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SUPERARMED GLYCOSYL DONORS IN CHEMICAL GLYCOSYLATION

By

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A DISSERTATION

Submitted to the Graduate School of the

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DOCTOR OF PHILOSOPHY

in

CHEMISTRY

November 11th 2011

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ABSTRACT

Superarmed glycosyl donors in chemical glycosylation

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Prof. Alexei V. Demchenko, Advisor

Only recently has the tremendous biological significance and therapeutic potential of carbohydrates and conjugates thereof (glycoproteins, glycolipids, proteoglycans, etc.) begun to emerge. As the appreciation for the biological roles of carbohydrates a growing demand for efficient and scalable methods towards the synthesis of these challenging molecules has become even more imperative. This has led to the development of a variety of expeditious strategies for oligosaccharide assembly. Amongst these strategies, the so-called armed-disarmed strategy introduced by Fraser-Reid is of particular attractiveness as it allows for chemoselective oligosaccharide synthesis. Recently, the conformational changes as well as the strategic placement of common protecting groups have led to the discovery of new methods for “superarming” of glycosyl donors.

This doctoral dissertation is dedicated to the exploration of new methods and strategies for efficient oligosaccharide assembly. The main focus of this work is centered on the detailed study of the superarmed glycosyl donors and broadening their application to the chemoselective oligosaccharide assembly. This study was supplemented by the

discovery of new leaving groups and application to the synthesis of biologically important oligosaccharides containing residues of sialic acid.

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pursue my academic interests to the fullest extent, supporting me more than 100% of the way. My two younger brothers gave me all the moral support and love being the best brothers in the world. I would not achieve my goal without invaluable support, care and infinite love from my husband Mr. Chethiya Ranaweera, although I am thousand miles away from him for achieving my academic goals. Finally, I would like to thank all my friends in United States and Sri Lanka for their love and encouragement to achieve my goals.

LIST OF ABBREVIATIONS

Å.....		Angstrom
Ac.....		Acetyl
Ar.....		Aryl
AgOTf.....	Silver trifluoromethanesulfonate	
Bn.....		Benzyl
br.....		Broad
Bz.....		Benzoyl
BF ₃ (OEt) ₂	Boron trifluoride etherate	
Bu ₄ NBr.....	Tetrabutylammonium bromide	
Cu(OTf) ₂	Copper(II) trifluoromethanesulfonate	
Cbz.....		Benzyloxycarbonyl
CDA.....		Cyclohexane 1,2-diacetal
d.....		Doublet
1,2-DCE.....		1,2-Dichloroethane
DCM.....		Methylene chloride
dd.....		Doublet of doublets
DMF.....	<i>N,N</i> -Dimethylformamide	
DMTST.....	Dimethyl(methylthio)sulfonium trifluoromethanesulfonate	
Et.....		Ethyl
Gal.....		Galactose
Glc.....		Glucose

h.....	Hour(s)
HR-EI MS	High Resolution Electron Ionization mass spectrum
HR-FAB MS	High Resolution Fast Atom Bombardment mass spectrum
Hz.....	Hertz
IDCP.....	Iodonium(di- γ -collidine)perchlorate
KOH.....	Potassium hydroxide
LG.....	Leaving group
m	Multiplet
min	Minute(s)
m/z	Mass to charge ratio
Me.....	Methyl
MS.....	Molecular sieves
NIS	<i>N</i> -Iodosuccinimide
NMR	Nuclear magnetic resonance
PFBz.....	Pentafluorobenzoyl
Phth.....	Phthalimido
Pic.....	Picolinyl
Ph	Phenyl
ppm	Parts per million
RRV.....	Relative reactivity value
R_f	Retention factor
rt	Room temperature
SBox.....	<i>S</i> -Benzoxazolyl

STaz.....	S-Thiazolinyl
s.....	Singlet
t.....	Triplet
Tol.....	Tolyl
TBDMS.....	tert-Butyldimethylsilyl
TFA.....	Trifluoroacetic acid
TfOH.....	Trifluoromethanesulfonic (triflic) acid
TMS.....	Trimethylsilyl
TESOTf.....	Triethylsilyl trifluoromethanesulfonate (triflate)
TLC.....	Thin layer chromatography
TMSOTf.....	Trimethylsilyl trifluoromethanesulfonate

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CHAPTER 1

Superarmed and superdisarmed building blocks in expeditious oligosaccharide synthesis

H. D. Premathilake, A. V. Demchenko. Superarmed and superdisarmed building blocks in oligosaccharide synthesis. In "Topics in Current Chemistry, Vol. 301. Reactivity Tuning in Oligosaccharide Assembly." B. Fraser-Reid, J. Cristobal Lopez Eds., Springer-Verlag, Berlin-Heidelberg, **2011**, pp. 189-221

1.1 Background

Complex carbohydrates (polysaccharides or complex glycoconjugates in which oligosaccharides are connected to peptides, proteins, or fatty acids) are involved in a variety of biological processes.¹ Throughout the past two decades, the main scientific effort in the field of glycoscience has remained centered upon those carbohydrates associated with diseases that consistently rank among the leading causes of death worldwide, such as: cardiovascular disease, cancer, septicemia, bacterial, viral, and parasitic infections. The driving force behind this tremendous scientific and industrial effort is the belief that a comprehensive knowledge of the structural, conformational and other general properties of these carbohydrates will help scientists to understand the pathogenesis of the associated diseases. Consequently, this could lead to the development of new and effective strategies for the prevention, diagnosis, treatment of these diseases. Over the years, glycoscientists have mastered techniques necessary for isolating only certain classes of naturally occurring carbohydrates. Therefore, the availability of pure natural isolates cannot satisfy all of the challenges presented by modern glycoscience. As a result, glycoscientists have turned to both chemical and enzymatic synthesis as a means for accessing complex carbohydrates. While enormous progress in the areas of synthetic, biological, and analytical chemistry, have made many classes of organic compounds readily accessible through broadly applicable methods, carbohydrates of even moderate complexity still represent a significant challenge. A few representative examples of such oligosaccharide sequences are shown in Figure 1.1.

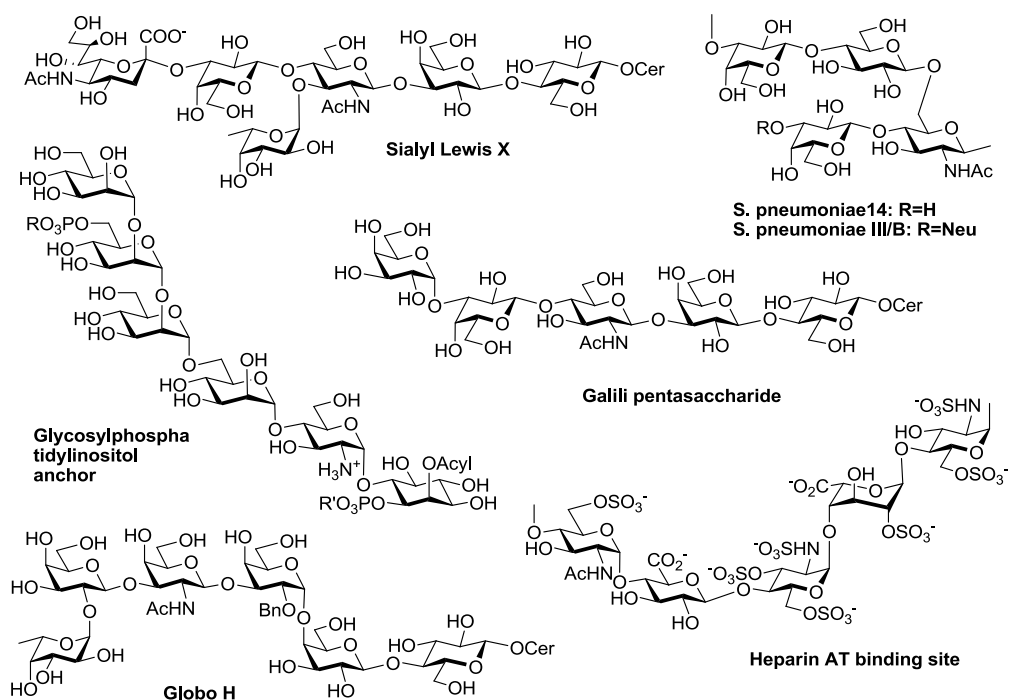
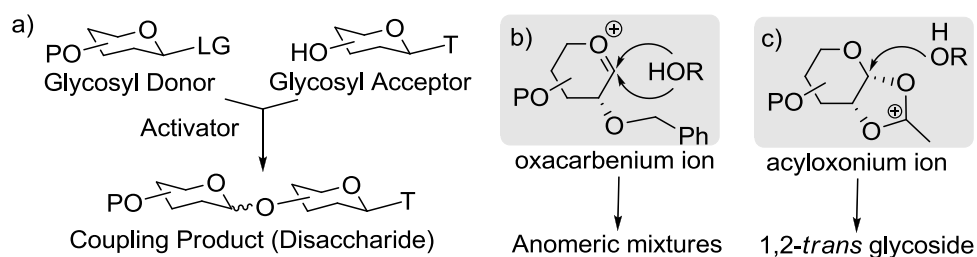


Figure 1.1. Representative examples of natural poly- and oligosaccharide sequences.

1.1.1 Principles of Chemical O-Glycosylation

Poly- or oligosaccharide sequences are constructed by connecting monosaccharide units via O-glycosidic bonds. In nature this linkage is formed by a coupling reaction known as glycosylation, the course and selectivity of which is controlled by glycosyltransferases. In the chemical laboratory, glycosylation typically involves a promoter (or activator)-assisted nucleophilic displacement, wherein a leaving group (LG = halogen, OH, O-alkenyl/imidoyl, S-alkyl/aryl/imidoyl, etc.) on the glycosyl donor is displaced by a hydroxyl moiety of the glycosyl acceptor (Scheme 1.1a).² Remaining functional groups on both the glycosyl donor and acceptor are temporarily masked with protecting groups (P, T), which, along with strategies for their installation and removal (protection-

deprotection), have become essential components of chemical syntheses of oligosaccharide molecules. Although protecting groups were initially applied to reduce unwanted side reactions by masking additional sites of reactivity, they can also affect the glycosylation in a variety of other ways; in other words, they “do more than protect.”³ Since the anomeric center is chiral, particular care has to be taken with regards to the stereoselectivity of glycosylation. Despite the significant progress made in the area of glycoside synthesis,² the necessity of forming either a 1,2-*cis* or a 1,2-*trans*-glycosidic bond with high stereocontrol remains the main reason that chemical O-glycosylation is ranked among the most critical challenges of modern synthetic chemistry.



Scheme 1.1. Outline of chemical glycosylation.

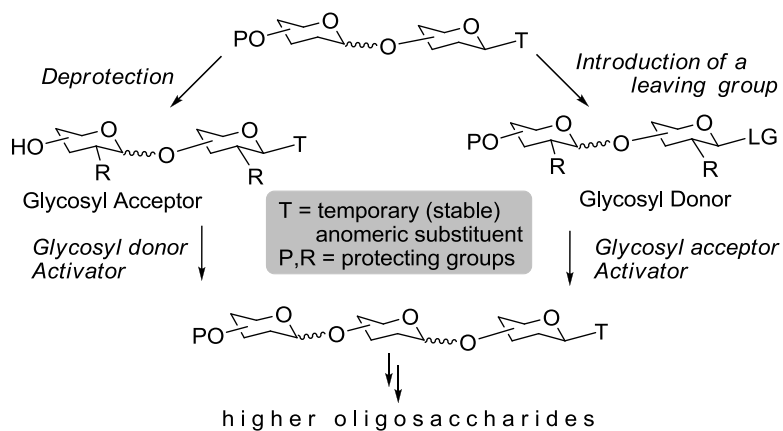
Although mechanistic rationalizations of the glycosylation reaction lack generality and consistency, and although studies dedicated to the reaction mechanism are still scarce, some conventions have already been well established.⁴ For instance, in the case of ether-type non-participating substituents, glycosylation proceeds via a flattened oxocarbenium ion⁵ (Scheme 1.1b), often leading to anomeric mixtures favoring 1,2-*cis* glycosides^{6,7} (for D-gluco/galacto series) due to the influence of the anomeric effect.^{8,9} Thus, variable factors such as temperature, pressure, structure, conformation, solvent, promoter, steric hindrance, protecting or leaving group are exceedingly important in influencing the

stereoselectivity of glycosylation. Amongst these, neighboring group participation¹⁰ is one of the most prominent effects dictating the stereochemical outcome of the glycosylation reaction (protecting groups do more than protect), as it is well established that 1,2-trans glycosides can be obtained from 2-acylated glycosyl donors. This selectivity arises from the acyloxonium intermediate formed as a result of the anchimeric assistance from the neighboring C-2 group (Scheme 1.1c).

1.1.2 Oligosaccharide Synthesis

The development of new leaving groups and efficient glycosylation methods is largely responsible for the progress that has been made in the area of oligosaccharide synthesis. When the arsenal of glycosylation techniques was limited to the Fischer (LG=OH)¹¹ and Koenigs–Knorr (LG = Cl, Br)^{12, 13} approaches (or their variations),^{14, 15} oligosaccharide assembly was limited to inefficient stepwise linear techniques. However, as more stable glycosyl donors, such as fluorides,¹⁶ thioglycosides¹⁷ and O-alkenyl glycosides were developed,¹⁸ the possibility of selective and/or chemoselective activation of one leaving group over another emerged. In linear oligosaccharide synthesis, the disaccharide product formed from the single step glycosylation reaction (see Scheme 1.1) is then converted into either a second-generation glycosyl acceptor or donor; this is accomplished via the liberation a specific hydroxyl group or installation of a suitable leaving group, respectively (Scheme 1.2). These second generation disaccharide building blocks are then allowed to react with an appropriate monosaccharide glycosyl donor or acceptor, resulting in the formation of a trisaccharide. The protecting/leaving group

manipulation and glycosylation sequence can be then reiterated until an oligosaccharide of the desired chain length is obtained.



Scheme 1.2. Conventional (linear) oligosaccharide synthesis.

It soon became apparent, however, that both the linear and convergent¹⁹⁻²¹ approaches were too inefficient, due to the extensive protecting or leaving group manipulations between each glycosylation step. Consequently, the past two decades have witnessed a dramatic improvement of the methods and strategies used for oligosaccharide synthesis, as scientists have persistently aimed to answer the key question: can oligosaccharides be obtained more expeditiously through the elimination of these unnecessary synthetic steps? The first attempts to address this challenge emerged in the mid-1980s and 1990s, which resulted in the development of a number of revolutionary approaches. Many of these innovative strategies involve selective activations, wherein different leaving groups are sequentially activated minimizing the need for protecting group manipulations between glycosylation steps; selective activation,^{19, 22} two-step activation^{19, 23-25} and the active-latent concept²⁶⁻²⁹ are just a few classifications of such approaches. One specific example, the orthogonal approach, makes use of two chemically distinct glycosyl donors,

wherein one of the leaving groups is selectively activated while the other remains intact, and *vice versa*, offering significant flexibility.³⁰ This activation sequence can then be reiterated to give straightforward access to larger oligosaccharides.

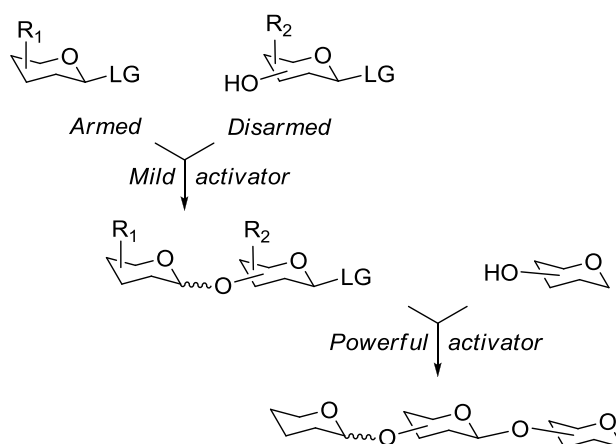
Another direction in expeditious oligosaccharide synthesis emerged with the discovery of the so-called armed-disarmed approach by Fraser-Reid and co-workers.³¹ This strategy, based on the chemoselectivity principle, utilizes only one class of leaving group, thus, glycosyl donor reactivity is modulated entirely through the choice of protecting group (protecting groups do more than protect). This effect allows for direct chemoselective coupling between an activated (armed) glycosyl donor and a deactivated (disarmed) glycosyl acceptor, and the resulting disaccharide can then be used directly in subsequent glycosidation.

With the main focus on the armed-disarmed concept, this chapter discusses the recent progress that has been made in the area of chemoselective oligosaccharide synthesis. The classic *armed-disarmed approach*, developed by Fraser-Reid, has created a solid basis for extensive studies and applications, and all strategies discussed in this chapter are directly related to (or derived from) this elegant concept. As recent improvements have significantly expanded the scope of the original chemoselective concept, a series of building blocks, the reactivity of which extends beyond the traditional armed-disarmed definition, have additionally been introduced. These “superarmed” and “superdisarmed” building blocks have helped to expand the scope of the original methodology so that it can now be applied to the synthesis of a much broader range of complex oligosaccharide sequences, in comparison to that of the classic armed-disarmed concept. These excellent

innovations have already been applied to the synthesis of various oligosaccharides and glycoconjugates, and some representative examples are presented herein.

1.2. Armed-disarmed strategy for oligosaccharide synthesis

The chemoselective approach and its variations discussed in this section make use of only one class of leaving group for both reaction components, which are either activated (armed donor) or deactivated (disarmed acceptor) by the influence of the protecting groups (R_1 , R_2 , Scheme 1.3). Usually, the protecting groups in both reaction components have to be taken into consideration to allow for direct chemoselective activation of the armed glycosyl donor over the disarmed glycosyl acceptor. As both components bear the same type of LG, the key factor for an armed–disarmed activation to take place is finding suitable reaction conditions that can efficiently differentiate between the activated and deactivated building blocks. In most cases, the differentiation is achieved by the choice of promoter, temperature, or solvent.³²



Scheme 1.3. Armed-disarmed strategy outline

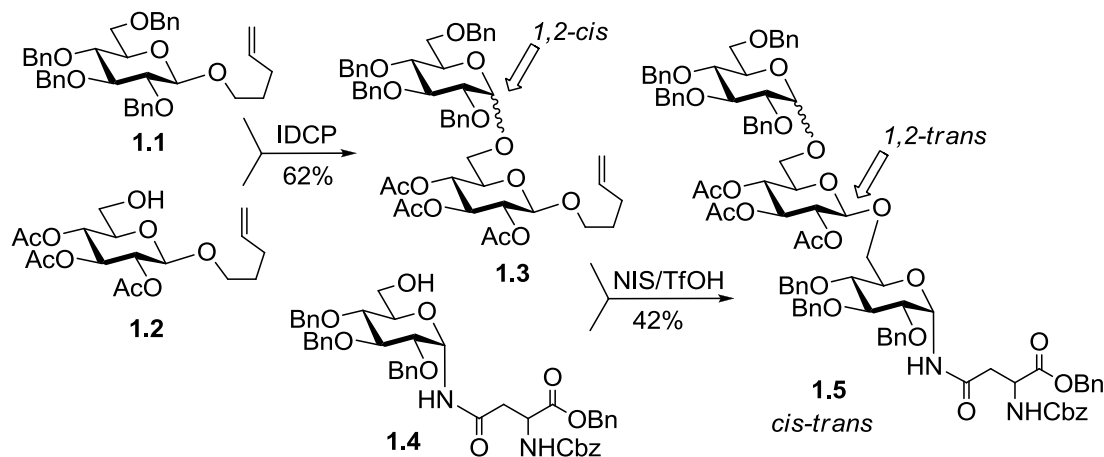
As aforementioned, the majority of strategies discussed in this subsection allow for efficient oligosaccharide assembly without the necessity to perform additional synthetic steps between the glycosylation steps. Accordingly, the disarmed leaving group of the resulting disaccharide can be activated directly, although, a more powerful promoter or elevated temperatures are typically required.

1.2.1. Classic concept: electron-withdrawing substituents and the synthesis of cis-trans-patterned oligosaccharides

Although the effect of protecting groups on reactivity had been noted,²⁰ it was Fraser-Reid who described, in 1988, a new manner by which the differential properties of protecting groups could be exploited, termed the “armed-disarmed strategy.”³³ It was noticed that ester-type protecting groups (OAc, OBz, etc.) strongly reduced, “disarmed”, the reactivity of the n-pentenyl glycosyl donor, in comparison to that of its alkylated (benzylated, OBn) “armed” counterpart.

One justification for such an observation is that the increased electron-withdrawing ability of ester protecting groups decreases the electron density (nucleophilicity) of the anomeric heteroatom, which translates into a diminished ability to interact with the electrophilic promoter. Resultantly, the armed leaving group reacts faster, with the disarmed leaving group reacting either much more slowly, or not at all. In order to achieve an efficient differentiation in reactivity, mild promoters have an advantage, as they are able to offer a more controlled activation. For example, iodonium(di- γ -collidine) perchlorate (IDCP) was found to be a suitable mild electrophilic activator for O-pentenyl glycosyl donor **1.1**, and corresponding disaccharide **1.3** was isolated in 62% yield

(Scheme 1.4).³³ As the anomeric configuration of the product is influenced by the protective group at O-2, a 1,2-*cis*-linked disaccharide is preferentially obtained in the first step, due to the use of the non-participating, ether-type (O-benzyl) arming substituent.



Scheme 1.4. Armed (**1.1**) and disarmed (**1.2**) O-pentenyl glycosides:

synthesis of *cis-trans*-patterned trisaccharide **1.5**.

Furthermore, the leaving group of disarmed building blocks (such as **1.2** or **1.3**) can also be activated, but this would typically require more time, higher temperature, and/or stronger promoters. For instance, the direct glycosidation of disaccharide **3** was readily achieved in the presence of a strong promoter system, NIS/TfOH. This glycosylation step was performed with glycosyl acceptor **1.4**, resulting in the stereoselective formation of a 1,2-*trans* glycosidic linkage. As aforementioned, glycosidation of 2-acetylated glycosyl donors typically proceeds via the formation of the bicyclic acyloxonium intermediate, which coordinates the 1,2-*cis* face of the ring. As a result of this two-step activation sequence, a *cis-trans*-patterned trisaccharide (**1.5**) is obtained, wherein the monosaccharide units are sequentially connected via a 1,2-*cis* and 1,2-*trans* linkage (Scheme 1.4).

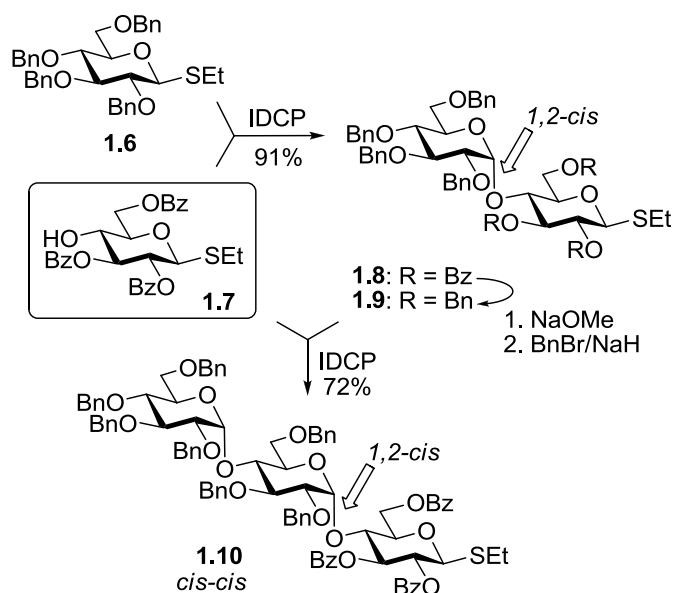
Although this discovery was made using *n*-pentenyl glycosides, this electronic effect ultimately proved to be of a general nature, and as such can be applied to nearly any class of glycosyl donor. This concept was further explored for the chemoselective glycosidations of thioglycosides,³⁴ selenoglycosides,³⁵ fluorides,³⁶ phosphoramidates,³⁷ substituted thioformimidates,³⁸ glycols,³⁹ and thioimidates.^{40, 41} The usefulness of this approach was realized in application toward expeditious oligosaccharide synthesis, as it circumvents the need for protecting group manipulations at the anomeric center.⁴²

1.2.2. Strategic updates to the original armed-disarmed method

Synthesis of the cis-cis-patterned oligosaccharides using reprotection of the intermediate disaccharide. To address the major limitation that the armed-disarmed strategy could only be applied to the synthesis of oligosaccharides having a *cis-trans* glycosylation pattern, van Boom and co-workers designed a method whereby the synthesis of *cis-cis*-linked derivatives could also be achieved.³⁴ In the first synthetic step the classic armed-disarmed activation was performed, however, the resulting disaccharide was then reprotected (OBz → OBn) prior to subsequent glycosidation. A representative example of this strategy is shown in Scheme 1.5.

Armed thioglycoside donor **1.6** was selectively activated over disarmed glycosyl acceptor **1.7** in the presence of IDCP to provide the disarmed 1,2-*cis* linked disaccharide (**1.8**) in 91% yield. The latter was then subjected to a two-step debenzoylation-benzoylation sequence, whereupon the resulting disaccharide donor (**1.9**) was glycosidated with disarmed acceptor **1.7**, to afford the *cis-cis*-linked trisaccharide (**1.10**) in 72% yield. The

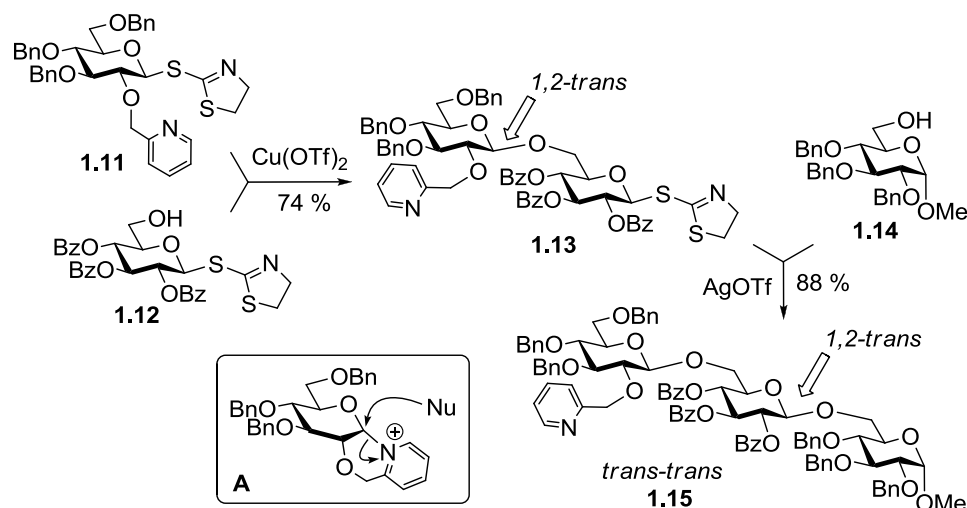
conversion of the second generation glycosyl donor **1.8** into the armed state **1.9**, allowed for the second coupling step to also be performed with the mild promoter IDCP.



Scheme 1.5. Synthesis of *cis-cis*-patterned trisaccharide **1.10**, via the modified armed–disarmed approach.³⁴

Synthesis of trans-trans patterned oligosaccharides using picolinyl arming participating group. Demchenko et al.⁴¹ demonstrated that with the use of a *O*-picolinyl substituent as an “arming participating group” at C-2 of the glycosyl donor, a 1,2-*trans* glycosidic linkage can be chemo- and stereo-selectively introduced in the first glycosylation step. For example, glycosidation of armed glycosyl donor **1.11** with disarmed acceptor **1.12** in the presence of Cu(OTf)₂, produced 1,2-*trans*-linked disaccharide **1.13** in 74% yield (Scheme 1.6). Due to the opposite stereochemical outcome of this glycosylation, in comparison to the 1,2-*cis* linkage formed in the first step of the classic armed–disarmed approach, this approach was called the *inverse armed–disarmed* strategy. Subsequent glycosidation of disarmed disaccharide **1.13** with the standard glycosyl acceptor **1.14**

could then be achieved in the presence of a more powerful activator AgOTf, and the resulting *trans-trans*-linked trisaccharide **1.15** was obtained in 88% yield.⁴¹ NMR experiments were utilized, showing the presence of the anticipated cyclic compound **A** as the key reaction intermediate (Scheme 1.6).



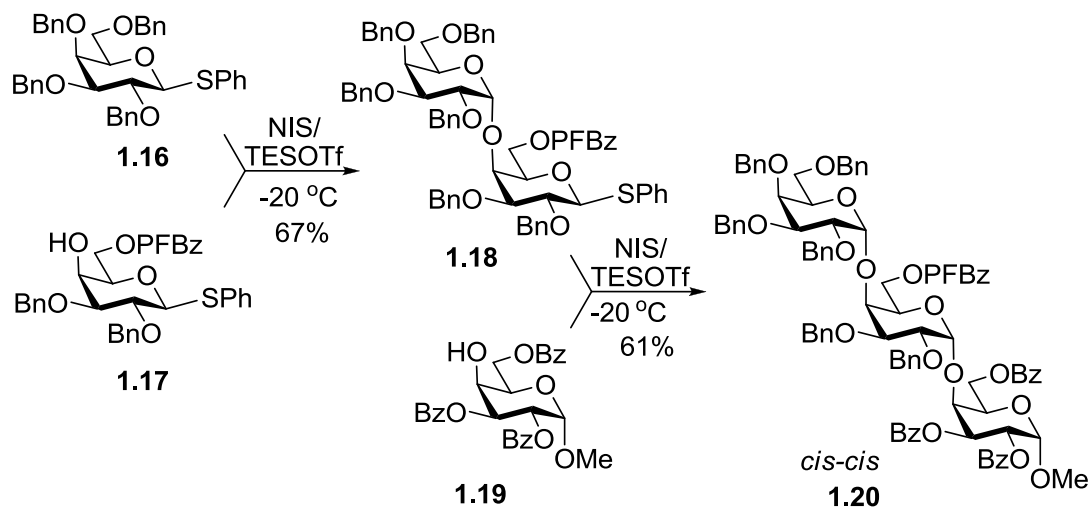
Scheme 1.6. Arming participating picolinyl group mediated synthesis of *trans-trans*-patterned trisaccharide **1.15**.

1.2.3. Conceptual updates to the original armed-disarmed method

Deactivation by a remote protecting group capable of powerful electron-withdrawal.

Madsen *et al.*⁴³ clearly demonstrated that a single electron-withdrawing moiety at the remote C-6 position will sufficiently disarm the leaving group of a glycosyl acceptor, in comparison to the per-alkylated glycosyl donor. This effect was especially pronounced with the use of a pentafluorobenzoyl (PFBz) ester, capable of a very powerful electron-withdrawal.⁴⁴ For example, armed benzylated thioglycoside **1.16** could be chemoselectively activated over the disarmed 6-*O*-pentafluorobenzoyl acceptor **1.17** in the presence of NIS/TESOTf to provide disaccharide **1.18** (Scheme 1.7). The latter

could then be glycosidated with glycosyl acceptor **1.19** in the presence of NIS/TESOTf to give trisaccharide **1.20** in 61% yield. It is important to highlight that this approach allows for the *cis-cis* oligosaccharide sequence to be obtained directly, without deprotection/reprotection of the intermediate disaccharide, as previously discussed for the synthesis reported by van Boom (see Scheme 1.5).

