m, 2H, H-6b, H-6a), 3.97-3.94 (m, 1H, H-5), 3.49-3.42 (m, 2H, H-2, H-4), 3.24 (dd, 1H, *J* = 8.4, 14.0 Hz, H-8a), 3.03 (dd, 1H, *J* = 5.1, 14.0 Hz, H-8b), 2.14 (s, 3H, COCH3), 2.02 (s, 3H, COCH3), 1.86 (s, 3H, COCH3) ; 13C NMR (75 MHz, CDCl3) *δ* 170.52, 169.72, 169.53, 139.96, 137.10, 136.41, 129.21, 128.98, 128.57, 128.14, 128.00, 127.93, 127.49, 127.09, 126.06, 88.67, 81.16, 75.63, 74.94, 74.76, 72.80, 70.55, 62.39, 41.32, 21.11, 21.08, 20.80; HR MALDI-TOF MS: m/z: calcd for C33H36O9S [M+Na]+: 631.2079; found: 631.2079.

3,6-Di-*O*-acetyl-4-*O*-benzyl-2-*O*-{(*S*)-2-(phenylthiomethyl)benzyl}-α-D-glucopyranosyl trichloroacetimidate (8). Hydrazine acetate (92 mg, 1.0 mmol) was added to a solution of **45** (304 mg, 0.5 mmol) in DMF (5 mL) at room temperature. The reaction mixture was stirred overnight and then quenched with saturated aqueous NaHCO3. The reaction mixture was extracted with ethyl acetate (20 mL). The organic phase was washed with saturated aqueous NH4Cl (20 mL) and dried (MgSO4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*- {(*S*)-2-(phenylthiomethyl)benzyl}-D-glucopyranose (**7**, 263 mg, 93%). Trichloroacetonitrile (0.46 mL, 4.6 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (28 μL, 0.19 mmol) were added to a solution of **7** (263 mg, 0.46 mmol) in

dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford **8** (300 mg, 91%): *Rf* = 0.45 (dichloromethane/acetone, 100/1); [α]20 D = -0.03° (*c* = 6.0, CHCl3); 1H NMR (300 MHz, CDCl3) *δ* 8.61 (s, 1H, N*H*), 7.37-7.16 (m, 15H, aromatic), 6.62 (d, 1H, *J* = 3.6 Hz, H-1), 5.57 (t, 1H, *J* = 9.6 Hz, H-3), 4.52-4.42 (m, 1H, H-7), 4.50 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.44 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.29-4.17 (m, 2H, H-6a, H-6b), 4.13-4.08 (m, 1H, H-5), 3.55 (dd, 1H, *J* = 3.6, 9.6 Hz, H-2), 3.49 (t, 1H, *J* = 9.6 Hz, H-4), 3.25 (dd, 1H, *J* = 6.9, 13.5 Hz, H-8a), 3.05 (dd, 1H, *J* = 6.6, 13.5 Hz, H-8b), 2.00 (s, 3H, COCH3), 1.81 (s, 3H, COCH3); 13C NMR (75 MHz, CDCl3) *δ* 170.44, 169.49, 161.08, 139.80, 137.07, 136,21, 129.35, 128.97, 128.54, 128.53, 128.13, 127.22, 126.11, 93.07, 80.86, 75.51, 75.47, 74.54, 72.70, 70.96, 62.33, 41.27, 20.95, 20.77; HR MALDI-TOF MS: m/z: calcd for C33H34Cl3NO8S [M+Na]+: 732.0968; found: 732.0957.

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CHAPTER III

STEREOSELECTIVE GLYCOSYLATIONS OF 2-AZIDO-2-DEOXY-GLUCOSIDES USING INTERMEDIATE SULFONIUM ION

3.1 ABSTRACT

TMSOTf-promoted glycosylations of 2-azido-2-deoxy-glucosyl trichloroacetimidates provide excellent α-anomeric selectivities when performed at a relatively high reaction temperature in the presence of PhSEt or thiophene. NMR and computation studies have shown that these glycosylations proceed through an equatorial anomeric sulfonium ion, which upon displacement by a sugar alcohol provides an axial glycoside. Computational studies have indicated that steric factors determine the selective formation of the β–anomeric sulfonium ion.

3.2 INTRODUCTION

The principal challenge presented by the synthesis of complex oligosaccharides of biological importance is the development of approaches for the stereoselective introduction of glycosidic linkages. A reliable method for stereoselective glycosylations is based on neighboring group participation of a 2-*O*-acyl functionality (**Figure 3.1a**).[1] In these reactions, a promoter activates an anomeric leaving group, which results in its departure and the formation of an oxacarbenium ion. Subsequent neighboring group participation of the 2-*O*-acyl protecting group will give a more stable dioxolenium ion. An alcohol can attack the anomeric center of the dioxolenium ion from only one face providing a 1,2-*trans* glycoside. Thus, in the case of glucosyl-type donors, β-linked products will be formed and mannosides will give α-glycosides. The introduction of 1,2-*cis* glycosidic linkages, such as α-glucosides and α-galactosides,

requires glycosyl donors with a nonassisting functionality at C-2. Invariably, the use of these glycosyl donors leads to the formation of mixtures of anomers.[2, 3] Separation of these anomers requires time-consuming purification protocols resulting in loss of material. It also limits the use of one-pot multistep glycosylations[4,5] and automated polymer-supported synthesis[6-8] to oligosaccharides that only contain 1,2-*trans* glycosides.

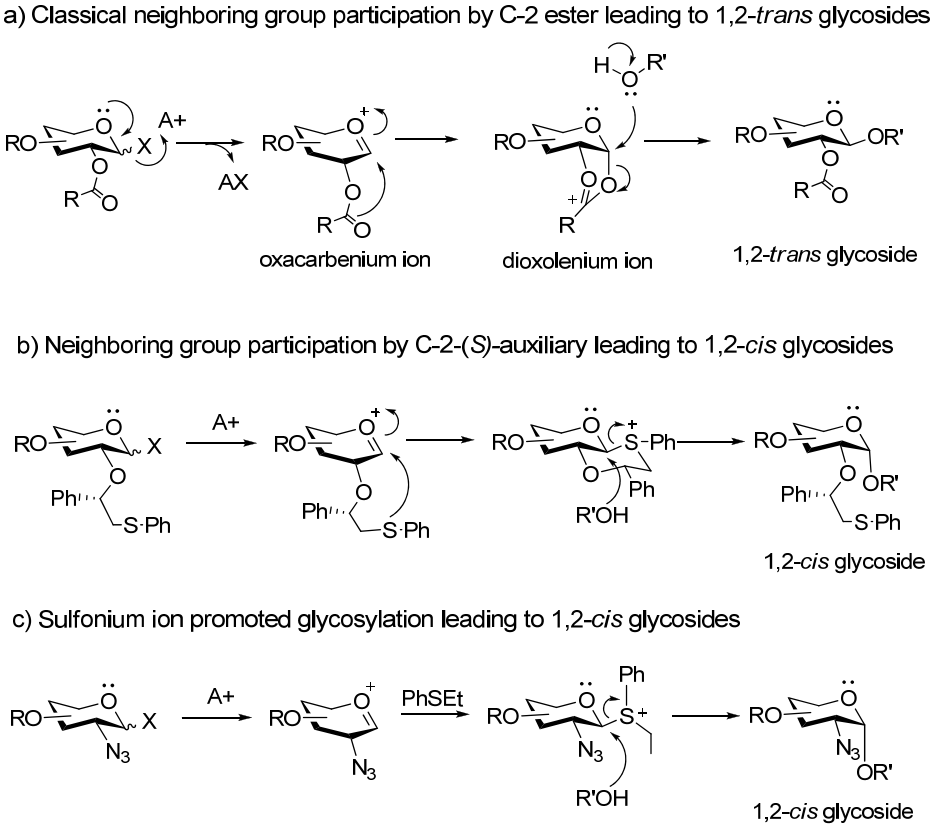


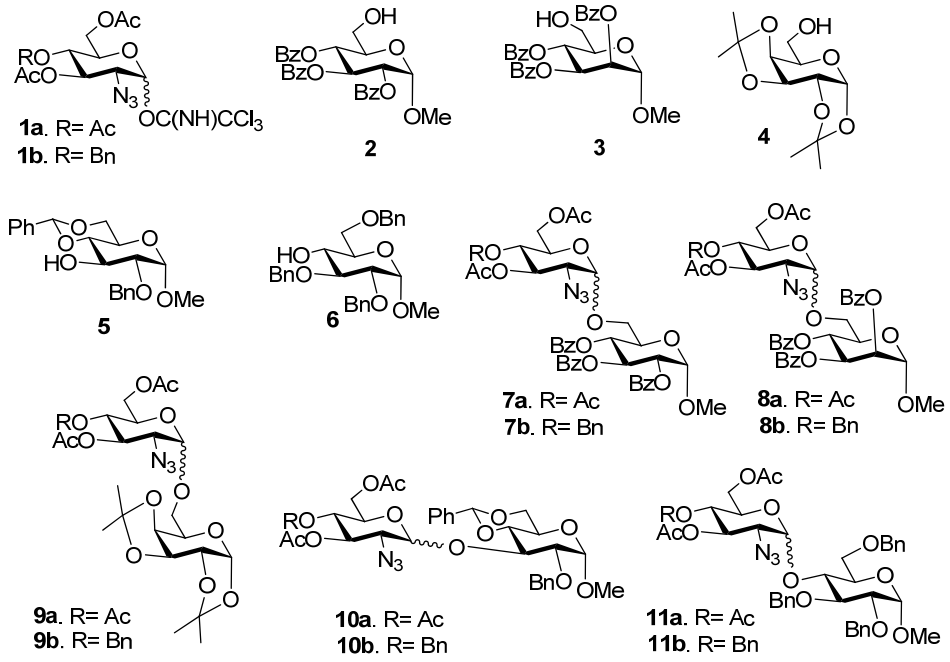
Figure 3.1. Conventional and sulfonium ion promoted stereoselective glycosylation.

Thus, the stereoselective formation of 1,2-*cis* glycosides is the principal challenge of complex oligosaccharide synthesis. Recently, we reported that a glycosyl donor substituted with a chiral auxiliary[9-11] such as an (*S*)-(phenylthiomethyl)-benzyl ether at C-2 can be employed for the stereoselective introduction of 1,2-*cis* glycosides such as α-glucosides and α-galactosides (**Figure 3.1b**). Neighboring group participation by the chiral auxiliary leads to a quasi-stable anomeric sulfonium ion. Due to steric and electronic factors, the sulfonium ion is formed as a

trans-decalin ring system. Displacement of the sulfonium ion by a hydroxyl leads to the stereoselective formation of α-glycosides.

3.3 RESULT AND DISCUSSION

We report here that glycosylations of 2-azido-2-deoxyglucosyl donors performed in the presence of a thioether provide glycosides with excellent α-selectivity. NMR and computational studies have shown that these glycosylations proceed through an intermediate sulfonium ion, which due to steric factors adopts an equatorial configuration. Displacement of the latter intermediate by a sugar hydroxyl results in the formation of an axial glycoside. 1,2-*Cis*-linked 2-amino-2-deoxy-glycosides are usually introduced by employing glycosyl donors having a nonparticipating azido moiety at C-2 of a glycosyl donor.[12,13] However, these glycosylations are rarely stereoselective and often provide mixtures of α/β-anomers (**Scheme 3.1**).



Scheme 3.1. Glycosylations of Glycosyl Donors **1a**,**b** and Acceptors **2**-**6**

It was anticipated that the application of the auxiliary based methodology for the preparation of α-linked 2-amino-2-deoxy-glycosides would be difficult. Therefore, we

investigated whether improvements in anomeric selectivities could be achieved by the addition of thioethers to glycosylations of 2-azido-2-deoxy-glycosyl donors. It was expected that activation of such glycosyl donors would lead to the formation of an oxacarbenium ion, which upon reaction with the thioether would give a sulfonium ion intermediate (**Figure 3.1c**). Due to steric factors, the later intermediate should be formed as a β-anomer. Subsequent displacement of the β-sulfonium ion by a sugar hydroxyl should then give an α-glycoside.

In the first instance, the effect of the addition of phenylthioethyl ether (PhSEt) on the anomeric outcome of TMSOTf-promoted glycosylations of 3,4,6-tri-*O*-acetyl-2- azido-2-deoxy-D-glucopyranosyl trichloroacetimidate (**1a**)[14,15] with glycosyl acceptors **2**-**4** was investigated. Phenylthioethyl ether was selected due to its structural resemblance to the (*S*)-(phenylthiomethyl)benzyl ether auxiliary, which has been shown to glycosylate through a sulfonium ion. Furthermore, primary sugar alcohols were selected because their use leads often to poor α-anomeric selectivities.[2] As can be seen in **Table 3.1**, the addition of PhSEt to glycosylation of **1a** with **2**-**4** performed at -78 °C in dichloromethane resulted in increases of α-anomeric selectivities. Interestingly, when the reactions were performed at 0 °C, further improvement of α-selectivity was observed, and in each case, the addition of PhSEt gave the best results. For example, a TMSOTf-promoted glycosylation of glycosyl donor **1a** with glycosyl acceptor **2** in dichloromethane at -78°C gave a poor anomeric selectivity of $\alpha/\beta = 2/1$. An improved anomeric selectivity of $\alpha/\beta = 5/1$ was achieved when the reaction was performed in the presence of PhSEt. Interestingly, increasing the reaction temperature to 0 °C resulted in a good α/β ratio of 8/1. However, at this reaction temperature, the addition of PhSEt gave an excellent α-anomeric selectivity of $\alpha/\beta = 20/1$.

Table 3.1. Stereoselective outcomes of glycosylations of glycosyl donor **1a** with glycosyl acceptors **2**-**6** in the presence or absence of a PhSEt or Thiophene.

acceptor	temp	thioether	product, α/β (yield)
2	-78 °C	none	**7a**, 2/1 (91%)
2	-78 °C	PhSEt	**7a**, 5/1 (83%)
2	0 °C	none	**7a**, 8/1 (92%)
2	0 °C	PhSEt	**7a**, 20/1 (94%)
2	0 °C	thiophene	**7a**, α-only (91%)
3	-78 °C	none	**8a**, 2/1 (76%)
3	-78 °C	PhSEt	**8a**, 4/1 (80%)
3	0 °C	none	**8a**, 10/1 (85%)
3	0 °C	PhSEt	**8a**, 14/1 (92%)
3	0 °C	thiophene	**8a**, 18/1 (95%)
4	-78 °C	none	**9a**, 1/3 (76%)
4	-78 °C	PhSEt	**9a**, 1/2 (80%)
4	0 °C	none	**9a**, 2/1 (85%)
4	0 °C	PhSEt	**9a**, 5/1 (92%)
4	0 °C	thiophene	**9a**, 14/1 (95%)
5	-78 °C	none	**10a**, 2/1 (45%)
5	0 °C	none	**10a**, 10/1 (56%)
5	0 °C	thiophene	**10a**, 15/1 (60%)
6	-78 °C	none	**11a**, α-only (33%)
6	0 °C	none	**11a**, α-only (40%)
6	0 °C	thiophene	**11a**, α-only (43%)

The anomeric ratios were determined by integration of the signals of the methyl glycoside after purification by size exclusion column chromatography. The observation that the addition of PhSEt led to improved α-anomeric selectivities provides support that the glycosylations proceed through an intermediate β-sulfonium ion. To confirm the presence of this intermediate, glycosyl donor **1a** and PhSEt (10 equiv) in $CDCl_3$ at -20 °C were treated with 1 equiv of TMSOTf, and after a reaction time of 10 min, 1H, 1H TOCSY, HSQC, and HMBC NMR spectra were recorded (**Figure 3.2**).