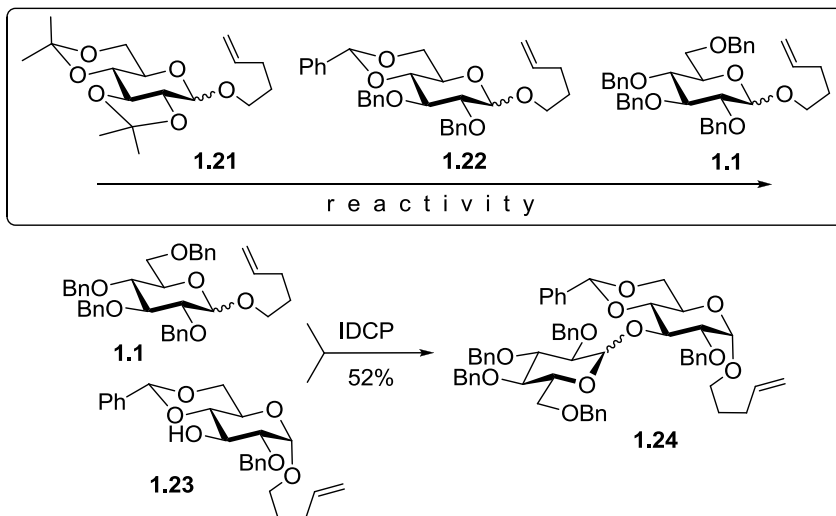


Scheme 1.7. Disarming the glycosyl acceptor with the remote 6-*O*-pentafluorobenzoyl moiety: direct synthesis of *cis-cis*-patterned trisaccharide **1.20**.⁴⁴

Crich et al.⁴⁵ also investigated the influence of the electron-withdrawal at the C-6 position on the reactivity of glycosyl triflates and stereoselectivity of their glycosidations. In exploring a series of mono-, di-, and tri-fluorinated 6-deoxy rhamnosides, a clear correlation between the strength of electron withdrawal at C-6 and stability of the anomeric triflates was established. While common rhamnosyl triflates undergo rapid decomposition at temperatures above -60 °C, it was shown that their 6,6,6-trifluorinated counterparts remained stable at temperatures up to +10 °C. Many related studies have

further demonstrated that the arming/disarming effect of the protecting groups may also be highly dependent upon their location (see Schemes 1.11 and 1.12 below), geometry, and core donor structure.^{46, 47}

Deactivation with cyclic ketals/acetals: torsional and electronic effects. Fraser-Reid and co-workers discovered that the deactivation of glycosyl donors could also be achieved through the strategic placement of cyclic acetal/ketal substituents that would lock the pyranose ring in the ⁴C₁ chair conformation. This type of deactivating effect was attributed to the increased rigidity of the fused ring system, prohibiting the oxacarbenium ion intermediate from achieving the requisite planar geometry about the (C-2)-(C-1)-(O-5)-(C-5) atoms.⁴⁸ As depicted in Scheme 1.8, in a series of O-pentenyl glycosides, reactivity was noted to increase from the tricyclic 2,3:4,6-diacetone ketal **1.21** to the bicyclic 4,6-benzylidene acetal **1.22** with the traditional armed O-pentenyl glycoside (**1.1**) being the most reactive. This relative reactivity trend was proven by direct chemoselective activation of armed glycosyl donor **1.1** over benzylidene-protected glycosyl acceptor **1.23**. As in case of the traditional armed-disarmed approach, IDCP was found to be a suitable promoter that allowed for efficient differentiation of the reactivity levels between the armed and torsionally disarmed building blocks (**1.1** and **1.23**, respectively). As a result, disaccharide **1.24** was isolated in 52% yield, with no observed by-products resulting from the self-condensation of glycosyl acceptor **1.23**. These results suggested that the disarming could be achieved by acetal/ketal protecting groups exclusively.

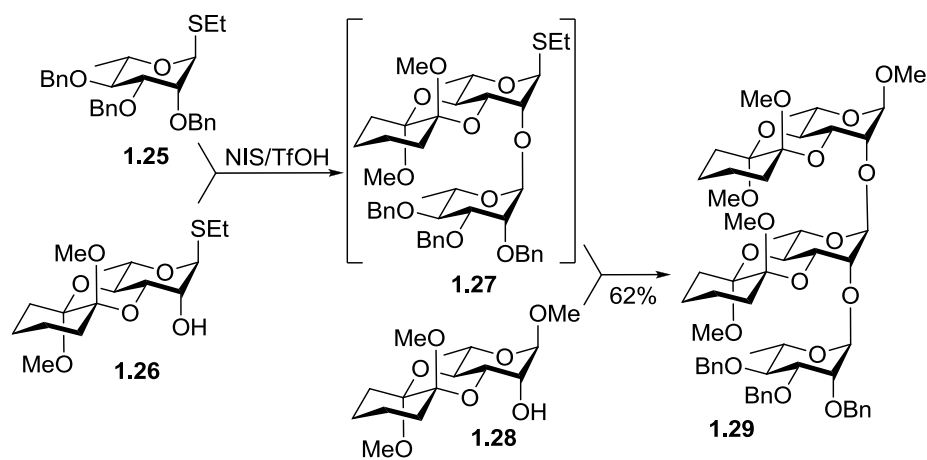


Scheme 1.8. The disarming of building blocks can be achieved with a benzylidene acetal or isopropylidene ketal.⁴⁸

This concept was expanded upon by Ley and co-workers, who clearly demonstrated that similar deactivation could be effectively achieved with the use of a variety of cyclic 1,2-diacetal/diketal systems.⁴⁹ And the example below highlights one such application, in which a two-step sequential activation was accomplished using a one-pot synthetic strategy. The one-pot approach allows for two (or more) sequential glycosylation reactions to be performed in a single flask (pot) without isolation and purification of the intermediate.⁵⁰ Thus, armed glycosyl donor **1.25**, of the L-rhamno series, was chemoselectively activated over torsionally disarmed rhamnosyl acceptor **1.26** in the presence of NIS/TfOH. The resulting disaccharide (**27**, not isolated) was then reacted directly with rhamnosyl acceptor **1.28**, and the final trisaccharide **1.29** was isolated in 62% yield over the two-step activation sequence. Clearly, one-pot strategies offer the fastest pathway to oligosaccharides, although to ensure successful isolation of the final

product, all steps need to proceed with particularly high diastereoselectivity and yield.⁵⁰

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Scheme 1.9. One-pot synthesis of trisaccharide **1.29** via torsional deactivation with cyclohexane 1,2-diacetal (CDA).

It should be noted, that the ester and acetal/ketal groups disarm building blocks following different considerations and mechanisms. Whereas ester disarming effect is purely electronic, benzylidene/isopropylidene groups were initially assumed to disarm exclusively through torsional strain. In further mechanistic probing, Bols and co-workers proposed that the disarming effect of the 4,6-acetal may also be due to the orientation of the electron-withdrawing C-6 substituent.⁵² From a series of model experiments, it was found that a basic torsional disarming effect does exist; however, the data suggested that the substituent configuration (stereoelectronic effect) *also* plays a significant role in the overall degree of disarming. For example, the reactivity of torsionally disarmed compound **1.32** (with an axially oriented 6-methoxy substituent) falls between that of per-methylated armed building block **1.33** and compounds **1.30/1.31** (in which the equatorially oriented 6-O-substituents are capable of more a geometrically directed

electron-withdrawal, Figure 1.2). Based on relative rates of hydrolysis (Figure 1.2), it was concluded that conformational restriction and stereoelectronics (charge-dipole interactions) were almost equally responsible for the observed disarming effect.

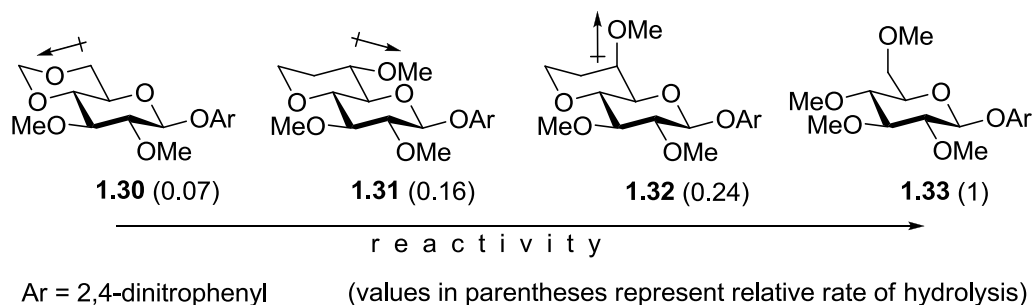
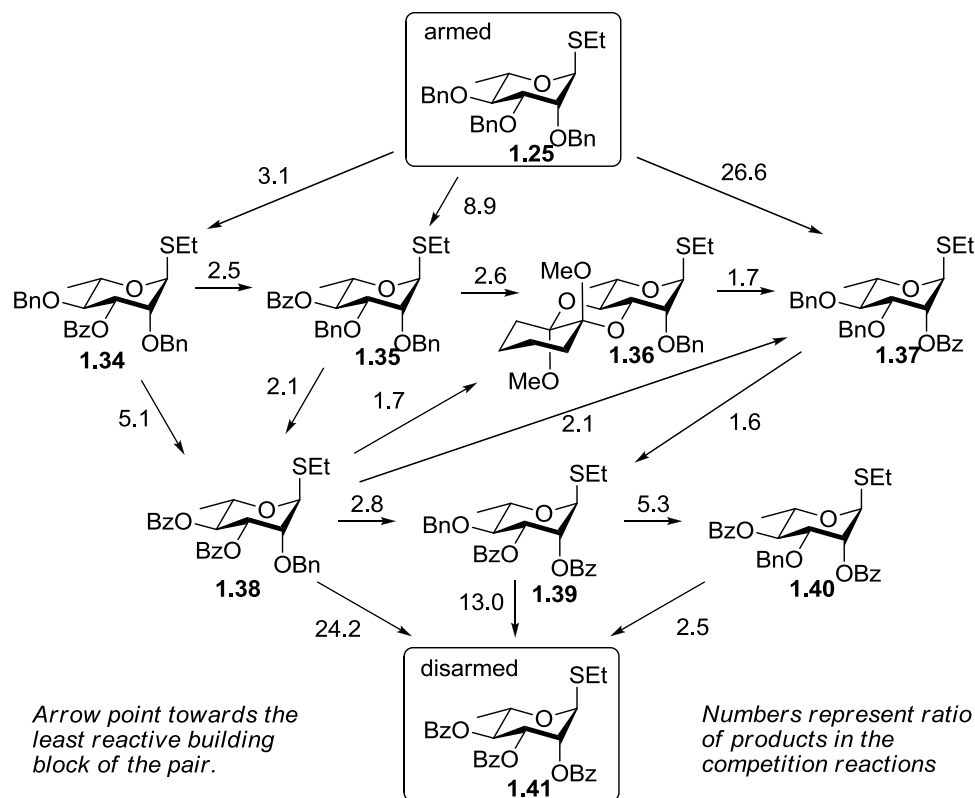


Figure 1.2. The disarming effects of the cyclic ketal/acetal are both conformational and electronic.

1.2.4. Going beyond the simple armed and disarmed building block combination

Many different reactivity levels revealed. Further progress in the area of chemoselective oligosaccharide synthesis emerged with the development of a programmable oligosaccharide strategy, which stemmed from the studies pioneered in Fraser-Reid's, van Boom's, Ley's, and Wong's groups. Subsequently, attempts to classify, and even predict, the outcome of a glycosylation reaction (or a sequence) led to the further development of approaches that attempted to quantify the reactivity of building blocks.^{46-48, 53, 54} For example, Ley et al. developed a new approach wherein building block reactivity could be "tuned."⁴⁶ In a series of competitive experiments, wherein two glycosyl donors were competing for one standard glycosyl acceptor, a series of relative reactivity ratios were established. Additionally, these ratios were found to correspond to various protecting group patterns. For instance, an important relationship between the

position of benzoyl groups and their effect on reactivity surfaced from these studies (Scheme 1.10).



Scheme 1.10. The reactivity of a series of partially benzoylated rhamnosides falls between the traditional armed (**1.25**) and disarmed (**1.41**) building blocks.

Thus, the greatest disarming effect was seen from the 2-benzoyl substituent in compound **1.37**, followed by the 4-benzoyl and 3-benzoyl substituents (in compounds **1.34** and **1.35**, respectively). In addition, cyclic ketal **1.36** was found closer in reactivity to the mono-benzoylated rather than the di-benzoylated series of compounds. Not surprisingly, reactivity levels recorded for the mono-benzoylated (**1.34-1.35**, **1.37**), di-benzoylated (**1.38-1.40**) and torsionally disarmed (**1.36**) glycosyl donors, fell in between the

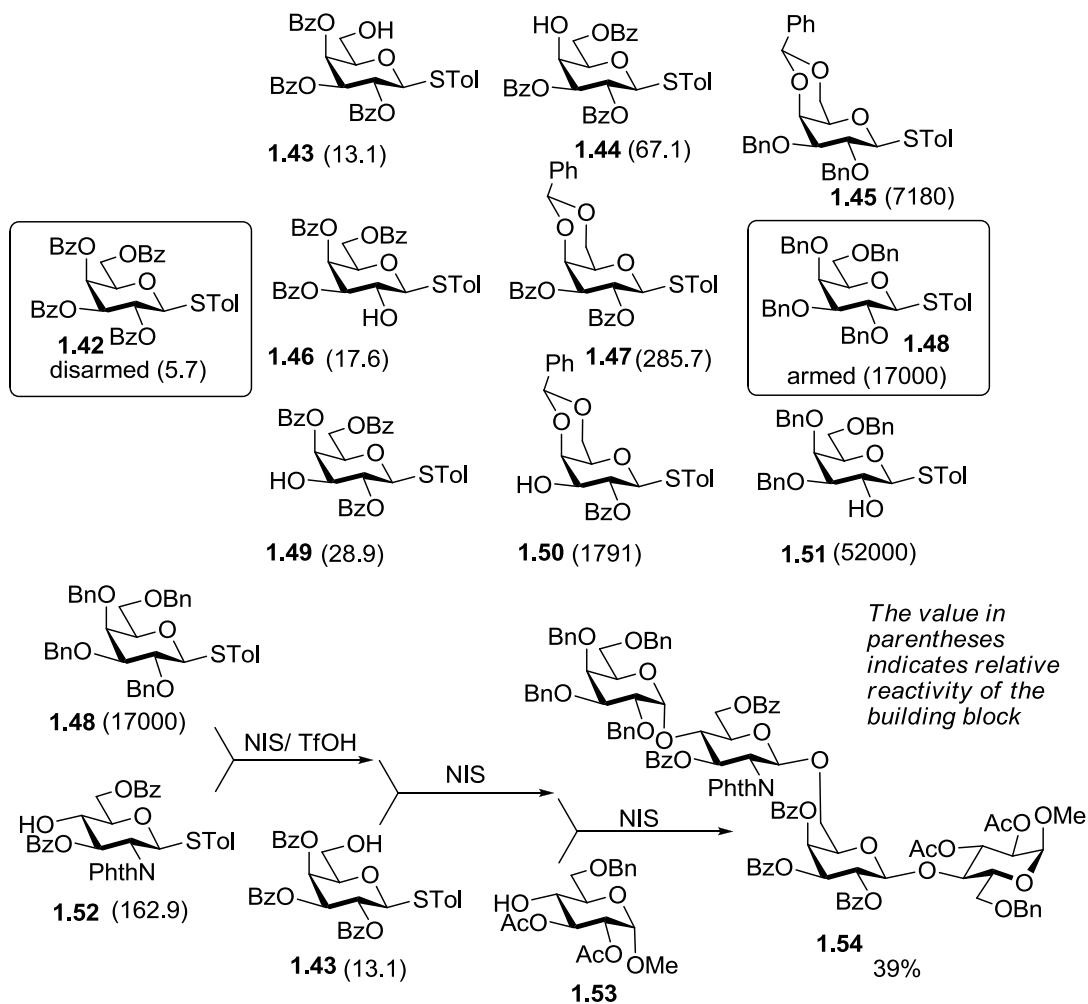
traditional per-benzylated armed rhamnoside **1.25** and its disarmed per-benzoylated counterpart **1.41**.

Wong *et. al.* devised a mathematical approach, assigning relative reactivity values (RRVs) to a wide library of building blocks.⁴⁷ The determination of RRVs was made in standardized reaction conditions, tolyl thioglycoside donors in the presence of an NIS/TfOH promoter system. The cumulative reactivity data was then compiled into a predictive computer program called Optimer.⁴⁷ Various intermediate reactivity levels were revealed during these studies, with nearly all compounds clearly situated between the armed (**1.42**) and disarmed (**1.48**) building blocks (Scheme 1.11). Similar to Ley's findings, the acetal-protected building blocks were also positioned between the armed and disarmed building blocks, being closer in reactivity to the former. For example, 4,6-benzylidene-2,3-dibenzoyl derivative **1.47** was approximately fifty times more reactive than its per-benzoylated disarmed counterpart **1.42** (Scheme 1.11).

Following these studies, a well-rounded technology for one-pot oligosaccharide synthesis based on RRVs emerged. A representative example is depicted in Scheme 1.11, wherein armed glycosyl donor **1.48** was chemoselectively activated over glycosyl acceptor **1.52** in the presence of NIS/TfOH. The resulting disaccharide intermediate was then reacted with added disarmed glycosyl acceptor **1.43**, to form a trisaccharide intermediate that was then glycosidated with added glycosyl acceptor **1.53** to provide tetrasaccharide **1.54** in 39% overall yield.⁴⁷ The reactivity difference between similarly protected sugars of different series has also to be taken into consideration. For example, the reactivity ratio between per-benzylated tolyl thioglycosides of the 6-deoxy-L-galacto, D-galacto, and D-gluco series was found to be 27.1/6.4/1 respectively.⁴⁷ Ley's studies also showed a

similar correlation between the reactivity of building blocks of different series.^{49, 55}

Accumulation of comparison data for reactivity of building blocks of 2-amino-2-deoxysugars and their neutral counterparts has also began to emerge.^{54, 56-60}



Scheme 1.11. Relative reactivity levels of differently protected

galactosides. Synthesis of tetrasaccharide **1.54** via the programmable one-

pot strategy.⁴⁷

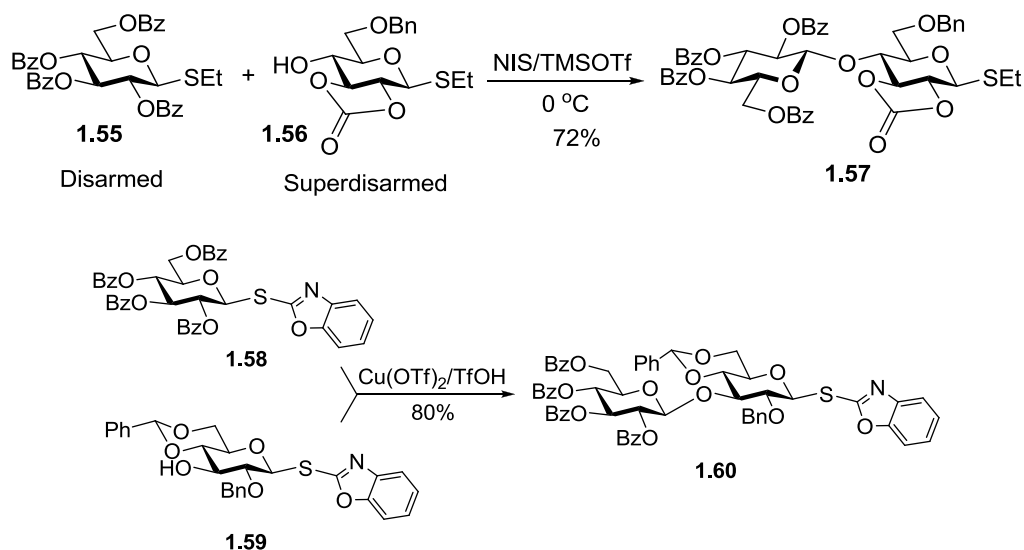
1.3. Superdisarmed building blocks

Although most reactivity levels in Fraser-Reid's, Ley's and Wong's studies fall between the traditional armed and disarmed building blocks, Wong's study revealed a number of building blocks that were extended beyond this boundary. For example, 2-hydroxyl galactoside **1.51** was found to be three times more reactive than the traditional armed galactoside **1.48** (Scheme 1.11). Indirectly, this discovery opened up a new avenue for studying building blocks that are either more reactive than armed ones (superarmed) or less reactive than disarmed ones (superdisarmed); the studies arising from these two directions are surveyed below. In this subchapter, those building blocks possessing a lower reactivity than their conventional per-acylated (per-benzoylated) disarmed counterparts will be discussed.

1.3.1. Superdisarming by torsional effect.

As aforementioned, Fraser-Reid,⁴⁸ Ley,⁶¹ and Bols⁵² found that anomeric deactivation can be achieved by the combination of the torsional and electronic effects of cyclic acetal/ketal protecting groups. The combination of two separate effects could lead one to believe that such systems would be less reactive than the pure-electronically disarmed, acylated building blocks. However, in the majority of cases investigated and surveyed in the previous subchapter, the acetal/ketal-protected derivatives were found to be of intermediate reactivity, falling between the traditional armed and disarmed building blocks (see Schemes 1.10 and 1.11). It was not until more recent studies by Boons,⁶² that it became apparent that thioglycosides protected with the cyclic 2,3-carbonate group

could be even less reactive (superdisarmed) than traditional disarmed acylated derivatives. The following example clearly illustrates this finding. Thus, disarmed perbenzoylated thioglycoside donor **1.55** was chemoselectively activated over superdisarmed glycosyl acceptor **1.56** in the presence of NIS/TMSOTf (Scheme 1.12).



Scheme 1.12. Chemoselective activation of disarmed donors **1.55** or **1.58** over superdisarmed acceptors **1.56** or **1.59**, respectively.

Along similar lines, Demchenko *et al.* performed the direct chemoselective activation of the electronically disarmed SBox glycoside **1.58** over torsionally/electronically disarmed (superdisarmed) glycosyl acceptor **1.59**. This direct chemoselective coupling resulted in the formation of disaccharide **1.60**, proving that even traditional benzylidene systems can superdisarm building blocks of the SBox series. It appears that there is certain inconsistency between this result and the comprehensive programmable approach which showed benzylidene derivatives to be more reactive than their disarmed counterparts. Although a direct investigation of these two findings is not yet available, studies reported

by Bols⁶³ offer the explanation that the disparity could be simply explained by the benzylidene orientation; axial – galactose (Wong *et al.*) vs. equatorial – glucose (Demchenko *et al.*). In order to access the electronic effects of various ring substituents, Bols *et al.* designed the following model study which showed equatorial substituents to be significantly more electron withdrawing (destabilizing, disarming) than their axial counterparts (Figure 1.3). The values shown are in pH units, and reflect the amount by which the pKa of the substituted amine decreases with respect to piperidine.

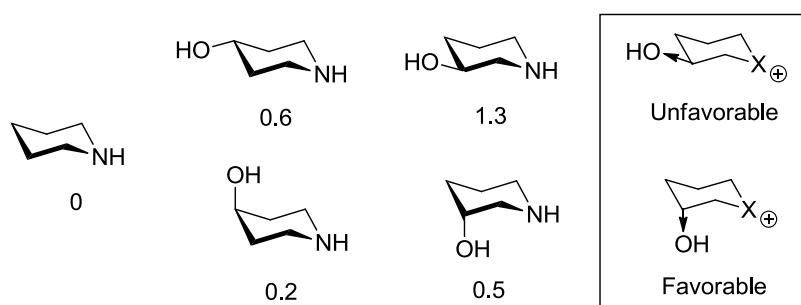


Figure 1.3. Effect of axial and equatorial electron-withdrawing substituents on basicity of piperidines.

It is believed that this result can help to visualize different relative reactivity found amongst 4,6-benzylidene building blocks of different series (gluco vs. galacto in this case). However, a more systematic study of this phenomenon, and perhaps a series of side-by-side chemoselective coupling experiments, would be needed to draw a more direct conclusion.

1.3.2. Superdisarming by electronic effects.

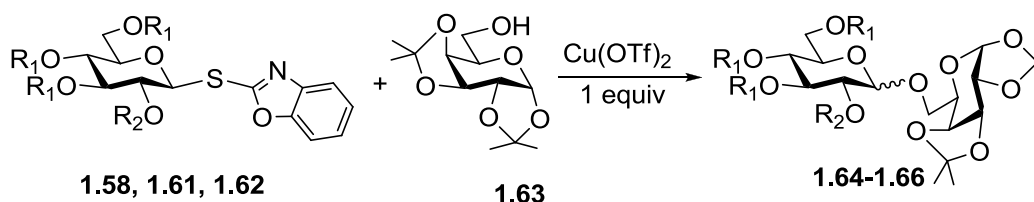
Demchenko *et al.* also reported that a mixed protecting group pattern can unexpectedly and profoundly affect the glycosyl donor reactivity.⁴⁰ Upon investigating S-benzoxazolyl (SBox) glycosides containing an “arming” benzyl group at C-2 and “disarming” acyl groups at the remaining hydroxyls, it was expected that reactivity would fall somewhere between that of the armed (per-benzylated) and the disarmed (per-benzoylated) glycosyl donors; similar to the results found in Ley’s studies for building blocks of the L-rhamnose series, as discussed above. However, the results acquired with the SBox glycosides of the D-gluco series revealed that these “mixed-patterned” glycosyl donors were the least reactive amongst the building blocks investigated (Table 1.1).⁴⁰

Thus, the reaction of armed SBox donor **1.61** with glycosyl acceptor **1.63** in the presence of copper(II) trifluoromethanesulfonate proceeded smoothly, and product **1.64** was isolated in a good yield of 89% (Entry 1, Table 1.1). Along similar lines, it was discovered that disarmed (per-benzoylated) SBox glycoside **1.58** also reacted readily, although this glycosylation was marginally slower in comparison to that of the armed per-benzylated building block **1.61**, never fully going to completion, resulting in a slightly lower, 70% yield of the disaccharide **1.65**. Interestingly, when essentially the same reaction conditions were applied to the glycosidation of 2-*O*-benzyl-tri-3,4,6-*O*-benzoyl protected SBox glucoside **1.62**, no formation of the expected disaccharide **1.66** was detected.

As Lemieux’s halide stability theory,⁶⁴⁻⁶⁶ Fraser-Reid’s armed-disarmed concept rationale,^{31, 33} Ley’s tuning reactivity studies,⁴⁶ and Wong’s programmable oligosaccharide synthesis⁴⁷ all predicted 2-*O*-benzylated glycosyl donor **1.62** to be more

reactive than its per-benzoylated counterpart **1.58**, these unanticipated results necessitated further studies.

Table 1.1. Comparative activation of differently protected SBox glycosides **1.58**, **1.61** and **1.62**.



Entry	Donor	Product	Yield	α/β ratio
1	<p style="text-align: center;">1.61</p>	1.64	89%	5.4/1
2	<p style="text-align: center;">1.58</p>	1.65	70%	β only
3	<p style="text-align: center;">1.62</p>	1.66	No reaction	--

This finding implies that a combination of electronic effects, beyond the recognized inductive effects of the C-2 protecting group, may exist. The observed reactivity pattern was rationalized by the occurrence of the so-called “O-2/O-5 Cooperative Effect.”⁴⁰ Thus, in addition to the “arming/disarming” nature of the protecting group at O-2, stabilization of the glycosyl cation intermediate must also be taken into consideration.

First, this stabilization can be achieved from the lone electron pair on the neighboring endocyclic ring oxygen (O-5) like in the armed glycosyl donor **A**, shown in Figure 1.4. However, if electron withdrawing protecting groups are placed near the O-5 ring oxygen (C-4 and C-6, like in the disarmed donors **B** or **C**), the electron density on O-5 will be decreased, effectively suppressing oxacarbenium ion formation. In this case, the ability of the system to stabilize via other plausible internal modes may become increasingly important.

A second type of stabilization may arise based on the availability of the lone electron pair on an acyl type protecting group at O-2, which is capable of providing stabilization via the formation of an acyloxonium ion intermediate, like in disarmed glycosyl donor **B**. Crich et al.⁶⁷ emphasized that the anchimeric assistance was particular to the 1,2-trans orientation of the 2-O-acyl and 1-SBox leaving group, as stabilization presumably takes place via the concerted displacement of the leaving group. However, if no source of secondary stabilization is available, as in case of 2-O-benzyl substituent in **C**, this combination will give rise to the overall “superdisarming” protecting group pattern.

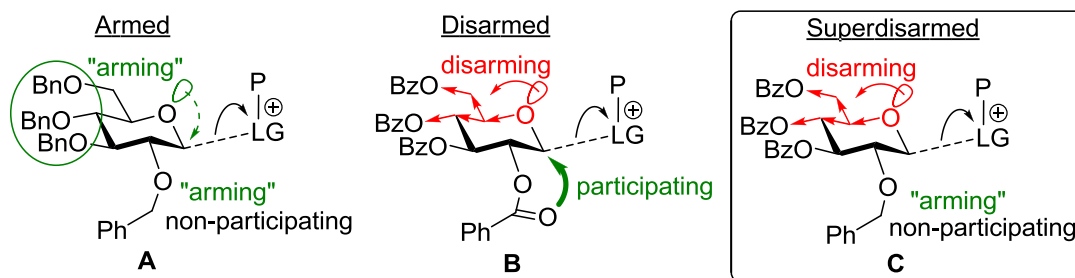


Figure 1.4. O-2/O-5 Cooperative effect in glycosidation of the superdisarmed building blocks

1.4. Superarmed building blocks

In contrast to superdisarmed building blocks, possessing reactivity even lower than that of the per-acylated disarmed building blocks, other super reactive glycosyl donors have also been discovered. The term superarmed was first coined by Bols for describing the reactivity of conformationally armed building blocks. Herein however, we apply the term superarmed to all building blocks that are more reactive than conventional per-alkylated armed building blocks.

1.4.1. Superarming by conformational effects.

As it was previously noted, the substituent orientation can have a strong effect on the reactivity of a molecule. A model study of the relative pK_a values for protonated heterocyclic amines showed that equatorial substituents are significantly more deactivating than their axial counterparts (compare **1.67** and **1.68** on Figure 1.5).⁶³ Further revealed by these findings, was that a perturbation of the equilibrium between ring conformations may also occur upon protonation of the heterocyclic amine.⁶⁸ This was found to result from the desire for substituents to reside axially, as they have a greater ability to provide charge stabilization through charge-dipole interactions. For example, cyclic amine derivative **1.68** was found to exist predominantly in the conformation wherein the electron-withdrawing hydroxyl substituents are axial. This study further suggests that positively charged oxacarbenium ion intermediates may also spontaneously undergo conformational changes in an attempt to maximize the number of axial substituents. If so, this conformational change would be made easier if the starting

material already had a number of axial substituents;⁶⁹ for example, galactose has been long known to be more reactive than glucose (compare hydrolysis rates for compounds **1.69** and **1.70**, Figure 1.5). Furthermore, when conformationally restricted 3,6-anhydroglucoside **1.71**, having all-axial hydroxyl groups, was investigated, it was shown to hydrolyze much faster than its all-equatorial counterpart **1.69**.⁷⁰

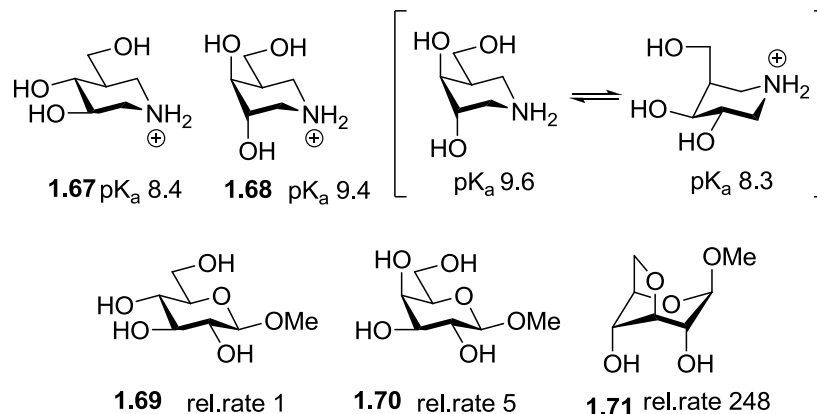
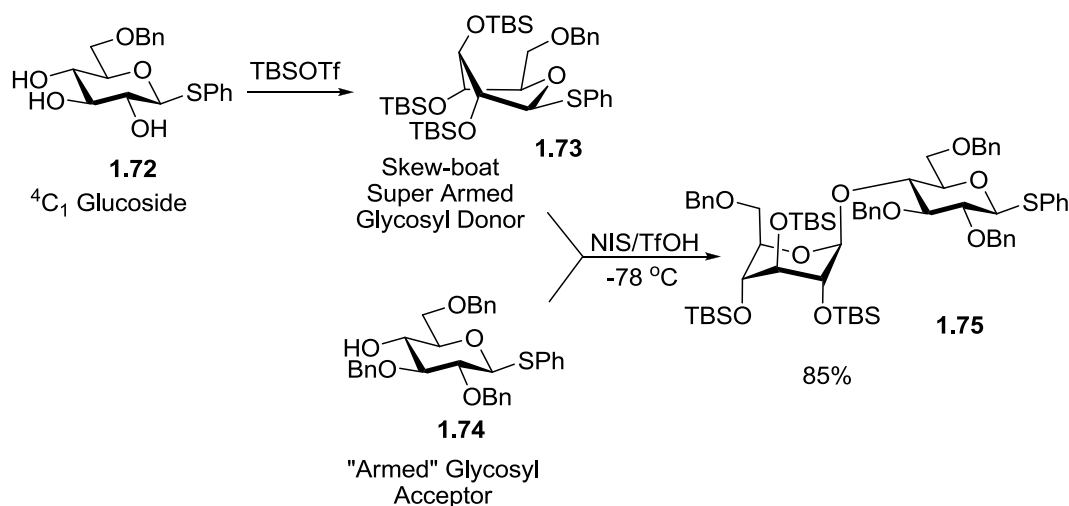


Figure 1.5. Basicity and reactivity increase with the increase of the number of axial hydroxyls: conformational change to increase reactivity

This result implies that if all-equatorial glucosyl donors were converted into their all-axial counterparts, the reactivity could be dramatically increased. Based on the knowledge that steric congestion at the equatorial C-3 and C-4 positions causes conformational changes,^{71, 72} Bols and co-workers were able to exploit this phenomenon.^{70, 73, 74} However, when TBS protection was applied to glucose derivative **1.72**, the product **1.73** was found to exist in more of a skew-boat conformation,⁷⁵ (Scheme 1.13) rather than the anticipated ¹C₄ conformation adopted by analogous xylopyranose derivatives,⁷⁶ perhaps due to the added steric bulk of the substituent at C-5. Nevertheless, a sufficient conformational change was induced, reconfiguring the

substituents perpendicular to the sugar ring. As such, this conformationally superarmed glucosyl donor **1.73** showed a dramatic 20-fold increase in reactivity, relative to the traditional armed benzylated derivatives, as shown by direct competition experiments.⁷³ Furthermore, superarmed glycosyl donor **1.73** could be successfully coupled with “armed” acceptor **1.74** to afford the resulting disaccharide **1.75** in 85% yield.⁷⁷ Similar observations have also been made with glycosyl donors of the manno, rhamno, and galacto series.⁷⁴



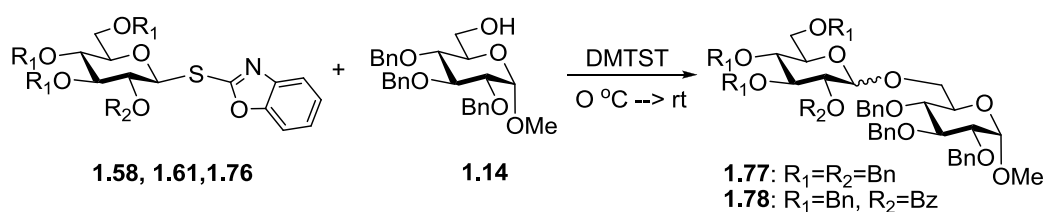
Scheme 1.14. Chemoselective activation of the conformationally superarmed glycosyl donor **1.73** over armed glycosyl acceptor **1.74**.