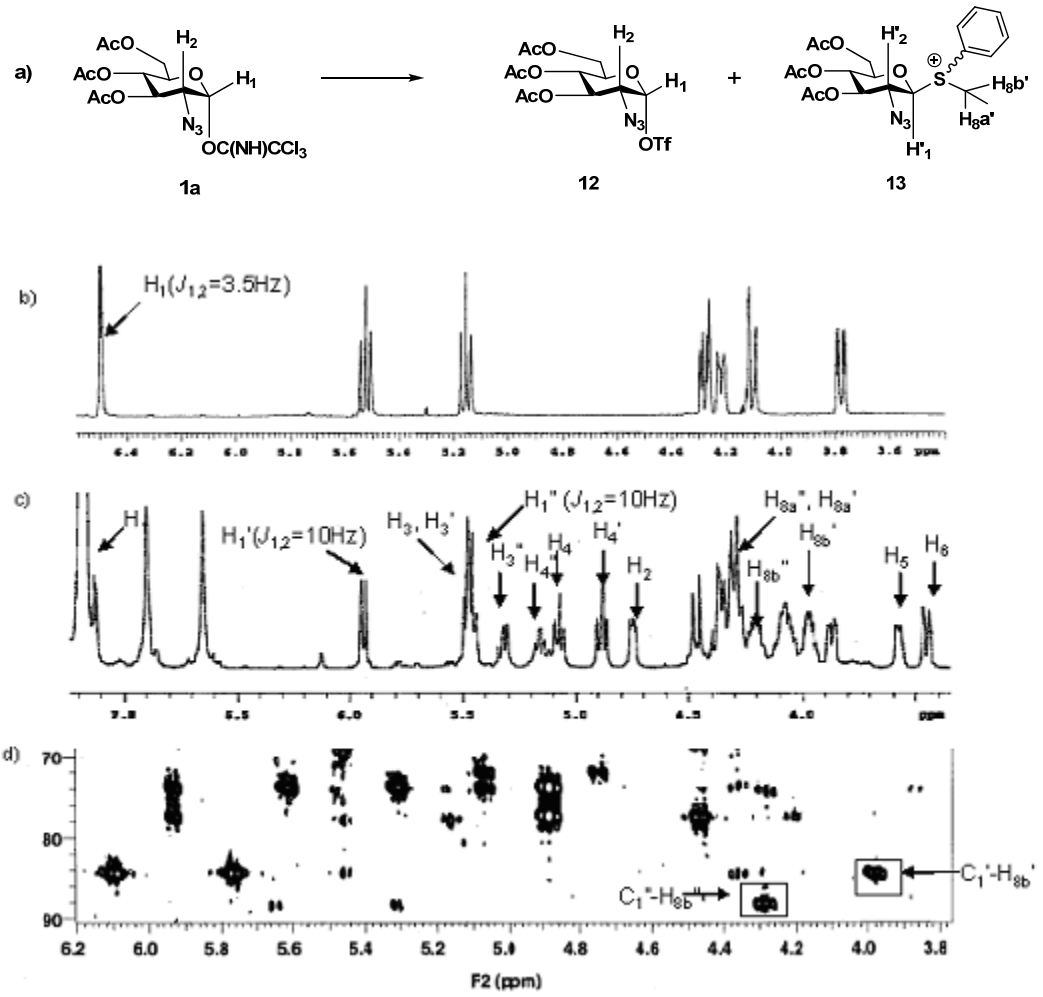


Figure 3.2. (a) α-Triflate **12** and β-sulfonium ions **13**. (b) ^{1}H NMR spectrum of glycosyl donor **1a**. (c) ^{1}H NMR spectrum of **12** and **13**. (d) HMBC spectrum of **12** and **13**.

The collected data showed the formation of three compounds, which were unambiguously assigned as the α-triflate **12** and two diastereoisomeric β-sulfonium ions **13**. Thus, H-1 of compound **12** exhibits a large downfield shift and a small vicinal coupling constant between H-1 and H-2, which is typical for an α-triflate (δ 6.50, d, $J_{1,2}$ = 3.5 Hz).[16] On the other hand, the large vicinal coupling constants between H-1 and H-2 of the two other compounds indicated that their anomeric substituents have β-configurations (δ 5.95, d, $J_{1,2}$ = 10.0 Hz; 5.48, d, $J_{1,2}$ = 10.0 Hz). Furthermore, the HMBC spectrum, which measures three-bond proton−carbon coupling, showed for each of the two compounds a correlation between H-1 and

H-8 of the ethyl moiety of the aglycon, which demonstrates that β-sulfonium ions were formed.

When the temperature of the sample was gradually raised to 0 °C, signals arising from the α-triflate and one of the β-sulfonium isomers disappeared and only peaks assigned to the other β-sulfonium isomer were observed. This compound exhibited a medium strong nuclear Overhauser enhancement (NOE) between H-1 and H-8. Furthermore, no NOEs were observed between H-1 and the aromatic protons of the aglycon, indicating that the phenyl substituent is *trans* to H-1.

The three possible rotamers of the β-sulfonium ion were optimized by DFT quantum mechanical calculations. A distance of 2.8 Å between H-1 and H-8 in the *tg* conformation as in compound **13** is in agreement with the observed NOE. This conformation places the phenyl ring *trans* to H-1 and explains the absence of NOEs between these protons. The *gg* and *gt* conformations predict NOEs between the aromatic ring of the aglycon and H-1, which indicates that the β-sulfonium ion is preferentially formed as a *tg* conformer.

Next, attention was focused on determining the origin of the stereoselective formation of the β-anomeric sulfonium ion. In this respect, it has been found that the equilibrium between anomers of pyranosides having a cationic functionality at their anomeric center often shifts toward the equatorial anomer, an effect that has been coined reverse anomeric effect (RAE). Lemieux and co-workers explained the preferential formation of the equatorial anomer by stabilizing monopole−dipole interactions arising from the positive charge, which is close to the negative end of the dipole.[17] However, this proposal fails to explain conformational preferences of several compounds which apparently are stabilized even though the positive charge has moved away from the negative end of the dipole.[18] Finch and Nagpurkar proposed that a RAE arises from a stabilizing homoallylic-type overlap between the oxygen lone pair and the π* orbital of the aromatic heterocycle because such an overlap is geometrically favorable in an equatorial conformation.[19] However, quantum mechanical calculations of the *N*-(hydroxymethyl)pyridinium ion indicated that the barrier to C−N^+ rotation is at best 0.3 kcal/mol

when the p and π* orbitals are parallel.[20] Moreover, UV spectra of 2-, 3-, or 4-(hydroxymethyl)pyridinium ions showed no evidence for such a p−π* orbital interaction. It appears that in these cases the β-anomer is preferred due to minimizing steric interactions.[21]

To examine the possible involvement of stereoelectronic effects in the preferential formation of β-anomeric sulfonium ions, molecular orbital calculations at the B3LYP/6-31G** level using the Jaguar program were performed on the *tg* conformer (**Figure 3.3**). If stereoelectronic factors are responsible for stabilizing the β-sulfonium ion, overlap between the lone pair electrons of the endocyclic oxygen (p-orbital) and the π* orbital of the C-1−S^+ bond would be expected. However, the calculations show that the HOMO-1 and LUMO molecular orbitals do not display any participation with the endocyclic oxygen. Thus, orbital interactions do not appear responsible for the greater stability of the β-sulfonium ion. Interestingly, a model of the axially substituted anomeric sulfonium ion in the *tg* conformation demonstrates steric hindrance between the anomeric substituent and H-3 and H-5 of the sugar ring. Thus, it is likely that the β-substituted sulfonium ion is selectively formed due to minimizing unfavorable steric interactions.

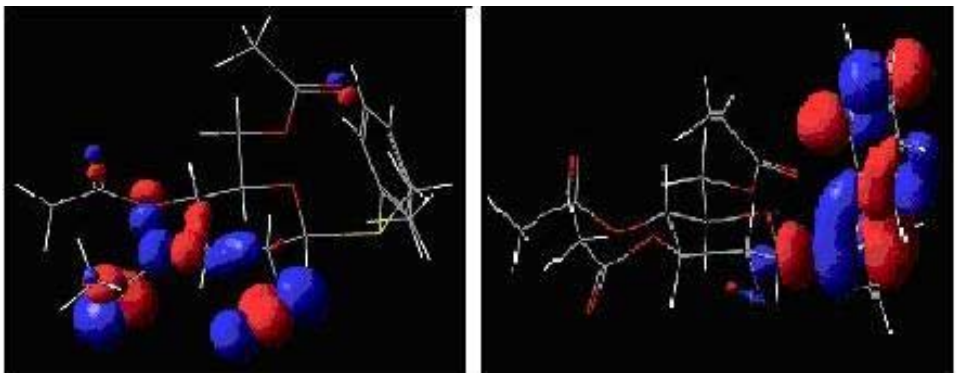


Figure 3.3. HOMO-1 and LUMO of *tg* conformer of β-sulfonium ion intermediates. The endocyclic oxygen does not participate in any orbital overlap. These molecular orbital calculations indicate that stereoelectronic effects are not responsible and that steric effects are the origin of selective formation of the β-anomeric sulfonium ion.

Having established that glycosylations performed in the presence of PhSEt proceed through a β-sulfonium ion intermediate, a number of thioethers were examined to improve the anomeric outcome of the glycosylations. As can be seen in **Table 1**, the use of thiophene resulted in further small increases in α-selectivity. Next, glycosyl donor **1a** was coupled with secondary sugar alcohols **5** and **6** at −78 °C and 0 °C in both the presence and absence of thiophene. In the case of **5**, a small increase in *α*-anomeric selectivity was observed, whereas the use of **6** gave in both conditions only the α-anomer. The yields were relatively low in part due to the formation of substantial quantities of anomeric trichloroacetamide byproduct due to reaction with the leaving group.[22] When a thiophenyl glycoside was employed in combination with Ph_2SO/Tf_2O as the promoter system, compounds **10a** and **11a** were obtained in better yields. To demonstrate the generality of the approach, glycosyl donor **1b** was coupled with **2**−**6** at −78 °C and 0 °C in the presence and absence of thiophene. As can be seen in **Table 2**, the α-anomeric selectivity was improved when the glycosylations were performed in the presence of thiophene. Also, a relatively high reaction temperature improved the anomeric outcome of the glycosylations. The improvements were most notable when primary sugar hydroxyls were employed (**Table 3.2**).

Finally, a number of glycosylations were performed with 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl trichloroacetimidate[22]. However, this glycosyl donor gave poor α-anomeric selectivities for primary as well as secondary sugar alcohols. Furthermore, the addition of thiophene resulted only in marginal improvements of anomeric selectivity. Probably, the high reactivity of the glucosyl donor promotes glycosylation of the intermediate oxacarbenium ion resulting in poor anomeric selectivities.

Table 3.2. Steroeselective outcomes of glycosylations of glycosyl donor **1b** with glycosyl acceptors **2**-**6** in the presence or absence of a PhSEt or thiophene.

acceptor	temp	thioether	product, α/β (yield)
2	-78 °C	none	**7b**, 5/1 (85%)
2	0 °C	none	**7b**, 12/1 (90%)
2	0 °C	thiophene	**7b**, 20/1 (93%)
3	-78 °C	none	**8b**, 4/1 (90%)
3	0 °C	none	**8b**, 10/1 (95%)
3	0 °C	thiophene	**8b**, 20/1 (92%)
4	-78 °C	none	**9b**, 4/1 (90%)
4	0 °C	none	**9b**, 10/1 (98%)
4	0 °C	thiophene	**9b**, 15/1 (96%)
5	-78 °C	none	**10b**, 3/1 (40%)
5	0 °C	none	**10b**, 11/1 (52%)
5	0 °C	thiophene	**10b**, 15/1 (50%)
6	-78 °C	none	**11b**, α-only (31%)
6	0 °C	none	**11b**, α-only (35%)
6	0 °C	thiophene	**11b**, α-only (37%)

3.4 CONCLUSION

In conclusion, glycosylations of 2-azido-2-deoxy-glycosyl trichloroacetimidates provide excellent α-anomeric selectivities when performed at relatively high reaction temperatures in the presence of thiophene. Mechanistic studies have shown that activation of a trichloroacetimidate in the presence of PhSEt results in the formation of a β-substituted anomeric sulfonium ion. Computational studies have indicated that the steric factors determine the selective formation of the β-anomer. Displacement of the β-sulfonium ion by an alcohol leads to the formation of an α-glycoside. Finally, the use of highly reactive glycosyl donors leads to a reduction of α-anomeric selectivity. Extension of the methodology to other glycosyl donors is in progress.

3.5 EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under a positive pressure of argon, unless otherwise noted. All chemicals were purchased from commercial suppliers and used without further purification. Dichloromethane was distilled from calcium hydride under N_2. Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh). Reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science) and the compounds were detected by examination under UV light and visualized by dipping the plates in a cerium sulfate-ammonium molybdate solution followed by heating. Organic solutions were concentrated by rotary evaporation below 40 ^{o}C under reduced pressure. Molecular sieves (4Å), used for reactions, were crushed and activated *in vacuo* at 390 °C during 8 h and then for 2-3 h at 390 °C directly prior to application. Optical rotations were measured with a 'Jasco P-1020' polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Inova 300 spectrometer and a Varian Inova 500 spectrometer equipped with Sun workstations. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Data are presented as follow: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = double of doublet, m = multiplet and/or multiple resonances), integration, coupling constant in Hertz (Hz). High-resolution mass spectra were run in a JMS SX/SX102A tandem mass spectrometer, equipped with FAB source. The matrix used was DHB and the internal standards ultramark 1621 and PEG.

General procedure for the glycosylation reactions employing glycosyl donor 1a and 1b.

Protocol A. A mixture of glycosyl donor **1a** or **1b** (0.042 mmol), glycosyl acceptor (0.063 mmol) and activated molecular sieves (4Å) in DCM (2 mL) was stirred for 20 min under an atmosphere of argon at rt, then cooled to -78 °C or 0 °C. After the addition of trimethylsilyl trifluoromethanesulfonate (0.76 μL, 0.0042 mmol), the reaction mixture was stirred at -78 °C or 0 °C. When the donor was consumed as detected by TLC analysis, the reaction mixture was quenched with aq. $NaHCO_3$ (5 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by size exclusion LH-20 column (eluent MeOH/DCM = 1/1, v/v) to determine the α/β ratio. Then further purification was completed by silicagel column chromatography (n-hexane/ethyl acetate = 2/1).

Protocol B. A mixture of glycosyl donor **1a** or **1b** (0.042 mmol), glycosyl acceptor (0.063 mmol), activated molecular sieves (4Å) and thioether (0.42 mmol) in DCM (2 mL) was stirred for 20 min under an atmosphere of argon at rt, then cooled to -78 °C or 0 °C. After the addition of trimethylsilyl trifluoromethanesulfonate (0.76 μL, 0.0042 mmol), the reaction mixture was stirred at -78 °C or 0 °C. When the donor was consumed as detected by TLC analysis, the reaction mixture was quenched with aq. $NaHCO_3$ (5 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by size exclusion LH-20 column (eluent MeOH/DCM = 1/1, v/v) to determine the α/β ratio. Then further purification was completed by silicagel column chromatography (n-hexane/ethyl acetate = 2/1).

Methyl (3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside(7a, α); $[\alpha]^{20}_D$ = +82.0° (*c* = 5.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.98-7.95 (m, 4H, aromatic), 7.88-7.86 (m, 2H, aromatic), 7.54-7.25 (m, 9H, aromatic), 6.18 (t, 1H, *J* = 9.0 Hz, H-3'), 5.54 (t, 1H, *J* = 10.0 Hz, H-3), 5.54 (t, 1H, *J* = 9.0 Hz, H-4'), 5.26-5.23 (m, 2H, H-1', H-2'), 5.04 (t, 1H, *J* = 10.0 Hz, H-4), 5.01 (d, 1H, *J* = 3.0 Hz, H-1), 4.33-4.30 (m, 1H, H-

5'), 4.21 (dd, 1H, *J* = 5.0, 12.0 Hz, H-6a), 4.18-4.15 (m, 1H, H-5), 4.07-4.00 (m, 1H, H-6b), 3.92 (dd, 1H, *J* = 3.5, 11.0 Hz, H-6a'), 3.69-3.67 (m, 1H, H-6b'), 3.51 (s, 3H, OCH_3), 3.32 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2), 2.09 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.57, 169.91, 169.74,165.81(2), 165.37, 133.56, 133.37, 133.15, 129.94, 129.89, 129.71, 129.18, 129.06, 128.77, 128.52, 128.43, 128.29, 128.01, 97.83, 96.91, 72.09, 70.34, 70.30, 69.48, 68.41, 68.33, 67.76, 66.87, 61.77, 60.96, 55.69, 20.71, 20.67(2). HRMS (FAB) *m/z* calcd for $C_{40}H_{41}N_3O_{16}$ $(M+Na)^+$: 842.2385; found: 842.2382

Methyl (3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (8a, α); $[\alpha]^{20}_D$ = -2.76° (*c* = 5.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 8.10-7.80 (m, 6H, aromatic), 7.51-7.23 (m, 9H, aromatic), 5.90 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3'), 5.85 (t, 1H, *J* = 10.0 Hz, H-4'), 5.68-5.67 (m, 1H, H-2'), 5.53 (t, 1H, *J* = 10.0 Hz, H-3), 5.05-4.99 (m, 3H, H-1, H-1', H-4), 4.37-4.34 (m, 1H, H-5'), 4.18-4.09 (m, 2H, H-5, H-6b), 4.01-3.97 (m, 2H, H-6a', H-6a), 3.73-3.71 (m, 1H, H-6b'), 3.57 (s, 3H, OCH_3), 3.35 (dd, 1H, *J* = 3.5, 10.0 Hz, H-2), 2.09 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.51, 169.83, 169.71,165.62(2), 165.38, 133.60, 133.53, 133.15, 129.94, 129.84, 129.72, 129.30, 129.06, 128.86, 128.63, 128.53, 128.28, 98.63, 97.62, 70.63, 70.38, 69.97, 69.40, 68.41, 67.75, 67.25, 67.10, 61.74, 60.95, 55.54, 20.71, 20.65, 20.58. HRMS (FAB) *m/z* calcd for $C_{40}H_{41}N_3O_{16}$ $(M+Na)^+$: 842.2385; found: 842.2388

3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (9a, α); $[\alpha]^{20}_D$ = +58.8° (*c* = 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 5.52 (d, 1H, *J* = 5.0 Hz, H-1'), 5.47 (t, 1H, *J* = 10.0 Hz, H-3), 5.06 (t, 1H, *J* = 10.0 Hz, H-4), 5.04 (d, 1H, *J* = 3.0 Hz, H-1), 4.63 (dd, 1H, *J* = 2.0, 7.5 Hz, H-3'), 4.33-4.30 (m, 2H, H-2', H-4'), 4.16-4.03 (m, 4H, H-5, H-5', H-6a, H-6b), 3.85-3.77 (m, 2H, H-6a', H-6b'), 3.30 (dd, 1H, *J* = 3.0, 10.0

Hz, H-2), 2.09 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 1.56 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.67, 170.01, 169.73, 109.38, 108.78, 98.18, 96.25, 70.86, 70.59(2), 70.35, 68.40, 67.76, 67.61, 66.50, 61.79, 60.99, 26.09, 25.97, 24.97, 24.36, 20.73, 20.73, 20.64. HRMS (FAB) *m/z* calcd for $C_{24}H_{35}N_3O_{13}$ $(M+Na)^+$: 596.2068; found: 596.2066

3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-β-D-galactopyranose (9a, β); $[\alpha]^{20}_D$ = -15.7° (*c* = 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.34 (d, 1H, *J* = 5.0 Hz, H-1'), 4.99 (t, 1H, *J* = 9.0 Hz, H-3), 4.98 (t, 1H, *J* = 9.0 Hz, H-4), 4.62-4.60 (m, 1H, H-6b), 4.57 (d, 1H, *J* = 9.0 Hz, H-1), 4.32-4.25 (m, 3H, H-2', H-3', H-6a), 4.13-4.04 (m, 3H, H-4', H-5', H-6a'), 3.85-3.81 (m, 1H, H-6b'), 3.66-3.65 (m, 1H, H-5), 3.50 (t, 1H, *J* = 9.0 Hz, H-2), 2.08 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.01 (s, 3H, $COCH_3$), 1.53 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.65, 169.97, 169.66, 109.43, 108.74, 102.27, 96.23, 72.53, 71.75, 71.24, 70.71, 70.39, 69.12, 68.49, 67.63, 63.73, 61.92, 25.98, 25.97, 24.94, 24.38, 20.71, 20.70, 20.60. HRMS (FAB) *m/z* calcd for $C_{24}H_{35}N_3O_{13}$ $(M+Na)^+$: 596.2068; found: 596.2068

Methyl (3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside(10a, α); $[\alpha]^{20}_D$ = +91.1° (*c* = 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46-7.35 (m, 10H, aromatic), 5.56 (s, 1H, C*H*Ph), 5.52 (d, 1H, *J* = 4.0 Hz, H-1), 5.50 (t, 1H, *J* = 10.0 Hz, H-3), 4.99 (t, 1H, *J* = 10.0 Hz, H-4), 4.74 (d, 1H, *J* = 3.5 Hz, H-1'), 4.67 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.62 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.40-4.38 (m, 1H, H-5), 4.29-4.23 (m, 2H, H-3', H-4'), 4.14-4.10 (m, 1H, H-6a'), 3.86-3.74 (m, 4H, H-6a, H-6b, H-6b', H-5'), 3.61 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2'), 3.41(s, 3H, OCH_3), 3.12 (dd, 1H, *J* = 4.0, 10.0 Hz, H-2), 2.09 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.66,

170.18, 169.55, 137.30, 137.09, 129.52, 128.72, 128.64, 128.54, 128.48, 128.40, 128.32, 128.04, 127.95, 127.84, 127.03, 128.64, 128.43, 128.28, 125.99, 101.49, 98.19, 97.80, 82.25, 77.76, 74.15, 72.70, 70.23, 68.94, 68.09, 67.40, 61.96, 61.18, 60.64, 55.33, 20.77, 20.69, 20.53; HRMS (FAB) *m/z* calcd for $C_{33}H_{39}N_3O_{13}$ $(M+Na)^+$: 708.2381; found: 708.2381

Methyl (3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside(10a, β); $[\alpha]^{20}_D$ = +8.8° (*c* = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.48-7.32 (m, 10H, aromatic), 5.50 (s, 1H, C*H*Ph), 5.00 (t, 1H, *J* = 9.0 Hz, H-3), 4.95 (t, 1H, *J* = 9.0 Hz, H-4), 4.89 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.83 (d, 1H, *J* = 9.0 Hz, H-1), 4.56 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.49 (d, 1H, *J* = 3.5 Hz, H-1'), 4.29-4.16 (m, 3H, H-3', H-6a, H-6b), 3.99-3.96 (m, 1H, H-4'), 3.82-3.67 (m, 3H, H-6a', H-5', H-2'), 3.62-3.52 (m, 3H, H-2, H-6b', H-5'), 3.12(s, 3H, OCH_3), 2.08 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.70, 170.01, 169.66, 137.34, 128.99, 128.66, 128.52, 128.30, 128.13, 126.05, 101.84, 101.05, 98.45, 80.23, 79.28, 77.22, 73.75, 72.73, 71.50, 68.89, 68.42, 63.91, 62.32, 62.08, 55.32, 20.74, 20.68, 20.60; HRMS (FAB) *m/z* calcd for $C_{33}H_{39}N_3O_{13}$ $(M+Na)^+$: 708.2381; found: 708.2387

Methyl (3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (11a, α); $[\alpha]^{20}_D$ = +14.2° (*c* = 5.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.36-7.27 (m, 15H, aromatic), 5.81 (d, 1H, *J* = 4.0 Hz, H-1), 5.40 (t, 1H, *J* = 10.0 Hz, H-3), 5.14 (d, 1H, *J* = 10.0 Hz, C*H*HPh), 4.99 (t, 1H, *J* = 10.0 Hz, H-4), 4.80 (d, 1H, *J* = 10.0 Hz, C*H*HPh), 4.74 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.63 (d, 1H, *J* = 3.0 Hz, H-1'), 4.61 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.58 (s, 2H, C*H*HPh), 4.13-4.08 (m, 2H, H-3', H-6a), 3.95-3.91 (m, 2H, H-5, H-6a'), 3.83-3.66 (m, 4H, H-6b, H-5', H-4', H-6b'), 3.58 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2'), 3.39(s, 3H, OCH_3), 3.23 (dd, 1H, *J* = 4.0, 10.0 Hz, H-2), 2.07 (s, 3H, $COCH_3$), 2.01 (s, 3H, $COCH_3$), 1.98 (s,

3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.42, 169.96, 169.46, 138.56, 137.86, 137.81, 131.03, 129.30, 128.50, 128.42, 128.35, 128.13, 128.01, 127.69, 127.47, 127.37, 124.75, 97.60, 97.35, 81.76, 80.52, 74.86, 73.54, 73.53, 73.20, 70.32, 69.30, 69.13, 68.18, 67.98, 61.44, 60.87, 55.35, 20.67, 20.66, 20.59; HRMS (FAB) *m/z* calcd for $C_{40}H_{47}N_3O_{13}$ $(M+Na)^+$: 800.3007; found: 800.3001

Methyl (3,6-Di-*O*-acetyl-4-*O*-benzyl-2-azido-2-deoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (7b, α); $[\alpha]^{20}_D$ = +137.8° (*c* = 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.98-7.96 (m, 4H, aromatic), 7.88-7.86 (m, 2H, aromatic), 7.52-7.27 (m, 14H, aromatic), 6.17 (t, 1H, *J* = 10.0 Hz, H-3'), 5.64 (t, 1H, *J* = 9.0 Hz, H-3), 5.20 (t, 1H, *J* = 10.0 Hz, H-4'), 5.26-5.23 (m, 2H, H-1', H-2'), 4.96 (d, 1H, *J* = 3.0 Hz, H-1), 4.63 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.57 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.33-4.16 (m, 3H, H-5', H-6a, H-6b), 4.10-4.07 (m, 1H, H-5), 3.92-3.89 (m, 1H, H-6a'), 3.64-3.62 (m, 1H, H-6b'), 3.58 (t, 1H, *J* = 9.0 Hz, H-4), 3.50 (s, 3H, OCH_3), 3.12 (dd, 1H, *J* = 3.0, 9.0 Hz, H-2), 2.07 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.54, 169.73, 165.79,165.77, 165.33, 137.35, 133.49, 133.30, 133.05, 129.94, 129.71, 129.21, 129.11, 128.80, 128.55, 128.45, 128.39, 128.26, 128.08, 127.98, 98.07, 96.86, 75.95, 74.34, 72.09, 71.95, 70.35, 69.53, 68.79, 68.36, 66.84, 62.59, 61.33, 55.72, 20.93, 20.79. HRMS (FAB) *m/z* calcd for $C_{45}H_{45}N_3O_{15}$ $(M+Na)^+$: 890.2748; found: 890.2748

Methyl (3,6-Di-*O*-acetyl-4-*O*-benzyl-2-azido-2-deoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (8b, α); $[\alpha]^{20}_D$ = +38.6° (*c* = 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H, aromatic), 7.96-7.94 (m, 2H, aromatic), 7.91-7.81 (m, 2H, aromatic), 7.61-7.22 (m, 14H, aromatic), 5.88 (dd, 1H, *J* = 3.0, 10.0 Hz, H-3'), 5.80 (t, 1H, *J* = 10.0 Hz, H-4'), 5.67 (dd, 1H, *J* = 2.0, 3.0 Hz, H-2'), 5.64 (dd, 1H, *J* = 10.0, 11.0 Hz, H-3), 4.96 (d, 1H, *J* = 2.0, Hz, H-1'), 4.96 (d, 1H, *J* = 3.0, Hz, H-1), 4.62 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.55 (d, 1H, *J* =

11.0 Hz, C*H*HPh), 4.36-4.33 (m, 1H, H-5'), 4.25-4.23 (m, 1H, H-6a), 4.14-4.05 (m, 2H, H-6b, H-5), 3.99-3.95 (m, 1H, H-6b'), 3.68-3.66 (m, 1H, H-6a'), 3.57 (t, 1H, *J* = 11.0 Hz, H-4), 3.55 (s, 3H, OCH_3), 3.14 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2), 2.07 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.50, 169.66, 165.61(2), 165.39, 137.31, 133.51, 133.48, 133.10, 129.96, 129.88, 129.73, 129.34, 129.11, 128.89, 128.62, 128.56, 128.47, 128.26, 128.12, 128.02, 98.60, 97.85, 75.93, 74.45, 72.04, 70.62, 69.99, 69.40, 68.84, 67.33, 67.07, 62.56, 61.33, 55.58, 20.94, 20.73. HRMS (FAB) *m/z* calcd for $C_{45}H_{45}N_3O_{15}$ $(M+Na)^+$: 890.2748; found: 890.2748

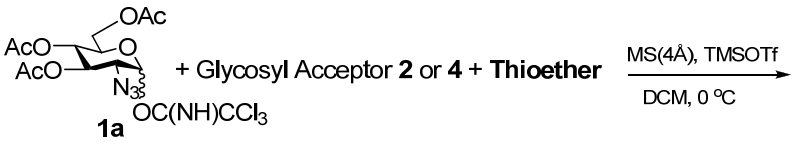
3,6-Di-*O*-acetyl-4-*O*-benzyl-2-azido-2-deoxy-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (9b, α); $[\alpha]^{20}_D$ = +104.8° (*c* = 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.38-7.22 (m, 5H, aromatic), 5.57 (dd, 1H, *J* = 9.0, 11.0 Hz, H-3), 5.50 (d, 1H, *J* = 5.0 Hz, H-1'), 5.00 (d, 1H, *J* = 3.0 Hz, H-1), 4.62-4.55 (m, 3H, H-3', H-4', C*H*HPh), 4.33-4.26 (m, 4H, H-2', H-6b', H-6a, C*H*HPh), 4.09-4.06 (m, 1H, H-5), 4.02-4.00 (m, 1H, H-5'), 3.82-3.80 (m, 1H, H-6a'), 3.75-3.73 (m, 1H, H-6b), 3.59 (t, 1H, *J* = 9.0 Hz, H-4), 3.12 (dd, 1H, *J* = 3.0, 11.0 Hz, H-2), 2.12 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 1.64 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.64, 169.82, 137.34, 128.55, 128.08, 127.95, 109.27, 108.76, 98.29, 96.22, 75.94, 74.17, 71.84, 70.77, 70.63, 70.57, 68.63, 67.23, 66.32, 62.70, 61.39, 26.11, 25.97, 24.97, 24.33, 20.94, 20.88; HRMS (FAB) *m/z* calcd for $C_{29}H_{39}N_3O_{12}$ $(M+Na)^+$: 644.2431; found: 644.2439