1.4.2. Superarming by electronic effects

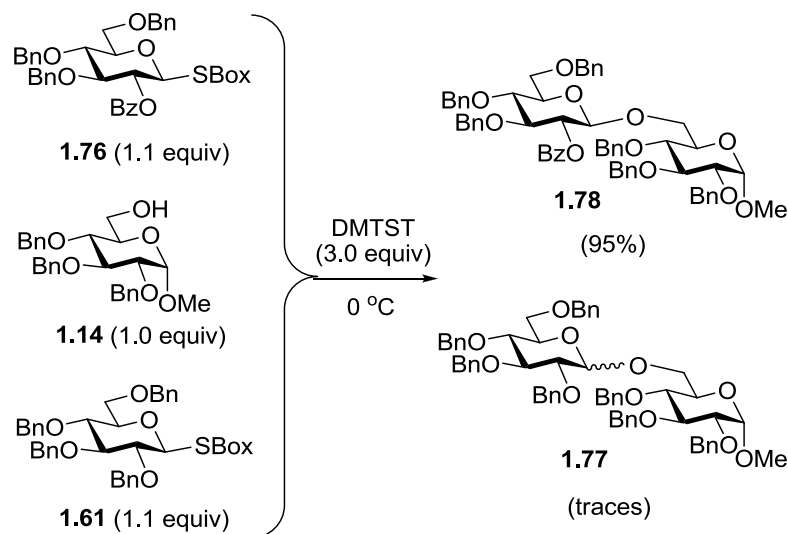
As aforementioned, a mixed protecting group pattern could unexpectedly and profoundly affect glycosyl donor reactivity.⁴⁰ Along these lines, a glycosyl donor containing a participating benzoyl group at C-2 and electron donating groups at the remaining positions, was also investigated. Interestingly, these glycosyl donors proved to be even more reactive (superarmed) than their armed per-benzylated counterparts.^{78, 79} Thus, the

reaction of armed SBox donor **1.61** with glycosyl acceptor **1.14** in the presence of dimethyl(thiomethyl)sulfonium trifluoromethanesulfonate (DMTST), proceeded smoothly, and product **1.77** was isolated in 91% yield (Entry 1, Table 1.2). Furthermore, it was discovered that the disarmed per-benzoylated SBox glycoside **1.58** failed to react under essentially the same reaction conditions. Unexpectedly, the glycosidation of 2-*O*-benzoyl-tri-3,4,6-*O*-benzyl protected SBox glucoside **1.76** proceeded almost instantaneously, and disaccharide **1.78** was obtained in 90% yield (for comparison, the glycosidation of armed donor **1.61** took 2 h).

Table 1.2. Comparative glycosidations of glycosyl donors **1.58**, **1.61** and **1.76**.



Entry	Donor	Time	Product	Yield	α/β ratio
1	 1.61	2 h	1.77	91%	1.2/1
2	 1.58	16 h	--	No reaction	
3	 1.76	< 5 min	1.78	90%	β only



Scheme 1.14. Superarmed (**1.76**) and armed (**1.61**) glycosyl donors in competitive glycosylation.

The reactivity of the superarmed donors was illustrated in a direct competitive glycosylation experiment, wherein both the superarmed and armed donors (**1.76** and **1.61**, respectively), were placed in the same reaction vessel with glycosyl acceptor **1.14**. As depicted in Scheme 1.14, superarmed glycosyl donor **1.76** proved to be significantly more reactive than its per-benzylated analogue **1.61**; this was reflected in the formation of disaccharide **1.78** (95%) with only trace amount of disaccharide **1.77** present (<5%). In addition, unreacted glycosyl donor **1.61** was recovered in 87% yield. Furthermore, this concept was found to be universal and applicable to glycosidation of O-pentenyl, S-ethyl, S-phenyl, S-tolyl and S-thiazolanyl building blocks.⁸⁰ This observed reactivity pattern was also rationalized by the occurrence of the “O-2/O-5 Cooperative Effect.”⁴⁰ As described in Figure 1.4, stabilization of the glycosyl cation can be achieved either from the lone electron pair on the neighboring endocyclic ring oxygen (O-5) or from the lone

electron pair on an acyl type protecting group at O-2, as it is capable of providing stabilization via the formation of the acyloxonium ion intermediate. If both sources of stabilization are available, as in case of 2-O-benzoyl-3,4,6-tri-O-benzyl, this combination gives rise to an overall “superarming” protecting group pattern. Alternatively, this type of superarmed glycosyl donor may be also viewed as an armed donor, capable of a 1,2-trans stereoselective glycosylation, allowing for the chemoselective introduction of a 1,2-trans linkage prior to other linkages.

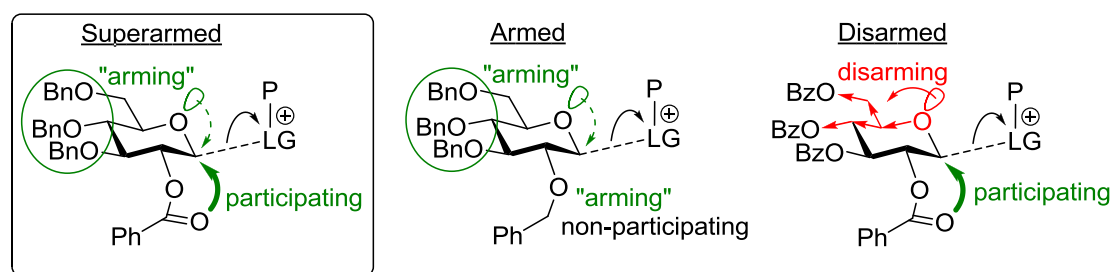
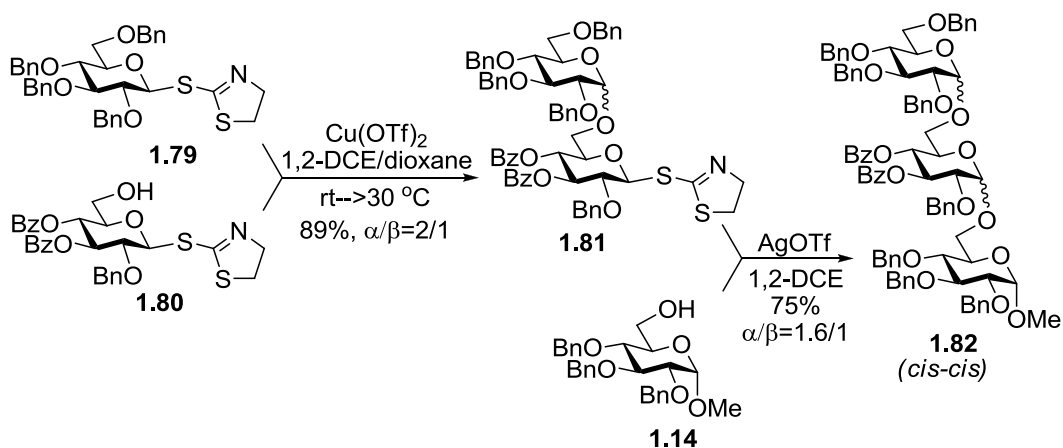


Figure 1.6. O-2/O-5 Cooperative effect in glycosidation of the superarmed building blocks

1.5. The involvement of superdisarmed and superarmed building blocks in oligosaccharide synthesis.

The expeditious preparation of complex oligosaccharides remains a significant challenge to synthetic organic chemistry. The combined demands of regio- and stereoselectivity in glycosidic bond formation, has led to complex synthetic schemes and extensive protecting group manipulations. As aforementioned, the use of a chemoselective activation strategy avoids such extraneous manipulations, thus offering significant

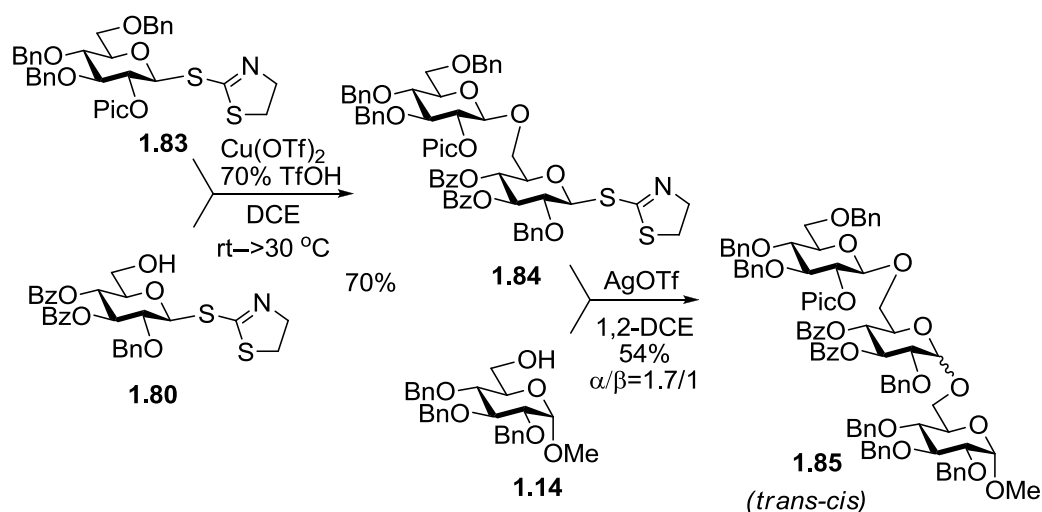
advantages for expeditious glycoside synthesis. Combining the strategic and conceptual updates to the original Fraser-Reid strategy for armed-disarmed oligosaccharide synthesis, with the novel concepts for superarming and superdisarming of building blocks, has expanded the applicability of chemoselective synthesis to encompass a variety of oligosaccharide sequences. For example, utilization of the cooperative effect allows for the acquisition of *cis-cis* linked oligosaccharides, similar to that discussed previously (see Scheme 1.7). As shown in Scheme 15, armed STaz glycosyl donor **1.79** was chemoselectively activated over superdisarmed 3,4-di-*O*-benzoyl-2-*O*-benzyl protected STaz glycosyl acceptor **1.80** in the presence of Cu(OTf)₂ to give disaccharide **1.81** in 89% yield.⁸¹ Superdisarmed disaccharide **1.81** was then glycosidated with standard glycosyl acceptor **1.14** in the presence of AgOTf to give the desired *cis-cis*-linked trisaccharide **1.82** in 75% yield.



Scheme 1.15. Sequential activation of armed \rightarrow superdisarmed building blocks for direct synthesis of *cis-cis*-linked oligosaccharide **1.82**

Along similar lines, it was demonstrated that a combination of the *trans*-directing picolinyl functionality of armed glycosyl donor **1.83** and the *cis*-directing functionality of

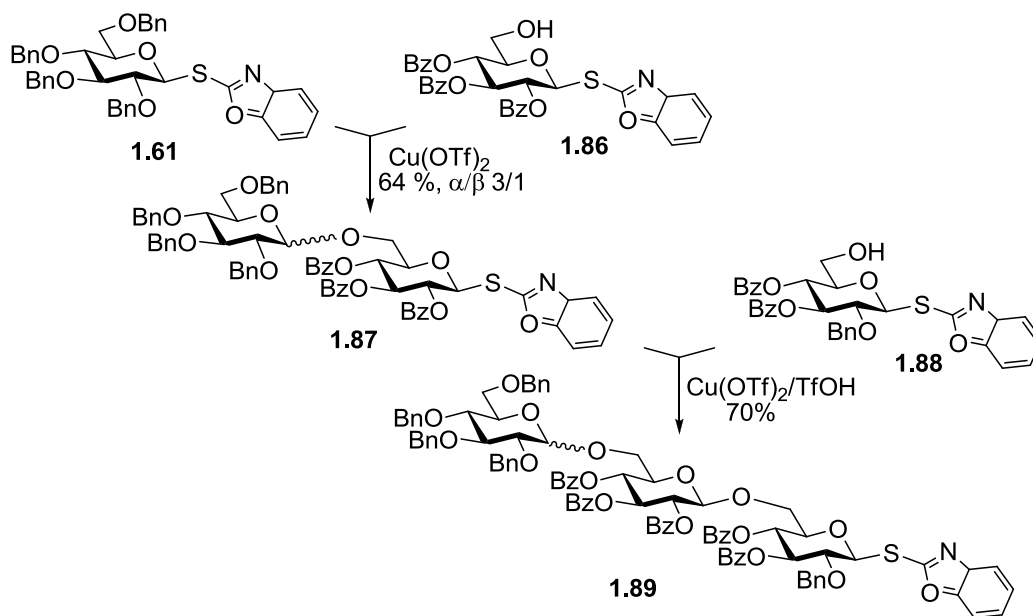
its subsequent superdisarmed disaccharide **1.84**, led to a *trans-cis* glycosylation pattern, inverse to that of the classic armed-disarmed approach which gives a *cis-trans* pattern.⁸¹ The coupling between building blocks **1.83** and **1.80** was performed in the presence Cu(OTf)₂/TfOH, to give *trans*-linked disaccharide **1.84** in 70% yield (Scheme 1.16). The superdisarmed disaccharide **1.84** was then coupled with glycosyl acceptor **1.14** in the presence of AgOTf, affording the desired inverse-patterned *trans-cis* trisaccharide **1.85** in 54% yield.



Scheme 1.16. Sequential activation of picolyated armed \rightarrow superdisarmed building blocks: synthesis of *trans-cis*-linked trisaccharide

1.85.

It was also demonstrated that disarmed disaccharide **1.87** (obtained by classic armed-disarmed approach from building blocks **1.61** and **1.86**, Scheme 1.17), could be further chemoselectively activated over superdisarmed building block **1.88**. Thus, disarmed disaccharide **1.87** was activated in the presence of Cu(OTf)₂/TfOH to produce trisaccharide **1.89** in 70% yield.⁴⁰

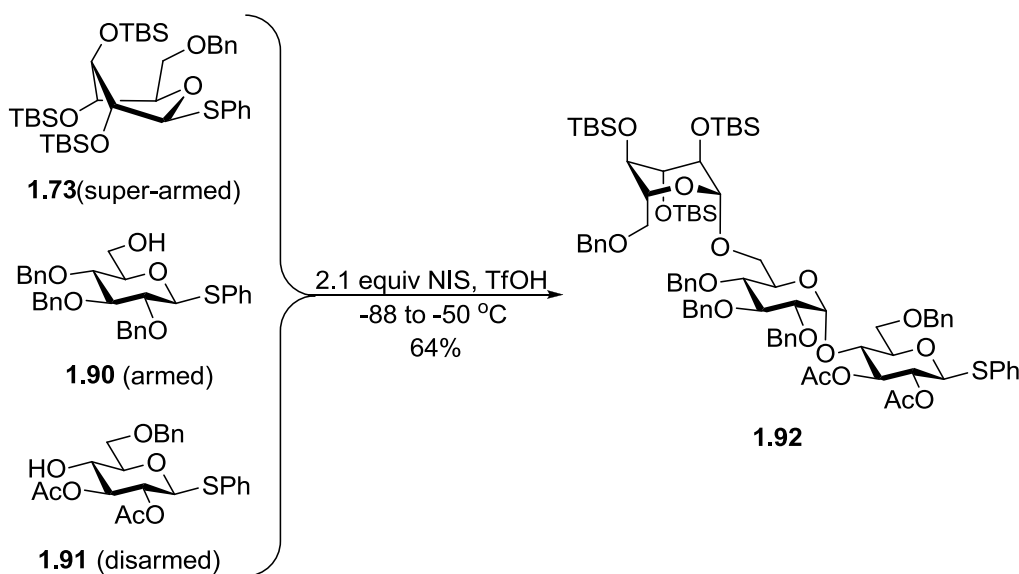


Scheme 1.17. Sequential activation of armed \rightarrow disarmed \rightarrow superdisarmed building blocks **1.61**, **1.86**, **1.88**, respectively.⁴⁰

This concept of conformational superarming was clearly demonstrated by performing a one-pot coupling wherein all three reaction components (thioglycosides **1.73**, **1.90**, and **1.91**) were mixed from the beginning (Scheme 1.18).⁷⁴ This type of one-pot technique requires differentiation between the reactivity levels of both glycosyl donors (**1.73** and **1.90**) and both glycosyl acceptors (**1.90** and **1.91**), while all bearing the same anomeric leaving group (phenylthio). The first reaction took place between the superarmed glycosyl donor **1.73** and the more reactive primary (and also more electron rich due to the neighboring benzyl substituents) glycosyl acceptor **1.90**. The resulting disaccharide derivative then reacted with the remaining glycosyl acceptor **1.91**. As a result of this one-pot coupling in the presence of NIS/TfOH, trisaccharide **1.92** was obtained in 64% yield.

A similar sequence, yet with the execution of the traditional stepwise approach, was

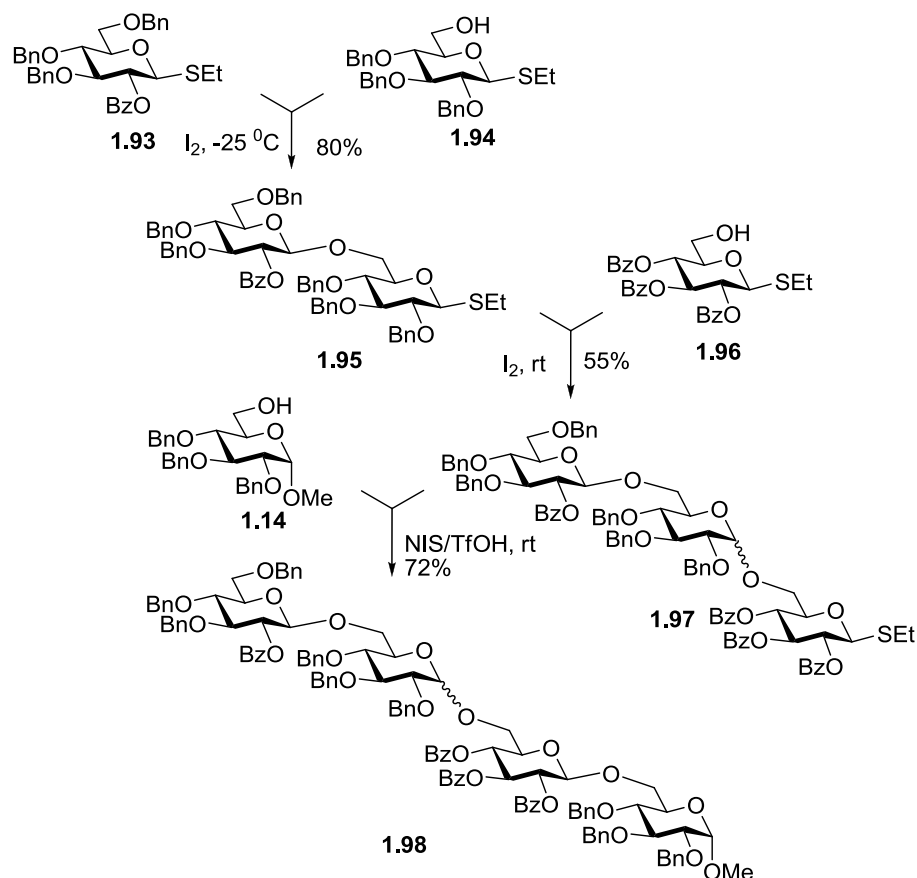
explored with the electronically superarmed glycosyl donors. Thus, the superarmed glycosyl donor **1.93** was activated over “armed” acceptor **1.94** in the presence of iodine to provide disaccharide **1.95** in 80% yield (Scheme 1.19). This disaccharide was then glycosidated with the disarmed acceptor **1.96** to provide trisaccharide **1.97** in 55% yield. The resultant trisaccharide was glycosidated with glycosyl acceptor **1.14** to obtain the target tetrasaccharide **1.98** in which monosaccharide residues are connected via alternating *trans-cis-trans* linkages.



Scheme 1.18. Superarmed → armed → disarmed activation for the synthesis of trisaccharide **1.92** in one-pot.

In principle, examples of using electronically superarmed building blocks are rather abundant; however, the use of these building blocks was not linked to their superarmed properties. These examples include the synthesis of HIV viral protein gp120 glycopeptide fragment;⁸² the synthesis of core tetrasaccharide corresponding to GPI-related mucins of *T. cruzi* Y-strain;⁸³ the synthesis of a complex branched

oligosaccharide of F1 α antigen 9;⁸⁴ etc.^{85, 86} The involvement of superdisarmed glycosyl donors in electrochemical glycosylations was also investigated.^{87, 88}



Scheme 1.19. Synthesis of tetrasaccharide **1.98** using superarmed \rightarrow armed \rightarrow disarmed sequential activations.⁸⁰

1.6. Conclusions and Outlook

It is critical to make complex carbohydrates more accessible to the general chemical, biochemical, and industrial audience to keep pace with the exploding area of glycobiology. This aim can be only achieved by the development of methods and strategies for efficient oligosaccharide synthesis that would be applicable for both

laboratory and industrial preparation. A number of excellent strategies that offer a reasonably efficient route to oligosaccharide assembly have already emerged and the armed-disarmed approach for chemoselective oligosaccharide synthesis is undoubtedly amongst them. Although recent advancements discussed herein have expanded the scope of the armed-disarmed methodology it is clear that further development of efficient and general methods for the expeditious synthesis of complex carbohydrates will remain an important and active arena for scientific endeavors during the 21st century.

Other remarkable improvements in oligosaccharide synthesis have also emerged, including one-pot protection⁸⁹ and glycosylation strategies,^{50, 51, 90} polymer-supported⁹¹⁻⁹³ and automated synthesis,^{94, 95} fluoros tag assisted synthesis in microreactors,⁹⁶ and surface-tethered iterative carbohydrate synthesis (STICS).⁹⁷ The chemoselective strategy, however, is still occupying an important niche in the arsenal of available methods. In the coming years, glycoscientists are expected to have developed simple, efficient, and flexible approaches to oligosaccharide assembly that will complement existing methodologies and bring our ability to obtain complex oligosaccharides up to a significantly higher level.

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CHAPTER 2

Superarming common glycosyl donors by electronic effects

Premathilake, H. D.; Mydock, L. K.; Demchenko, A. V., Superarming common glycosyl donors by simple 2-O-benzoyl-3,4,6-tri-O-benzyl protection. *J. Org. Chem.* **2010**, *75*, 1095-1100

2.1 Introduction

Traditional strategies for oligosaccharide synthesis often require extensive protecting and/or leaving group manipulations between each glycosylation step, thereby increasing the total number of synthetic steps while decreasing both the efficiency and yield. In contrast, expeditious strategies allow for the rapid chemical synthesis of complex carbohydrates by minimizing extraneous chemical manipulations. The armed-disarmed approach for chemoselective oligosaccharide synthesis is one such strategy that addresses these challenges. The significant improvements that have recently emerged in the area of chemoselective activation were discussed in Chapter 1. These advancements have expanded the scope of the armed-disarmed methodology so that it can now be applied to a wider range of oligosaccharide sequences, in comparison to the original concept. Surveyed in this chapter, is the superarmed glycosyl donors developed by electronic effects and the versatility of this developed technique in application to a sequential chemoselective oligosaccharide synthesis

According to the initially developed armed –disarmed strategy introduced by Fraser-Reid¹, any glycosyl donor bearing all ether-protecting groups (i.e. OBn) will be significantly more reactive than its ester-protected (i.e. OBz) analog,² and are thus referred to as “armed” and “disarmed,” respectively (Figure 2.1). Furthermore, it is thought that this effect predominates from the neighboring substituent at C-2,³ and in addition, it is presumed that the overall reactivity of the glycosyl donor corresponds to the total number of ether substituents.^{2,4}

The strategic placement of common protecting groups opens up a new method for “superarming” the glycosyl donors. Thus, the story became interesting to us, when glycosyl donors containing mixed protecting group patterns, such as 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl derivative **2.1**, were considered. As per the total number and location of the benzyl substituent(s), it was believed that the reactivity of compound **2.1** would lie in between that of the fully ether-protected, armed donor **2.2** and the fully ester-protected, disarmed donor **2.3**. Unexpectedly, however, glycosyl donor **2.1** was experimentally determined to be more reactive (superarmed) than the classic armed donors, **2.2**. Superarming glycosyl donors by the simple 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protection was first pioneered in our laboratory with *S*-benzoxazolyl (SBox) glycosyl donors.⁵ To this end, we have explored the reactivities with D-glucose, D-galactose and D-mannose series. (e.g. glycosyl donors **2.4-2.6**, Figure 2.1).

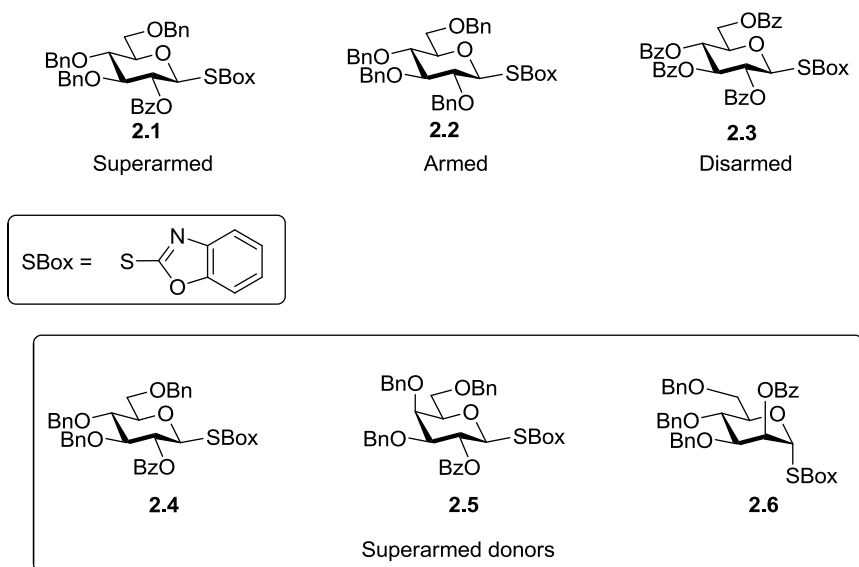


Figure 2.1 Superarmed glycosyl donors

Conceptualized from our studies on the O-2/O-5 Cooperative Effect,⁶ (Figure 2.2) it was determined that *S*-benzoxazolyl (SBox) glycosides possessing both a participating moiety at O-2 (benzoyl) and remote benzyl substituents that electronically arm the lone pair at O-5 (e.g., glycosyl donors **2.4-2.6**, Figure 2.1) are exceptionally reactive⁵ and they have been appropriately titled as “superarmed.” (first coined by Bols)^{7, 8} Furthermore, these building blocks possess the desirable quality of being both arming and participating glycosyl donors, traits not commonly found in other systems.⁹ We have now been able to broaden the scope of possible linkages obtained in chemoselective activation strategies, through the use of our “superarmed” donors, allowing for the efficient installation of any and all linkage sequences, *cis-trans*, *cis-cis*, *trans-cis*, and *trans-trans*.^{6, 10}

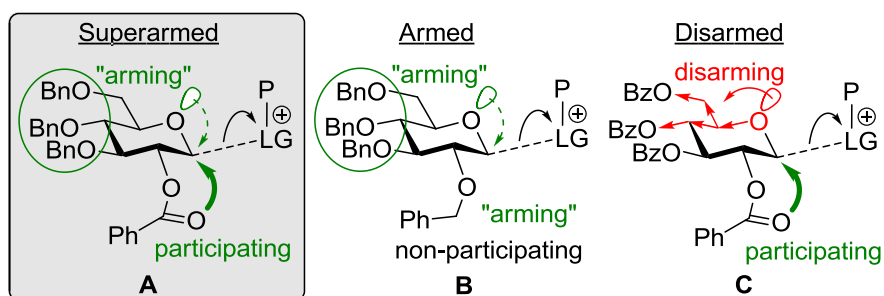


Figure 2.2. Cooperative arming and disarming effects

2.2 Comparative glycosylations

However it remained unclear whether this principle could be applied to other classes of leaving group. Herein, we describe the investigation of stable glycosyl donors of the armed (**2.7**) and superarmed (**2.8**) series, bearing common leaving groups: *O*-pentenyl, *S*-ethyl, *S*-phenyl, *S*-tolyl, and *S*-thiazolanyl (STaz, Figure 2.3). All test glycosylations were performed with the standard glycosyl acceptor **2.9**¹¹ to afford disaccharides **2.10**¹² and **2.11**¹² from the armed and superarmed

glycosyl donors, respectively (Table 2.1). Additionally, the obtained results were compared to the previously investigated SBox glycosides **2.7a**¹³ and **2.8a**.⁵

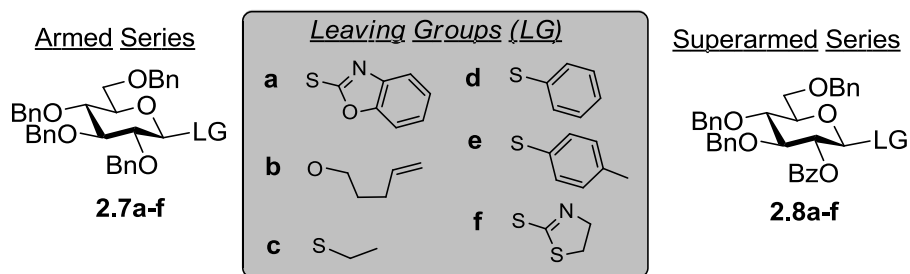


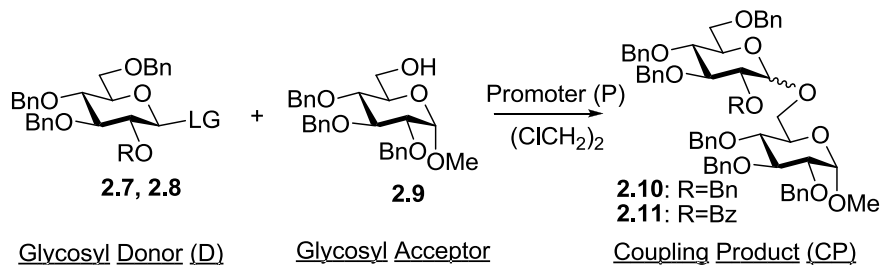
Figure 2.3. Glycosyl donors of the armed and superarmed series

It should be noted that the key feature of any chemoselective activation is the application of mild promoter/reaction conditions that allows for the efficient differentiation of the reactivity levels among the building blocks. However, establishing a reactivity differentiation becomes increasingly difficult with the highly reactive superarmed and armed glycosyl donors. In our earlier work, we described that the reactivity of armed and superarmed SBox glycosides, **2.7a** and **2.8a**, respectively, can be effectively separated in the presence of dimethyl(methylthio)sulfonium trifluoromethanesulfonate¹⁴ (DMTST) as promoter (Table 2.1, Entries 1 and 2).⁵ Herein, we also determined that an equally successful differentiation can be achieved in the presence of copper(II) trifluoromethanesulfonate (Entries 3 and 4). This result offers further significance, as $\text{Cu}(\text{OTf})_2$ is a promoter unique to thioimidoyl leaving groups.

In order to differentiate between armed and superarmed O-pentenyl glycosides, **2.7b**¹⁵ and **2.8b**,¹⁶ respectively, we chose iodonium(di- γ -collidine)perchlorate¹⁷ (IDCP), as this mild promoter has proven effective for chemoselectively activating armed pentenyl glycosides over their disarmed counterparts at rt.¹ However, these reaction conditions

were found to be too powerful, as both glycosyl donors **2.7b** and **2.8b** were activated in a matter of minutes at rt. Additionally, no significant difference in reactivity was observed when O-pentenyl glycosides were investigated in the presence of NIS (rt), NBS (45 °C), or NIS/TfOH (-20 °C), albeit in a majority of comparative glycosylations, super-armed donor **2.7b** was slightly more reactive (the extended experimental results are available as a part of the SI). Ultimately, the application of IDCP at low temperature (-10 °C) was deemed the most successful in terms of the differential activation of O-pentenyl glycosides. Thus, 20 h was required for the glycosidation of **2.7b**, whereas the glycosidation of **2.8b** was complete in about 3 h (Entries 5 and 6). The yields obtained with both armed and superarmed pentenyl glycosides under these reaction conditions, however, remained unimpressive (62% and 53%, respectively).