Methyl (3,6-Di-*O*-acetyl-4-*O*-benzyl-2-azido-2-deoxy-α-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside(10b, α); $[\alpha]^{20}_D$ = +173.6° (*c* = 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.47-7.22 (m, 15H, aromatic), 5.60 (dd, 1H, *J* = 9.0, 11.0 Hz, H-3), 5.56 (s, 1H, C*H*Ph), 5.48 (d, 1H, *J* = 3.5 Hz, H-1), 4.70 (d, 1H, *J* = 3.5 Hz, H-1'), 4.62 (s, 2H, C*H*HPh), 4.55 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.49 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.35-4.26 (m,

2H, H-5, H-5'), 4.22 (t, 1H, *J* = 9.0 Hz H-3'), 4.08-4.06 (m, 1H, H-6a), 3.99 (dd, 1H, *J* = 3.5, 12.0 Hz, H-6b), 3.79-3.72 (m, 3H, H-4', H-6a', H-6b'), 3.59 (dd, 1H, *J* = 3.5, 9.0 Hz, H-2'), 3.55(t, 1H, *J* = 11.0 Hz, H-4), 3.88(s, 3H, OCH_3), 2.98 (dd, 1H, *J* = 3.5, 9.0 Hz, H-2), 2.06 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.74, 170.24, 137.89, 137.41, 129.17, 128.83, 128.65, 128.45, 128.13, 128.07, 126.21, 101.64, 98.53, 98.41, 82.46, 78.07, 75.92, 74.61, 74.56, 73.24, 72.36, 69.17, 68.75, 62.44, 62.16, 61.22, 55.53, 21.20, 21.05; HRMS (FAB) *m/z* calcd for $C_{38}H_{43}N_3O_{12}$ $(M+Na)^+$: 756.2744; found: 756.2740

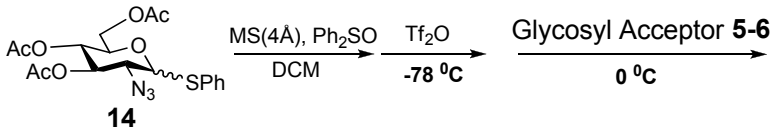
Methyl (3,6-Di-*O*-acetyl-4-*O*-benzyl-2-azido-2-deoxy-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (11b, α); $[\alpha]^{20}_D$ = +79.6° (*c* = 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.34-7.20 (m, 20H, aromatic), 5.76 (d, 1H, *J* = 4.0 Hz, H-1), 5.47 (t, 1H, *J* = 10.0 Hz, H-3), 5.11 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.78 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.71 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.61 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.62-4.47 (m, 5H, H-1', C*H*HPh), 4.11 (t, 1H, *J* = 10.0 Hz, H-3'), 4.07-3.99 (m, 2H, H-6a, H-5'), 3.89-3.79 (m, 3H, H-6b, H-4', H-5), 3.72 (dd, 1H, *J* = 3.5, 11.0 Hz, H-6a'), 3.64-3.54 (m, 2H, H-6b', H-2'), 3.49 (t, 1H, *J* = 10.0 Hz, H-4), 3.38 (s, 3H, OCH_3), 3.04 (dd, 1H, *J* = 4.0, 10.0 Hz, H-2), 2.06 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.37, 169.79, 138.71, 137.88, 137.85, 137.33, 129.45, 129.21, 128.99, 128.83, 128.63, 128.54, 128.51, 128.39, 128.32, 128.17, 128.12, 128.03, 127.74, 127.56, 127.42, 126.23, 124.27, 97.60, 97.59, 81.84, 80.55, 77.22, 75.70, 74.81, 74.65, 73.49, 73.23(2), 72.14, 69.28, 69.12, 62.43, 61.25, 55.32, 20.93, 20.81; HRMS (FAB) *m/z* calcd for $C_{45}H_{51}N_3O_{12}$ $(M+Na)^+$: 848.3370; found: 848.3377

Table 3.3. Glycosylation of acceptors **2** and **4** in the presence of various thioethers.



Thioether	Glycosyl Acceptor **2** product, α/β (yield)	Glycosyl Acceptor **4** product, α/β (yield)
PhSEt	**7a**, 20/1 (94%)	**9a**, 5/1 (92%)
PhSPh	**7a**, 12/1 (97%)	**9a**, 3/1 (95%)
$PhSCH_2Cl$	**7a**, 9/1 (92%)	**9a**, 5/1 (97%)
Thiophene	**7a**, α-only (91%)	**9a**, 14/1 (95%)
Selenophene	**7a**, 15/1 (94%)	**9a**, 4/1 (93%)
$PhSPh\text{-}NO_2$	**7a**, 10/1 (77%)	**9a**, 3/1 (85%)
CH_3SCH_3	Donor decomposition only	Donor decomposition only

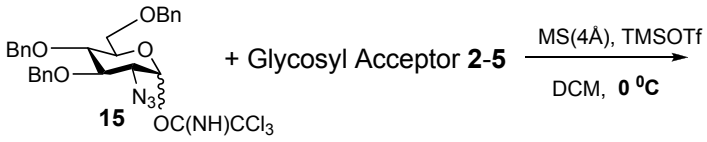
Table 3.4. Glycosylations of thioglycosyl donor **14** with secondary glycosyl acceptors **5** and **6** in the presence or absence of thioethers.



14

Accept.	Thioether	product, α/β (yield)
5	none	**10a**, 2/1 (60%)
5	PhSET	**10a**, 14/1 (76%)
5	thiophene	**10a**, 17/1 (74%)
6	none	**11a**, α only (40%)
6	PhSEt	**11a**, α only (45%)
6	thiophene	**11a**, α only (40%)

Table 3.5. Glycosylations of 2-deoxy-2-azido-3,4,6-*O*-tri-benzyl-D-glucopyranose trichloroacetimidate **15** with glycosyl acceptors **2**-**5** in the presence or absence of thiophene



Accept.	Temp.	Thioether	product, α/β (yield)
2	0 °C	none	3/1 (80%)
2	0 °C	thiophene	3/1 (82%)
3	0 °C	none	3/1 (83%)
3	0 °C	thiophene	4/1 (81%)
4	0 °C	none	1/2 (95%)
4	0 °C	thiophene	1/2 (96%)
5	0 °C	none	1/2 (45%)
5	0 °C	thiophene	1/1 (48%)

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CHAPTER IV

DIRECT AND STEREOSELECTIVE SYNTHESIS OF α-LINKED 2-DEOXYGLYCOSIDES

4.1 ABSTRACT

α-Linked 2-deoxyglycosides were conveniently obtained by employing a glycosyl donor having a participating (*S*)-(phenylthiomethyl)benzyl moiety at C-6, whereas 2,6-dideoxy-α-glycosides could be prepared by $BF_3 \cdot OEt_2$-promoted activation of allyl glycosyl donors.

4.2 INTRODUCTION

Many medically important natural products are modified by oligosaccharides composed of 2-deoxysugars, and examples of such compounds include antibiotics such as erythromycin, antiparasite agents such as amphotericin, insecticides such as the avermectins, and anticancer drugs such as doxorubicin.[1-4] The sugar moiety of these compounds can wield a remarkable influence on pharmacological and pharmacokinetic properties and can dictate the molecular recognition at the drug target site. Not surprisingly, considerable efforts are directed at the development of tools that make it possible to diversify natural product glycosylation.[5-7] This approach, which has been coined glycodiversification or glycorandomization, can be achieved by metabolic, enzymatic, and chemical means.[8-14]The stereochemical introduction of 2-deoxyglycosides is a key step in chemical glycodiversification and has mainly been achieved by indirect methods that employ a participating functionality as C-2 of a glycosyl donor such as halides and aryl selenyl and sulfenyl derivatives.[15-18] The drawback of this approach is that the introduction and removal of the participating functionality requires additional steps that need to be performed in a stereoselective manner, often leading to time-consuming synthetic

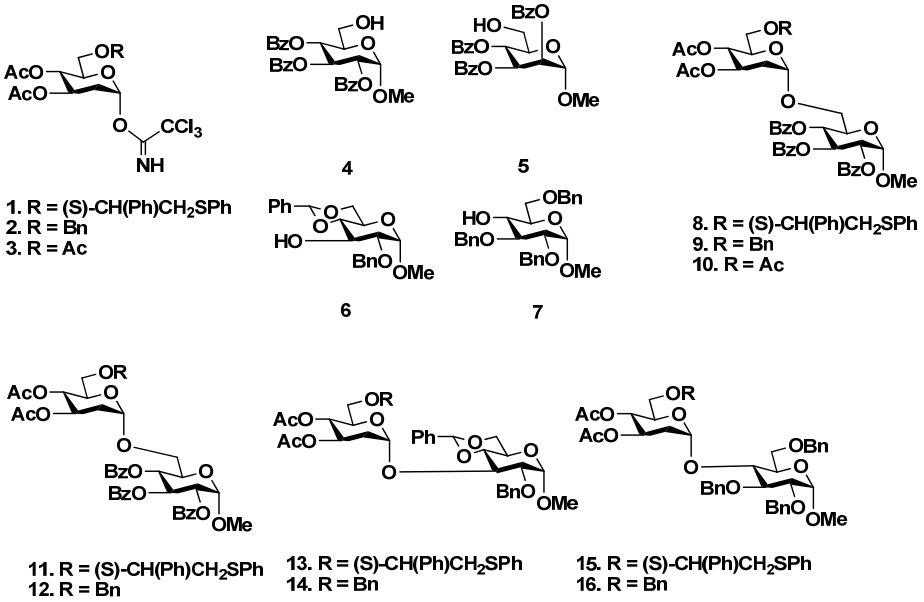
procedures. On the other hand, several methods are available for direct β-selective glycosylation in which α-glycosyl halides, glycosyl phosphites, and trichloroacetimidates are employed as glycosyl donors in combination with a mild promoter.[19-24] α-Glycosides of 2-deoxysaccharides have been obtained in moderate yield by acid-catalyzed activation of glycals, anomeric esters, and silyl ethers.[25-28] Furthermore, diastereoselective Pd-promoted glycosylations followed by reduction of a 2,3-double bond of the resulting compound has been employed to prepare unnatural 2,3-dideoxyglycosides.[29, 30] Reasonable anomeric selectivities have also been achieved by remote assistance of a *p*-methoxybenzoyl ester at C-3 of a glycosyl donor. Remote participation has also been implicated in the stereoselective introduction of α-galactosides, α-glucosides, and β-mannosides.[31-37] Recently, we demonstrated that glycosylations with glycosyl donors modified at C-2 with a (*S*)-(phenylthiomethyl)benzyl moiety give exclusively α-anomeric selectivity due to neighboring group participation resulting in an intermediate *trans*-fused 1,2-sulfonium ion.[38-40]

4.3 RESULT AND DISCUSSION

We were curious to explore whether remote participation by a (*S*)-(phenylthiomethyl)benzyl moiety can be exploited in the stereochemical synthesis of 2-deoxyglycosides. Thus, trichloroacetimidates **1**−**3** were prepared that have either a (*S*)-(phenylthiomethyl)benzyl, a benzyl ether, or an acetyl ester at C-6 (**Table 4.1**). Interestingly, a TMSOTf-mediated glycosylation of donor **1** with glycosyl acceptor **4** gave the expected disaccharide **8** in good yield as almost exclusively the α-anomer. Similar glycosylations employing glycosyl donors **2** and **3**, having a benzyl ether or acetyl ester at C-6, provided the disaccharides **9** and **10**, respectively, as mixtures of anomers. The use of (*R*)-(phenylthiomethyl)benzyl ether at C-6 of the glycosyl donor also led to excellent anomeric selectivity indicating that the chirality of the auxiliary did not influence the anomeric outcome of the glycosylation. We were unable to identify the intermediate sulfonium ion by NMR

experiments in which **1** was activated with TMSOTf probably due to the high reactivity of the intermediate. However, glycosylations of **1** with **5**−**7** led to the isolation of the corresponding disaccharides **11**, **13** and **15** in excellent yields with almost exclusively α-anomeric selectivity. The alternative use of benzylated derivative **2** gave the disaccharides **12**, **14** and **16** as mixtures of anomers. Glycosylations of **2** and **3** promoted by $BF_3{\cdot}OEt_2$ did not lead to an improvement of anomeric selectivity. Thus, it appears that a (phenylthiomethyl)benzyl ether at C-6 promotes high α-selectivity.

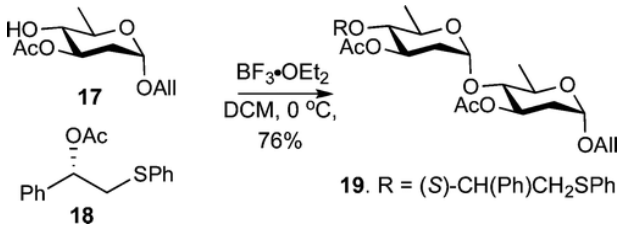
Table 4.1. Glycosylations with trichloroacetimidate donors **1**-**3**[a]



donor	acceptor	product	yield (%)	α/β
1	**4**	**8**	94	15:1
1	**5**	**11**	93	12:1
1	**6**	**13**	95	10:1
1	**7**	**15**	92	8:1
2	**4**	**9**	96	1:1
2	**5**	**12**	95	1:1
2	**6**	**14**	92	5:1
2	**7**	**16**	93	4:1
3	**4**	**10**	90	4:1

[a] All reactions were performed at -78 °C in DCM

Next, attention was focused on anomeric control by employing a glycosyl donor that has a (*S*)-(phenylthiomethyl)benzyl ether at C-4. Surprisingly, an attempt to introduce the auxiliary at C-4 by treatment of sugar alcohol **17** with (*S*)-(phenylthiomethyl)benzyl acetate **18** in the presence of $BF_3{\cdot}OEt_2$ led to the formation of disaccharide **19** (**Scheme 4.1**). Thus, unexpected activation of the allyl glycoside of **17** led to self-condensation. However, the allyl glycoside of disaccharide **19** did not undergo further activation indicating that **17** (or its auxiliary modified counterpart) is more reactive than **19**.