Consequently, we investigated *S*-ethyl glycosides **2.7c**¹⁸ and **2.8c**¹⁹ in the presence of relatively mild promoters, including IDCP, DMTST, and MeOTf at reduced temperatures (Table 2.1, Entries 7-12). While reactions in the presence of IDCP or MeOTf showed insufficient difference in reactivity (Table 2.1, Entries 7-8), the best differentiation was achieved with MeOTf at 0 °C or DMTST at -20 °C, wherein three-fold and six-fold increase in reactivity was achieved, respectively (Table 2.1, Entries 9-12). Additionally, the yields for both armed and disarmed glycosyl donors were good to excellent across the board. The reactivity difference, however, still rendered these conditions insufficient for any subsequent chemoselective activation studies, which are essential for applying this methodology toward oligosaccharide synthesis. Therefore, we continued to search for even milder reaction conditions to activate the *S*-ethyl glycosides.

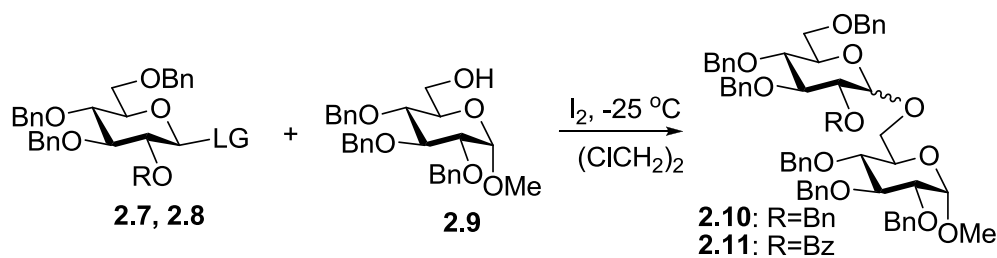
Table 2.1. Comparative activation of armed (2.7) and superarmed (2.8) glycosyl donors

Entry	D	P	Temp.	Time	CP	Yield	$\alpha:\beta$
1	2.7a	DMTST	0 °C	2 h	2.10	92%	2:1
2	2.8a	DMTST	0 °C	5 min	2.11	86%	β only
3	2.7a	Cu(OTf) ₂	0 °C	2 h	2.10	99%	2:1
4	2.8a	Cu(OTf) ₂	0 °C	20 min	2.11	96%	β only
5	2.7b	IDCP	-10 °C	20 h	2.10	62%	3:1
6	2.8b	IDCP	-10 °C	3 h	2.11	53%	β only
7	2.7c	IDCP	-10 °C	96 h	2.10	82%	2:1
8	2.8c	IDCP	-10 °C	96 h	2.11	78%	β only
9	2.7c	MeOTf	0 °C	18 h	2.10	95%	2:1
10	2.8c	MeOTf	0 °C	6 h	2.11	96%	β only
11	2.7c	DMTST	-20 °C	1 h	2.10	90%	2:1
12	2.8c	DMTST	-20 °C	10 min	2.11	89%	β only

Upon investigating a variety of other known thioglycoside promoters,²⁰⁻²² we found results with molecular iodine, introduced by Field as a mild promoter for the activation of methyl thioglycosides,²³ at -25 °C to be the most impressive. Thus, while activation of the armed glycosyl donor **2.7c** required at least 10 h, the reaction of its superarmed counterpart **2.8c** completed in less than 1 h, displaying a ten-fold reactivity increase (Table 2.2, Entries 1 and 2). Encouraged by these results, iodine was chosen as the promoter for the subsequent studies with *O*-pentenyl donors (1b and 2b), as well as common classes of thioglycosides donors,²⁰⁻²² *S*-phenyl (**2.7d**²⁴ and **2.8d**²⁵), *S*-tolyl (**2.7e**²⁶ and **2.8e**), and STaz glycosides (**2.7f**²⁷ and **2.8f**). Although, we observed that the superarmed glycosyl donors of both the *S*-phenyl and *S*-tolyl series reacted faster (Table 2.2, Entries 3-6), no differentiation that would be of practical application to chemoselective oligosaccharide synthesis was achieved at this stage.

Furthermore, no reactivity differentiation could be established in the presence of iodine between the armed and superarmed STaz glycosyl donors **2.7f** and **2.8f**, nor between *O*-pentenyl glycosides **2.7b** and **2.8b**, respectively (Entries 7-10). Under these conditions, both armed and superarmed glycosyl donors of these classes reacted smoothly, but at a similar pace. Although both *O*-pentenyl and STaz glycosides easily react in accordance with the conventional armed-disarmed activation scheme,^{1, 9} we have found the differentiation between the more closely positioned superarmed and armed glycosides, to be challenging. It is possible, that the protecting group effect is decreased in cases of remote activation,²⁸ typical for both the *O*-pentenyl and STaz glycosides (alkene²⁹ and nitrogen atom of the thiazoline ring,³⁰ respectively); opposite to that of the direct activation¹³ cases (i.e. *S*-ethyl or SBox glycosyl donors).

Table 2.2. Activation of armed (**2.7**) and superarmed (**2.8**) glycosyl donors in the presence of iodine (3 mol equiv)



Entry	Donor	Time	Product	Yield	Ratio $\alpha:\beta$
1	2.7c	10 h	2.10	89%	1:4
2	2.8c	1 h	2.11	93%	β only
3	2.7d	15 h	2.10	74%	1:2
4	2.8d	8 h	2.11	78%	β only
5	2.7e	15 h	2.10	63%	1:2
6	2.8e	12 h	2.11	72%	β only
7	2.7f	19 h	2.10	87%	1:2
8	2.8f	19 h	2.11	85%	β only
9	2.7b	17 h	2.10	82%	1:2.8
10	2.8b	17 h	2.11	84%	β only
11	2.7a	48 h	2.10	NR ^a	-
12	2.8a	20 h	2.11	95%	β only

^a NR – no reaction; although glycosyl donor **2.7a** smoothly reacted at rt in 13 h

affording disaccharide **2.10** in 95% ($\alpha:\beta=1:2$)

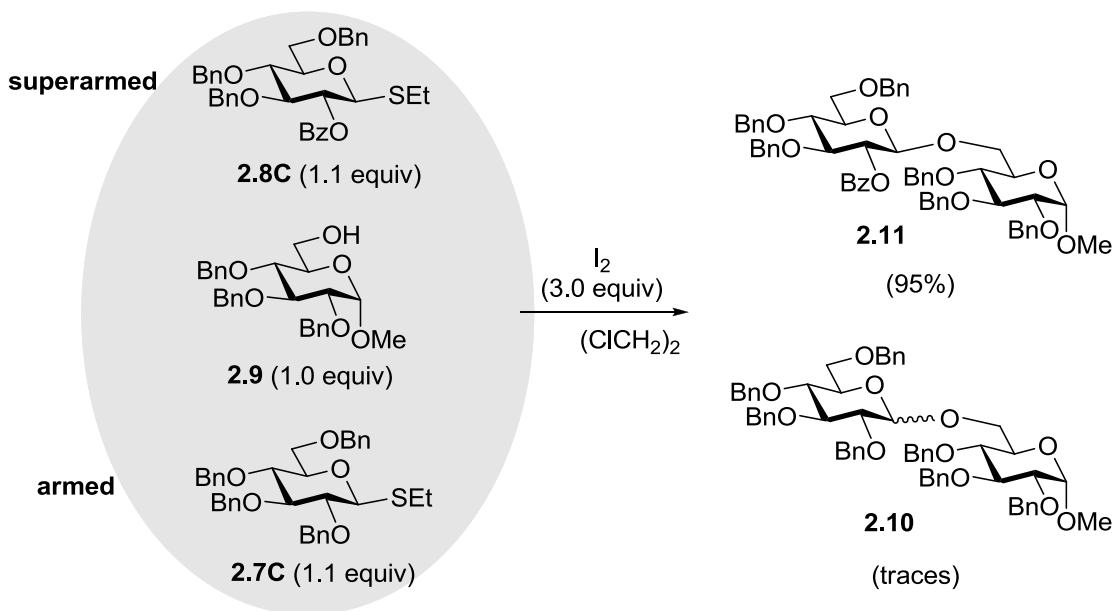
Following this rationale, we found that the reactivity difference between the armed and superarmed SBox derivatives **2.7a** and **2.8a** was remarkable in the presence of iodine at -25 °C (Entries 11 and 12). While no reaction took place with the armed glycosyl donor **2.7a**, the superarmed glycosyl donor **2.8a** reacted very smoothly, and afforded the corresponding disaccharide **2.11** in 20 h (95%). It should be noted that the armed SBox glycoside **2.7a** could also be activated with iodine, but this could be only accomplished at rt. The fact that the SBox glycosides reacted much slower than their *S*-ethyl counterparts was rather unanticipated, as SBox glycosides are typically much more reactive and can be selectively activated in the presence of alkyl/aryl thioglycosides.^{13,31}

2.3 Competitive glycosylations

As verification of the promising results obtained with *S*-ethyl glycosides in the presence of iodine, we set up direct competitive glycosylations. To optimize the reaction conditions for a chemoselective oligosaccharide assembly, the competitive glycosylations were investigated at a variety of reaction temperatures (Table 2.3). These reactions were carried out by placing equimolar amounts (1.1 equiv each) of the armed **2.7c** and superarmed **2.8c** glycosyl donors in the same reaction vessel with glycosyl acceptor **2.9** (1 equiv). Upon the addition of iodine (3 equiv), both glycosyl donors competed for the same acceptor to form either disaccharide **2.10** or **2.11**. The highest product ratio in these competitive glycosylations was also obtained at -25 °C, wherein the 1,2-*trans*-linked disaccharide **5** (derived from superarmed glycosyl donor **2.8c**) was isolated in 62% yield

(entry 3). Conversely, the disaccharide **2.10** (derived from armed glycosyl donor **2.7c**) was isolated in only 14% yield ($\alpha/\beta = 1/4$).

Table 2.3. Competitive activations of S-ethyl glycosyl donors: **2.7c** (armed) vs. **2.8c** (superarmed)



Entry	Temp.	Time	Ratio	Yield 2.10	Yield 2.11
			2.10:2.11	(α/β)	(α/β)
1	rt	1 h	56:44	53%	45%
				(1:1.7)	(β only)
2	-10 °C	1 h	29:71	22%	51%
				(1:4)	(β only)
3	-25 °C	3 h	20:80	14%	62%
				(1:4)	(β only)
4	-35 °C	24 h	40:60	11%	26%
				(1:5)	(β only)

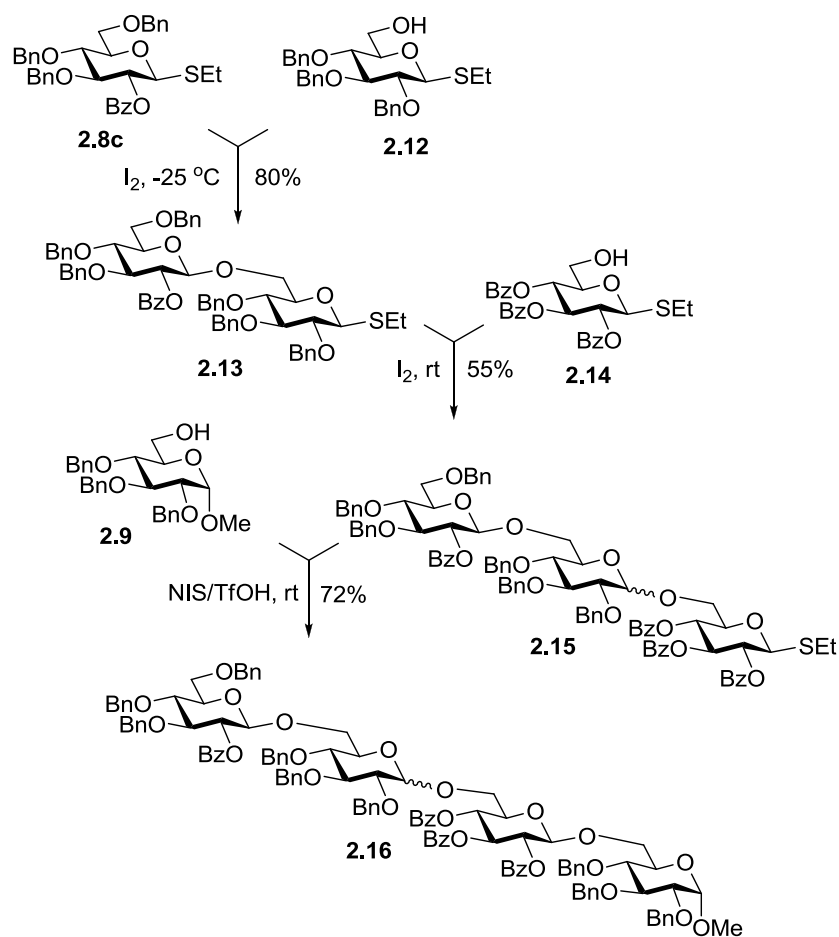
2.4 Chemoselective oligosaccharide synthesis

Having investigated the superarming and arming effects in direct competitive glycosylations with glycosyl donors of the *S*-ethyl series, we now turned our attention to a sequential tetrasaccharide synthesis. To begin, the chemoselective activation of the superarmed glycosyl donor **2.8c** over the “armed” glycosyl acceptor **2.12**³² was successfully carried out in the presence of iodine, at -25 °C (Scheme 1). Subsequently, the resulting armed disaccharide **2.13**, obtained in 80% yield, was directly coupled with “disarmed” glycosyl acceptor **2.14**.³³ This chemoselective activation was also performed in the presence of iodine, but this time at rt. The resulting trisaccharide **2.15**, obtained in 55% yield ($\alpha/\beta = 1:2.6$), was then reacted with glycosyl acceptor **2.9** in the presence of NIS/TfOH, and the resulting tetrasaccharide **2.16** was isolated in 72% yield. Overall, this synthesis serves as ultimate proof of the utility of this superarmed approach in chemoselective oligosaccharide synthesis.

2.5 Conclusion

In conclusion, a promising new concept for superarming glycosyl donors through the use of common protecting groups has now been extended to encompass a range of common glycosyl donors. Although it was initially necessary to fine-tune the reaction conditions and carefully select an adequate (mild) promoter, once established, the reactivity of the superarmed glycosyl donors was able to be exploited. This approach ultimately provides an additional synthetic building block that can be integrated into the conventional

chemoselective armed-disarmed strategy. Results obtained herein were both consistent and high yielding, thus, offering this approach as a general method whereby a 1,2-*trans* linkage has to be introduced prior to other linkages. Additionally, the superarmed glycosyl donors can be easily obtained by conventional synthetic methods. Currently, the application of the superarmed glycosyl donor concept toward selective activation and orthogonal approaches to oligosaccharide synthesis is under pursuit in our laboratory.



Scheme 2.1. Sequential activation of differently protected *S*-ethyl building blocks:
synthesis of tetrasaccharide **2.16**

2.6 Experimental

Preparation of superarmed glycosyl donors 2.8e and 2.8f

***p*-Methylphenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio- β -D-glucopyranoside (2.8e).**

The title compound was obtained using a modified protocol similar to that previously reported.^{7,8,14} CH₂Cl₂ (9.0 mL) and *p*-toluenethiol (1.6 g, 13.03 mmol) were added to 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-methoxybenzylidene)- α -D-glucopyranose¹⁴ (740 mg, 1.31 mmol) and molecular sieves (3Å, 850 mg), and the resulting mixture was stirred under argon for 45 min. Trimethylsilyl trifluoromethanesulfonate (6 μ L, 0.328 mmol) was added and the reaction mixture was stirred under argon for 16 h at rt. After that, the reaction mixture was neutralized by the addition of triethylamine (~0.1 mL), diluted with CH₂Cl₂, the solid was filtered-off and was rinsed successively with CH₂Cl₂. The combined filtrate (~30 mL) was washed with water (10 mL), 20% aq. NaHCO₃ (10 mL), and water (3 x 10 mL). The organic phase was separated, dried, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/hexanes gradient elution) to afford the title compound **2.8e** as a white solid in 70% yield. Analytical data for **2.8e**: R_f = 0.54 (ethyl acetate/hexanes, 3/7, v/v); m. p. 134-135 °C (diethyl ether/hexanes); [α]_D²² +32.5° (c = 1, CHCl₃); ¹H-n.m.r: δ , 2.18 (s, 3H, SPhCH₃), 3.48 (m, 1H, J_{5,6a} = 1.9 Hz, J_{5,6b} = 3.6 Hz, H-5), 3.62 (dd, 1H, J_{4,5} = 9.5 Hz, H-4), 3.65-3.78 (m, 3H, H-3, 6a, 6b), 4.42-4.75 (m, 6H, 3 \times CH₂Ph), 4.61 (d, 1H, J_{1,2} = 10.0 Hz, H-1), 5.14 (dd, 1H, J_{2,3} = 9.0 Hz, H-2), 6.80-8.00 (m, 24H aromatic) ppm; ¹³C-n.m.r.: δ , 21.3, 69.1, 72.7, 73.7, 75.2, 75.5, 76.8, 77.2, 77.4, 77.7, 78.0, 79.7, 84.5, 86.4, 127.7 (\times 3), 127.8 (\times 3), 127.8 (\times 3), 128.0, 128.1 (\times 2), 128.3, 128.4 (\times 2), 128.5 (\times 2),

128.7 (×2), 128.8 (×2), 128.9 (×2), 128.9 (×3), 129.1, 130.0 (×2), 130.3 (×2), 130.4, 133.6, 133.9 (×3), 138.1, 138.4, 138.5, 138.7, 165.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{41}H_{40}O_6SNa^+$ 683.2443, found 683.2624.

Thiazolinyl 2-O-benzoyl-3,4,6-tri-O-benzyl-1-thio-β-D-glucopyranoside (2.8f). The title compound was obtained using a modified protocol similar to that previously reported.³⁴ 3,4,6-tri-O-benzyl-1,2-O-(1-methoxybenzylidene)-α-D-glucopyranose¹⁴ (200 mg, 0.35 mmol) was mixed with molecular sieves (3Å, 0.8 g) and 2-mercaptothiazoline (420 mg, 3.52 mmol), and dried *in vacuo* for 15 min. Acetonitrile (2.6 mL) was added and the resulting mixture was stirred under argon for 1 h. Mercuric bromide (13 mg, 0.035 mmol) was added and the resulting reaction mixture was heated at reflux for 16 h. The volatiles have been evaporated under reduced pressure, the residue was diluted with CH_2Cl_2 , the solid was filtered-off and rinsed successively with CH_2Cl_2 . The combined filtrate (30 mL) was washed with 1N aq. NaOH (10 mL) and water (3 x 10 mL). The organic phase was separated, dried, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane gradient elution) to afford the title compound **2.8f** as a white solid in 70% yield. Analytical data for **2.8f**: $R_f = 0.47$ (ethyl acetate/hexane, 4/6, v/v); m. p. 141-143 °C (diethyl ether-hexanes); $[\alpha]_D^{22} +81.2^\circ$ (c = 1, $CHCl_3$); 1H -n.m.r.: δ , 3.43 (m, 2H, NCH_2), 3.82 (m, 1H, H-5), 3.88-3.98 (m, 2H, H-6a, 6b), 4.03 (dd, 1H, $J_{4,5} = 9.1$ Hz, H-4), 4.05 (dd, 1H, $J_{3,4} = 8.8$ Hz, H-3), 4.30 (m, 2H, CH_2S), 4.75 (dd, 2H, $J^2 = 11.9$ Hz, CH_2Ph), 4.85 (dd, 2H, $J^2 = 10.9$ Hz, CH_2Ph), 4.87 (dd, 2H, $J^2 = 11.0$ Hz, CH_2Ph), 5.55 (dd, 1H, $J_{2,3} = 8.5$ Hz, H-2), 5.67 (d, 1H, $J_{1,2} = 10.3$ Hz, H-1), 7.22-8.20 (m, 20H, aromatic) ppm; ^{13}C -n.m.r.: δ , 35.6, 64.3, 68.8, 72.4, 73.6,

75.3, 75.5, 77.8, 80.0, 83.1, 84.3, 127.8, 127.9, 128.0, 128.1 (×2), 128.1 (×2), 128.2 (×2), 128.5 (×2), 128.6 (×3), 128.6 (×2), 129.7, 130.1 (×2), 133.5, 137.9, 138.2, 138.3, 163.7, 165.4 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{37}H_{37}NO_6S_2Na^+$ 678.1959, found 678.1977.

Preparation of di- and oligosaccharides (2.10, 2.11, 2.13, 2.15, and 2.16)

Method A: Typical DMTST-promoted glycosylation procedure: A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 200 mg) in 1,2-dichloroethane (DCE, 1.6 mL) was stirred under argon for 1 h. The mixture was chilled to 0 or -20 °C (see Table 1), DMTST¹⁴ (0.33 mmol) was added and the reaction mixture was stirred for 5 min – 2 h (see Table 1). Upon completion, the mixture was diluted with CH₂Cl₂, the solid was filtered-off and rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 20% aq. NaHCO₃ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution).

Method B: Typical Cu(OTf)₂-promoted glycosylation procedure: A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 1 h followed by the addition of freshly conditioned Cu(OTf)₂ (0.22 mmol). The reaction mixture was stirred for 20 min - 2h at 0 °C (see Table 1) then diluted with CH₂Cl₂, the solid was filtered-off and rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was

washed with 20% aq. NaHCO₃ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution).

Method C: Typical IDCP-promoted glycosylation procedure: A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 1 h. The reaction mixture was then chilled to -10 °C, IDCP¹⁷ (0.22 mmol) was added and the reaction mixture was stirred for 3 -96 h (see Table 1). Upon completion, the mixture was diluted with CH₂Cl₂, the solid was filtered-off and rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 20% NaHCO₃ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution).

Method D: Typical MeOTf-promoted glycosylation procedure: A mixture containing the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 1 h. The mixture was chilled to 0 °C, MeOTf (0.39 mmol) was added and the reaction mixture was stirred for 6-18 h (see Table 1). The mixture was then diluted with CH₂Cl₂, the solid was filtered-off and the residue was rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 20% aq. NaHCO₃ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution).

Method E: Typical iodine-promoted glycosylation procedure: A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 16 h. The mixture was chilled to -25 °C (or as indicated in Table 3 or Scheme 1), iodine (0.33 mmol) was added and the reaction mixture was stirred for 1 – 48 h (see Table 2). Upon completion, the mixture was quenched with Et₃N and diluted with CH₂Cl₂, the solid was filtered-off and the residue was rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 10% aq.Na₂S₂O₃ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution).

Method F: Typical NIS/TfOH-promoted glycosylation procedure: A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 16 h. NIS (0.22 mmol) and TfOH (0.022 mmol) were added and the reaction mixture was stirred for 1 h. Upon completion, the mixture was diluted with CH₂Cl₂, the solid was filtered-off and the residue was rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 10% aq.Na₂S₂O₃ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution).

Methyl *O*-(2,3,4,6-tetra-*O*-benzyl-*D*-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl- α -*D*-glucopyranoside (2.10). The spectroscopic and analytical data for the title compound were in good agreement with those reported previously.¹²

Methyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -*D*-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl- α -*D*-glucopyranoside (2.11). The spectroscopic and analytical data for the title compound were in good agreement with those reported previously.¹²

Ethyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -*D*-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-1-thio- β -*D*-glucopyranoside (2.13). The title compound was obtained as a colorless syrup from **1c**¹⁸ and **6**³² by method E in 80% yield. Analytical data for **7**: R_f = 0.4 (ethyl acetate/hexanes, 3/7, v/v); $[\alpha]_D^{23} +18.4^\circ$ (c=1, CHCl₃); ¹H-n.m.r: δ , 1.13 (t, 3H, J = 8.0 Hz, SCH₂CH₃), 2.51 (m, 2H, SCH₂CH₃), 3.31 (dd, 1H, J_{2,3} = 9.0 Hz, H-2), 3.32-3.46 (m, 2H, H-4, 5), 3.48-3.65 (m, 3H, H-3, 5', 6a), 3.67-3.82 (m, 4H, H-3', 4', 6a', 6b'), 4.10 (d, 1H, J_{5,6b} = J_{6a,6b} = 10.5 Hz, H-6b), 4.32 (d, 1H, J_{1,2} = 9.7 Hz, H-1), 4.40-4.87 (m, 13H, H-1', 6 x CH₂Ph), 5.31 (br dd, 1H, H-2'), 7.05-8.00 (m, 35H, aromatic) ppm; ¹³C-n.m.r.: δ , 15.2, 24.7, 29.9, 68.4, 69.2, 74.0, 75.4, 75.7, 75.8, 75.8, 76.0, 77.6, 78.4, 79.1, 82.0, 83.3, 84.9, 86.9, 101.4, 128.0 (×2), 128.1 (×4), 128.2 (×3), 128.2 (×4), 128.4 (×4), 128.4 (×4), 128.6 (×3), 128.8 (×6), 128.8 (×5), 128.8 (×5), 130.2 (×2), 138.2, 138.4 (×2), 138.5, 166.0 ppm; HR-FAB MS [M+Na]⁺ calcd for C₆₃H₆₆O₁₁SNa⁺ 1053.4224, found 1053.4238

Ethyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-glucopyranosyl)-(1 \rightarrow 6)-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyl)-(1 \rightarrow 6)-2,3,4-tri-*O*-benzoyl-1-thio- β -D-glucopyranoside

(2.15). The title compound was obtained as a pale-yellow syrup from **2.13** and **2.14**³³ by method E (rt) in 55% yield (α : β = 1:2.6). Analytical data for **2.15**: R_f = 0.3 (ethyl acetate/hexane, 3/7, v/v); ¹H-n.m.r. (selected data for β -**9**): δ , 1.13 (t, 3H, J = 8.0 Hz, SCH₂CH₃), 2.65 (m, 2H, SCH₂CH₃), 3.26 (dd, 1H, $J_{2',3'}$ = 8.9 Hz, H-2'), 3.30-3.58 (m, 4H, H-3', 4', 5', 6a), 3.62-4.20 (m, 9H, H-3'', 4'', 5, 5'', 6a', 6a'', 6b, 6b', 6b''), 4.35 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1'), 4.35-4.95 (m, 14H, H-1, 1'', 12 x CH₂Ph), 5.32 (dd, 1H, $J_{2'',3''}$ = 9.5 Hz, H-2''), 5.38 (dd, 1H, $J_{4,5}$ = 7.0 Hz, H-4), 5.49 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 5.86 (dd, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 7.05-8.15 (m, 50H aromatic) ppm; ¹³C-n.m.r.: δ , 15.0 (\times 2), 24.4, 29.9, 69.0, 70.4, 70.9, 73.7 (\times 2), 74.1, 74.4, 74.9 (\times 2), 75.2, 75.2, 75.4, 75.6, 77.7, 78.1, 78.4 (\times 2), 82.3, 83.0, 83.9, 84.6, 101.4, 103.9, 127.6 (\times 2), 127.8 (\times 2), 127.8 (\times 2), 127.9, 128.0, 128.1 (\times 4), 128.2 (\times 2), 128.4, 128.4 (\times 4), 128.5 (\times 4), 128.6 (\times 5), 128.7, 129.0, 129.1, 129.5, 129.9 (\times 2), 130.0, 130.0 (\times 2), 130.1, 133.2, 133.4 (\times 2), 133.6 (\times 2), 138.1 (\times 2), 138.2 (\times 2), 138.3, 138.4 (\times 2), 138.8 (\times 4), 165.3 (\times 2), 165.4 (\times 2), 165.6 (\times 3), 166.0 (\times 2) ppm; HR-FAB MS [M+Na]⁺ calcd for C₉₀H₈₈O₁₉SNa⁺ 1527.5538, found 1527.5558.

Methyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-glucopyranosyl)-(1 \rightarrow 6)-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyl)-(1 \rightarrow 6)-*O*-(2,3,4-tri-*O*-benzoyl- β -D-glucopyranosyl)-

(1 \rightarrow 6)-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside (2.16). The title compound was obtained as colorless syrup **3** and **9** by method F in 72% yield. Selected analytical data for β -**2.16**: R_f = 0.66 (ethyl acetate/hexane, 2/3, v/v); ¹H-n.m.r.: δ , 4.24 (d, 1H, $J_{1'',2''}$ =

7.8 Hz, H-1''), 4.29 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1), 4.44 (d, 1H, H-1'), 4.47 (d, 1H, H-1'') ppm; ^{13}C -n.m.r.: δ , 55.7, 67.7, 68.4, 68.8, 69.8, 70.0, 72.2, 73.3, 73.9, 74.3, 74.8, 74.9, 75.0, 75.4, 75.6, 75.8, 77.6 ($\times 2$), 77.9, 78.2, 79.6 ($\times 2$), 80.1, 82.2, 83.1, 98.3, 98.5, 101.0, 101.6, 127.4 ($\times 3$), 127.8, 128.0 ($\times 3$), 128.2 ($\times 6$), 128.3 ($\times 4$), 128.3 ($\times 4$), 128.4, 128.5 ($\times 3$), 128.7 ($\times 5$), 128.7 ($\times 6$), 128.8 ($\times 7$), 128.8 ($\times 7$), 128.8 ($\times 6$), 129.0 ($\times 5$), 129.1, 129.2, 129.4 ($\times 3$), 129.4, 129.6, 130.0, 130.1 ($\times 3$), 130.3, 130.4, 133.5, 133.6, 133.9, 136.2, 138.1, 138.3, 138.4, 138.6, 138.8, 139.3, 165.2, 165.4, 165.8, 166.1 ppm; HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{116}\text{H}_{114}\text{O}_{25}\text{Na}^+$ 1929.7547, found 1929.7583.

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CHAPTER 3

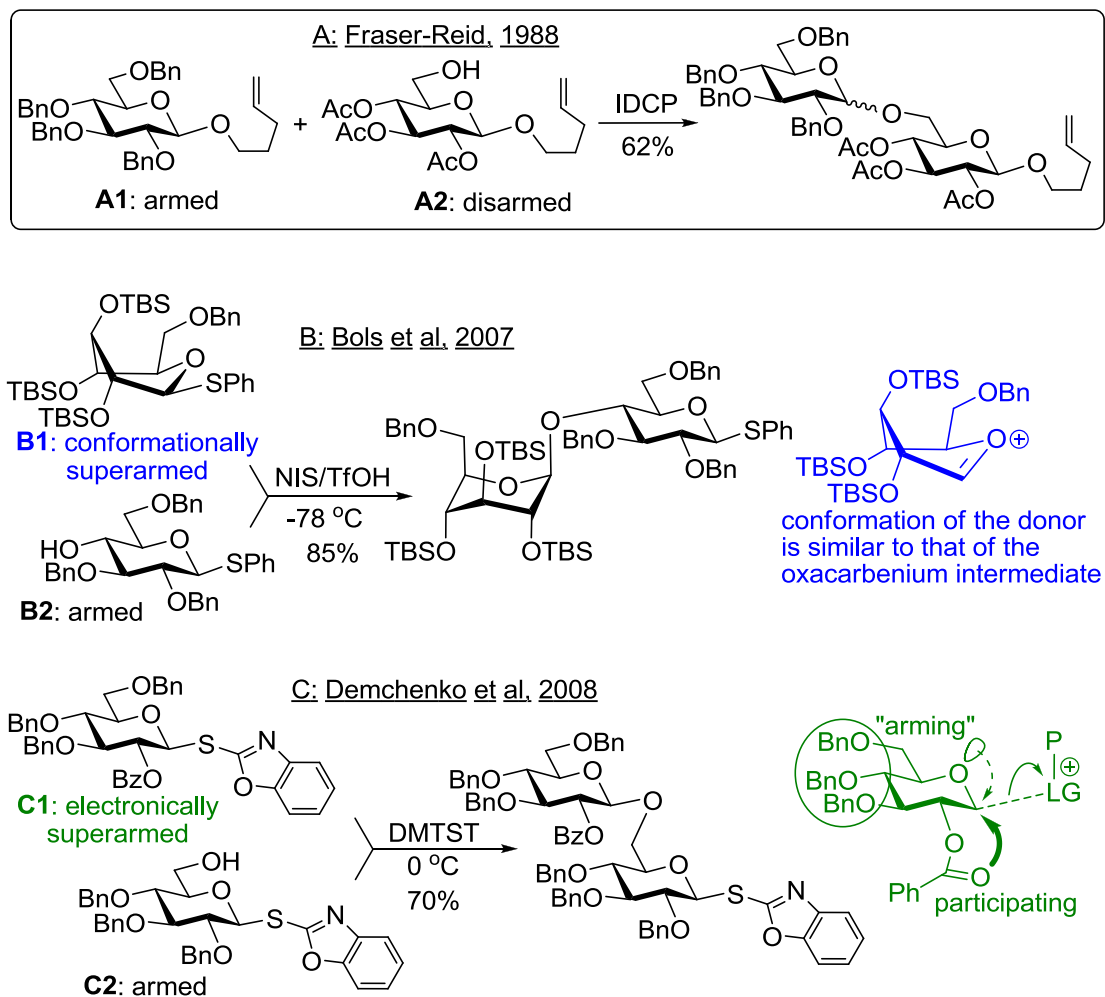
Superarming of glycosyl donors by cooperative electronic and conformational effects

3.1 Introduction

Traditional strategies for oligosaccharide synthesis often require extensive protecting and/or leaving group manipulations between each glycosylation step, thereby leading to the increase in the total number of synthetic steps and, consequently, decrease in both efficiency and over-all yield. The past two decades have witnessed a dramatic improvement of the methods and strategies used for oligosaccharide synthesis.^{1,2} These developments include but are not limited to one-pot protection³ and glycosylation strategies,^{4,6} orthogonal assembly,^{7,8} polymer-supported⁹⁻¹¹ and automated synthesis,^{12,13} ionic liquid supported,^{14,15} fluororous tag assisted,^{16,17} and surface-tethered synthesis (STICS).¹⁸

The armed-disarmed approach for chemoselective oligosaccharide synthesis is occupying an important niche in the arsenal of available methods.^{19,20} for oligosaccharide synthesis. This strategy, introduced by Fraser-Reid et al., utilizes only one leaving group, and the building block reactivity is modulated entirely through the choice of protecting groups to allow the direct chemoselective coupling between an activated (armed) glycosyl donor **A1** and a deactivated (disarmed) glycosyl acceptor **A2** (Scheme 3.1A).¹⁹ Since the anomeric configuration of the product is influenced by the protecting group at O-2, a 1,2-*cis*-linked disaccharide is preferentially obtained in the first step, due to the use of the non-participating, ether-type (O-benzyl) arming substituent. The resulting disaccharide can then be used directly in subsequent glycosidation to form *cis-trans*-patterned oligosaccharides. Recent improvements have expanded the scope of the armed-disarmed methodology so that it can now be applied to a wider range sequences: *cis-cis* by using a

remote protecting group capable of powerful electron-withdrawal,^{21,22} *trans-trans* using picolinyl arming participating group,²³ and *trans-cis* patterned oligosaccharides by O2/O5 cooperative effect in glycosylation as we demonstrated in the previous chapter.²⁴



Scheme 3.1. Chemoselective strategies for oligosaccharide synthesis: A. Armed-disarmed; B. Conformational superarming; C. Electronic superarming

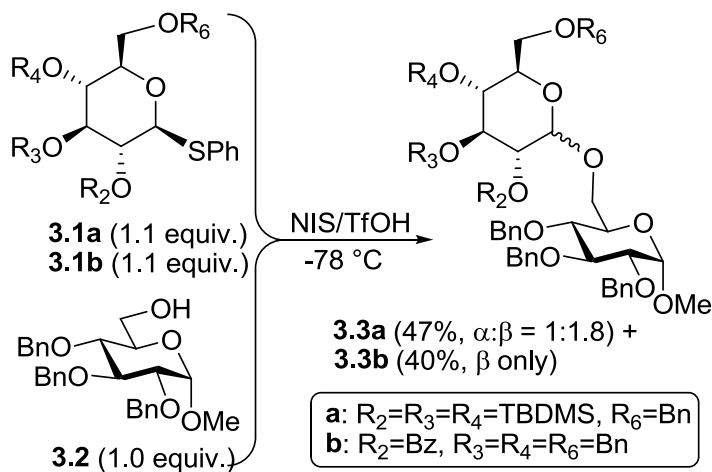
Derived from the discovery of the O2/O5 cooperative effect in glycosylation that showed how the mixed protecting group pattern could unexpectedly and profoundly affect glycosyl donor reactivity,²⁴ our group reported in 2008 that a glycosyl donor containing a

participating benzoyl group at C-2 and electron donating groups at the remaining positions is significantly more reactive (superarmed) than their armed per-benzylated counterparts.^{39,40} Thus, the glycosidation of 2-*O*-benzoyl-tri-3,4,6-*O*-benzyl protected SBox glucoside **C1** was affected with the corresponding armed glycosyl acceptor **C2** in the presence of dimethyl(methylthio)sulfonium triflate (DMTST), and the resulting disaccharide was isolated in 70% yield (Scheme 3.1C). This concept for superarming was found to be universally applicable to glycosidation of *O*-pentenyl, *S*-ethyl, *S*-phenyl, *S*-tolyl and *S*-thiazolanyl building blocks as investigated in chapter 2.⁴¹

Springing from a model study of the relative pK_a values for protonated heterocyclic amines wherein it was shown that equatorial substituents are significantly more deactivating than their axial counterparts,³¹ Bols' group reported in 2007 that conformationally modified glycosyl donors are significantly more reactive than their respective counterparts residing in ⁴C₁ conformation.³²⁻³⁴ In this study conformational changes were induced by creating steric congestion at the equatorial C-3 and C-4 positions.^{35,36} As such, the modified to a skew-boat conformation³⁷ glycosyl donor **B1** showed a dramatic 20-fold increase in reactivity relative to the traditional armed benzylated derivatives.³³ Furthermore, superarmed glycosyl donor **B1** could be successfully coupled with "armed" acceptor **B2** in the presence of NIS/TfOH at -78 °C to afford the corresponding disaccharide in 85% yield (Scheme 3.1B).³⁸

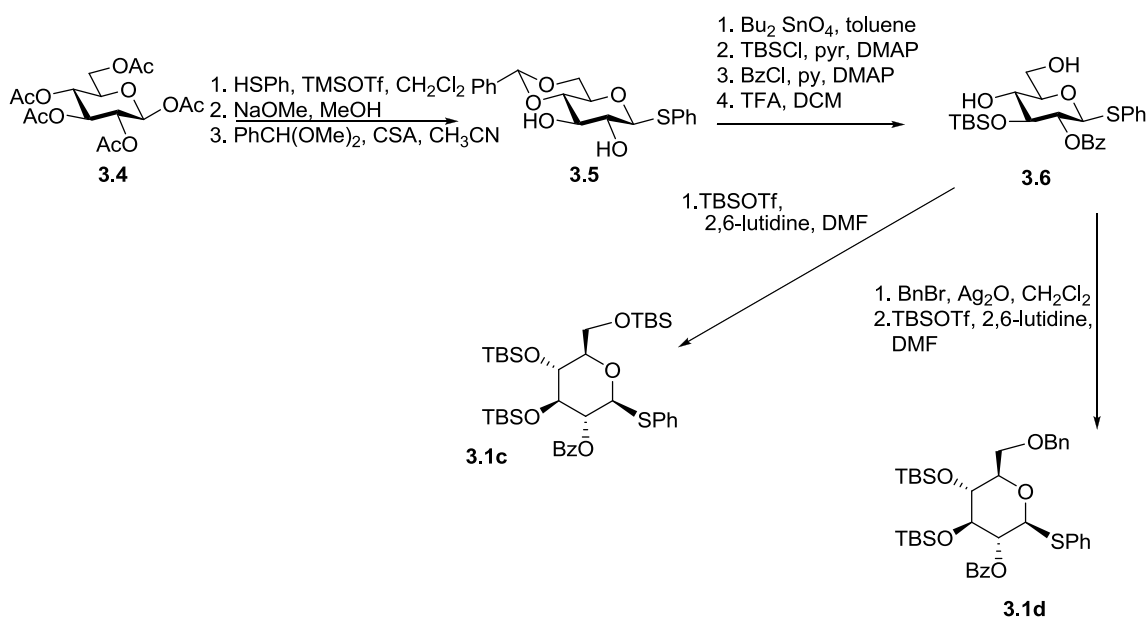
3.2 Comparing the reactivities of electronically and conformationally superarmed donors

With two different approaches to superarming of glycosyl donors, we wondered which superarmed donor is more reactive. To investigate this, we performed direct competition experiment wherein the conformationally superarmed glycosyl donor **3.1a** was set to compete with electronically superarmed glycosyl donor **3.1b** for glycosyl acceptor **3.2**⁴² (Scheme 3.2). The most reliable comparison was achieved in the NIS/TfOH-promoted competition experiment at $-78\text{ }^{\circ}\text{C}$, essentially the same reaction conditions as reported in Bols'et al. study, wherein the rate of the formation of disaccharide **3.3a** derived from the conformationally superarmed glycosyl donor **3.1a** was slightly higher. Ultimately, this was reflected in a slightly higher yield for disaccharide **3.3a** (47%), whereas disaccharide **3.3b** derived from the electronically superarmed donor **3.1b** was isolated in 40% yield.



Scheme 3.2. Competition experiment between conformationally superarmed donor **3.1a** and electronically superarmed donor **3.1b**

This result made us wonder whether further enhancement in reactivity could be achieved by using conventions of both conformational and electronic superarming approaches. To address this question and with the goal of incorporating all key structural features from both approaches into a single building block, we obtained glycosyl donors equipped with 2-O-benzoyl substituent and remote O-TBDMS substituents either at all remaining 3,4,6-positions (glycosyl donor **3.1c**) or at 3,4-positions in combination with 6-O-benzyl (glycosyl donor **3.1d**, Scheme 3.3).



Scheme 3.3 Synthesis of glycosyl donor **3.1c** and **3.1d**

Since the new building blocks are equipped with 2-O-benzoyl substituents, the stereoselectivity was expected to be excellent, which would be of benefit because the stereoselectivity obtained with donor **3.1a** bearing TBDMS at C-2 could be poor. From preliminary NMR experiments it has become apparent that the conformations of new glycosyl donors **3.1c** and **3.1d** have departed from the basic ⁴C₁ chair conformation, typical for most glucopyranose derivatives. The ¹H-NMR spectra recorded at room

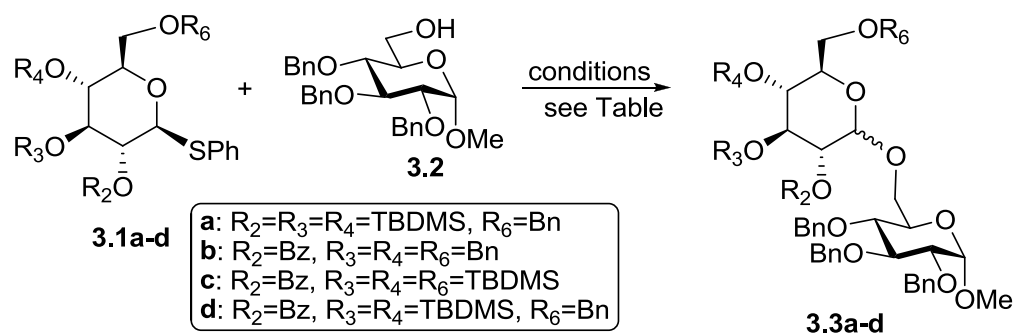
temperature showed sets of poorly resolved broad signals presumably due to the relatively slow equilibration between several conformers. The resolution of spectra recorded in DMSO could be enhanced at 80 °C presumably due to significantly faster equilibration between different conformations. Recording spectra at -40 °C in order to elucidate the conformational features of different contributors was proven cumbersome. Therefore, we turned our efforts toward computational methods that could reveal a number of energy minima conformers. Examination of the most stable conformations of these donors is still underway.

3.3 Comparative glycosylations

Having synthesized new glycosyl donors **3.1c** and **3.1d**, which indicated that the induced structural changes would be sufficient to enhance the reactivity of **3.1c** and **3.1d** via the conformational superarming concept, we turned our attention to investigating their glycosyl donor properties. For this purpose, we performed initial side-by-side comparison of glycosyl donors **3.1a-d** under standard reaction conditions (NIS/TfOH, -78 °C). The results of this study are summarized in Table 3.1. Somewhat unexpectedly, reaction of **3.1a** was significantly faster than that of **3.1b** performed at essentially the same reaction conditions (Entries 1 and 2). This large difference in reactivity was not clearly evident from our preliminary competition experiment (*vide supra*, Scheme 3.2) wherein similar reaction rates and yields of the resulting products have been observed. Consequent in-situ NMR monitoring of these reactions showed that the seemingly large difference in reactivity judged by the reaction time listed in Table 3.1 can be explained as follows.

While both reactions start relatively fast, glycosidation of **3.1a** gets surpassed by competing hydrolysis of the glycosyl donor (or a preactivated intermediate derived therefrom) resulting in a rapid consumption of **3.1a**. However, only 60% gets converted into the corresponding disaccharide **3.6a**, which was formed as a mixture of diastereomers since no participating group is present at C-2 (Entry 1). Very differently, after the initial fast reaction, further glycosidation of donor **3.1b** can be smoothly driven to completion with minimal or no side reactions observed or by-product formation detected. Resultantly, disaccharide **3.3b** was isolated in 96% yield (Entry 2).

Table 3.1. Comparative study of glycosyl donors **3.1a-d**.



Entry	donor	Conditions	time	Product, yield (α/β ratio)
1	3.1a	NIS/TfOH, -78 °C	10 min	3.3a , 60% (1:1.8)
2	3.1b	NIS/TfOH, -78 °C	2.5 h	3.3b , 96% (β only)
3	3.1c	NIS/TfOH, -78 °C	45 min	3.3c , 20% (1:1.0) ^[b]
4	3.1d	NIS/TfOH, -78 °C	10 min	3.3d , 70% (β only) ^[a]
5	3.1b	NIS/TMSOTf, -78 °C	3 h	3.3b , 95% (β only)
6	3.1d	NIS/TMSOTf, -78 °C	30 min	3.3d , 86% (β only) ^[a]

7	3.1b	MeOTf, 0 °C→rt	48 h	3.3b , 88% (β only)
8	3.1b	I ₂ , 0 °C	8 h	3.3b , 95% (β only)
9	3.1d	I ₂ , 0 °C	30 min	3.3d , 30% (β only)
10	3.1b	DMTST, -30 °C	2 h	3.3b , 90% (β only)
11	3.1d	DMTST, -30 °C	2 h	3.3d , 85% (β only) ^[a]
12	3.1a	NIS, rt	3 h	3.3a , 55% (1:1.0)
13	3.1b	NIS, rt	22 h	3.3b , 88% (β only)
14	3.1d	NIS, rt	3 h	3d , 85% (β only)

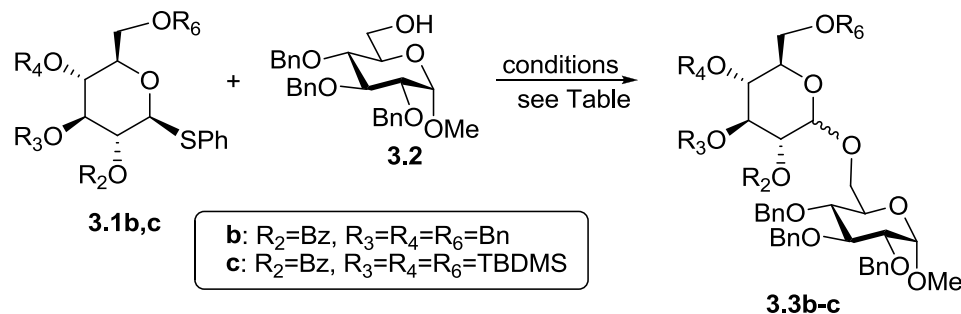
^[a] Presented yields are combined total yields for **3d** and partially desilylated disaccharide. The latter accounts for: entry 4 - 14%, entry 6 - 11%, and entry 11 - 45%. ^[b] 1,6-anhydride was observed in 75%.

Further experiments showed rather limited practicality of glycosyl donor **3.1c**, which showed very high propensity toward 6-O-silyl transfer to the 6-hydroxyl of glycosyl acceptor **3.2** followed by rapid self-condensation of the donor to afford the corresponding 1,6-anhydro derivative. Similar observations were made using methyl triflate and DMTST as promoters. To our surprise, disaccharide **3.3c** was forming as a mixture of anomers, sometimes with no stereoselectivity at all (Table 3.2).

To our understanding this was an indication that the participation of the 2-O-benzoyl substituent in **3.1c** is not sufficiently strong to provide anchimeric assistance to form β -glycosides stereoselectively. Hence, the superarming by electronic effect would be also very weak if at all possible. Therefore, further study of glycosyl donor **3.1c** was abandoned and we refocused our attention on studying glycosyl donor **3.1d** equipped

with stable 6-O-benzyl substituent. Very rapidly it has become apparent that glycosyl donor **3.1d** is able to provide higher yields for the formation of disaccharide **3.3d** (70%, Entry 4, Table 3.1). In addition, disaccharide **3.3d** was obtained with complete β -stereoselectivity.

We also noticed that some TBDMS groups would still migrate post-glycosylationally, for example disaccharide **3.3d** (Entry 4) contained about 14% of partially desilylated disaccharide. This finding served as a motivation for us to conduct a systematic search of other suitable reaction conditions that would have a positive impact on our comparative study. First, we were interested in identifying the reaction conditions that would allow for efficient differentiation of reactivity levels of different glycosyl donors. Second, from the practicality standpoint these conditions should provide high yields and clean reactions across the entire series of superarmed glycosyl donors. Upon screening common reaction conditions for the activation of thioglycosides^[43] we determined that NIS/TMSOTf, MeOTf, or I₂ allow for efficient differentiation of the reactivity levels of **3.1b** and **3.1d**. In all of these experiments glycosidation of donor **3.1d** was significantly faster than that of electronically superarmed donor **3.1b** (Entries 5-10, Table 3.1). And it is only in the presence of DMTST, donors **3.1b** and **3.1d** showed comparable rates of glycosylation (Entries 11 and 12). Iodine-promoted glycosidation of **3.1d** gave very modest result (30% of **3.3d**, Entry 10) because of a rapid transfer of a 3-O-TBDMS group of the donor to the primary hydroxyl of glycosyl acceptor **3.2**. Presumably, this was mediated by TBDMSI formed in situ.

Table 3.2: Comparative glycosylation studies of donor **3.1b** and **3.1c**

Entry	Donor	Promoter	Temp/ Time	Product	Yield (α/β ratio)
1	3.1b	DMTST	-30 °C/ 2 h	3.3b	90 (β only)
2	3.1c	DMTST	-30 °C/ 30 min	3.3c	65 (1:16.1)
3	3.1b	MeOTf	0 °C-rt/ 2 days	3.3b	88 (β only)
4	3.1c	MeOTf	0 °C-rt/ 2 days	3.3c	67 (1:1.3)
5	3.1b	NIS/TfOH	-30 °C/ 10 min	3.3b	90 (β only)
6*	3.1c	NIS/TfOH	-30 °C/ 10 min	3.3c	-

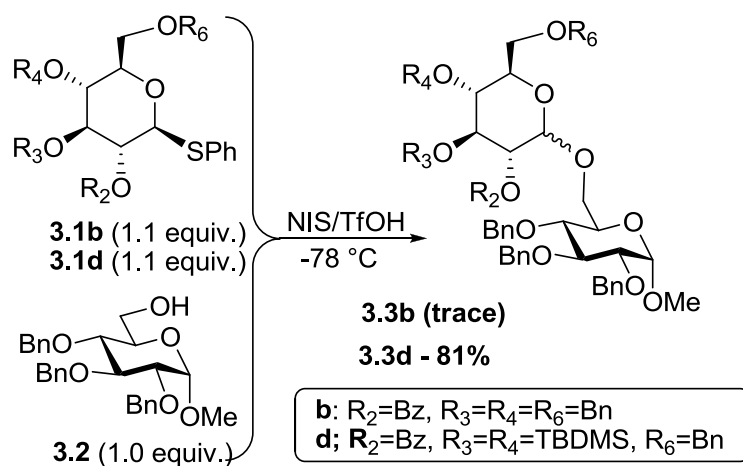
*1,6-anhydrosugar was isolated in 75% yield

General drawback of most glycosidations of **3.1d** is the presence of a partially desilylated disaccharide product. The amount of the deprotected products formed varied and in most reactions would not exceed 10-15%. Occasionally, significant amount of the deprotected disaccharide was observed (45%) like in DMTST-promoted glycosylation (Entry 12). And it is only in the presence of NIS with no additives at room temperature high yields and no desilylation was observed. Resultantly, the requisite disaccharide **3.3d** was

isolated in 85% yield (Entry 15). Based on the reaction times required to glycosidate donors **3.1a**, **3.1b**, and **3.1d** (Entries 13-15), one could assume that **3.1d** is closer in reactivity to the conformationally superarmed donor **3.1a** (both glycosylation were complete in 3 h) rather than that of the electronically superarmed donor **1b**, which required 22 h. As a verification of these results, we also deemed it necessary to carry out a series of competitive glycosylations where **3.1b**, **3.1d** and **3.1a** compete for the common acceptor.

3.4 Competitive glycosylation

In this study, glycosyl donor **3.1b** set to compete with donor **3.1d** for glycosyl acceptor **3.2** leading to the formation of disaccharide **3.3d** in 81%, while only trace amounts of disaccharide **3.3b** (<10%) could be detected (Scheme 3.4). In addition, the unreacted glycosyl donor **3.1b** was recovered in 86% yield.



Scheme 3.4 Competitive experiment between **3.1b** and **3.1d**

3.5 Conclusion

In conclusion, we have discovered differently reactive glycosyl donors through the use of bulky silyl protecting groups which allows for the conformational change in superarmed glycosyl donors. So far, the results evident that the donor **3.1d** is clearly more reactive than the previously discovered electronically superarmed donor **3.1b**. However, it shows almost similar reactivity to the conformationally superarmed donor **3.1a**. Further exploration of these superarming methods is very important in the field for chemoselective oligosaccharide synthesis.

3.6 Experimental

General remarks. Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F₂₅₄ (EM Science). The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at < 40 °C. CH₂Cl₂ and ClCH₂CH₂Cl were distilled from CaH₂ directly prior to application. Anhydrous DMF (EM Science) was used as is. Methanol was dried by refluxing with magnesium methoxide, distilled and stored under argon. Pyridine was dried by refluxing with CaH₂ and then distilled and stored over molecular sieves (3 Å). Molecular sieves (3 Å or 4 Å), 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. AgOTf (Acros) was co-evaporated with toluene (3 x 10 mL) and dried *in vacuo* for 2-3 h directly prior to application. DMTST was prepared in accordance to previously reported methods. Optical

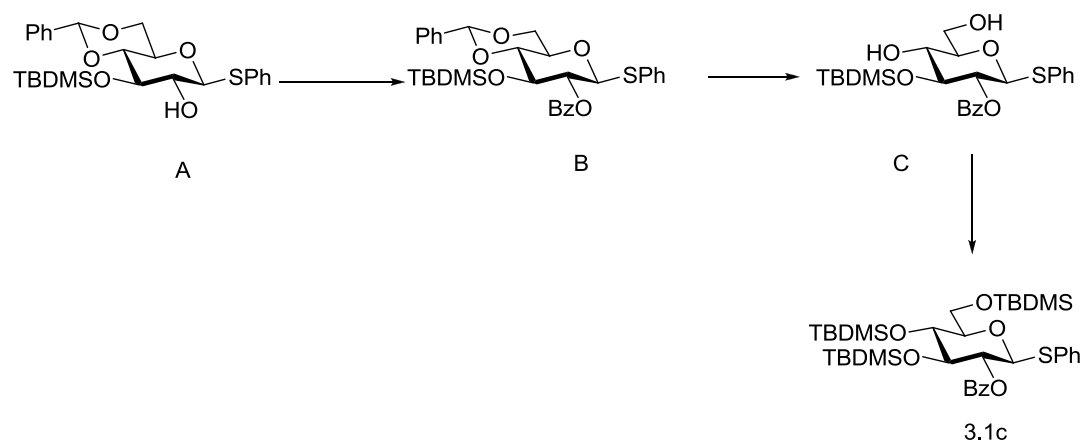
rotations were measured at 'Jasco P-1020' polarimeter. ^1H -n.m.r. spectra were recorded in CDCl_3 at 300 MHz, DMSO at 500 MHz, ^{13}C -NMR spectra were recorded in CDCl_3 at 500 MHz unless otherwise noted. HR FAB-MS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer, matrix *m*-nitrobenzyl alcohol, with NaI as necessary.

Synthesis of glycosyl donors

Phenyl 2-O-benzoyl-3,4,6-tri-O-benzyl-1-thio- β -D-glucofuranoside (3.1b) was obtained from the orthoester 3.2⁴⁰ in a procedure similar to that previously reported . Analytical data for the title compound was essentially the same as previously described¹⁰

Phenyl 6-O-benzyl-2,3,4-tri-O-tert-butyldimethylsilyl-1-thio- β -D-glucofuranoside (3.1a). Analytical data for the title compound was essentially the same as previously described⁴⁴

Methyl 6-O-(2-O-benzoyl-3,4,6-tri-O-benzyl- β -D-glucofuranosyl)-2,3,4-tri-O-benzyl- α -D-glucofuranoside (3.15) was obtained from 3.3 and 3.14 as a clear film. Analytical data for 3.15 is the same as reported previously.³⁴

Phenyl 2-O-benzoyl-3,4,6-tri-O-tert-butyldimethylsilyl-1-thio-β-D-glucopyranoside**(3.6)****Phenyl 3-O-tert-butyldimethylsilyl-4,6-O-benzylidene-1-thio-β-D-glucopyranosid A:**

The solution of phenyl 4,6-benzylidene-1-thio-β-D-glucopyranoside **3.5** (4.0 g, 12.82 mmol) was heated under reflux with Bu_2SnO (3.5 g, 14.10 mmol) in a flask equipped with a Dean-Stark device in anhydrous toluene (200 mL) for 3h and concentrated to approximately 50 mL. After cooling the reaction mixture down to room temperature, anhydrous DMF (77 mL) was added followed by addition of imidazole (3.1 g, 44.87mmol) and TBDMSCl (2.13 g, 14.10 mmol) and the obtained solution was stirred for 48 h at 130 °C. After the reaction was complete, DMF was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with water (100 mL), saturated NaHCO_3 (100 mL) and water (3×100 mL). The organic phase was dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford compound **A** in 92% yield. Analytical data for **A**: $R_f = 0.69$ (ethyl acetate-hexane, 2/3, v/v). ^1H -n.m.r (300 MHz, CDCl_3 , rt): δ , -0.05 (s, 3H), 0.02 (s, 3H), 0.79 (s, 9H), 2.48 (d, 1H, J =

2.6 Hz, OH), 3.31-3.39 (m, 3H, H-2, H-6a, H-6b), 3.633.71 (m, 2H, H-3, H-5), 4.26 (dd, 1H, $J_{2,3} = 4.23\text{Hz}$, H-2), 4.55 (d, 1H, $J_{1,2} = 9.84\text{ Hz}$, H-1), 5.41 (s, 1H, *CHPh*), 7.21-7.40 (m, 10H, aromatic) ppm.

Phenyl 2-O-benzoyl-3-O-tert-butyldimethylsilyl-4,6-O-benzylidene-1-thio- β -D-glucopyranosid (B). To a stirred solution of **A** (6.2 g, 14.55 mmol) and DMAP (0.5 g) in pyridine (24 mL) at 0 °C, was added dropwise benzoyl chloride (3.4 mL, 29.11 mmol). The reaction was stirred under argon for 30 minutes, upon which it was allowed to warm to 60 °C and continue stirring for 24 h. The reaction was quenched with dry MeOH (2 mL), and concentrated *in vacuo*. The residue was then diluted with CH_2Cl_2 (300 mL) and washed successively with water (50 mL), saturated NaHCO_3 (50 mL), water (3 x 50 mL), dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (Acetone – toluene gradient elution) to afford compound **B** in 89% yield. Analytical data for **B**: $R_f = 0.68$ (acetone-toluene, 1/19, v/v). $^1\text{H-n.m.r}$ (300 MHz, CDCl_3 , rt): δ -0.24 (s, 3H), -0.19 (s, 3H), 0.59 (s, 9H), 3.46-3.56 (m, 2H, H-4, H-5), 3.85-3.94 (m, 2H, H-6a, H-6b), 4.16-4.24 (m, 1H, H-3), 5.03 (d, 1H, $J_{1,2} = 10.1\text{Hz}$, H-1), 5.18 (dd, 1H, $J_{2,3} = 8.7\text{ Hz}$, H-2), 5.46 (s, 1H, *CHPh*), 7.19-7.99 (m, 15H, aromatic) ppm.

Phenyl 2-O-benzoyl-3-O-tert-butyldimethylsilyl-1-thio- β -D-glucopyranoside (C). Starting material **B** (3.4 g) was dissolved in 10% trifluoroacetic acid in CH_2Cl_2 (34 mL), followed by the addition of H_2O (0.1 mL). The reaction was stirred at room temperature for 2 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (100 mL),

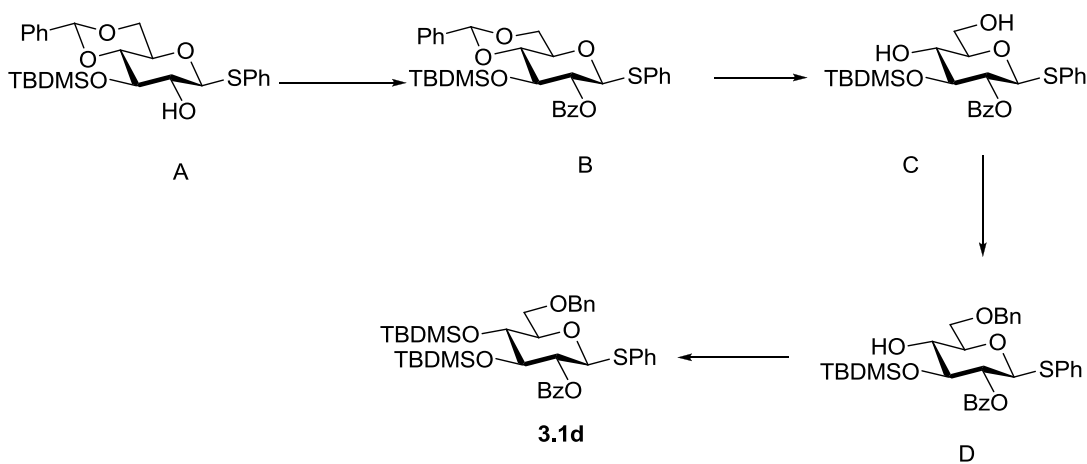
washed with water (50 mL), saturated NaHCO₃ (50 mL) and water (3×50 mL) dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford compound **C** in 75% yield. Analytical data for **C**: R_f = 0.38 (ethyl acetate-hexane, 2/3, v/v). ¹H-n.m.r (300 MHz, CDCl₃, rt): δ -0.14 (s, 3H), 0.07 (s, 3H), 0.75 (s, 9H), 2.37 (s, 1H, OH), 2.65 (s, 1H, OH), 3.46-3.49 (m, 1H, H-5), 3.67 (dt, 1H, H-4), 3.79-3.86 (m, 2H, H-6a, H-6b), 3.94-3.98 (m, 1H, H-3), 4.83 (d, 1H, J_{1,2} = 10.0Hz, H-1), 5.16 (t, 1H, J_{2,3} = 9.5Hz, H-2), 7.24-8.06 (m, 10H, aromatic) ppm.

Phenyl 2-O-benzoyl-3,4,6-tri-O-tert-butyldimethylsilyl-1-thio-β-D-glucopyranoside (3.1c). To a stirred solution of a **C** (0.5 g, 1.05 mmol) in DMF (5 mL) was added *tert*-butyldimethylsilyl triflate (0.96 mL, 4.20 mmol) at 0 °C, then 2,6-lutidine (0.25 mL, 2.10 mmol) was added. The resulting mixture was then heated to 150 °C. After 24 h the reaction was quenched with saturated NaHCO₃, and extracted with Et₂O (3× 50 mL). The organic layer was washed with water, HCl (1 N), and brine. The organic phase was dried over Mg₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane gradient elution) to afford the title compound as colorless syrup (0.660 g, 88 %). Analytical data for 3.6: R_f = 0.69 (ethyl acetate-hexanes, 1/4, v/v); ¹H-n.m.r (500 MHz, CDCl₃, rt): δ, 0.01 (br. s, 8H), 0.68 (br. s, 27H), 3.69 (br. m, 5H), 5.02 (m, 2H), 7.04-7.87 (m, 10H, aromatic) ppm. ¹³C NMR (300 MHz, CDCl₃): δ, -5.0, -4.3, -4.2, -4.0, -3.7, 18.1, 18.2, 18.6, 26.0 (×3), 26.1 (×3), 26.2 (×3), 64.0, 70.5, 74.5, 75.5, 83.5, 83.9, 127.3, 128.4 (×2), 128.9 (×2), 130.1 (×2), 130.2 (×2), 131.5 (×2), 133.3, 134.6, 165.6 ppm.

$^1\text{H-n.m.r}$ (500 MHz, DMSO, 50 °C): δ , 0.04 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.12 (s, 3H), 0.81 (s, 3H), 0.84 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 0.88 (s, 3H), 0.89 (s, 3H), 3.73-3.78 (m, 2H, H-5, H-6a), 3.83 (t, 1H, $J_{4,5} = 9.7$ Hz, H-4), 3.86-3.90 (m, 1H, H-6b), 4.03 (t, 1H, $J_{3,4} = 4.9$ Hz, H-3), 5.01 (dd, $J_{2,3} = 4.5$ Hz, H-2), 5.29 (d, 1H, $J_{1,2} = 8.7$ Hz, H-1), 7.27-7.97 (m, 10H, aromatic) ppm.