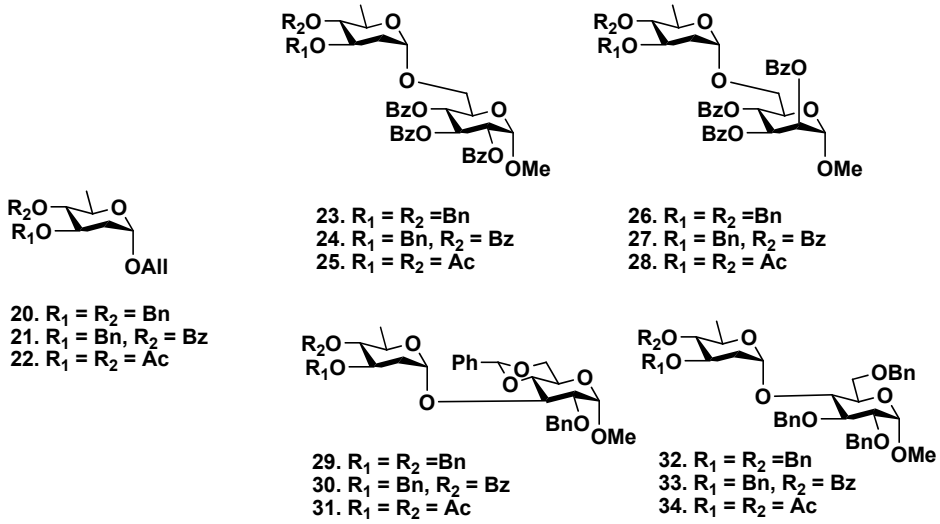
Scheme 4.1. Direct Activation of a 2,6-Dideoxy Allyl Glycoside

Allyl glycosides are attractive building blocks in glycoside chemistry because the allyl moiety provides convenient protection of the anomeric center but can easily be removed by isomerization to a vinyl glycoside, which can be hydrolyzed under mild conditions to give a lactol. The latter compound can be converted into various glycosyl donors such as trichloroacetimidates, phosphites, and halides. The intermediate vinyl glycoside can also directly be employed as a glycosyl donor in TMSOTf-promoted glycosylations.[41, 42]

We envisaged that allyl 2-deoxyglycosides would be interesting building blocks for oligosaccharide assembly because the results presented here indicate that these compounds can be employed in direct glycosylations using $BF_3{\cdot}OEt_2$ as the promoter or converted into various conventional glycosyl donors using standard procedures. To explore the direct glycosylation of allyl 2-deoxyglycosides in more detail, compounds **20**, **21**, and **22**, which have either benzyl ether or ester at C-3 and C-4, were employed in $BF_3{\cdot}OEt_2$-mediated glycosylations with glycosyl acceptors **4**−**7** to give the corresponding disaccharides **23**−**34** (**Table 4.2**). Interestingly, the highly activated glycosyl donor **20** having benzyl ethers at C-3 and

C-4 could be activated at −78 °C to provide the expected disaccharides **23**, **26**, **29**, and **32** in excellent yields (**Table 4.2**). The somewhat less reactive glycosyl donor **21**, having a benzoyl ester C-4, required a temperature of −30 °C for activation, whereas the least reactive derivative **22** was only reactive at 0 °C.

Table 4.2. Glycosylations with allyl glycosyl donors **20**−**22**[a]

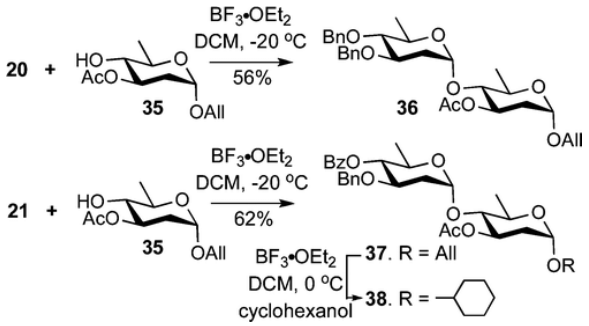


donor	acceptor	T (°C)	product	yield (%)	α/β
20	**4**	-78	**23**	85	8:1
20	**5**	-78	**26**	80	5:1
20	**6**	-78	**29**	68	7:1
20	**7**	-78	**32**	62	5:1
21	**4**	-30-0	**24**	83	10:1
21	**5**	-30-0	**27**	82	8:1
21	**6**	-30-0	**30**	68	11:1
21	**7**	-30-0	**33**	65	10:1
22	**4**	0 to rt	**25**	85	14:1
22	**5**	0 to rt	**28**	82	13:1
22	**6**	0 to rt	**31**	73	15:1
22	**7**	0-to rt	**34**	72	10:1

[a]All reactions were performed in DCM

Importantly, each glycosylation resulted in the formation of the expected disaccharide (**23**−**34**) as mainly the α-anomer. Thus, these results indicated that the high α-anomeric selectivity observed in the formation of disaccharide **19** is not due to participation by the C-4 (*S*)-(phenylthiomethyl)benzyl ether but probably a result of the $BF_3{\cdot}OEt_2$-promoted activation of the allyl glycoside. Furthermore, it was observed that the corresponding methyl glycosides of **20**−**22** were less reactive than allyl glycosides because higher reaction temperatures and a larger excess of $BF_3{\cdot}OEt_2$ (4 equiv) was required for activation. The use of catalytic TMSOTf as the promotor to activate **20**−**22** led to good anomeric selectivities; however, the yields were significantly lower compared to $BF_3{\cdot}OEt_2$-promoted glycosylations. Attempts were also made to introduce β-glycosides by treatment of compounds **20**−**22** with TMSI or TMSBr to form the intermediate halides, which can then be displaced by a sugar alcohol to form β-glycosides.[24] However, these attempts led to formation of disaccharides in good yields but with poor anomeric selectivities. Finally, the direct activation of allyl 2-deoxyglycosides was employed in an armed−disarmed strategy to synthesize more complex compounds.[43-45] Thus, it was envisaged that benzylated 2,6-dideoxyglycoside **20** would be more reactive than compound **35**, which has a deactivating acetyl ester at C-3. Indeed, a $BF_3{\cdot}OEt_2$-mediated glycosylation of **20** with **35** in DCM at −20 °C gave clean formation of disaccharide **36**, which was isolated in a yield of 56% (α/β = 6/1) and led to the recovery of a small amount of starting materials (**Scheme 4.2**). However, further activation of allyl glycoside **36** at a higher reaction temperature led to decomposition of the disaccharide. It is possible to convert the allyl glycoside of the latter compound into another leaving group for conventional glycosylation. We aimed, however, to minimize manipulations during oligosaccharide assembly, and therefore, the less reactive glycosyl donor **21** was employed in a coupling with glycosyl acceptor **35** and in this case disaccharide **37** was obtained in a yield of 62% (α/β = 8/1). The successful formation of this compound indicates that the benzoyl ester at C-4 of **21** is less deactivating than the acetyl ester

at C-3 of **35**. Fortunately, the allyl glycoside of **37** could be activated with $BF_3{\cdot}OEt_2$ at 0 °C, and coupling with cyclohexanol, which was used as a mimic of the aglycon of compounds such as avermectin B_{1a}, gave disaccharide **38** as mainly the α-anomer.



Scheme 4.2. Armed−disarmed glycosylation strategy

4.4 CONCLUSION

In conclusion, it has been demonstrated that 2-deoxyglycosyl donors having a (*S*)-(phenylthiomethyl)benzyl moiety at C-6 can be employed for the chemical synthesis of α-linked glycosides. In addition, it was found that allyl 2,6-dideoxyglycosides could easily be activated with $BF_3{\cdot}OEt_2$ and couplings with a variety of sugar alcohol provided mainly α-glycosides. It is to be expected that the methodology will be attractive for glycorandomization of medically important natural products.

4.5 EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under a positive pressure of argon, unless otherwise noted. All chemicals were purchased from commercial suppliers and used without further purification. DCM was distilled from calcium hydride under N_2. Column chromatography was performed on silica gel G60 (SiliCycle, 60-200μm 60 Å). Reactions were monitored by TLC on Kieselgel 60 F_{254} (EMD Chemicals Inc.) and the compounds were detected by examination under UV light and visualized by charring with 10% sulfuric acid in methanol or cerium ammonium molybdate in 20% aq. sulfuric acid. Organic solutions were concentrated by rotary evaporation below 40 ^{o}C under reduced pressure. Molecular sieves (4Å), used for reactions, were crushed and activated in *vacuo* at 390 °C during 8h. Optical rotations were measured with a 'Jasco P-1020' polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Inova 300 spectrometer and a Varian Inova 500 spectrometer equipped with Sun workstations. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Data are presented as follow: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = double of doublet, m = multiplet and/or multiple resonances), integration, coupling constant in Hertz (Hz). High-resolution mass spectra were obtained using MALDI-ToF (Applied Biosystems 4700 Proteomics Analyzer). The matrix used was DHB and the internal standards ultramark 1621 and PEG.

General procedure for glycosylations employing glycosyl donor 1, 2, and 3.

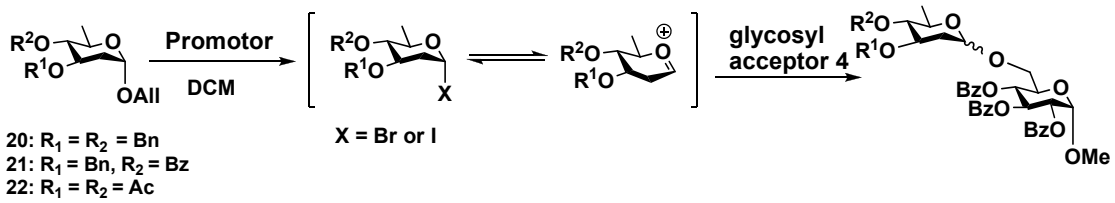
A mixture of glycosyl donor **1, 2,** or **3** (0.046 mmol), glycosyl acceptor (0.055 mmol) and activated molecular sieves (4Å) in DCM (3 mL) was stirred for 20 min under an atmosphere of argon at rt, then cooled to -78 ^{o}C. After the addition of trimethylsilyl trifluoromethanesulfonate (8.0 μL, 0.046 mmol for **1** and 2.5 μL, 0.014 mmol for **2** and **3**), the reaction mixture was stirred at -78 ^{o}C. When the donor was consumed as detected by TLC analysis, the reaction mixture

was quenched with saturated aq. $NaHCO_3$ (5 mL). The organic phase was dried ($MgSO_4$), filtered, and the filtrate was concentrated in *vacuo*. Purification of the residue was done by silicagel column chromatography (n-hexane/ethyl acetate = 2/1, v/v).

General procedure for glycosylations employing glycosyl donor 20, 21, and 22.

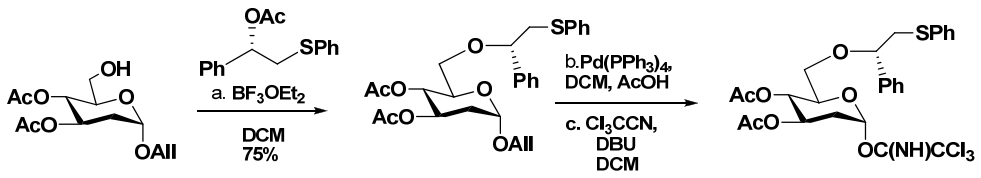
A mixture of glycosyl donor **20, 21** or **22** (0.074 mmol), glycosyl acceptor (0.089 mmol), and activated molecular sieves (4Å) in DCM (3 mL) was stirred for 20 min under an atmosphere of argon at rt, then cooled (-78 ^oC for **20**, -30 ^oC for **21**, and 0 ^oC for **22**). After the addition of boron trifluoride diethyl etherate (19 µL, 0.147 mmol), the reaction mixture was allowed to warm to -30 ^oC for **20**, 0 ^oC for **21,** and rt for **22**. When the donor was consumed as detected by TLC analysis, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (5 mL). The organic phase was dried ($MgSO_4$), filtered, and the filtrate was concentrated in *vacuo*. Purification of the residue was done by silica gel column chromatography (n-hexane/ethyl acetate = 2/1, v/v).

Table 4.3. β-Selective glycosylations employing TMSI or TMSBr as a promoter.



20: $R_1 = R_2 = Bn$
21: $R_1 = Bn$, $R_2 = Bz$
22: $R_1 = R_2 = Ac$

donor	promotor	temp.	product, α/β(yield)
20	**TMSI**	**-78 ^oC**	**10:1 (74%)**
20	**TMSBr**	**-78 ^oC**	**3:1 (64%)**
21	**TMSI**	**-20 ^oC**	**1:2 (68%)**
21	**TMSBr**	**-20 ^oC**	**No reaction**
22	**TMSI**	**0 ^oC**	**No reaction**
22	**TMSBr**	**0 ^oC**	**No reaction**



Scheme 4.3. Preparation of glycosyl donor1

3,4-Di-*O*-acetyl-6-*O*-[(1*S*)-phenyl-2-(phenylsulfanyl)ethyl]-2-deoxy-α-D-glucopyranosyl trichloroacetimidate (1): **a**: Boron trifluoride diethyl etherate (870 μL, 6.94mmol) was added to a solution of allyl 3,4-di-*O*-acetly-2-deoxy-α-D-glucopyranose (2 g, 6.94 mmol), acetic acid (1*S*)-phenyl-2-(phenylsulfanyl)ethyl ester (2.83 g, 10.41 mmol), and activated molecular sieves (4Å) in dichloromethane (20 mL) at 0 ^{o}C. After 30 min, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$), filtered, and the filtrate was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1, v/v).

b: Tetrakis(triphenylphosphine)palladium (3.9 g, 3.38 mmol) was added to a solution of allyl 3,4-di-*O*-acetly-6-*O*-[(1*S*)-phenyl-2-(phenylsulfanyl)ethyl]-2-deoxy-α-D-glucopyranose (1.5 g, 3.38 mmol) in acetic acid (20 mL) and DCM (10 mL) at room temperature. The reaction mixture was stirred overnight and then diluted with dichloromethane (20 mL) and quenched with saturated aq. $NaHCO_3$. The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1, v/v).

c: Trichloroacetonitrile (1.99 mL, 19.9 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (119 μL, 0.8 mmol) were added to a solution of 3,4-di-*O*-acetly-6-*O*-[(1*S*)-phenyl-2-(phenylsulfanyl)ethyl]-2-deoxy-α-D-glucopyranose (915 mg, 1.99 mmol) in DCM (10 mL) at 0^{o}C. The reaction mixture was stirred at the same temperature for 1h and then concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1,

v/v) to afford **1** (1.36 g, 68% over 2 steps): R_f = 0.45 (n-hexane/ethyl acetate = 2/1, v/v); $[\alpha]^{20}_D$ = +52.6° (*c* = 23.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.52 (s, 1H, N*H*), 7.28-7.05 (m, 10H, aromatic), 6.30 (d, 1H, *J* = 3.0 Hz, H-1), 5.30-5.26 (m, 1H, H-3), 5.15 (t, 1H, *J* = 9.6 Hz, H-4), 4.36-4.31 (m, 1H, H-7), 4.01-3.96 (m, 1H, H-5), 3.82-3.29 (m, 3H, H-6a, H-6b, H-8a), 3.03 (dd, 1H, *J* = 6.0, 13.5 Hz, H-8b), 2.39-2.32 (m, 1H, H-2a), 1.95 (s, 3H, $COCH_3$), 1.83 (s, 3H, $COCH_3$), 1.92-1.85 (m, 1H, H-2b); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.56, 169.94, 160.71, 140.26, 136.89, 129.45, 129.07, 128.75, 128.49, 127.37, 126.12, 95.69, 81.98, 71.95, 69.24, 69.14, 67.08, 41.10, 33.67, 21.22, 21.07.