$^1\text{H-n.m.r}$ (500 MHz, CDCl_3 , -40 °C): δ , -0.05 (s, 6H), 0.03 (s, 6H), 0.08 (s, 6H), 0.71 (s, 9H), 0.90 (s, 18H), 3.63 (m, 2H, H-6a, H-6b), 3.70 (m, 1H, H-5), 3.84 (t, 1H, $J_{4,5} = 7.0$ Hz, H-4), 3.96 (m, 1H, H-3), 4.98 (d, 1H, $J_{1,2} = 9.8$ Hz, H-1), 5.19 (dd, 1H, $J_{2,3} = 7.2$ Hz, H-2), 7.21-8.04 (m, 10H, aromatic) ppm. HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{37}\text{H}_{62}\text{O}_6\text{SSi}_3\text{Na}^+$ 741.3473, found 741.3464.

Phenyl 2-O-benzoyl-6-O-benzyl-3,4-di-O-tert-butyldimethylsilyl-1-thio- β -D-glucopyranoside (3.1d)



Phenyl 2-O-benzoyl-6-O-benzyl-3,-O-tert-butyldimethylsilyl-1-thio- β -D-glucopyranoside (D). To a stirred solution of a C (2.0 g, 4.08 mmol) in CH_2Cl_2 (26 mL) was added Ag_2O (1.89 g, 8.16 mmol) followed by benzyl bromide (0.60 mL, 4.90 mmol).

The resulting mixture was heated to 30 °C. After 24 h the reaction mixture was filtered through Celite and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane gradient elution) to afford the title compound as colorless syrup (1.9 g, 80 %). Analytical data for **D**: $R_f = 0.78$ (ethyl acetate-hexanes, 2/3, v/v); $^1\text{H-n.m.r}$: δ , -0.25 (s, 3H, CH₃), -0.05 (s, 3H, CH₃), 0.62 (s, 9H, C(CH₃)₃), 2.45 (d, 1H, J = 4.7 Hz, OH), 3.44-3.54 (m, 2H, H-6a, H-6b), 3.66-3.72 (m, 3H, H-3, H-4, H-5), 4.47 (dd, 2H, $^2J = 10.2$ Hz, CH₂Ph), 4.67 (d, 1H, $J_{1,2} = 10.1$ Hz, H-1), 5.06 (t, 1H, $J_{2,3} = 9.9$ Hz, H-2), 7.07-7.95 (m, 15H, aromatic) ppm.

Phenyl 2-O-benzoyl-6-O-benzyl-3,4,-di-O-tert-butyltrimethylsilyl-1-thio- β -D-glucopyranoside (3.1d). To a stirred solution of a **D** (1.5 g, 2.59 mmol) in DMF (16 mL) was added *tert*-butyltrimethylsilyl triflate (1.19 mL, 5.17 mmol) at 0 °C, then 2,6-lutidine (0.60 mL, 5.17 mmol) was added. The resulting mixture was then heated to 150 °C. After 48 h the reaction was quenched with saturated NaHCO₃, and extracted with Et₂O (3 \times 100 mL). The organic layer was washed with water, HCl (1 N), and brine. The organic phase was dried over Mg₂SO₄ and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane gradient elution) to afford the title compound as colorless syrup (1.12 g, 62 %). Analytical data for 3.7: $R_f = 0.65$ (ethyl acetate-hexanes, 1/4, v/v); $^1\text{H-n.m.r}$ (500 MHz, DMSO, rt): δ , -0.01 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.73 (s, 9H), 0.81 (s, 9H), 3.56 (dd, 1H, $J_{5,6a} = 7.6$ Hz, $J_{6a,6b} = 10.1$ Hz, H-6a), 3.69-3.75 (m, 2H, H-4, H-6b), 3.87-3.91 (m, 1H, H-5), 4.06 (t, 1H, $J_{2,3} = 6.6$ Hz, H-3), 4.53 (dd, 2H, $^2J = 12.1$ Hz, CH₂Ph), 5.00 (dd, 1H, H-2), 5.29 (d, 1H, $J_{1,2} = 9.1$ Hz, H-1), 7.23-7.97 (m, 15H, aromatic) ppm.

$^1\text{H-n.m.r}$ (500 MHz, DMSO, 80 °C): δ , 0.05 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.84 (s, 18H), 3.69 (dd, 1H, $J_{6a-6b} = 10.2$ Hz, $J_{5,6a} = 6.6$ Hz, H-6a), 3.77 (dd, 1H, $J_{5,6b} = 5.36$ Hz, H-6b) 3.87 (t, 1H, $J_{4,5} = 4.2$ Hz, H-4), 3.98 (m, 1H, H-5), 4.03 (t, 1H, $J_{3,4} = 4.3$ Hz, H-3), 4.54 (dd, 2H, $^2J = 12.2$ Hz, CH_2Ph), 5.06 (dd, 1H, $J_{2,3} = 3.45$ Hz, H-2), 5.30 (d, 1H, $J_{1,2} = 8.1$ Hz, H-1), 7.23-7.98 (m, 15H, aromatic) ppm. HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{38}\text{H}_{54}\text{O}_6\text{SSi}_2\text{Na}^+$ 717.3076, found 717.3083.

Synthesis of glycosides

Method A: Typical DMTST-promoted glycosylation procedure: A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 200 mg) in $(\text{ClCH}_2)_2$ (1.6 mL) was stirred under an atmosphere of argon for 1 h. The mixture was chilled to 0 °C and DMTST (0.30 mmol) was added and the reaction mixture was stirred at 0 °C. Upon completion, the mixture was diluted with CH_2Cl_2 , the solid was filtered-off and the residue was washed with CH_2Cl_2 . The combined filtrate (30 mL) was washed with NaHCO_3 (10 mL) and water (3 x 10 mL). The organic phase was separated, dried with MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution).

Method B: Typical MeOTf-promoted glycosylation procedure: A mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3Å, 300 mg) in 1,2-dichloroethane (1.4 mL) was stirred under argon for 1 h. MeOTf (0.33 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Tables), the solid was filtered off and the residue was rinsed successively

with CH_2Cl_2 . The combined filtrate (30 mL) was washed with 20% NaHCO_3 (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO_4 and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate- hexane gradient elution) to afford the corresponding oligosaccharide.

Method C: Typical TMSOTf-promoted glycosylation procedure: A mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 150 mg) in 1,2-dichloroethane (2.5 mL) was stirred under argon for 1 h. TMSOTf (0.22 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Tables), the solid was filtered off and the residue was rinsed successively with CH_2Cl_2 . The combined filtrate (30 mL) was washed with 20% NaHCO_3 (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO_4 and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate- hexane gradient elution) to afford the corresponding oligosaccharide.

Method D: Typical NIS/TfOH-promoted glycosylation procedure: A mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 150 mg) in 1,2-dichloroethane (1.6 mL) was stirred under argon for 1 h. NIS (0.22 mmol) and TfOH (0.022 mmol) was added and the reaction mixture was monitored by TLC. Upon completion, the mixture was diluted with CH_2Cl_2 , the solid was filtered off, and the residue was rinsed successively with CH_2Cl_2 . The combined filtrate (30 mL) was washed with 10% $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO_4 and concentrated in *vacuo*. The residue was purified by

silica gel column chromatography (ethyl acetate- hexane gradient elution) to afford the corresponding oligosaccharide.

Method E: Typical NIS promoted glycosylation procedure: A mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 150 mg) in 1,2-dichloroethane (1.6 mL) was stirred under argon for 1 h. NIS (0.33 mmol) was added and the reaction mixture was monitored by TLC. Upon completion, the mixture was diluted with CH₂Cl₂, the solid was filtered off, and the residue was rinsed successively with CH₂Cl₂, The combined filtrate (30 mL) was washed with 10% Na₂S₂O₃ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate- hexane gradient elution) to afford the corresponding oligosaccharide.

Method F: Typical NIS/TMSOTf-promoted glycosylation procedure: A mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 150 mg) in 1,2-dichloroethane (1.6 mL) was stirred under argon for 1 h. NIS (0.22 mmol) and TMSOTf (0.022 mmol) was added and the reaction mixture was monitored by TLC. Upon completion, the mixture was diluted with CH₂Cl₂, the solid was filtered off, and the residue was rinsed successively with CH₂Cl₂, The combined filtrate (30 mL) was washed with 10% Na₂S₂O₃ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate- hexane gradient elution) to afford the corresponding oligosaccharide.

Method G: Typical iodine-promoted glycosylation procedure: A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3Å, 200 mg) in 1,2-DCE (1.6 mL) was stirred under an atmosphere of argon overnight. Iodine (0.30 mmol) was added and the reaction mixture was stirred at -25 °C, Upon completion, the reaction mixture was quenched with TEA, diluted with CH₂Cl₂ and the solid was filtered-off and the residue was washed with CH₂Cl₂. The combined filtrate (30 mL) was washed with Na₂S₂O₃ (10 mL) and water (3 x 10 mL), the organic phase was separated, dried with MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution).

Methyl 6-O-(2-O-Benzoyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (3.3b) was obtained from **3.1b** and **3.2** as a clear film. Analytical data for **3.3b** was essentially the same as previously described.⁴⁴

Methyl 6-O-(2-O-Benzoyl-3,4,6-tri-O-tert-butyldimethylsilyl-β-D-glucopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (3.3c) The title compound was obtained from **3.1c** and **3.2** by method A, B or D as a clear film. Selected analytical data for **3.3c**: R_f= 0.52 (ethyl acetate-hexanes, 1/4, v/v); ¹H-n.m.r (300 MHz, CDCl₃, rt): δ, 0.02 (s, 6H), 0.04 (s, 6H), 0.05 (s,6H), 0.07 (s, 6H), 0.08 (s, 6H), 0.12 (s, 6H), 0.86 (s, 27H), 0.89 (s, 27H), 3.24 (s, OCH₃), 3.37 (s, OCH₃), 3.99 (t, 1H, H-3), 4.13 (m, 1H, H-6b), 4.61 (s, 1H, H-1), 4.95 (s, 1H, H-1'), 5.06 (dd, 1H, H-2'), 7.09-7.97 (m, 40H, aromatic) ppm. ¹³C NMR (300 MHz, CDCl₃): δ, -5.3, -5.2, -4.3, -4.1, -4.0, -3.7, 18.1, 18.8, 19.2, 25.8 (×8), 55.2, 67.9, 69.8, 71.1, 71.2, 73.5, 73.6, 75.1, 75.2, 75.7, 77.4, 79.6, 79.9, 82.2,

98.5, 100.1, 127.6, 127.7 ($\times 3$), 128.3 ($\times 4$), 128.4 ($\times 3$), 128.5 ($\times 4$), 128.6 ($\times 4$), 130.8 ($\times 2$), 133.1, 138.4, 138.5, 138.6, 139.1, 166.4 ppm. HR-FAB MS $[M+Na]^+$ calcd for $C_{59}H_{88}O_{12}Si_3Na^+$ 1095.5481, found 1095.5479.

Methyl 6-O-(2-O-Benzoyl-6-O-Benzyl-3,4-di-O-tert-butyldimethylsilyl- β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (3.3d). The title compound was obtained from **3.1d** and **3.2** by method A, D-G as a clear film. Analytical data for **3.3d**: $R_f = 0.51$ (ethyl acetate-hexanes, 1/4, v/v); 1H -n.m.r (300 MHz, $CDCl_3$, rt): δ , -0.02 (s, 3H), 0.01(s, 3H), 0.02 (s, 3H), 0.08 (s, 3H). 0.80 (s, 9H), 0.81 (s, 9H), 3.20 (s, 3H, OCH₃), 3.40-3.46 (m, 2H, H-2, H-4), 3.62-3.95 (m, 8H, H-3, H-5, H-6a, H-3', H-4', H-5', H-6'a H-6'b), 4.12 (d, 1H, $J = 9.1$ Hz, H-6b), 4.46 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1), 4.36 (d, 1H, $^2J = 10.7$ Hz, $\frac{1}{2} CH_2Ph$), 4.48-4.73 (m, 7H, $\frac{7}{2} CH_2Ph$), 4.91 (d, 1H, $J_{1,2'} = 6.5$ Hz, H-1'), 5.06 (dd, 1H, H-2'), 7.06-7.95 (m, 25H, aromatic) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ , -4.3, -4.1, 4.0, -3.8, 18.1, 18.2, 26.1 ($\times 5$), 55.2, 67.9, 69.8, 71.1, 71.2, 73.5, 73.6, 75.1, 75.2, 75.7, 77.4, 79.6, 79.9, 82.2, 98.1, 100.2, 127.6, 127.7 ($\times 3$), 128.0 ($\times 4$), 128.3 ($\times 4$), 128.4 ($\times 4$), 128.5 ($\times 4$), 128.6 ($\times 4$), 130.8 ($\times 2$), 133.1, 138.4, 138.5, 138.6, 139.1, 165.4 ppm. HR-FAB MS $[M+Na]^+$ calcd for $C_{60}H_{80}O_{12}Si_2Na^+$ 1071.5086, found 1070.5070.

Methyl 6-O-(6-O-Benzyl-2,3,4-tri-O-tert-butyldimethylsilyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (3.3a). The title compound was obtained from **3.1a** and **3.2** by method D or E as a clear film. Selected analytical data for **3.3a β** : $R_f = 0.49$ (ethyl acetate-hexanes, 1/4, v/v); 1H -n.m.r (300 MHz, $CDCl_3$, rt): δ , -0.02 (s, 3H),

0.01(s, 3H), 0.02 (s, 3H), 0.08 (s, 3H). 0.79 (s, 9H), 0.80 (s, 9H), 0.81 (s, 9H), 3.20 (s, 3H, OCH₃), 3.42-3.47 (m, 2H, H-2, H-4), 4.46 (d, 1H, J_{1,2} = 3.3 Hz, H-1), 4.66 (t, 1H, J_{2,3} = 5.9 Hz, H-3'), 4.94 (d, 1H, J_{1',2'} = 11.0 Hz, H-1'), 7.06-7.95 (m, 20H, aromatic) ppm. HR-FAB MS [M+Na]⁺ calcd for C₅₉H₉₀O₁₁Si₃Na⁺ 1081.5791, found 1081.5702.

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CHAPTER 4

Toward a better understanding of the reactivity of sialosides

4.1 Introduction

While the prior three chapters have focused on the reactivity variations of neutral sugars (glucose, galactose and mannose) by the electronic nature of the O-2/O-5 cooperative effect and the conformational effects, this chapter explores the reactivity of the sialic acids donors and the ultimate goal is to compare those reactivities with neutral sugars. Sialic acids structure is different from neutral sugars and these are nine carbon monosaccharides which is a diverse family of naturally occurring 2-keto-3-deoxy-nononic acids that are involved in wide range of biological processes.^{1,2} Their unique structure is characterized by the presence of a carboxylic group (ionized at physiological pH), deoxygenated C-3, glycerol chain at C-6, and differently functionalized C-5 (figure 4.1). The sugar ring of Neu5Ac has a ²C₅ conformation in which the bulky side chain and C-5 acetamido moiety adopt equatorial orientations (figure 4.1).

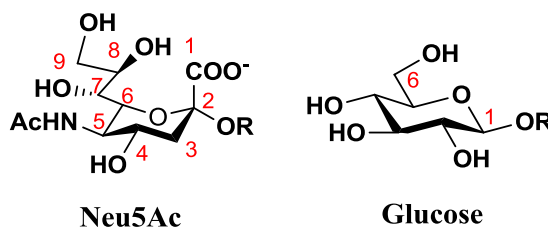


Figure 4.1 Sialic acid and glucose

Among the 50 derivatives so far reported, N-acetylneuraminic acid (5-acetamido-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosonic acid, Neu5Ac) is the most widespread, although N-glycolylneuraminic acid (Neu5Gc) and 2-keto-3-deoxy-D-glycero-D-galacto-non-2-ulopyranosonic acid (KDN) which is an important form of

sialic acid that does not have an amino functionality are also commonly found in biological systems (Figure 4.2).^{1, 2}

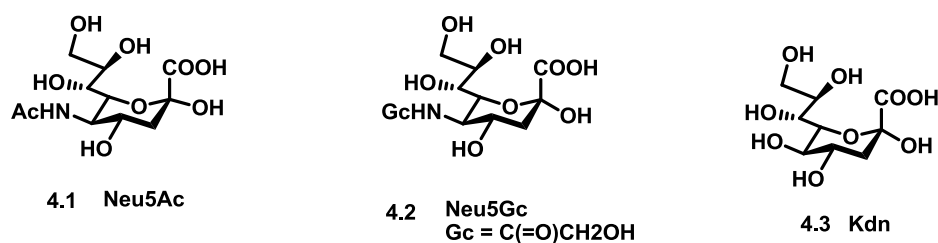


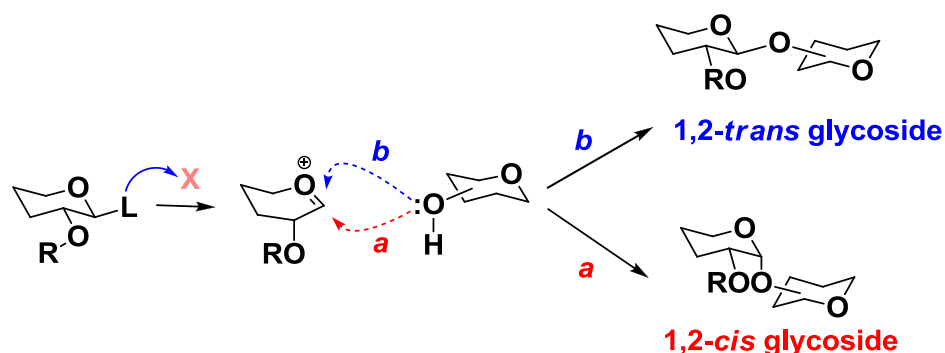
Figure 4.2 Major naturally occurring sialic acids.

Most sialic acids occur as glycosides of oligosaccharides, glycoproteins and glycolipids. Sialic acids appear essentially at the terminal position, in which they are most commonly found (α 2-3) - or (α 2-6)-glycosidically linked to galactose or (α 2-6)-linked to N-acetylgalactosamine. Being at the terminus of natural cell-surface glycoconjugates, sialic acids are ideally positioned to mediate carbohydrate-protein interactions in cell-cell recognition phenomena. For example, sialic acids are involved in the sialyl Lewis X-section binding that occurs in the recruitment of leukocytes during the inflammation process. Also sialic acids act as receptors for some microbial toxins, for microbial adhesion which mediate attachment to a host cell and for animal lectins that are important for cell-cell adhesion. Sialic acids also play important roles as masks to prevent biological recognition.³ For example, acetylation of the C-9 hydroxyl prevents this monosaccharide to be a receptor for the attachment of influenza A and B viruses.⁴ Modifications of sialic acids can interfere with the mode of cell interaction. For example, O-acetylation or N-acetyl hydroxylation hinders the action of sialidases leading to a longer lifespan of rat erythrocytes.⁵ Advances in both chemical and enzymatic synthesis have provided reliable routes to the production of many complex sialosides. These

compounds are of key importance to determine the biological roles of these glycoconjugates.

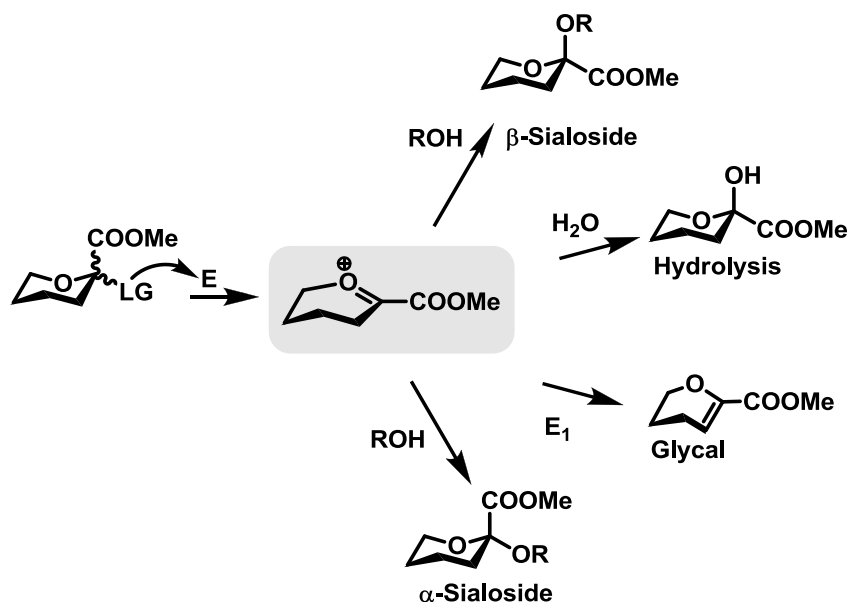
4.2 Chemical synthesis and reactivity of sialosides

Glycosidic bond formation is generally achieved by condensing a fully protected glycosyl donor, which bears a potential leaving group at its anomeric center, with a suitably protected glycosyl acceptor that often contains only one free hydroxyl group. The nature of the protecting group at C-2 of the glycosyl donor is a major determinant of the anomeric reactivity as we discussed in the previous chapters. The C-2 protecting group which performs neighboring group participation can favor the 1, 2-trans glycosidic linkage. If no participating functionality is present at C-2, the reaction conditions (solvent, temperature, and promoter) will become main factors to determine the anomeric selectivity. Also, the constitution of the glycosyl donor and acceptor (e.g., type of saccharide donor, leaving group at the anomeric center, protection and substitution pattern) have a major effect on the stereoselectivity (Scheme 4.1).



Scheme 4.1 Typical glycosylation reaction

Glycosylations of sialic acid donors which is called chemical sialylation is an important method used to synthesize homogeneous sialylated glycoconjugates. Glycosides of N-acetylneuraminic acid can be introduced by similar glycosylation approaches, and these coupling procedures are classified as direct methods. The direct method of O-sialylation happens in one synthetic step involving a coupling of glycosyl accepter having free hydroxyl group and a donor with an appropriate leaving group at C-2. The use of glycosyl donor of Neu5Ac is, however, complicated by the fact that no neighboring C-3 functionality is present to direct the stereochemical outcome of glycosylations. In fact, upon leaving group departure, the oxacarbenium ion is destabilized by the electron-withdrawing carboxylate functionality at C-1. In addition, the lack of a participating group at C-3 results in nucleophilic attack from the top or bottom of the intermediate (Scheme 4.2). The other possible side reactions are hydrolysis, as well as the synthesis of a 2,3-dehydro derivative due to elimination.



Scheme 4.2 Typical sialylation reaction

To be summarized, the accomplishment of sialylation reactions in high yields with excellent stereoselectivity is still a challenge due to the peculiar structure of sialic acid:

1. No neighboring C-3 functionality that can direct the stereochemical outcome of glycosylations;
2. The electron withdrawing carboxylic acid at the anomeric center, which may favor the formation of glycal (2,3-dehydro derivative);
3. Sterically hindered C-2 position that blocks the approach to the hydroxyl group of an acceptor.

To address these problems alternative chemical methodologies and strategies focusing on the structure of sialyl donor have been developed in the field, primarily focusing on solvent, leaving groups and promoters. The introduction of participating auxiliaries at the C-3 position (indirect method) also has been investigated.^{6, 7} In addition, modifications of the C-1 carboxyl group^{8, 9} as well as modification of C-5 acetamido group,^{10,11,12} have been reported as alternative strategies to optimize chemical sialylation. Among these, C-5 modifications have been probably the most exploited. N-acetylacetamido (NAC₂)¹⁰, azido (N₃)¹³, N-trifluoroacetyl (NHTFA)¹⁴, N-trichloroethoxycarbonyl (NHTroc)¹⁵, 5-N,4-O-oxazolidinone¹⁶ and its N-acetylated version¹¹ are the common C-5 structural modifications available in the area.

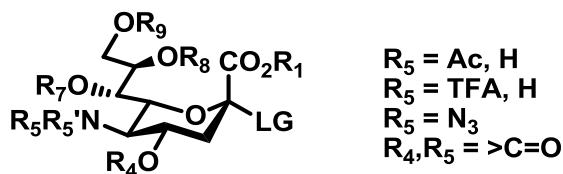


Figure 4.3 modifications of C-5 acetamido group

Herein we are interested in 5,4-N,O-oxazolidinone protected sialosides which are generally considered more reactive than N-acetylacetamido derivative but slightly lower than the corresponding N-trifluoroacetamido derivative (NTFA). It has also demonstrated that the oxazolidinone fused ring enhances the stereoselectivity of glycosylation reactions with the large number of acceptors. Thus 5,4-N,O-oxasolidinine donors are established as a versatile intermediate for the stereoselective synthesis of a (2, 3) and a (2, 6)-linked sialosides.

4.3 Effect of C-5 modification (5,4-N,O-oxazolidinone) on the reactivity of sialyl donors

4.3.1 Comparative studies with neutral sugars

4.3.1.1 Comparative studies with glucose

To complement classic armed-disarmed theory, our recent studies revealed that certain mixed protecting group patterns of neutral sugars can significantly affect reactivity of building blocks in glycosylation (detailed discussion on chapter 1-3). Thus the discovery of superarmed glycosyl donors^{17,18,19}, which along with an earlier discovery of O-2/O-5 cooperative effect in glycosylation (superdisarmed donors)²⁰ created an excellent toolkit for expeditious oligosaccharide synthesis. Superarmed glycosyl donors are more reactive than the traditional armed donors and Superdisarmed donors even less reactive than additional disarmed donors as shown in Figure 4.4. Certain observations of the reactivity have already been made with building blocks of other.^{17,21} It is well known that deoxy sugars are much more reactive than the corresponding neutral sugars. Furthermore, the

acidic sugars (uronic acids) are much less reactive than their neutral counterparts. To this end the reactivity of glycosyl donors derived from sialic acids has been deemed low in comparison to the neutral sugars (galactose). Recent advances in the field discovered modified sialic acid donors (Figure 4.3) which are significantly more reactive than classic sialosyl donors (NAc). It still remains uncertain how their reactivity would compare to neutral sugars.

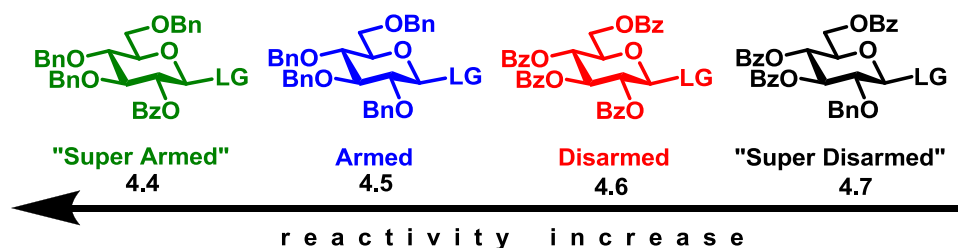
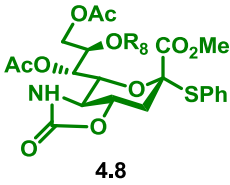
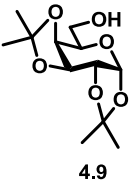
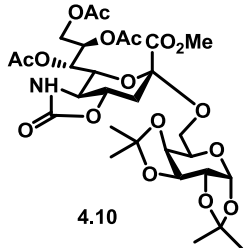
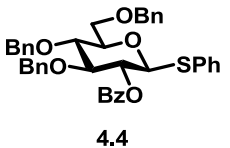
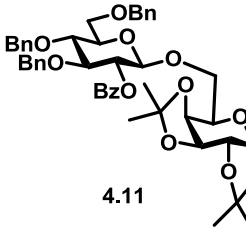
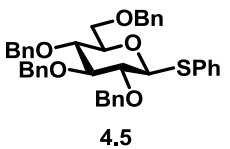
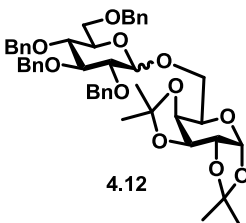
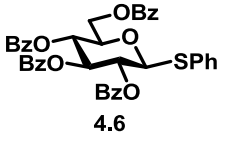
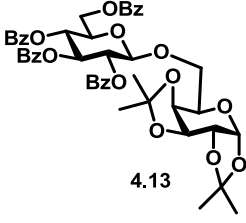
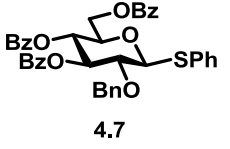
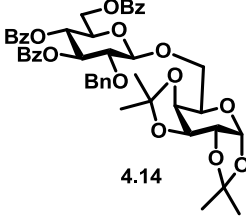


Figure 4.4 Reactivity sequences of neutral sugars (glucose)

We would like to address this challenge by investigating the relative reactivities of 5-N-4-O-oxazolidinone protected phenylthio donor and neutral sugars through comparative glycosidations. We have synthesized 5,4-N,O-oxazolidinone protected phenylthio donor **4.8**¹⁶ and the series of glucose donors (**4.4-4.7**) by the well-known procedures. It is important to note, that in order to easily differentiate among the reactivity levels of the various substrates, the choice of activator (promoter) is key. Thus upon investigating a range of activators we selected N-iodosuccinimide (NIS) and triflic acid to be the most suitable promoter. As such, the results of the NIS/ TfOH mediated glycosylations in 1, 2-dichloroethane are summarized in Table 4.1. These comparative glycosylations were performed in acetonitrile at -40 °C which are the established conditions for a better α -stereoselectivity (kinetic product) and good yields¹⁶. Glycosylation of the 5,4-N,O-oxazolidinone protected donor **4.8**²² with glycosyl acceptor **4.9** proceeded smoothly and

Table 4.1 Comparative glycosylation studies of 5,4-N,O-oxazolidinone donor **4.8** with neutral sugars (glucose)

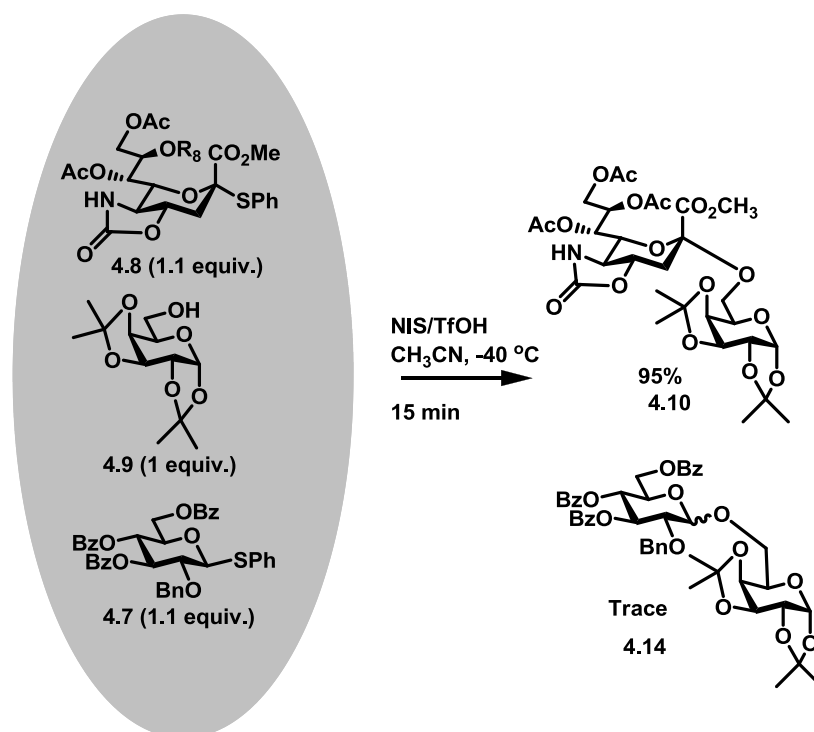
Entry	Donor	Acceptor	Temp/Time	Disaccharide	Yield/Ratio
1	 <p>4.8</p>	 <p>4.9</p>	-40 °C/ 30 min	 <p>4.10</p>	99% (16.0:1)
2	 <p>4.4</p>	4.9	-40 °C/ 5 min	 <p>4.11</p>	85% (β only)
3	 <p>4.5</p>	4.9	-40 °C/ 10 min	 <p>4.12</p>	83% (1:7.4)
4	 <p>4.6</p>	4.9	-40 °C/ 30 min	 <p>4.13</p>	88% (β only)
5	 <p>4.7</p>	4.9	-40 °C/ 2 days	 <p>4.14</p>	80% (1:12.0)

was completed in 30 minutes affording the corresponding disaccharide **4.10** in 99% yield with very good α selectivity (Entry 1, Table 4.1). Then the reactions of the superarmed, armed, disarmed and superdisarmed glycosyl donors (**4.4** - **4.7** respectively) with glycosyl acceptor **4.9** were set up under essentially the same reaction conditions in order to compare the reactivities. As expected our superarmed donor **4.4**²³ reacted nearly instantaneously, to provide disaccharide **4.11** in 85% yield with β stereoselectivity due to the participating group at C-2 position (Entry 2). Glycosylation of armed donor **4.5**²⁴ with the acceptor **4.9** proceeded smoothly within 10 minutes to afford the disaccharide **4.12** in 83% yield and good α -stereoselectivity due to the solvent effect. However, the disarmed donor **4.6**²⁵ showed the same reactivity as the sialyl donor **4.4** to afford the disaccharide **4.13** in 88% yield (Entry 4). Interestingly the superdisarmed donor **4.7** was clearly less reactive than the sialyl donor **4.4** and obtained 80% of the corresponding disaccharide **4.14** within 2 days (Entry 5). According to these comparative glycosylation experiments, it is clear that the 5,4-N,O-oxazolidinone protected sialyl donor **4.8** is more reactive than the superdisarmed donor **4.7** in the glucose series, While showing similar reactivity to the disarmed donor **4.6**²⁵ these reaction conditions.

4.3.1.2 Competitive glycosylations

As a verification of these results, we also deemed it necessary to carry out a series of competitive glycosylations, wherein both the superdisarmed donor and sialyl donor (**4.7** and **4.8** respectively), would be placed in the same reaction vessel with the glycosyl acceptor **4.9**. Upon addition of the promoter (NIS/TfOH) at -40 °C, the two glycosyl donors would then compete to react with the one equivalent glycosyl acceptor **4.9**. As depicted in Scheme 4.3, the 5-N-4-O-oxazolidinone protected glycosyl donor **4.8** was

clearly significantly more reactive than its superdisarmed glucose analogue **4.7** and led to the formation of the corresponding disaccharide **4.10** which contained trace amount of disaccharide **4.14**²⁶ for a combined yield of 95%. In addition, the unreacted glycosyl donor **4.7** was recovered in 96% yield.

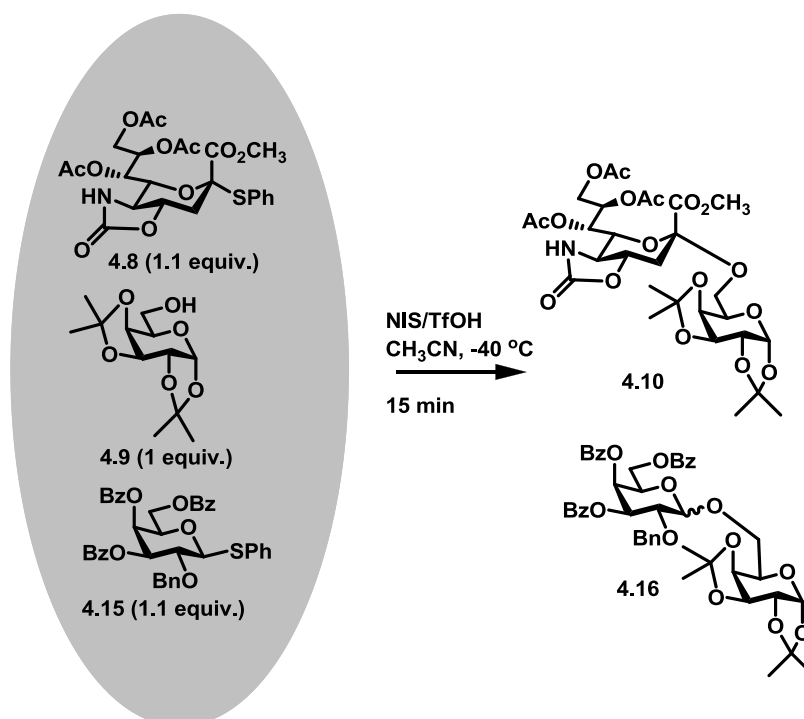


Scheme 4.3 Competitive glycosidations of glycosyl donors **4.7** and **4.8** with glycosyl acceptor **4.9** in the presence of NIS/TfOH

4.3.1.3 Comparative studies with galactose

Having compared the reactivity with glucose donors, our attention turned to the comparative studies of 5,4-N,O-oxazolidinone protected sialyl donor with galactose moieties. It is well known that galactose sugars are more reactive than their glucose counterparts and N-acetylneuraminic acid is less reactive than galactose. Therefore the reactivity comparison between 5,4-N,O-oxazolidinone protected sialyl donor and

galactose sugars are equally important for the establishment of the reactivity of C-5 modified sialyl donors. Investigation into the reactivity of 5,4-N,O-oxazolidinone protected sialyl donor **4.8** with superdisarmed galactose donor **4.15**²⁷ in a similar fashion to that of our competitive studies with the superdisarmed glucose moiety.



Scheme 4.4 Competitive glycosidations of glycosyl donors **4.8** and **4.15** with glycosyl acceptor **4.9** in the presence of NIS/TfOH

As seen in Scheme 4.4, upon addition of the promoter (NIS/TfOH) at -40 °C, the two glycosyl donors (**4.8** and **4.15**) would compete to react with the one equivalent glycosyl acceptor **4.9**. From the results of that experiment the 5,4-N,O-oxazolidinone protected glycosyl donor **4.8** was clearly significantly more reactive than its superdisarmed galactose analogue **4.15** as well. It led to the formation of the corresponding disaccharide

4.10 which contained trace amount (~10%) of disaccharide **4.16** for a combined yield of 60%. In addition, the unreacted glycosyl donor **4.15** was recovered in 76% yield.

4.3.2 Rationalization

Overall, the results of these investigations strongly suggest that the 5,4-N,O-oxazolidinone protected sialyl donor is more reactive than the superdisarmed glucose and galactose counterparts. This is evident that the C-5 modifications can enhance the reactivity of sialyl donors and it will be very important synthetic targets towards the biologically important sialylations.

4.4 Study of the C-5 modification effect on the stereoselectivity

Having investigated the effect of C-5 modifications on reactivity of sialosides we subsequently turned our attention towards the stereoselective synthesis of sialosides through the use of C-5 modifications. From the first modification as N-acetylacetamido and N-trifluoroacetamido by Boons et al.;¹⁴ to the azido modification by Wong; to the oxazolidinone trans-fused ring and its N-acetyl derivative, investigated by Tahakashi, De Meo and Crich, it has been a general belief that C-5 modifications can dramatically improve the synthesis of α -sialosides. Thus, we were extremely intrigued by coming across a modification as N-benzoyl acetamido that led to the unnatural β -anomer in all of the sialylations reactions tested with per-benzoylated donor **4.17**, as reported by Ye et al.¹² The use of per-benzoylated donor, which is not so common in sialic acid chemistry, raises the question if it is the C-5 modification or rather the presence of O benzoyl groups

that actually lead to the β stereoselectivity. To answer this question we synthesized serious of sialyl donors **4.17** and **4.18-4.20** which are benzoylated only at C-5 with different leaving groups and primary glycosyl acceptors for initial screening experiments (Figure 4.5).

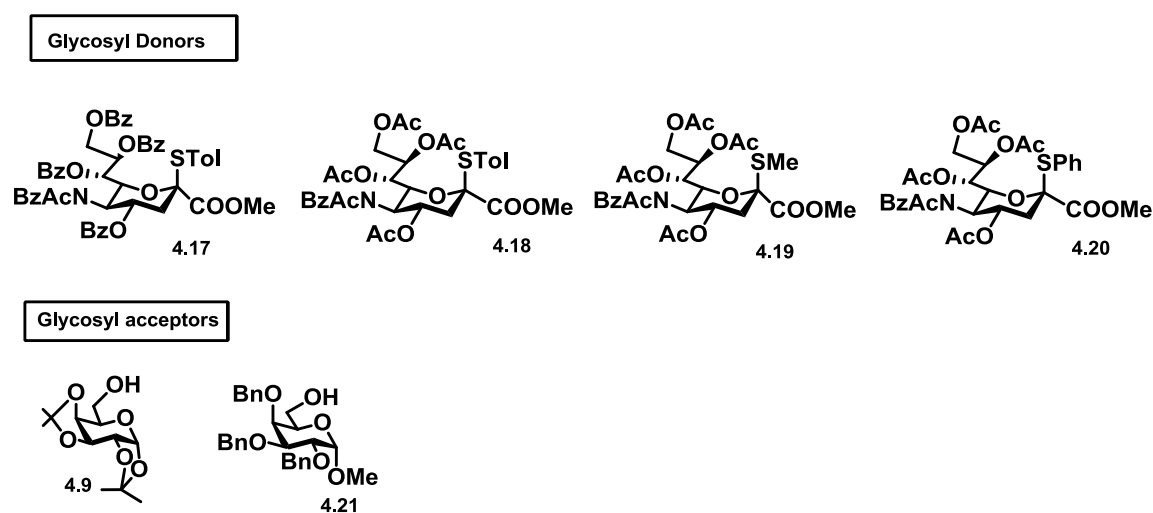
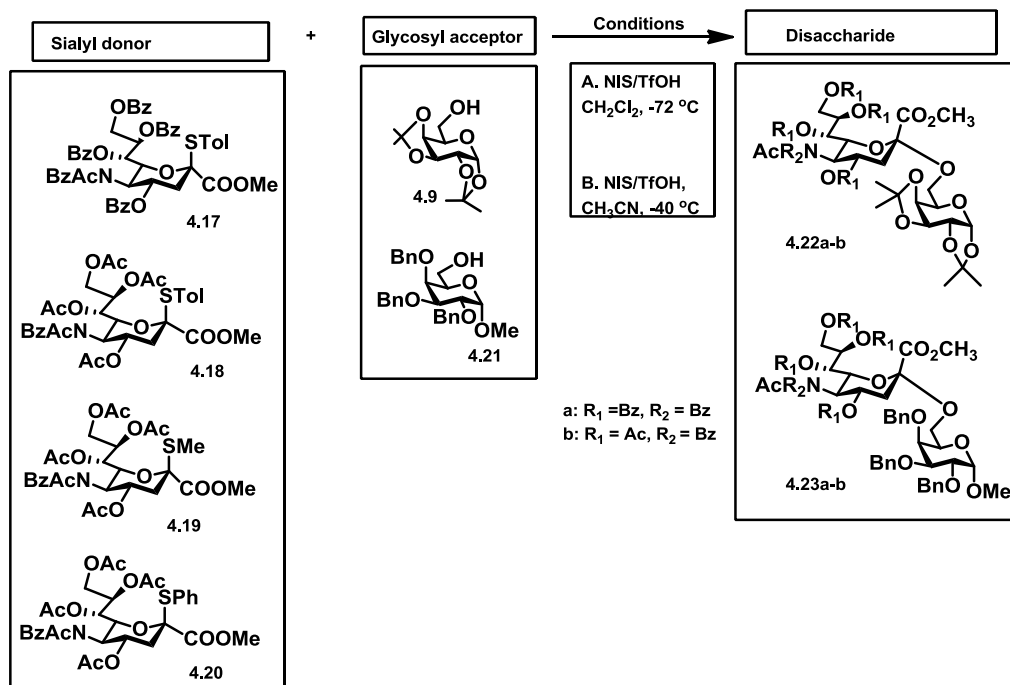


Figure 4.5. Sialyl donors and primary glycosyl acceptors for initial screening.

In fact, the coupling between per-benzoylated S-tolyl (STol) sialyl donor **4.17** with glycosyl acceptor **4.9** and **4.21** led to high yields of the β -anomer in the presence of different promoters (Table 4.2, Entries 1 and 2). Sialosyl donors **4.17 to 4.20** were coupled with acceptors **4.9** and **4.21** under various reaction conditions. The reactions performed in acetonitrile were carried out at $-40\text{ }^{\circ}\text{C}$, while the reactions in dichloromethane were performed at $-72\text{ }^{\circ}\text{C}$. Each reaction was performed using NIS/TfOH as promoter and in the presence of molecular sieves 3 \AA in order to minimize hydrolysis. It is noteworthy to mention that the introduction of a benzoyl group at C-5 creates two rotamers at the C-5-N bond. Hence in order to achieve high resolution of

signals, all ^1H NMR spectra were recorded at 80 °C in DMSO, whereas spectra recorded at -40 °C clearly show two distinctive groups of signals corresponding to each rotamer.

Table 4.2 Comparison of donors **4.18-4.20** with donor **4.17** by coupling with acceptor **4.9** and **4.21**.



Entry	Donor	Acceptor	Conditions	Product	Yield	Ratio ($\alpha:\beta$)
1	4.17	4.9		4.22a	86	1:6.7
2	4.17	4.21		4.23a	90	β
3	4.18	4.9		4.22b	62	2.0:1
4	4.18	4.21	A	4.23b	86	1.0:1

5	4.19	4.9	4.22b	64	5.8:1
6	4.19	4.21	4.23b	85	1.7:1
7	4.20	4.9	4.22b	65	1:1.2
8	4.20	4.21	4.23b	70	1.0:2
<hr/>					
9	4.17	4.9	4.22a	94	1:1.8
10	4.17	4.21	4.23a	95	1:1.6
11	4.18	4.9	4.22b	75	1.7:1
12	4.18	4.21	4.23b	80	1.3:1
13	4.19	4.9	4.22b	74	1.4:1
14	4.19	4.21	4.23b	86	1.0:1
15	4.20	4.9	4.22b	75	1.4:1
16	4.20	4.21	4.23b	79	1.2:1

The initial comparative testing of sialosyl donors **4.17-4.20** with glycosyl acceptors **4.9** and **4.21** (1.5 equiv.) were performed using the conditions **A** and **B**. These comparative studies clearly show that while per-N,O-benzoylated donor **4.17** provides superior β -selectivity (Entries 1 and 2), partially benzoylated STol donor **4.18**, SPh donor **4.20** and SMe donor **4.19** showed significantly lower preference for the beta-sialylation.(Table 4.2). Since a vast majority of chemical sialylations are performed in CH₃CN, and the solvent effect is known to be the most significant factor to obtain high α stereoselectivity in sialylations, we decided to investigate whether the participating solvent can significantly impact the stereoselectivity of these sialylation reactions. Under the reaction condition **B** (in the presence of participating solvent) sialosyl donor **4.17** again showed

more β selectivity (Entries 9, 10). However, other partially benzoylated donors (**4.18-4.20**) did not observe that trend (Entries 11-16). According to these results we do not see any trend of getting good β stereoselectivity due to the C-5 modification (NAcBz). We only observed good β stereoselectivity with the per-benzoylated donor **4.17**.

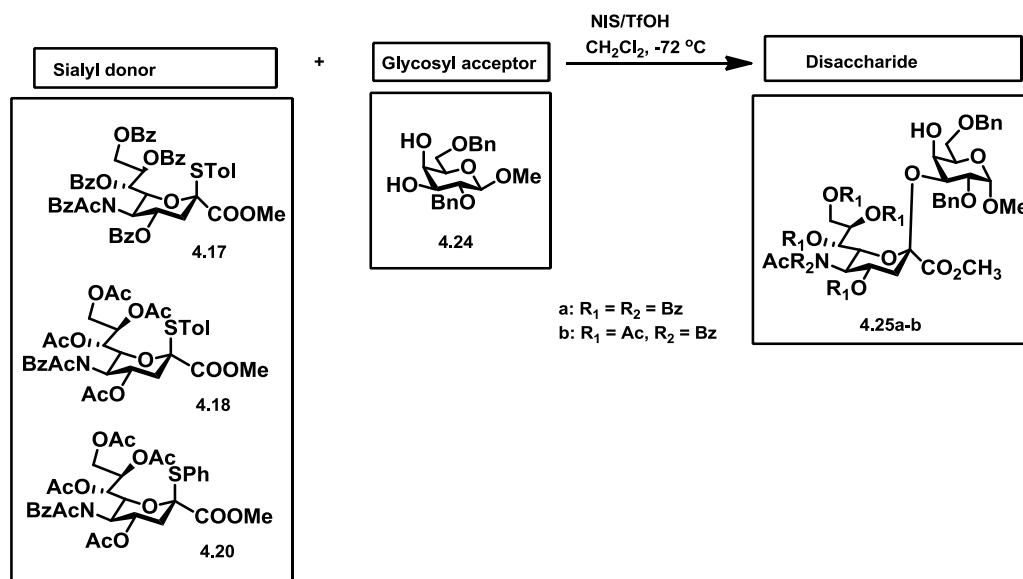
Having investigated the effect of primary acceptors, we turned our attention to the secondary hydroxyl acceptors to get the broader view of this effect. Partially protected galactoside acceptor **4.24**²⁸ was selected for these studies. As reported by Ye et al.,¹² again we observed pure β -selectivity with of the per-benzoylated donor **4.17** (Entry 1, Table 4.3). However, as expected we did not see considerable selectivity of partially benzoylated donor **4.18** and **4.20** with the secondary acceptor **4.24**. Donor **4.18** gave 1:1 and donor **4.20** gave 1.8:1 mixtures of diastereomers (Entries 2 and 3, respectively). These observations follow the same trend observed with the coupling of primary acceptors (Table 4.2).

4.5. Conclusion

Based on these sialylation experiments performed with modified donors, it is very clear that there is no direct effect on C-5 modification (NAcBz) itself on the stereoselectivity of sialosides. However, bulky O-protecting group manipulations at O-4 and at the glycerol chain might be an important factor. The nature of this effect is uncertain, and it can be steric, electronic or a combination of both. To our knowledge, no systematic study of O-modifications has been reported for sialyl donors, and resultantly the impact of such modifications on the stereoselectivity of sialylations is yet unknown. To fill this gap, the

investigation of the effect of O-substitution on the stereoselectivity of sialosides is ongoing in our laboratory.

Table 4.3 Comparison of donors **4.18** and **4.20** with donor **4.17** by coupling with the secondary acceptor **4.24**



Entry	Donor	Yield*	Ratio (α : β)
1	4.17	52	β only
2	4.18	57	1.0:1
3	4.20	85	1.8:1

*Reactions performed with 2 equivalent of acceptor

4.6 Experimental

General remarks. Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh) and size exclusion column chromatography was performed on Sephadex LH-20 (MeOH-CH₂Cl₂, 1:1, v:v elution). Reactions were monitored by TLC on Kieselgel 60 F₂₅₄ (EM Science). The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at < 40 °C. CH₂Cl₂ and ClCH₂CH₂Cl were distilled from CaH₂ directly prior to application. Anhydrous DMF (EM Science) was used as is. Methanol was dried by refluxing with magnesium methoxide, distilled and stored under argon. Pyridine was dried by refluxing with CaH₂ and then distilled and stored over molecular sieves (3 Å). Molecular sieves (3 Å or 4 Å), 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 at 'Jasco P-1020' polarimeter. ¹H-n.m.r. spectra were recorded in CDCl₃ at 300 MHz, DMSO at 80 °C and ¹³C-NMR spectra were recorded in CDCl₃ at 500 MHz unless otherwise noted. HR FAB-MS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer, matrix *m*-nitrobenzyl alcohol, with NaI as necessary.

Synthesis of glycosyl donors

Methyl (phenyl 7,8,9-tri-O-acetyl-4,5-O,N-carbonyl-3,5-dideoxy-2-thio-D-glycero- α -D-galacto-non-2-ulopyranoside)onate (4.8). Analytical data for the title compound was essentially the same as previously reported.¹⁶

Phenyl 2-O-benzoyl-3,4,6-tri-O-benzyl-1-thio- β -D-glucofuranoside (4.4). Analytical data for the title compound was essentially the same as previously reported.²³

Phenyl 2,3,4,6-tetra-O-benzyl-1-thio- β -D-glucofuranoside (4.5). Analytical data for the title compound was essentially the same as previously reported.²⁴

Phenyl 2,3,4,6-tetra-O-benzoyl-1-thio- β -D-glucofuranoside (4.6). Analytical data for the title compound was essentially the same as previously reported.²⁵

Phenyl 3,4,6-tri-O-benzoyl-2-O-benzyl-1-thio- β -D-galactofuranoside (4.15). Analytical data for the title compound was essentially the same as previously reported.²⁷

Methyl (*p*-methylphenyl 5-acetamido-4,7,8,9-tetra-O-benzoyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-uloofuranoside)onate (4.17). Analytical data for the title compound was essentially the same as previously reported.¹²

Methyl (*p*-methylphenyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-uloofuranoside)onate (4.18). To a stirring solution of methyl (*p*-methylphenyl 5-acetamido-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-uloofuranoside)onate²⁹ (1.5 g, 2.51 mmol) and 4-dimethylaminopyridine (0.09 g, 0.75 mmol) in pyridine (10 mL) at 0 °C, was added drop wise benzoyl chloride (0.58 mL, 5.02 mmol). The reaction was allowed to stir under argon for 15 minutes, upon

which it was allowed to warm to 60 °C and continued stirring for 6 hours. The reaction was then cooled to 0 °C, quenched with dry MeOH (0.15 mL), and concentrated in vacuo. The residue was then diluted with CH₂Cl₂ (50 mL) and washed successively with water (20 mL), 1N aq. HCl (20 mL), water (3× 20 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone-hexane gradient elution) to afford compound **4.18** in 90% yields. Analytical data for **4.18**: R_f = 0.46 (acetone/hexane, 2/3 v/v); ¹H NMR (500 MHz, DMSO-d₆, 80 °C) δ 7.66 (m, 3H; Ar), 7.56 (t, J₁ = 4.6 Hz, J₂ = 4.4 Hz, 2H; Ar), 7.35 (d, J = 4.9 Hz, 2H; Ar), 7.19 (d, J = 4.8 Hz, 2H; Ar), 5.88 (dt, J_{3e,4} = 2.8 Hz, J_{3a,4} = J_{4,5} = 6.2 Hz, 1H; H-4), 5.40 (dd, J_{5,6} = 6.1 Hz, J_{6,7} = 1.0 Hz, 1H; H-6), 5.30 (m, 1H; H-7), 4.90 (m, 1H; H-8), 4.61 (t, J_{4,5} = J_{5,6} = 6.1 Hz, 1H, H-5), 4.29 (dd, J_{8,9a} = 1.8 Hz, J_{9a,9b} = 7.3 Hz, 1H; H-9a), 4.06 (dd, J_{8,9b} = 4.5 Hz, J_{9b,9a} = 7.3 Hz, 1H; H-9b), 3.59 (s, 3H, OCH₃), 2.69 (dd, J_{3e,3a} = 8.3 Hz, J_{3e,4} = 2.9 Hz, 1H, H-3e), 2.32 (s, 3H, OCH₃), 2.10 (dd, J_{3a,3e} = 8.3 Hz, J_{3a,4} = 6.5 Hz, 1H; H-3a), 2.09 (s, 3H; PhCH₃), 1.94 (s, 9H, 3×OCH₃), 1.77 (s, 3H, OCH₃)ppm. ¹³C NMR 20.9 (×2), 21.1(×2), 21.5(×2), 38.1, 52.8, 62.5, 68.1, 68.5, 68.8, 69.6, 70..5, 72.1, 72.7, 88.5, 125.8, 129.2 (×3), 130.0 (×3), 136.7(×2), 140.2, 168.4, 169.6, 169.9, 170.4, 170.5, 171.0, 173.6, ppm; HR-FAB MS [M+Na]⁺ calcd for C₃₄H₃₉NO₁₃SNa⁺ 724.2040, found 724.2023.

Methyl (methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero-β-D-galacto-non-2-ulopyranoside)onate (4.19). To a stirring solution of methyl (methyl 5-acetamido-3,5-dideoxy-2-thio-D-glycero-β-D-galacto-non-2-ulopyranoside)onate (1.5 g, 2.51 mmol) and 4-dimethylaminopyridine (0.09 g, 0.75 mmol) in pyridine (10 mL) at 0 °C, was added drop wise benzoyl chloride (0.58 mL, 5.02

mmol). The reaction was allowed to stir under argon for 15 minutes, upon which it was allowed to warm to 60 °C and continued stirring for 6 hours. The reaction was then cooled to 0 °C, quenched with dry MeOH (0.15 mL), and concentrated in vacuo. The residue was then diluted with CH₂Cl₂ (50 mL) and washed successively with water (20 mL), 1N aq. HCl (20 mL), water (3 × 20 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone-hexane gradient elution) to afford compound **4.19** in 89% yields. Analytical data for **4.19**: R_f = 0.46 (acetone/toluene, 1/4 v/v); [α]_D = +5.5 (c 1, CHCl₃); ¹H NMR (500 MHz, DMSO-d₆, 80 °C); δ 7.53-7.68 (m, 5H; Ar), 5.73 (dt, J_{3e,4} = 2.8 Hz, J_{3a,4} = J_{4,5} = 6.2 Hz, 1H; H-4), 5.28 (dd, J_{6,7} = 0.8 Hz, J_{7,8} = 3.1 Hz, 1H; H-7), 5.19 (dd, J_{5,6} = 6.1 Hz, J_{6,7} = 0.8 Hz, 1H; H-6), 5.11 (m, 1H; H-8), 4.57 (t, J_{4,5} = J_{5,6} = 6.1 Hz, 1H; H-5), 4.48 (dd, J_{8,9a} = 1.7 Hz, J_{9a,9b} = 7.4 Hz, 1H; H-9a), 4.13 (dd, J_{8,9b} = 3.9 Hz, J_{9a,9b} = 7.4 Hz, 1H; H-9b), 3.77 (s, 3H; OCH₃), 2.63 (dd, J_{3a,3e} = 8.3 Hz, J_{3e,4} = 2.9 Hz, 1H; H-3e), 2.14 (dd, J_{3a,3e} = 8.3 Hz, J_{3a,4} = 2.9 Hz, 1H; H-3a), 2.11 (s, 3H; SCH₃), 2.04 (s, 3H; OCH₃), 1.97 (s, 3H; OCH₃), 1.95 (s, 3H; OCH₃), 1.92 (s, 3H; OCH₃), 1.76 (s, 3H; OCH₃). ¹³C NMR (300 MHz, CDCl₃, 25 °C) δ 174.9, 174.1, 173.2, 170.6, 170.5, 169.4, 168.1, 136.1, 133.3, 133.0, 129.7, 129.0, 128.9, 128.6, 84.6, 76.5, 72.2, 71.2, 69.2, 68.5, 68.3, 68.1, 67.7, 62.0, 57.0, 56.0, 52.7, 38.1, 37.7, 28.7, 27.8, 20.93, 20.9, 20.7, 11.6. HR-FAB MS [MH]⁺ calcd for C₂₈H₃₅NO₁₃S [M+Na]⁺ 648.1829 found: 648.1800.

Methyl (phenyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero-β-D-galacto-non-2-ulopyranoside)onate (4.20). To a stirring solution of methyl (phenyl 5-acetamido-3,5-dideoxy-2-thio-D-glycero-β-D-galacto-non-2-

ulopyranoside)onate³⁰ (1.5 g, 2.51 mmol) and 4-dimethylaminopyridine (0.09 g, 0.75 mmol) in pyridine (10 mL) at 0 °C, was added drop wise benzoyl chloride (0.58 mL, 5.02 mmol). The reaction was allowed to stir under argon for 15 minutes, upon which it was allowed to warm to 60 °C and continued stirring for 6 hours. The reaction was then cooled to 0 °C, quenched with dry MeOH (0.15 mL), and concentrated in vacuo. The residue was then diluted with CH₂Cl₂ (50 mL) and washed successively with water (20 mL), 1N aq. HCl (20 mL), water (3× 20 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone-hexane gradient elution) to afford compound **4.20** in 88% yields. Analytical data for **4.20**: R_f = 0.48 (acetone/toluene, 1/4 v/v); [α]_D = -37.7 (c 1, CHCl₃); ¹H NMR (500 MHz, DMSO-d₆, 80 °C) δ 1.77 (s, 3H, OCH₃), 1.94 (s, 9H, 3 × OCH₃), 2.12 (dd, 1H, J_{3e,3a} = 8.3 Hz, J_{3a,4} = 1.8 Hz, H-3a), 2.72 (dd, 1H, J_{3e,4} = 2.9 Hz, H-3e), 3.59 (s, 1H, OCH₃), 4.04 (dd, 1H, J_{8,9b} = 4.5 Hz, J_{9a,9b} = 7.3 Hz, H-9b), 4.30 (dd, 1H, J_{8,9a} = 1.8 Hz, H-9a), 4.62 (t, 1H, J_{4,5} = J_{5,6} = 6.1 Hz, H-5), 4.92 (m, 1H, H-8), 5.31 (m, 1H, H-7), 5.45 (dd, 1H, J_{6,7} = 1.0 Hz, H-6), 5.89 (dt, 1H, J_{3e,4} = 2.8 Hz, J_{3a,4} = 6.1 Hz, H-4), 7.387.68 (m, 10H, aromatic) ppm. ¹³C NMR: δ: 169.6, 169.1, 135.2, 132.2, 128.4, 128.0, 127.8, 127.5, 127.3, 87.2, 69.1, 67.3, 66.6, 61.1, 54.6, 51.4, 36.9, 19.7, 19.6 ppm. HR-FAB MS [M+Na]⁺ calcd for C₃₃H₃₇NO₁₃SNa 710.1886 found: 710.1864.

Synthesis of glycosyl acceptors

1,2,3,4-di-O-isopropylidene-α-D-galactopyranoside (4.9). Analytical data for the title compound was essentially the same as previously reported.³¹

Methyl 2,3,4-tri-O-benzyl- α -D-galactopyranoside (4.21). Analytical data for the title compound was essentially the same as previously reported.³²

Methyl 2,6-di-O-benzyl- β -D-galactopyranoside (4.24). Analytical data for the title compound was essentially the same as previously reported.²⁸

Synthesis of glycosides.

Typical NIS/TfOH-promoted glycosylation procedure in dichloromethane. A mixture of glycosyl donor (0.15 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3Å, 300 mg) in dichloromethane (1.6 mL) was cooled down to -72 °C and stirred under argon for 16 h. NIS (0.30 mmol) and TfOH (0.03 mmol) were added and the reaction mixture was monitored by TLC. Upon completion, the mixture was diluted with CH₂Cl₂, the solid was filtered off, and the residue was rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 10% Na₂S₂O₃ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (acetone - dichloromethane gradient elution) to afford the corresponding oligosaccharide.

Typical NIS/TfOH-promoted glycosylation procedure in acetonitrile. A mixture of glycosyl donor (0.15 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3Å, 300 mg) in acetonitrile (1.6 mL) was cooled down to -40 °C and stirred under argon for 16 h. NIS (0.30 mmol) and TfOH (0.03 mmol) were added and the reaction mixture was monitored by TLC. Upon completion, the mixture was diluted

with CH₂Cl₂, the solid was filtered off, and the residue was rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 10% Na₂S₂O₃ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (acetone - dichloromethane gradient elution) to afford the corresponding oligosaccharide.

O-(Methyl 5-acetamido-4,7,8,9-tetra-O-benzoyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (4.22a). Analytical data for the title compound was essentially the same as previously described.¹²

O-(Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (4.22b). Selected analytical data for **4.22b**: R_f = 0.57 (acetone/dichloromethane, 1/19, v/v); ¹H NMR (500 MHz, DMSO-d₆, 80 °C) δ 7.53-7.65 (m, 5H; Ar), 5.44 (d, J_{1,2} = 4.9 Hz, 1H; H-1), 5.23 (m, 1H; H-7'), 5.18 (m, 1H, H-8'), 4.79 (dd, 1H; H-3), 4.59-4.57 (m, 2H; H-2, H-4), 4.32-4.30 (m, 2H; H-5', H-9a'), 4.12 (dd, J_{8,9b} = 3.4 Hz, J_{9a,9b} = 7.3 Hz, 1H; H-9b'), 3.81 (s, 3H, COOCH₃), 3.73-3.77 (m, 2H; H-5, H-6a), 3.61 (dd, J_{5,6b} = 3.7 Hz, J_{6a,6b} = 6.0 Hz, 1H, H-6b), 2.76 (dd, J_{4,3e} = 3.0 Hz, J_{3a,3e} = 7.7 Hz, 1H, H-3e), 2.12 (s, 3H), 2.00 (s, 3H), 1.92 (s, 3H), 1.76 (s, 3H), 1.46 (s, 3H), 1.30-1.35 (m, 15H). ¹³C NMR (500 MHz, DMSO-d₆, 25 °C); 19.0, 20.6, 20.8, 24.3, 24.8, 25.8, 28.4, 52.8, 66.5, 69.9, 95.4, 98.1, 99.6, 107.7, 108.4, 128.6, 128.7, 129.2,

129.6, 167.5, 169.8, 170.0, 177.7 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{39}H_{51}NO_{19}Na^+$ 860.2955, found 860.2947.

Methyl O-(methyl 5-acetamido-4,7,8,9-tetra-O-benzoyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→6)-2,3,4-tri-O-benzyl- α -D-galactopyranoside (4.23a). Analytical data for the title compound was essentially the same as previously described.¹²

Methyl O-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→6)-2,3,4-tri-O-benzyl- α -D-galactopyranoside (4.23b). Selected analytical data for **4.23b**: $R_f = 0.61$ (acetone/dichloromethane, 1/9, v/v); 1H NMR (500 MHz, DMSO- d_6 , 80 °C) δ 7.30-7.68 (m, 20H; aromatic), 5.20 (m, 1H, H-4'), 4.46-4.60 (m, 2H; H-6', H-8'), 4.29 (dd, $J_{8,9a} = 3.0$ Hz, $J_{9a,9b} = 12.2$ Hz, 1H; H-9a'), 3.76 (s, 3H; $COOCH_3$), 3.32 (s, 3H; OCH_3), 2.75 (dd, $J_{4,3e} = 5.2$ Hz, $J_{3a,3e} = 13.0$ Hz, 1H, H-3'e α), 2.59 (dd, $J_{4,3e} = 5.0$ Hz, $J_{3a,3e} = 13.0$ Hz, 1H, H-3'e β) ppm. ^{13}C NMR (500 MHz, DMSO- d_6 , 25 °C) 20.4, 20.6, 20.7, 20.8, 20.9, 27.1, 52.7, 52.9, 54.2, 54.6, 55.1, 55.3, 56.2, 61.4, 61.6, 63.4, 66.6, 66.7, 66.9, 67.6, 68.6, 68.7, 69.0, 70.1, 71.5, 71.6, 73.9, 74.3, 74.6, 75.3, 75.6, 75.77.9, 97.3, 97.6, 98.2, 98.3, 98.4, 100.8, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 128.7, 129.2, 129.5, 131.0, 131.7, 133.4, 135.4, 135.9, 136.0, 138.8, 138.9, 166.7, 167.5, 169.3, 169.4, 169.5, 169.7, 169.8, 170.0, 170.1, 173.0, 173.1, 174.1, 174.3, 174.5 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{55}H_{63}NO_{19}Na^+$ 1064.3984, found 1064.3917.