3,4-Di-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranosyl trichloroacetimidate (2): $[\alpha]^{20}_D$ = +29.6° (*c* = 9.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.62 (s, 1H, N*H*), 7.35-7.27 (m, 5H, aromatic), 6.43 (d, 1H, *J* = 3.0 Hz, H-1), 5.40-5.36 (m, 1H, H-3), 5.22 (t, 1H, *J* = 10.0 Hz, H-4), 4.60 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.47 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.16-4.14 (m, 1H, H-5), 3.58-3.56 (m, 2H, H-6a, H-6b), 2.52-2.46 (m, 1H, H-2a), 2.06-2.02 (m, 1H, H-2b), 2.03 (s, 3H, $COCH_3$), 1.94 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.53, 169.99, 160.75, 137.81, 128.68, 128.59, 128.43, 128.23, 127.98, 95.62, 73.69, 72.06, 69.43, 68.91, 68.31, 33.74, 21.19, 20.94.

3,4,6-Tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl trichloroacetimidate (3): $[\alpha]^{20}_D$ = +17.6° (*c* = 37.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.59 (s, 1H, N*H*), 6.35 (d, 1H, *J* = 3.0 Hz, H-1), 5.35-5.24 (m, 1H, H-3), 5.06 (t, 1H, *J* = 9.9 Hz, H-4), 4.23 (dd, 1H, *J* = 4.2, 12.0 Hz, H-6a), 4.20-4.09 (m, 1H, H-5), 4.03 (dd, 1H, *J* = 2.7, 12.0 Hz, H-6b), 2.48-2.41 (m, 1H, H-2a), 2.06-2.02 (m, 1H, H-2b), 2.01 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 1.94 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.89, 170.33, 170.01, 160.65, 95.33, 70.85, 68.80, 68.68, 62.10, 33.77, 21.13, 20.91(2).

Methyl (3,4,-di-*O*-acetyl-6-*O*-[(1*S*)-phenyl-2-(phenylsulfanyl)ethyl]-2-deoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (8): $[\alpha]^{20}_{D}$ = -66.1° (*c* = 2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.00-7.99 (m, 2H, aromatic), 7.96-7.94 (m, 2H, aromatic), 7.89-7.88 (m, 2H, aromatic), 7.53-7.16 (m, 19H, aromatic), 6.14 (t, 1H, *J* = 10.0 Hz, H-3), 5.58 (t, 1H, *J* = 10.0 Hz, H-4), 5.27-5.24 (m, 3H, H-1, H-2, H-3'), 5.04 (t, 1H, *J* = 10.0 Hz, H-4'), 4.94 (d, 1H, *J* = 3.0 Hz, H-1'), 4.35-4.32 (m, 1H, H-7'), 4.28-4.22 (m, 1H, H-5), 3.89-3.84 (m, 2H, H-5', H-6a'), 3.58-3.56 (m, 1H, H-6b'), 3.49 (s, 3H, OCH_3), 3.49-3.10 (m, 4H, H-6a, H-6b, H-8a', H-8b'), 2.21-2.11 (m, 1H, H-2a'), 2.01 (s, 3H, $COCH_3$), 1.89 (s, 3H, $COCH_3$), 1.88-1.74 (m, 1H, H-2b'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.40, 170.05, 166.04(2), 165.41, 140.44, 136.99, 133.55, 133.50, 133.27, 130.17, 130.08, 129.93, 129.50, 129.43, 129.33, 129.28, 129.25, 129.18, 129.06, 128.66, 128.62, 128.48, 128.34, 127.17, 125.99, 97.08(2), 82.15, 72.44, 72.80, 72.04, 69.87, 69.57, 69.42, 68.54, 68.16, 66.13, 55.77, 41.08, 34.88, 21.26, 21.05; HR-MALDI-ToF/MS: *m/z* calcd for $C_{52}H_{52}O_{15}S$ $(M+Na)^+$: 971.3027; found: 971.3021

Methyl (3,4,-di-*O*-acetyl-6-*O*-[(1*S*)-phenyl-2-(phenylsulfanyl)ethyl]-2-deoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (11): $[\alpha]^{20}_{D}$ = -119.2° (*c* = 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.13-8.11 (m, 2H, aromatic), 7.97-7.96 (m, 2H, aromatic), 7.85-7.83 (m, 2H, aromatic), 7.61-7.15 (m, 19H, aromatic), 5.97 (t, 1H, *J* = 10.0 Hz, H-4), 5.87 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3), 5.68-5.67 (m, 1H, H-2), 5.35-5.25 (m, 1H, H-3'), 5.05 (t, 1H, *J* = 10.0 Hz, H-4'), 4.99-4.97 (m, 2H, H-1', H-1), 4.29-4.27 (m, 2H, H-7', H-5), 3.91 (dd, 1H, *J* = 5.0, 10.0 Hz, H-6a'), 3.82-3.78 (m, 1H, H-5'), 3.62 (dd, 1H, *J* = 3.0, 10.0 Hz, H-6b'), 3.54 (s, 3H, OCH_3), 3.34 (dd, 1H, *J* = 7.0, 14.0 Hz, H-8a'), 3.22-3.16 (m, 2H, H-6a, H-6b), 3.04 (dd, 1H, *J* = 7.00, 14.0 Hz, H-8b'), 2.19-2.14 (m, 1H, H-2a'), 2.02 (s, 3H, $COCH_3$), 1.89 (s, 3H, $COCH_3$), 1.89-1.72 (m, 1H, H-2b'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.23, 170.04, 165.82, 165.69, 165.61, 140.39, 136.94, 133.69, 133.51, 133.31, 130.14, 130.02, 129.98, 129.55, 129.44,

129.37, 129.23, 129.04, 128.99 ,128.90, 128.62, 128.49, 128.32, 127.16, 126.00, 98.82, 97.11, 82.11, 70.78, 70.42, 69.98, 69.71, 69.58, 69.43, 68.13, 67.54, 66.32, 55.68, 40.99, 34.88, 21.28, 21.05; HR-MALDI-ToF/MS: *m/z* calcd for $C_{52}H_{52}O_{15}S$ $(M+Na)^+$: 971.3027; found: 971.3024

Methyl (3,4,-di-*O*-acetyl-6-*O*-[(1*S*)-phenyl-2-(phenylsulfanyl)ethyl]-2-deoxy-α-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (13): $[\alpha]^{20}_D$ = -131.7° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.45-7.17 (m, 20H, aromatic), 5.51 (s, 1H, C*H*Ph), 5.42 (d, 1H, *J* = 3.0 Hz, H-1'), 5.36-5.28 (m, 1H, H-3'), 5.12 (t, 1H, *J* = 10.0 Hz, H-4'), 4.69 (d, 1H, *J* = 3.0 Hz, H-1), 4.63 (s, 2H, C*H*HPh), 4.35-4.32 (m, 1H, H-7'), 4.28-4.23 (m, 2H, H-6a, H-6b), 4.21-4.18 (m, 1H, H-5), 3.86-3.79 (m, 1H, H-5'), 3.71 (t, 1H, *J* = 10.0 Hz, H-3), 3.59 (t, 1H, *J* = 10.0 Hz, H-4), 3.52-3.44 (m, 2H, H-2, H-8a'), 3.39 (s, 3H, OCH_3), 3.20-3.04 (m, 3H, H-6a', H-6b', H-8b'), 2.24-2.18 (m, 1H, H-2a'), 2.19 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 1.82-1.74 (m, 1H, H-2b'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.83, 169.91, 140.37, 137.81, 137.46, 136.95, 129.49, 129.28, 128.93, 128.62, 128.58, 128.51, 128.26, 128.18, 127.72, 126.24, 125.96, 101.66, 98.74, 97.23, 83.02, 81.40, 78.26, 73.30, 73.13, 70.12, 69.70, 69.27, 68.66, 66.66, 62.13, 55.56, 40.71, 35.08, 21.34, 21.10; HR-MALDI-ToF/MS: *m/z* calcd for $C_{45}H_{50}O_{12}S$ $(M+Na)^+$: 837.3023; found: 837.3022

Methyl (3,4-di-*O*-acetyl-6-*O*-[(1*S*)-phenyl-2-(phenylsulfanyl)ethyl]-2-deoxy-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (15): $[\alpha]^{20}_D$ = -94.5° (*c* = 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.36-7.14 (m, 25H, aromatic), 5.40 (d, 1H, *J* = 3.0 Hz, H-1'), 5.22-5.18 (m, 1H, H-3'), 5.07 (d, 1H, *J* = 10.0 Hz, C*H*HPh), 5.00 (t, 1H, *J* = 10.0 Hz, H-4'), 4.77 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.66 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.63 (d, 1H, *J* = 10.0 Hz, C*H*HPh), 4.61 (d, 1H, *J* = 3.0 Hz, H-1), 4.55 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.48 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.28-4.25 (m, 1H, H-7'), 3.92 (t, 1H, *J* = 9.0 Hz, H-3), 3.77-3.67 (m, 5H, H-6b', H-5',

H-5, H-4, H-6a'), 3.54 (dd, 1H, *J* = 3.0, 9.0 Hz, H-2), 3.42 (s, 3H, OCH_3), 3.37 (dd, 1H, *J* = 7.0, 14.0 Hz, H-8a'), 3.14-3.05 (m, 3H, H-6a, H-6b, H-8b'), 2.22-1.98 (m, 1H, H-2a'), 2.00 (s, 3H, $COCH_3$), 1.88 (s, 3H, $COCH_3$), 1.68-1.62 (m, 1H, H-2b'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.82, 170.27, 140.25, 137.97, 137.52, 137.11, 129.47, 129.16, 128.81, 128.77, 128.73, 128.40, 128.23, 127.67, 126.26, 125.99, 98.95, 96.95, 83.00(2), 81.63, 77.90, 73.86, 73.51, 72.97, 72.70, 69.28, 68.36, 63.08, 62.14(2), 55.50, 40.71, 35.08, 21.61, 20.86; HR-MALDI-ToF/MS: *m/z* calcd for $C_{52}H_{58}O_{12}S$ $(M+Na)^+$: 929.3649; found: 929.3644

Methyl (3,4-di-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (16): $[\alpha]^{20}_D$ = -82.0° (*c* = 5.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.29-7.16 (m, 20H, aromatic), 5.37 (d, 1H, *J* = 3.0 Hz, H-1'), 5.16-5.11 (m, 1H, H-3'), 4.97 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.93 (t, 1H, *J* = 10.0 Hz, H-4'), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.58 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.56-4.53 (m, 2H, H-1, C*H*HPh), 4.49-4.37 (m, 3H, C*H*HPh), 4.23 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 3.86 (t, 1H, *J* = 9.0 Hz, H-3), 3.75-3.67 (m, 2H, H-5', H-5), 3.64-3.60 (m, 3H, H-4, H-6a', H-6b'), 3.45 (dd, 1H, *J* = 4.0, 9.0 Hz, H-2), 3.33 (s, 3H, OCH_3), 3.20-3.19 (m, 2H, H-6a, H-6b), 1.96-1.93 (m, 1H, H-2a'), 1.91 (s, 3H, $COCH_3$), 1.82 (s, 3H, $COCH_3$), 1.61-1.56 (m, 1H, H-2b'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.12, 169.90, 138.02, 137.87, 137.52, 137.11, 129.88, 129.16, 128.81, 128.77, 128.33, 128.10, 128.01, 126.97, 99.54, 97.75, 79.93, 77.62, 74.26, 73.87, 71.85, 70.65, 69.88, 69.36, 67.18, 65.10, 62.08, 60.36, 55.80, 40.93, 35.44, 21.08, 20.06; HR-MALDI-ToF/MS: *m/z* calcd for $C_{45}H_{52}O_{12}$ $(M+Na)^+$: 807.3459; found: 807.3451

Allyl (3-*O*-acetyl-4-*O*-[(1*S*)-phenyl-2-(phenylsulfanyl)ethyl]-2,6-dideoxy-α-D-glucopyranosyl)-(1→4)-3-*O*-acetyl-2,6-dideoxy-α-D-glucopyranoside (19): $[\alpha]^{20}_D$ = +13.5° (*c* = 2.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.35-7.11 (m, 10H, aromatic), 5.89-5.86 (m, 1H, OCH_2CHCH_2), 5.28-5.02 (m, 5H, H-3, H-3', H-1, OCH_2CHCH_2), 4.81 (d, 1H, *J* = 3.0 Hz, H-1'),

4.80-4.28 (m, 1H, H-7), 4.12-4.09 (m, 1H, OC*H*$_2$CHCH$_2$) 3.93-3.89 (m, 1H, OC*H*$_2$CHCH$_2$), 3.78-3.69 (m, 2H, H-5, H-5'), 3.39-3.31 (m, 2H, H-4, H-4'), 3.13-2.98 (m, 2H, H-8a', H-8b'), 2.24-2.21 (m, 1H, H-2a), 2.12-2.10 (m, 1H, H-2a'), 1.97 (s, 3H, COCH$_3$), 1.90 (s, 3H, COCH$_3$), 1.66-1.59 (m, 2H, H-2b, H-2b'), 1.24 (d, 3H, *J* = 5.0, H-6), 0.91 (d, 3H, *J* = 5.0, H-6'); ^{13}C NMR (75 MHz, CDCl$_3$) *δ* 170.04, 169.91, 140.16, 136.89, 134.32, 129.23, 129.12, 128.78, 128.69, 128.03, 126.16, 117.35, 97.64, 95.97, 81.20, 80.07, 78.90, 72.81, 72.17, 68.01, 67.46, 66.69, 40.74, 35.46, 34.60, 21.51, 21.38, 18.54, 18.27; HR-MALDI-ToF/MS: *m/z* calcd for $C_{33}H_{42}O_9S$ $(M+Na)^+$: 637.2550; found: 637.2555

Allyl 3,4-di-*O*-benzyl-2,6-dideoxy-α-D-glucopyranoside (20): $[\alpha]^{20}_D$ = +23.0° (*c* = 9.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 7.28-7.16 (m, 10H, aromatic), 5.84-5.76 (m,1H, OCH$_2$C*H*CH$_2$), 5.24-5.06 (m, 2H, OCH$_2$CHC*H*$_2$), 4.89 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.80 (d, 1H, *J* = 3.5 Hz, H-1), 4.62-4.52 (m, 3H, C*H*HPh), 4.06-4.00 (m, 1H, OC*H*$_2$CHCH$_2$), 3.94-3.86 (m, 1H, H-3), 3.84-3.76 (m, 1H, OC*H*$_2$CHCH$_2$), 3.72-3.64 (m, 1H, H-5), 3.06 (t, 1H, *J* = 10.0 Hz, H-4), 2.24-2.30 (m, 1H, H-2a), 1.65-1.58 (m, 1H, H-2b), 1.22 (d, 3H, *J* = 6.0 Hz, H-6); ^{13}C NMR (75 MHz, CDCl$_3$) *δ* 138.98, 138.85, 134.48, 128.63, 128.32, 128.25, 127.96, 127.88, 127.78, 117.25, 96.63, 84.56, 77.71, 75.48, 72.03, 67.86, 67.51, 35.99, 18.42; HR-MALDI-ToF/MS: *m/z* calcd for $C_{23}H_{28}O_4$ $(M+Na)^+$: 391.1988; found: 391.1988

Allyl 3-*O*-benzyl-4-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranoside (21): $[\alpha]^{20}_D$ = -121.3° (*c* = 1.6, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 8.12-8.08 (m, 2H, aromatic), 7.64-7.58 (m, 1H, aromatic), 7.52-7.46 (m, 2H, aromatic), 7.22-7.16 (m, 5H, aromatic), 6.02-5.84 (m, 1H, OCH$_2$C*H*CH$_2$), 5.38-5.24 (m, 2H, OCH$_2$CHC*H*$_2$), 5.09 (t, 1H, *J* = 10.0 Hz, H-4), 5.02 (d, 1H, *J* = 3.0 Hz, H-1), 4.65 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.52 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.24-4.16 (m, 1H, OC*H*$_2$CHCH$_2$), 4.10-3.84 (m, 3H, H-3, H-5, OC*H*$_2$CHCH$_2$), 2.42-2.38 (m, 1H, H-2a), 1.92-1.84

(m, 1H, H-2b), 1.26 (d, 3H, *J* = 6.0 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 166.06, 138.56, 134.38, 133.28, 130.34, 130.02, 128.69, 128.61, 128.42, 128.10, 127.81, 127.69, 127.62, 117.43, 96.74, 77.11, 74.29, 71.58, 68.18, 66.43, 35.82, 17.89; HR-MALDI-ToF/MS: *m/z* calcd for $C_{23}H_{26}O_5$ $(M+Na)^+$: 405.1780; found: 405.1788

Allyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-D-glucopyranoside (22): $[\alpha]^{20}_D$ = +104.4° (*c* = 11.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 5.86-5.82 (m, 1H, OCH_2CHCH_2), 5.32-5.24 (m, 2H, OCH_2CHCH_2), 5.20-5.16 (m, 1H, H-3), 4.90 (d, 1H, *J* = 3.5 Hz, H-1), 4.72 (t, 1H, *J* = 10.0 Hz, H-4), 4.14-4.08 (m, 1H, OCH_2CHCH_2), 3.96-3.90 (m, 2H, H-5, OCH_2CHCH_2), 2.25-2.20 (m, 1H, H-2a), 2.08 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 1.82-1.74 (m, 1H, H-2b), 1.15 (d, 3H, *J* = 6.0 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.36(2), 134.13, 117.33, 96.04, 75.02, 69.24, 68.04, 65.84, 35.42, 21.17, 20.99, 17.99; HR-MALDI-ToF/MS: *m/z* calcd for $C_{13}H_{20}O_6$ $(M+Na)^+$: 295.1260; found: 295.1261

Methyl (3,4-di-*O*-benzyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (23): $[\alpha]^{20}_D$ = -129.9° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*. 7.92-7.86 (m, 4H, aromatic), 7.82-7.79 (m, 2H, aromatic), 7.46-7.21 (m, 19H, aromatic), 6.06 (t, 1H, *J* = 10.0 Hz, H-3), 5.54 (t, 1H, *J* = 10.0 Hz, H-4), 5.20 (dd, 1H, *J* = 3.5, 10.0 Hz, H-2), 5.16 (d, 1H, *J* = 3.5 Hz, H-1), 4.84 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.78 (d, 1H, *J* = 3.5 Hz, H-1'), 4.53 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.41 (s, 2H, C*H*HPh), 4.15-4.11 (m, 1H, H-5), 3.82-3.74 (m, 2H, H-3', H-6a), 3.57-3.50 (m, 2H, H-5', H-6b), 3.37 (s, 3H, OCH_3), 2.98 (t, 1H, *J* = 10.0 Hz, H-4'), 2.11-2.08 (m, 1H, H-2a'), 1.58-1.51 (m, 1H, H-2b'), 1.03 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 166.10, 166.08, 165.38, 139.01, 138.95, 133.57, 133.47, 133.27, 130.17, 130.13, 130.04, 129.92, 129.54, 129.44, 129.34, 128.78, 128.63, 128.56, 128.50, 128.29, 128.13, 127.93, 127.75, 127.72, 97.68, 97.12, 84.33, 75.20, 72.40, 71.84, 70.79, 70.22, 68.37, 67.55, 66.29,

55.77, 35.71, 29.93, 18.14; HR-MALDI-ToF/MS: *m/z* calcd for $C_{48}H_{48}O_{12}$ $(M+Na)^+$: 839.3146; found: 839.3146

Methyl (3-*O*-benzyl-4-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (24): $[\alpha]^{20}_D$ = -150.3° (*c* = 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.01-7.99 (m, 2H, aromatic), 7.93-7.83 (m, 6H, aromatic), 7.53-7.09 (m, 17H, aromatic), 6.07 (t, 1H, *J* = 10.0 Hz, H-3), 5.60 (t, 1H, *J* = 10.0 Hz, H-4), 5.23 (dd, 1H, *J* = 3.5, 10.0 Hz, H-2), 5.18 (d, 1H, *J* = 3.5 Hz, H-1), 4.89 (t, 1H, *J* = 10.0 Hz, H-4'), 4.87 (d, 1H, *J* = 3.0 Hz, H-1'), 4.47 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.35 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.20-4.16 (m, 1H, H-5), 3.95-3.90 (m, 1H, H-3'), 3.80 (dd, 1H, *J* = 4.0, 11.0 Hz, H-6a), 3.68-3.65 (m, 1H, H-5'), 3.53 (dd, 1H, *J* = 2.5, 11.0 Hz, H-6b), 3.38 (s, 3H, OCH_3), 2.23 (dd, 1H, *J* = 5.5, 14.0 Hz, H-2a'), 1.92-1.67 (m, 1H, H-2b'), 0.89 (d, 3H, *J* = 12.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 166.14, 166.12, 166.06, 165.35, 138.53, 133.62, 133.34, 133.27, 130.35, 130.18, 130.07, 130.01, 129.97, 129.55, 129.36, 129.28, 128.68, 128.60, 128.52, 128.40, 127.83, 127.63, 97.67, 97.30, 77.46, 73.93, 72.35, 71.64, 70.94, 69.60, 68.46, 66.45, 65.78, 55.77, 35.59, 17.57; HR-MALDI-ToF/MS: *m/z* calcd for $C_{48}H_{46}O_{13}$ $(M+Na)^+$: 853.2938; found: 853.2939

Methyl (3,4-di-*O*-acetyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (25): $[\alpha]^{20}_D$ = -10.2° (*c* = 1.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.92-7.87 (m, 4H, aromatic), 7.82-7.77 (m, 2H, aromatic), 7.45-7.19 (m, 9H, aromatic), 6.07 (t, 1H, *J* = 10.0 Hz, H-3), 5.51 (t, H-1, *J* = 10.0 Hz, H-4), 5.22-5.15 (m, 3H, H-1, H-2, H-3'), 4.80 (d, 1H, *J* = 3.5 Hz, H-1'), 4.62 (t, 1H, *J* = 10.0 Hz, H-4'), 4.21-4.18 (m, 1H, H-5), 3.78- 3.74 (m, 2H, H-5', H-6a), 3.49 (dd, 1H, *J* = 3.0, 10.0 Hz, H-6b), 3.42 (s, 3H, OCH_3), 2.12 (dd, *J* = 5.0, 12.0 Hz, H-2a'), 1.98 (s, 3H, $COCH_3$), 1.92 (s, 3H, $COCH_3$), 1.70-1.59 (m, 1H, H-2b'), 0.85 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.48, 170.33, 166.07, 166.06, 165.44, 133.57, 133.28,

130.17, 130.08, 129.94, 129.88, 129.50, 129.33, 129.27, 128.63, 128.50, 97.12, 96.99, 74.92, 72.45, 70.80, 69.87, 69.14, 68.55, 66.12, 65.91, 55.78, 35.25, 21.24, 21.10, 17.56; HR-MALDI-ToF/MS: *m/z* calcd for $C_{38}H_{40}O_{14}$ $(M+Na)^+$: 743.2418; found: 743.2411

Methyl (3,4-di-*O*-benzyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (26): $[\alpha]^{20}_D$ = -121.3° (*c* = 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.13-8.11 (m, 2H, aromatic), 8.01-7.98 (m, 2H, aromatic), 7.89-7.85 (m, 2H, aromatic), 7.59-7.27 (m, 19H, aromatic), 5.97 (t, 1H, *J* = 10.0 Hz, H-4), 5.89 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3), 5.68-5.67 (m, 1H, H-2), 4.98-4.91 (m, 3H, H-1, H-1', C*H*HPh), 4.63 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.44 (s, 2H, C*H*HPh), 5.25-4.21 (m, 1H, H-5), 3.90-3.87 (m, 2H, H-5', H-6a), 3.71 (m, 2H, H-3', H-6b), 3.51 (s, 3H, OCH_3), 3.08 (t, 1H, *J* = 10.0 Hz, H-4'), 2.18 (dd, 1H, *J* = 5.0, 14.0 Hz, H-2a'), 1.64-1.58 (m, 1H, H-2b'), 1.15 (d 3H, *J* = 6.0 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 165.75(2), 165.63, 138.97, 138.92, 133.72, 133.50, 133.33, 130.10, 130.06, 129.98, 129.70, 129.58, 129.44, 128.81, 128.66, 128.57, 128.52, 128.16, 127.80, 127.78, 127.73, 98.77, 97.59, 84.35, 77.42, 75.25, 71.75, 70.85, 70.33, 69.52, 68.09, 67.09, 66.61, 55.67, 35.66, 18.22; HR-MALDI-ToF/MS: *m/z* calcd for $C_{48}H_{48}O_{12}$ $(M+Na)^+$: 839.3146; found: 839.3141

Methyl (3-*O*-benzyl-4-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (27): $[\alpha]^{20}_D$ = -111.6° (*c* = 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.05-8.04 (m, 2H, aromatic), 7.98-7.96 (m, 2H, aromatic), 7.92-7.90 (m, 2H, aromatic), 7.80-7.79 (m, 2H, aromatic), 7.53-7.04 (m, 17H, aromatic), 5.95 (t, 1H, *J* = 10.0 Hz, H-4), 5.80 (dd, 1H, *J* = 3.0, 10.0 Hz, H-3), 5.61 (dd, 1H, *J* = 1.5, 3.0 Hz, H-2), 4.93-4.88 (m, 3H, H-1, H-1', H-4'), 4.42 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.29 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.21-4.18 (m, 1H, H-5), 3.95-3.90 (m, 1H, H-3'), 3.86-3.83 (m, 1H, H-6a), 3.77-3.72 (m, 1H, H-5'), 3.62-3.44 (m, 1H, H-6b), 3.44 (s, 3H, OCH_3), 2.24 (dd, 1H, *J* = 5.0, 13.0 Hz, H-2a'), 1.73-1.67 (m, 1H, H-2b'),

0.95 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 166.03, 165.76, 165.74, 165.60, 138.51, 133.77, 133.61, 133.34, 133.28, 130.09, 130.04, 129.96, 129.70, 129.52, 129.44, 128.82, 128.69, 128.59, 128.52, 129.40, 127.65, 127.58, 98.88, 97.63, 76.91, 74.22, 71.48, 70.89, 70.47, 69.72, 67.59, 66.48, 66.23, 55.66, 35.57, 17.66; HR-MALDI-ToF/MS: *m/z* calcd for $C_{48}H_{46}O_{13}$ $(M+Na)^+$: 853.2938; found: 853.2933

Methyl (3,4-di-*O*-acetyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (28): $[\alpha]^{20}_D$ = -178.0° (*c* = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*. 8.06-8.04 (m, 2H, aromatic), 7.91-7.90 (m, 2H, aromatic), 7.77-7.76 (m, 2H, aromatic), 7.54-7.17 (m, 9H, aromatic), 5.89 (t, 1H, *J* = 10.0 Hz, H-4), 5.78 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3), 5.61-5.60 (m, 1H, H-2), 5.20-5.17 (m, 1H, H-3'), 4.92 (d, 1H, *J* = 5.0 Hz, H-1), 4.84 (d, 1H, *J* = 3.0 Hz, H-1'), 4.63 (t, 1H, *J* = 10.0 Hz, H-4'), 4.22-4.18 (m, 1H, H-5), 3.82 (dd, *J* = 5.0, 11.0 Hz, 1H, H-6a), 3.74-3.69 (m, 1H, H-5'), 3.54 (dd, 1H, *J* = 2.5, 11.0 Hz, H-6b), 3.47 (s, 3H, OCH_3), 2.15 (dd, 1H, *J* = 5.0, 12.0 Hz, H-2a'), 1.91 (s, 3H, $COCH_3$), 1.93 (s, 3H, $COCH_3$), 1.67-1.62 (m, 1H, H-2b'), 0.91 (d, 3H, *J* = 6.5 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.46, 170.17, 165.82, 165.71, 165.43, 133.73, 133.57, 133.33, 130.17, 130.00, 129.58, 129.41, 128.93, 128.66, 128.51, 98.87, 97.05, 74.84, 70.79, 70.42, 69.71, 69.17, 67.51, 66.31, 65.94, 53.65, 35.28, 21.27, 21.11, 17.53; HR-MALDI-ToF/MS: *m/z* calcd for $C_{38}H_{40}O_{14}$ $(M+Na)^+$: 743.2418; found: 743.2417

Methyl (3,4-di-*O*-benzyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (29): $[\alpha]^{20}_D$ = -127.1° (*c* = 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.46-7.44 (m, 2H, aromatic), 7.39-7.26 (m, 18H, aromatic), 5.52 (s, 1H, C*H*Ph), 5.40 (d, 1H, *J* = 3.0 Hz, H-1'), 4.95 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.78 (d, 1H, *J* = 12.0 Hz, C*H*HPH), 4.69-4.56 (m, 5H, C*H*HPh, H-1), 4.28-4.23 (m, 2H, H-3, H-5), 4.13-4.10 (m, 1H, H-5'), 4.00-3.95 (m, 1H, H-3'), 3.85-3.80 (m, 1H, H-6a), 3.70 (t, 1H, *J* = 10.0 Hz, H-4), 3.58-3.55 (m, 1H, H-6b),

3.45 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2), 3.40 (s, 3H, OCH_3), 3.13 (t, 1H, *J* = 10.0 Hz, H-4'), 2.34 (dd, 1H, *J* = 5.0, 14.0 Hz, H-2a'), 1.69-1.65 (m, 1H, H-2b'), 1.03 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 139.23, 139.04, 138.05, 137.50, 129.25, 128.78, 128.67, 128.56, 128.49, 128.44, 128.17, 129.94, 127.83, 127.69, 127.63, 127.26, 101.66, 99.20, 97.63, 84.87, 83.25, 78.27, 75.15, 74.07, 73.25, 71.77, 69.34, 67.71, 62.11(2), 55.49, 35.91, 18.55; HR-MALDI-ToF/MS: *m/z* calcd for $C_{41}H_{46}O_9$ $(M+Na)^+$: 705.3142; found: 705.3143

Methyl (3-*O*-benzyl-4-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (30): $[\alpha]^{20}_D$ = -136.7° (*c* = 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ*. 7.87-7.86 (m, 2H, aromatic), 7.51-7.05 (m, 18H, aromatic), 5.45 (s, 1H, C*H*Ph), 5.40 (d, 1H, *J* = 3.0 Hz, H-1'), 4.94 (t, 1H, *J* = 10.0 Hz, H-4'), 4.68 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.56 (d, 1H, *J* = 3.5 Hz, H-1), 4.52 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.50 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.37 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.20-4.17 (m, 3H, H-6a, H-6b, H-5), 3.97-3.92 (m, 1H, H-3'), 3.78-3.73 (m, 1H, H-5'), 3.67 (t, 1H, *J* = 10.0 Hz, H-3), 3.50 (t, 1H, *J* = 10.0 Hz, H-4), 3.41 (dd, 1H, *J* = 3.5, 10.0 Hz, H-2), 3.33 (s, 3H, OCH_3), 2.30 (dd, 1H, *J* = 5.5, 14.0 Hz, H-2a'), 1.73-1.68 (m, 1H, H-2b'), 1.05 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 165.98, 138.62, 138.06, 137.42, 133.18, 130.41, 130.01, 129.93, 129.31, 128.71, 128.54, 128.41, 129.26, 128.38, 128.26, 127.87, 127.69, 127.61, 126.24, 105.00, 99.07, 97.28, 83.32, 78.11, 73.78, 73.64, 72.67, 71.05, 69.32, 66.42, 62.16, 55.53, 35.58, 29.92, 17.99; HR-MALDI-ToF/MS: *m/z* calcd for $C_{41}H_{44}O_{10}$ $(M+Na)^+$: 719.2934; found: 719.2938

Methyl (3,4-di-*O*-acetyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (31): $[\alpha]^{20}_D$ = -37.7° (*c* = 2.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ*. 7.44-7.31 (m, 10H, aromatic), 5.51 (s, 1H, C*H*Ph), 5.38 (d, 1H, *J* = 3.0 Hz, H-1'), 5.36-5.30 (m, 1H, H-3'), 4.80 (t, 1H, *J* = 7.0 Hz, H-4'), 4.74-4.69 (m, 3H, H-1, C*H*HPh), 4.30-4.15 (m, 3H, H-5, H-6a, H-6b), 3.85-3.80 (m, 1H, H-5'), 3.71 (t, 1H, *J* = 10.0 Hz, H-3), 3.60 (t, 1H, *J* =

10.0 Hz, H-4), 3.52 (dd, 1H, *J* = 3.5, 10.0 Hz, H-2), 3.41 (s, 3H, OCH_3), 2.29 (dd, 1H, *J* = 5.0, 12.0 Hz, H-2a'), 2.02 (s, 6H, $COCH_3$), 1.76-1.70 (m, 1H, H-2b'), 1.05 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.70, 170.44, 137.99, 137.44, 135.01, 129.45, 129.27, 128.84, 128.71, 128.60, 128.52, 128.41, 128.22, 126.56, 126.22, 101.63, 98.96, 96.94, 83.17, 78.10, 75.08, 73.75, 73.18, 69.43, 69.29, 65.93, 62.08, 55.53, 35.51, 21.34, 21.12, 17.81; HR-MALDI-ToF/MS: *m/z* calcd for $C_{31}H_{38}O_{11}$ $(M+Na)^+$: 609.2414; found: 609.2411

Methyl (3,4-di-*O*-benzyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (32): $[\alpha]^{20}_D$ = -90.0° (*c* = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ*. 7.32-7.24 (m, 25H, aromatic), 5.30 (d, 1H, *J* = 3.5 Hz, H-1'), 5.02 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.89 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.73 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.64-4.49 (m, 8H, H-1,C*H*HPh), 3.87 (t, 1H, *J* = 9.0 Hz, H-3), 3.88-3.80 (m, 1H, H-3'), 3.73-3.52 (m, 4H, H-4, H-5, H-5', H-6a), 3.51 (dd, 1H, *J* = 3.5, 10.0 Hz, H-6b), 3.39 (s, 3H, OCH_3), 3.05 (t, 1H, *J* = 9.0 Hz, H-4'), 2.08 (dd, 1H, *J* = 5.0, 14.0 Hz, H-2a'), 1.55-1.50 (m, 1H, H-2b'), 1.16 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 138.88, 138.86, 138.44, 138.24, 129.42, 128.68, 128.65, 128.60, 128.56, 128.50, 128.36, 128.19, 128.15, 127.83, 127.78, 127.74, 127.67, 99.33, 97.99, 84.34, 82.35, 80.28, 76.35, 75.66, 75.24, 73.57, 73.45, 71.87, 69.98, 68.31, 55.45, 31.81, 22.88, 18.36, 14.35; HR-MALDI-ToF/MS: *m/z* calcd for $C_{48}H_{54}O_9$ $(M+Na)^+$: 797.3768; found: 797.3769

Methyl (3-*O*-benzyl-4-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (33): $[\alpha]^{20}_D$ = -23.2° (*c* = 2.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ*. 7.96-7.85 (m, 2H, aromatic), 7.54-7.03 (m, 23H, aromatic), 5.26(d, 1H, *J* = 2.0 Hz, H-1'), 4.97 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.87 (t, 1H, *J* = 10.0 Hz, H-4'), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.59-4.54 (m, 4H, H-1, C*H*HPh), 4.43 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.40 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.31 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 3.84-3.70 (m, 5H, H-3', H-3, H-4, H-5, H-5'), 3.65

(dd, 1H, *J* = 2.0, 11.0 Hz, H-6a), 3.60-3.56 (m, 1H, H-6b), 3.47 (dd, 1H, *J* = 3.0, 10.0 Hz, H-2), 3.35 (s, 3H, OCH_3), 2.05 (dd, 1H, *J* = 5.0, 14.0 Hz, H-2a'), 1.62-1.56 (m, 1H, H-2b'), 0.99 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 164.72, 137.49, 137.26, 137.13, 136.95, 132.08, 129.07, 128.75, 127.47, 127.37, 127.32, 127.19, 127.14, 126.97, 126.64, 126.53, 126.48, 126.45, 126.43, 98.31, 96.78, 80.92, 79.08, 74.48, 72.80, 72.39, 72.26, 70.22, 68.80, 68.41, 65.97, 54.27, 34.91, 28.69(2), 16.62; HR-MALDI-ToF/MS: *m/z* calcd for $C_{48}H_{52}O_{10}$ $(M+Na)^+$: 811.3560; found: 811.3563

Methyl (3,4-di-*O*-acetyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (34): $[\alpha]^{20}_D$ = +14.1° (*c* = 2.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ*. 7.35-7.26 (m, 15H, aromatic), 5.35 (d, 1H, *J* = 3.0 Hz, H-1'), 5.22-5.17 (m, 1H, H-3'), 5.05 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.75 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.68 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.66-4.63 (m, 4H, H-1, H-4', C*H*HPh), 4.54 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 3.95 (t, 1H, *J* = 10.0 Hz, H-3), 3.82-3.77 (m, 2H, H-5, H-5'), 3.76-3.69 (m, 3H, H-4, H-6a, H-6b), 3.54 (dd, 1H, *J* = 3.5, 10.0 Hz, H-2), 3.43 (s, 3H, OCH_3), 2.08-2.02 (m, 1H, H-2a'), 2.06 (s, 3H, $COCH_3$), 2.00 (s, 3H, $COCH_3$), 1.66-1.60 (m, 1H, H-2b'), 1.02 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.45, 170.32, 138.84, 138.40, 138.21, 128.70, 128.61, 128.55, 128.36, 128.18, 127.74, 127.68, 98.64, 98.02, 82.14, 80.32, 76.40, 75.60, 74.94, 73.58, 73.45, 69.88, 69.46, 69.05, 66.69, 55.49, 35.78, 21.24, 21.08, 17.70; HR-MALDI-ToF/MS: *m/z* calcd for $C_{38}H_{46}O_{11}$ $(M+Na)^+$: 701.3040; found: 701.3049

Allyl (3,4-di-*O*-benzyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→4)-3-*O*-acetyl-2,6-dideoxy-α-D-glucopyranoside (36): $[\alpha]^{20}_D$ = +26.2° (*c* = 2.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ*. 7.35-7.26 (m, 10H, aromatic), 5.94-5.86 (m, 1H, OCH_2CHCH_2), 5.31-5.30 (m, 1H, OCH_2CHCH_2), 5.26-5.21 (m, 1H, H-3), 5.20-5.13 (m, 1H, OCH_2CHCH_2), 5.13-5.12 (m, 1H, H-1'), 4.92 (d, 1H, *J* =

11.0 Hz, C*H*HPh), 4.86 (d, 1H, *J* = 3.0 Hz, H-1), 4.66-4.61 (m, 3H, C*H*HPh), 4.14-4.10 (m, 1H, OC*H*$_2$CHCH$_2$), 3.96-3.91 (m, 1H, OC*H*$_2$CHCH$_2$), 3.88-3.73 (m, 3H, H-3', H-5, H-5'), 3.70 (t, 1H, *J* = 10.0 Hz, H-4), 3.12 (t, 1H, *J* = 10.0 Hz, H-4'), 2.25-2.15 (m, 2H, H-2a', H-2a), 2.03 (s, 3H, COCH$_3$), 1.71-1.65 (m, 2H, H-2b', H-2b), 1.29-1.26 (m, 6H, H-6, H-6'); ^{13}C NMR (75 MHz, CDCl$_3$) *δ* 170.10, 138.85, 134.35, 128.62, 128.61, 128.26, 127.93, 127.83, 127.76, 117.30, 98.74, 95.99, 84.26, 80.72, 77.23, 75.35, 72.77, 72.07, 68.28, 68.02, 66.73, 36.18, 35.55, 21.48, 18.56, 18.15; HR-MALDI-ToF/MS: *m/z* calcd for $C_{31}H_{40}O_8$ $(M+Na)^+$: 563.2723; found: 563.2721

Allyl (3-*O*-benzyl-4-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→4)-3-*O*-acetyl-2,6-dideoxy-α-D-glucopyranoside (37): $[\alpha]^{20}_D$ = -2.58° (*c* = 1.2, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) *δ*. 7.97-7.94 (m, 2H, aromatic), 7.53-7.07 (m, 8H, aromatic), 5.89-5.81 (m, 1H, OCH$_2$C*H*CH$_2$), 5.26-5.24 (m, 1H, OCH$_2$CHC*H*$_2$), 5.22-5.17 (m, 1H, H-3), 5.12-5.09 (m, 2H, OCH$_2$CHC*H*$_2$, H-1'), 4.95 (t, 1H, *J* = 10.0 Hz, H-4'), 4.81 (d, 1H, *J* = 3.5 Hz, H-1), 4.51 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.39 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.09-3.72 (m, 5H, H-5, H-5', H-3', OC*H*$_2$CHCH$_2$), 3.32 (t, 1H, *J* = 10.0 Hz, H-4), 2.20-2.12 (m, 2H, H-2a', H-2a), 1.99 (s, 3H, COCH$_3$), 1.77-1.61 (m, 2H, H-2b', H-2b), 1.25 (d, 3H, *J* = 6.0 Hz, H-6), 1.13 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C NMR (75 MHz, CDCl$_3$) *δ* 170.13, 166.01, 138.46, 134.37, 133.33, 130.24, 129.99, 128.62, 128.44, 127.74, 127.69, 117.29, 99.10, 96.05, 81.58, 76.81, 74.18, 72.57, 71.75, 68.08, 67.18, 66.69, 36.17, 35.39, 21.49, 18.58, 17.69; HR-MALDI-ToF/MS: *m/z* calcd for $C_{31}H_{38}O_9$ $(M+Na)^+$: 577.2516; found: 577.2512

Cyclohexyl (3-*O*-benzyl-4-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranosyl)-(1→4)-3-*O*-acetyl-2,6-dideoxy-α-D-glucopyranoside (38): $[\alpha]^{20}_D$ = -145.5° (*c* = 0.2, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) *δ*. 8.06-8.04 (m, 2H, aromatic), 7.60-7.17 (m, 8H, aromatic), 5.32-5.27 (m, 1H, H-3), 5.20 (d, 1H, *J* = 3.0 Hz, H-1'), 5.06-5.01 (m, 2H, H-4', H-1), 4.61 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.59

(d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.04-3.89 (m, 3H, H-5, H-5', H-3'), 3.55-3.51 (m, 1H, OC*H*CH_2), 3.39 (t, 1H, *J* = 10.0 Hz, H-4), 2.25-2.21 (m, 2H, H-2a', H-2a), 2.07 (s, 3H, $COCH_3$), 1.86-1.76 (m, 2H, H-2b', H-2b), 1.86-1.22 (m, 10H, OCHC*H*$_2$), 1.33 (d, 3H, *J* = 6.0 Hz, CCH_3), 1.22 (d, 3H, *J* = 6.0 Hz, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.22, 166.11, 133.33, 130.25, 129.99, 128.62, 128.43, 127.67, 99.07, 94.63, 81.83, 77.44, 74.96, 74.26, 72.77, 72.44, 71.75, 67.15, 66.54, 36.18, 33.70, 31.69, 29.92, 25.91, 24.49, 21.53, 18.57, 17.68; HR-MALDI-ToF/MS: *m/z* calcd for $C_{34}H_{44}O_9$ $(M+Na)^+$: 619.2985; found: 619.2988

4.6 REFERENCES

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CHAPTER V

CONCLUSIONS

In this study, we envisioned that a (*S*)-(phenylthiomethyl)benzyl chiral auxiliary at the C-2 position of a glycosyl donor can direct the formation of α-gluco and α-galactosides. It has been shown that the chiral auxiliary of the C-2 functionality performs neighboring group participation to generate a quasi-stable β-anomeric sulfonium ion. Due to steric and electronic effects, the sulfonium ion is only formed as a *trans*-decalin. Displacement of the sulfonium ion by a glycosyl acceptor leads exclusively to the formation of an α-glycoside. NMR experiments (TOCSY, HSQC and HMBC) confirmed the presence of the cyclic β-anomeric sulfonium ion. It has been demonstrated that the chiral auxiliary can be introduced and removed under mild reaction conditions by exploiting the high reactivity of an episulfonium ion. The combination of a new methodology to introduce α-glycosides and traditional neighboring group participation by C-2 ester to give β-glycosides provides a general strategy for the synthesis of a wide variety of oligosaccharides.

We also have introduced new strategy, which can use PhSEt externally as an additive to generate a similar sulfonium ion intermediate, for the 2-amino sugar. It has been shown that glycosylations of 2-azido-2-deoxy-glycosyl donors with various glycosyl acceptors provide excellent α-anomeric selectivities when performed at relatively high reaction temperatures in the presence of thioethers such as PhSEt or thiophene. Mechanistic studies have shown that activation of a trichloroacetimidate donor in the presence of PhSEt result in the formation of the β-anomeric sulfonium ion selectively. Furthermore, computational studies have indicated that the steric factors determine the selective formation of β-anomer. Thus, ensuing displacement of the β-anomeric sulfonium ion by glycosyl acceptors leads to the formation of α-glycosides.

Finally, to explore the possibility of remote participation of the chiral auxiliary, we have synthesized 2-deoxyglycosyl donors having the chiral auxiliary at the C-6 position. Furthermore, it has been found that the chiral auxiliary at C-6 of 2-deoxy glycosyl donors aids the generation of α-linked glycosides. In addition, allyl 2,6-dideoxyglycosides, which are important component in natural products, could easily be activated by $BF_3{\cdot}OEt_2$ and glycosylations with various glycosyl acceptors provides mainly α-glycosides. In order to show the practical application of this method, we have demonstrated armed-disarmed glycosylation strategy for the synthesis of a mimic of the aglycon of compounds such as avermectin B_{1a}.