Methyl O-(methyl 5-acetamido-4,7,8,9-tetra-O-benzoyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→3)-2,6-di-O-benzyl-β-D-galactopyranoside (4.25a). Analytical data for the title compound was essentially the same as previously described.¹²

Methyl O-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→3)-2,6-di-O-benzyl-β-D-galactopyranoside (4.25b). Analytical data for the title compound was essentially the same as previously described.²⁷

6-O-(2-O-Benzoyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (4.11). Analytical data for the title compound was essentially the same as previously described.³³

6-O-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (4.13). Analytical data for the title compound was essentially the same as previously described.³⁴

6-O-(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside (4.12). Analytical data for the title compound was essentially the same as previously described.³⁵

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CHAPTER 5

2-Allylphenyl glycosides as complementary building blocks for oligosaccharide and glycoconjugate synthesis

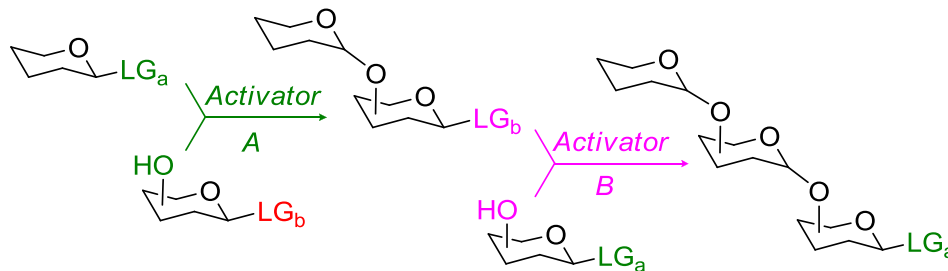
5.1 Introduction

Current knowledge about the key roles of carbohydrates is still limited. However, thanks to the explosive growth of the field of glycobiology in recent years, we have already learned that carbohydrates are involved in a broad range of vital biological processes (e.g., fertilization, anti-inflammation, immunoresponse, joint lubrication, antigenic determination).¹ Carbohydrates are also involved in many harmful processes (e.g., bacterial and viral infections, development of tumors, metastasis, tissue rejection, congenital disorders). The fact that many of these processes are directly associated with pathogenesis of deadly diseases including AIDS, cancer, pneumonia, septicemia, hepatitis and malaria²⁻⁴ has been particularly stimulating for major scientific efforts in the field of modern glycosciences. The development of novel and efficient methodologies to construct the glycosidic bond has gained an immense attention in the field. Most of the efforts have focused on the invention of new glycosyl donors, the discovery of reagent combinations for their activation, and the applications in expeditious oligosaccharide synthesis.

5.1.1 Orthogonal activation strategy

Traditional chemical assembly of oligosaccharides is lengthy because it involves multiple protecting and/or leaving group manipulations between glycosylation steps.⁵ Many advanced strategies that streamline the oligosaccharide assembly by minimizing or even eliminating additional manipulations between coupling steps are based either on chemoselective or on selective activation of leaving groups.⁶ The use of selective

activation⁷ offers more flexibility than that of the chemoselective activation that relies on the nature of protecting groups,⁸ and Ogawa's orthogonal strategy is conceptually the most attractive strategy developed to date.⁹⁻¹² This technique implies the use of two orthogonal leaving groups, LG_a and LG_b, selective activation of which can be reiterated to give streamlined access to oligosaccharide sequences (Scheme 5.1).



Scheme 5.1. Outline of the orthogonal strategy introduced by Ogawa et al.^[9]

Yet, the orthogonal strategy remains somewhat underdeveloped with too few known examples to become universally applicable. Only the original Ogawa's S-phenyl (SPh) vs. fluoride^{9,10,13} and thioimidate-based approaches¹⁴⁻¹⁶ developed by our group are known. A very good promise of orthogonality was shown for O-pentenyl vs. O-propargyl glycosides by Hotha et al.¹⁷ and for S-glycosyl O-methyl phenylcarbamothioate (SNea) vs. thioglycosides/thioimidates by our group.¹⁸ These approaches, however, still remain underdeveloped to clearly state their utility for multi-step synthesis. Working to expand this concept, our group reported a related, albeit less flexible, semi-orthogonal approach with the use of S-ethyl (SEt) and O-pentenyl leaving groups,¹⁹ which was extended to fluoride/O-pentenyl combination by Fraser-Reid and Lopez.²⁰

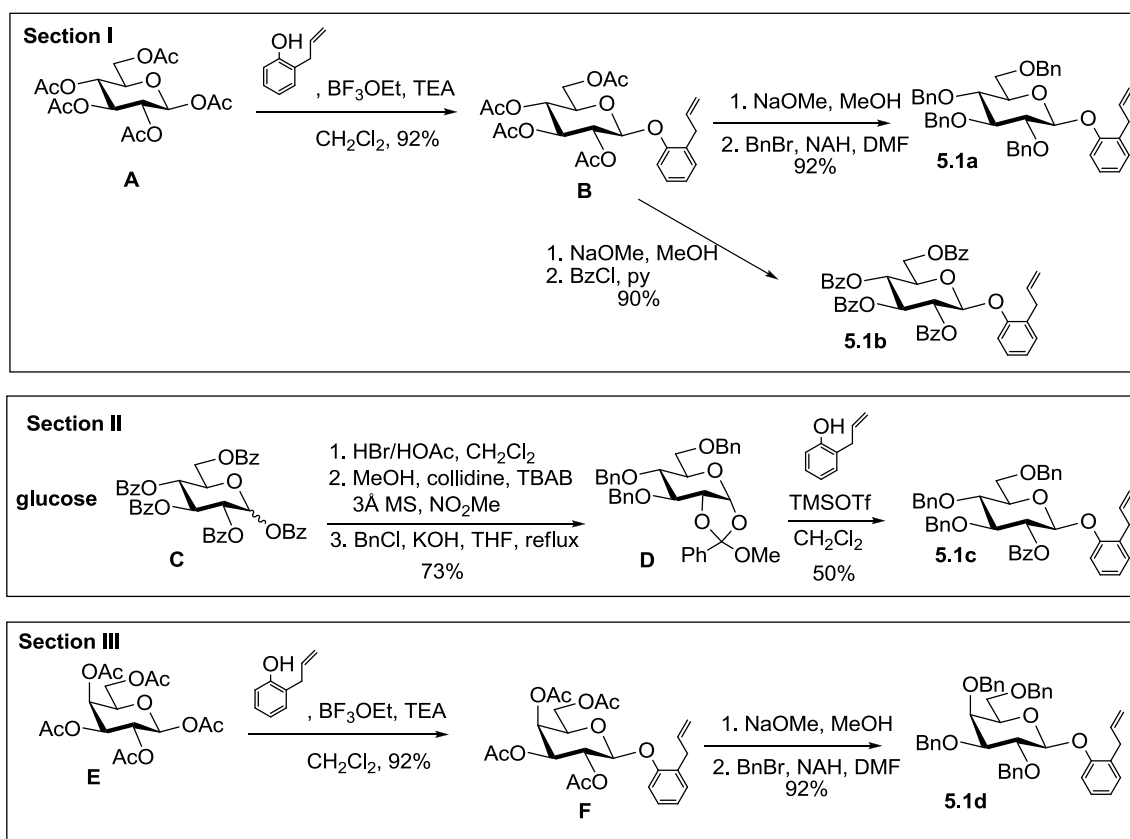
5.1.2 Involvement of oxygen based and sulfur based leaving groups in orthogonal strategy

Oxygen²¹ and sulfur-based²² leaving groups have found broad application in synthesis and fit into many expeditious strategies.⁶ However, suitable reaction conditions for orthogonal activation of these two classes leaving groups are yet to be found. Commonly, O-glycosides are too stable to be used as effective glycosyl donors.²¹ Pent-4-enyl O-glycosides introduced by Fraser-Reid are unique in this category of leaving groups because they can be glycosidated under mild conditions using I^+ generated *in situ*. Being a distinguishing feature of these O-glycosyl donors, these activation conditions also represent a noticeable limitation of this leaving group in the context of oligosaccharide synthesis. That is because no other promoters for O-pentenyl activation are known, and since I^+ can also activate thioglycosides, only a semi-orthogonality of O-pentenyl and S-Et leaving groups could be established.¹⁹ Additionally, 4-pentenol is rather expensive (\$323/50g, Aldrich), and although O-pentenyl can be introduced from the anomeric acetate directly, the most economical synthesis includes three-step protocol – halide, orthoester, and the rearrangement of the latter to glycoside.

5.2 Investigation of new O-based leaving group: *ortho*-allylphenyl (AP) leaving group

As a part of the ongoing research effort in our laboratory to develop versatile building blocks for chemical glycosylation and expeditious oligosaccharide synthesis, presented herein is the development of a new *ortho*-allylphenyl (AP) leaving group. This leaving

group was specifically designed with the purpose to address drawbacks of the *O*-pentenyl leaving group and to create a more flexible and economical approach both for glycosylation and for oligosaccharide synthesis. The following considerations were of particular relevance to aid in our design. First, chemists have been making aryl glycosides for some 130 years,²³ and many excellent protocols for their synthesis are available.²⁴ Indeed, we determined that AP glycosides can be readily obtained from the corresponding per-acetate using inexpensive 2-allylphenol (\$35/100g, Aldrich) in the presence of $\text{BF}_3\text{-Et}_2\text{O}$. For instance AP β -D-glucopyranoside was obtained in 92% yield (Scheme 5.2).

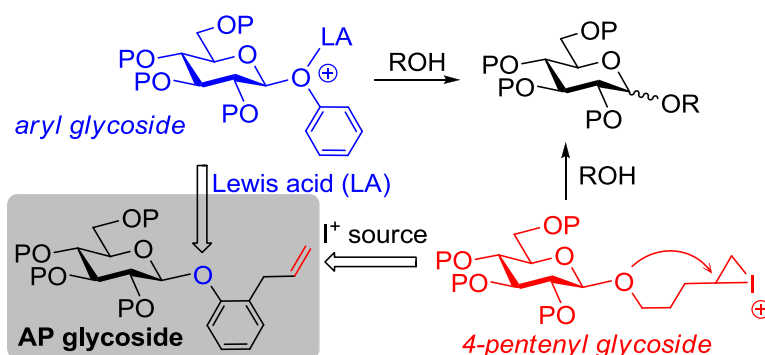


Scheme 5.2 Synthesis of the *ortho*-allylphenyl analogues

Second, we anticipated that promoters used for O-pentenyl activation²⁵ can also activate the AP leaving group. However, since AP glycosides bear structural features of both aryl and pentenyl glycosides they would offer a more versatile activation profile than either class of the leaving group (Scheme 5.3).

5.3 Activation pathways of AP glycosides

Our working hypothesis is that activation of the AP leaving group with I^+ takes place via the formation of epi-iodonium ion, which is then opened with the anomeric oxygen, similarly to that known for O-pentenyl glycosides.²⁵ It is possible that the activation of AP can be also achieved with Lewis acids, such as TMSOTf. This activation pathway, typical for aryl glycosides, is expected to become the key feature of the AP-mediated glycosylation approach because Lewis acids alone neither can activate O-pentenyl nor thioglycosides. Resultantly, this pathway may offer a suitable platform for developing a fully orthogonal approach in combination with thioglycosides that was not feasible for O-pentenyl glycosides.



Scheme 5.3. Anticipated pathways for activation of AP glycosides in glycosidation

5.3.1 Glycosylations of *ortho*-allylphenyl donor under different conditions

To pursue this concept we obtained a range of differently protected AP glucosides including per-benzylated **5.1a**, per-benzoylated **5.1b** (Section I, Scheme 5.2), and derivative **5.1c** (Section II) equipped with the superarming protecting group pattern (2-benzoyl-3,4,6-tribenzyl).²⁶ For comparison, we also obtained AP donors of the D-galacto derivative **5.1d** (Section III). With glycosyl donors **5.1a-d** in hand, we began evaluating their applicability to chemical glycosidation using a range of standard glycosyl acceptors **5.2-5.5**.¹⁸ Aryl glycosides show high propensity towards hydrolysis that may occur as the main side reaction to glycosylation. Therefore, particular care was taken to ensure strictly anhydrous reaction conditions, which is a common requirement for most glycosylations. Encouragingly, reaction of glycosyl donor **5.1a** with the primary glycosyl acceptor **5.2** in the presence of TMSOTf was completed in 15 min and provided the corresponding disaccharide **5.6a** in 82% yield (Table 5.1, entry 1). Expectedly, when a control experiment was set up with MeOTf, no glycosidation of **5.1a** took place (Entry 2). *The fact that the AP leaving group in 5.1a can be activated with TMSOTf, but not with MeOTf offers a basis for exploring its orthogonality with thioglycosides.* This is because thioglycosides show completely opposite reactivity trend under these activation conditions: no reaction with TMSOTf and smooth glycosidation with MeOTf.²⁷

N-Iodosuccinimide (NIS) in combination with TMSOTf is a very powerful promoter system for the activation of both O-pentenyl and thioglycosides. It was also found effective for the activation of AP glycosyl donor **5.1a**, upon which disaccharide **5.6a** was obtained in 80%. Even faster reaction and higher yield was obtained using NIS/TfOH promoter system, wherein the resulting disaccharide **5.6a** was obtained in 90% yield

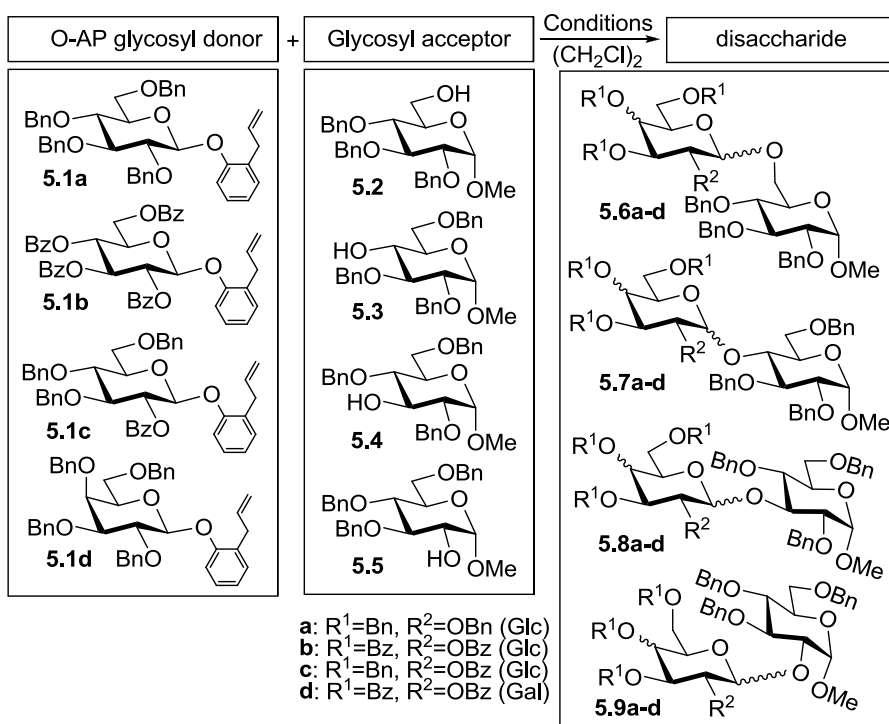
(Entry 4). The latter reaction conditions were chosen to investigate glycosylation of the secondary glycosyl acceptors **5.3-5.5**. These couplings were also proven feasible, and the corresponding disaccharides **5.7a-5.9a** were obtained in 72-82% yield (Entries 5-7).

Having investigated the reactivity of per-benzylated (armed) glycosyl donor **5.1a**, we turned our attention to testing its per-benzoylated (disarmed) counterpart **5.1b**. As anticipated, the reactivity of **5.1b** was significantly lower than that of **5.1a**, and particularly NIS-promoted glycosidations were proven of preparative value. Thus, the desired disaccharides **5.6b** and **5.9b** were isolated in 71-78% yield (Entries 10-12). Expectedly, no reaction took place in the presence of MeOTf (Entry 8); less predictably TMSOTf-promoted glycosidation of **5.1b** was practically ineffective either (Entry 9). *The observation that the armed AP leaving group in 5.1a can be readily activated with TMSOTf (Entry 1), whereas the disarmed AP leaving group in 5.1b remains inert under essentially the same reaction conditions suggests that AP glycosides can be applied in accordance with the classic armed-disarmed strategy (vide infra).*²⁸

In order to develop a flexible route to the synthesis of 1,2-trans glycosides we also investigated AP glycosyl donor **5.1c**, bearing a superarming protecting group pattern²⁶ As expected, all previously established reaction conditions were very effective and glycosidation of **5.1c** with acceptor **5.2** readily produced disaccharide **5.6c** (Entries 13-15). Again, particularly efficient was NIS/TfOH-promoted reaction wherein disaccharide **5.6c** was produced in 93% yield (Entry 15). In order to broaden the scope of the AP glycosylation approach, we tested its applicability to the synthesis of D-galactosides and 2-amino-2-deoxygalactosides, highly important and abundant sugar series.²⁹⁻³¹ Glycosidation of AP galactosyl donor **5.1d** with glycosyl acceptors **5.2-5.5** in the

presence of NIS/TfOH preceded smoothly and the corresponding disaccharides **5.6d-5.9d** were obtained in 80-85% yield (Entries 16-19).

Table 5.1. Glycosidation of AP glycosyl donors **5.1a-d** with glycosyl acceptors **5.2-5.5**.



Entry	Donor + acceptor	Conditions ^[a]	Time	Product (yield, α/β ratio)
1	5.1a + 5.2	TMSOTf, rt	15 min	5.6a (82%, 2.7/1)
2	5.1a + 5.2	MeOTf, rt	24 h	No reaction
3	5.1a + 5.2	NIS/TMSOTf, 0 °C	40 min	5.6a (80%, 1.4/1)
4	5.1a + 5.2	NIS/TfOH, 0 °C	15 min	5.6a (90%, 1/1.5)
5	5.1a + 5.3	NIS/TfOH, 0 °C	4 h	5.7a (73%, 1.2/1)
6	5.1a + 5.4	NIS/TfOH, 0 °C	30 min	5.8a (82%, 1.0/1)

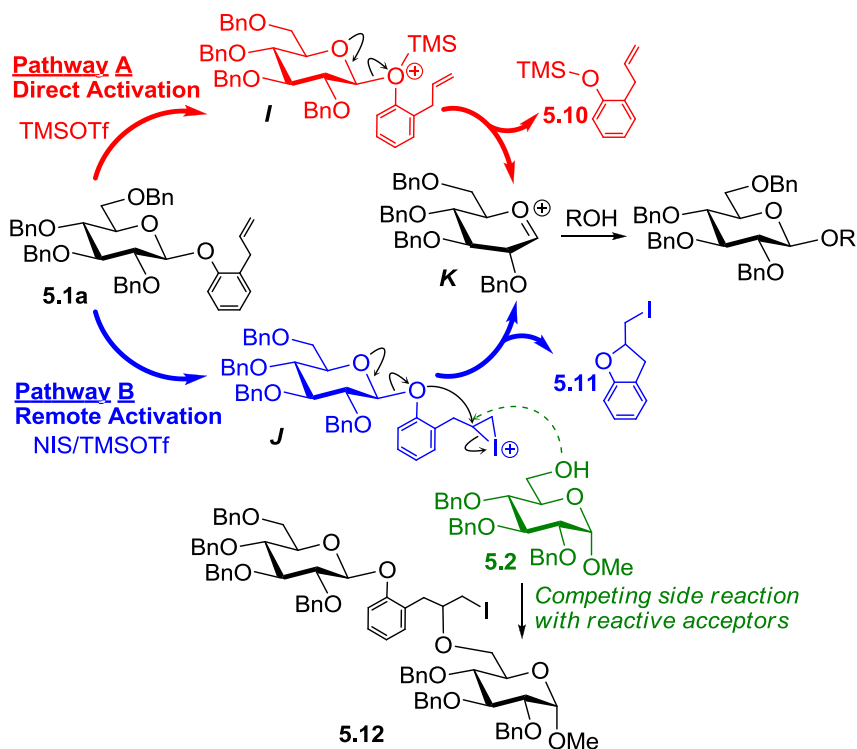
7	5.1a + 5.5	NIS/TfOH, 0 °C	3 h	5.9a (72%, 1/1.3)
8	5.1b + 5.2	MeOTf, rt	24 h	No reaction
9	5.1b + 5.2	TMSOTf, rt	24 h	No reaction
10	5.1b + 5.2	NIS/TMSOTf, 0 °C	6 h	5.6b (77%, β only)
11	5.1b + 5.2	NIS/TfOH, 0 °C	2 h	5.6b (71%, β only)
12	5.1b + 5.5	NIS/TfOH, 0 °C	3 h	5.9b (78%, β only)
13	1c + 2	MeOTf, rt	24 h	No reaction
14	5.1c + 5.2	TMSOTf, -20 °C	2.5 h	5.6c (73%, β only)
15	5.1c + 5.2	NIS/TMSOTf, 0 °C	10 min	5.6c (84%, β only)
16	5.1c + 5.2	NIS/TfOH, -20 °C	15 min	5.6c (93%, β only)
17	5.1d + 5.2	NIS/TfOH, 0 °C	15 min	5.6d (85%, 1.5/1)
18	5.1d + 5.3	NIS/TfOH, 0 °C	4 h	5.7d (81%, 1.2/1)
19	5.1d + 5.4	NIS/TfOH, 0 °C	30 min	5.8d (82%, 1.0/1)
20	5.1d + 5.5	NIS/TfOH, 0 °C	2 h	5.9d (80%, 2.0/1)

^[a] performed in the presence of molecular sieves 4 Å or 3 Å (MeOTf);

5.3.2 Rationalization of direct and remote activation pathways

In order to verify the two anticipated activation pathways by which the AP group may depart we repeated the two key experiments wherein glycosyl donor **5.1a** reacted with glycosyl acceptor **5.2** in the presence of TMSOTf and NIS/TMSOTf (Entries 1 and 3, respectively, Table 5.1). Upon completion of the reactions, judged by the disappearance of **5.1a** and formation of **5.6a**, we separated and analyzed all components of the reaction mixture. In the first reaction, (*o*-allylphenoxy) trimethylsilane **5.10** was isolated and its

identity was proven by comparison with the authentic commercial sample. The result of this test reaction indicated that the activation of the AP moiety under Lewis acid promotion takes place via the anomeric oxygen atom (I, Pathway A, Scheme 5.4) similarly to that of O-aryl glycosides.



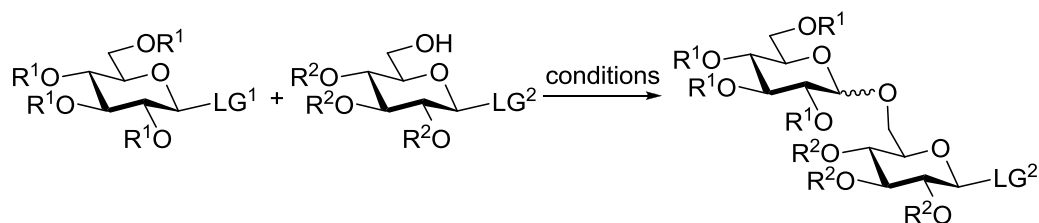
Scheme 5.4. Determination of the direct and remote activation pathways for glycosidation of AP glycosyl donors

In the NIS/TMSOTf-promoted reaction, 2-iodomethyl-2,3-dihydrobenzofuran **5.11**³² was isolated and its identity was proven by spectral methods. The result of this test reaction indicates that activation of the AP moiety under iodonium ion promotion takes place via the remote allyl moiety (**J**, Pathway B, Scheme 5.4) similarly to that found previously for O-pentenyl glycosides.²⁵ In addition, in the latter experiment we detected the presence of adduct **5.12** that has been formed as a result of a competing attack of the glycosyl

acceptor oxygen as opposed to endocyclization of **J** via the anomeric oxygen of glycosyl donor leading to oxacarbenium intermediate **K**. Although still remains to be confirmed, it is also possible that if the anomeric oxygen is too deactivated, such as in disarmed or superdisarmed glycosyl donors, the epi-iodonium ring would be preferentially opened by the intermolecular attack of glycosyl acceptor or other nucleophiles present in the reaction mixture.

5.4 Armed-diarmed activation

Results presented in Table 5.1 (compare entries 1 and 9) indicate that the reactivity of AP can be adjusted by varying protecting groups on the sugar ring, similar to the method established for O-pentenyl glycosides.³³ Thus, in accordance with Fraser-Reid's *armed-disarmed approach*, electronically activated (armed) glycosyl donor is chemoselectively activated over deactivated (disarmed) glycosyl acceptor bearing the same type of a leaving group.^{25,33} To explore this venue we obtained a disarmed (benzoylated) 6-OH AP glycosyl acceptor **5.13** (see the SI for the synthesis of all building blocks), which was coupled with the armed AP glycosyl donor **5.1a** in the presence of TMSOTf. As anticipated, this reaction was feasible and the expected disaccharide **5.14** was obtained in 78% yield (Table 5.2, Entry 1).

Table 5.2. AP glycosides in selective activations.

Entry	Donor + Acceptor ^[a]	Promoter	Time	Product (yield, α/β ratio)
1	5.1a (LG ¹ =OAP, R ¹ =Bn)	TMSOTf	10 min	5.14 (78%, 1.0/1)
	5.13 (LG ² =OAP, R ² =Bz)			
2	5.1a (LG ¹ =OAP, R ¹ =Bn)	TMSOTf	15 min	5.16 (71%, 1.0/1)
	5.15 (LG ² =SEt, R ² =Bn)			
3	5.1a (LG ¹ =OAP, R ¹ =Bn)	TMSOTf	1 h	5.18 (75%, 4.2/1)
	5.17 (LG ² =STol, R ² =Bz)			
4	5.1a (LG ¹ =OAP, R ¹ =Bn)	TMSOTf	1 h	5.20 (90%, 1.4/1)
	5.19 (LG ² =SPh, R ² =Bn)			
5	5.1a (LG ¹ =OAP, R ¹ =Bn)	TMSOTf	2 h	5.22 (98%, 1.8/1)
	5.21 (LG ² =SPh, R ² =Bz)			
6	5.23 (LG ¹ =SEt, R ¹ =Bn)	MeOTf	2 h	5.25 (82%, 1.0/1)
	5.24 (LG ² =OAP, R ² =Bn)			
	5.26 (LG ¹ =STaz, R ¹ =Bn)			
7	5.24 (LG ² =OAP, R ² =Bn)	MeOTf	1 h	5.25 (78%, 1.0/1)
	5.27 (LG ¹ =STol, R ¹ =Bn)			
8	5.24 (LG ² =OAP, R ² =Bn)	MeOTf	4 h	5.25 (97%, 1.2/1)
	5.28 (LG ¹ =SPh, R ¹ =Bn)			
9	5.24 (LG ² =OAP, R ² =Bn)	MeOTf	6 h	5.25 (90%, 1.0/1)

^[a] Performed in the presence of molecular sieves 4 Å (TMSOTf) or 3 Å (MeOTf) at rt;

5.5 Orthogonal activation strategy

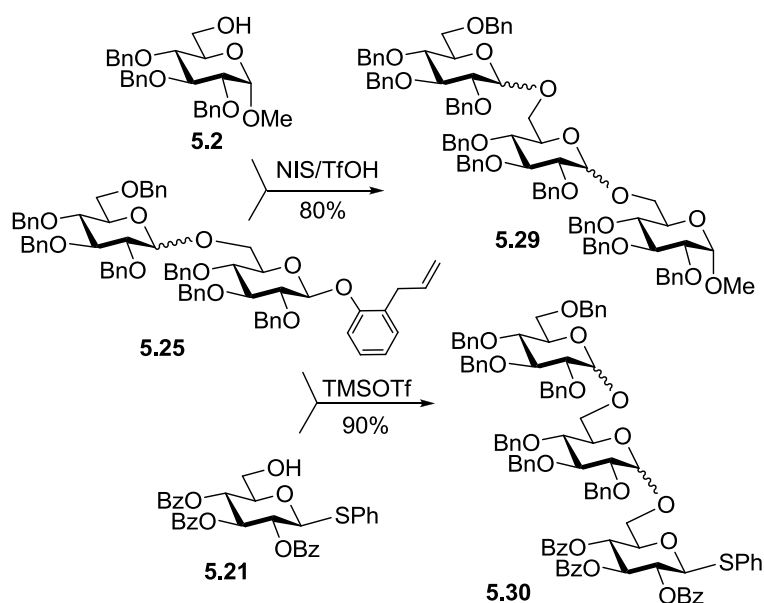
5.5.1 Selective activation of AP glycosides

With the ultimate goal of developing an efficient and distinct orthogonal differentiation of AP and thioglycosides, we next obtained acceptor **5.15** equipped with ethylthio leaving group. Very encouragingly, TMSOTf-promoted glycosylation between building blocks **5.1a** and **5.15** produced the expected disaccharide **5.16** in 71% yield (Entry 2). In a similar fashion, glycosyl acceptors **5.17** and **5.19** equipped with S-tolyl (STol) and SPh leaving groups, respectively, were glycosylated with glycosyl donor **5.1a**. Resultantly, disaccharides **5.18** and **5.20** were obtained in 75 and 90% respective yields (Entries 3 and 4). Also the disarmed SPh acceptor **5.21** was found quite usable in this coupling and the resulting disaccharide **5.22** was isolated in 98% yield. This series of experiments clearly demonstrates that the AP leaving group can be reliably activated with TMSOTf in the presence of S-alkyl/aryl leaving group. We next investigated glycosyl acceptor **5.24** equipped with the AP leaving group. Very encouragingly, MeOTf-promoted glycosidation of SEt, STaz, STol, and SPh glycosyl donors **5.23**,³⁴ **5.26**,¹⁴ **5.27**,³⁵ and **5.28**,³⁶ respectively, with glycosyl acceptor **5.24** was uneventful, and the respective disaccharide **5.25** was isolated in 78-97% yield (Entries 6-9).

5.5.2 Orthogonality of 2-allylphenyl and thioglycosides

These results, along with results on selective activation of AP over thioglycosides acceptors (*vide supra*), indicate a possibly completely orthogonal character of these two classes of leaving groups. To expand this observation further in the context of

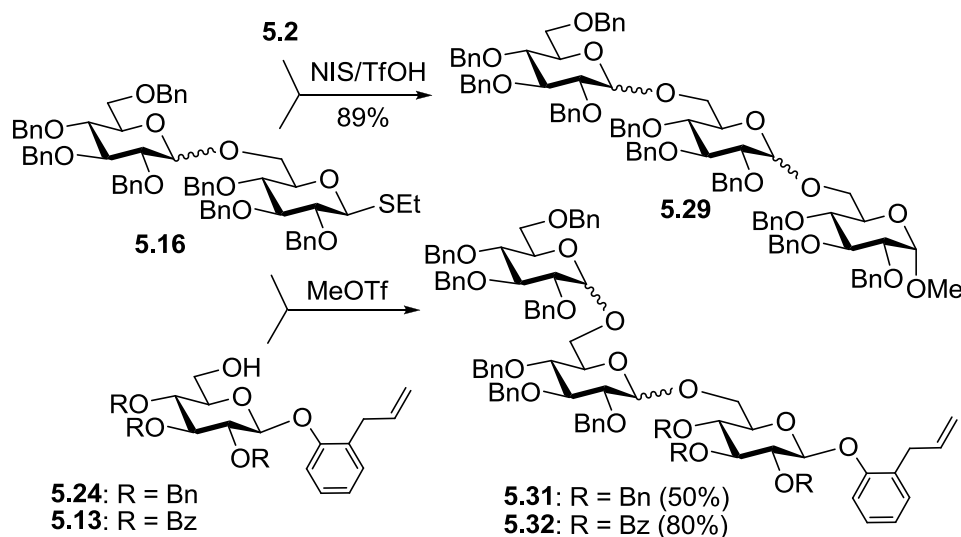
oligosaccharide synthesis we investigated the activation of the disaccharide building block **5.25**. Thus, its NIS/TfOH-promoted coupling with model acceptor **5.2** resulted in the formation of trisaccharide **5.29** in 80% yield (Scheme 5.5). The coupling of disaccharide **5.25** with thioglycoside acceptor **5.21** required a NIS-free activation conditions and TMSOTf-promoted reaction led to the corresponding trisaccharide **5.30** in 90%. Since trisaccharide **5.30** is equipped with the SPh anomeric leaving group, it is available for further chain elongation directly.



Scheme 5.5. Activation of AP disaccharide donor **5.25** over standard acceptor **5.2** or thioglycoside acceptor **5.21** (proof of orthogonality)

In a similar fashion, thioglycoside disaccharide **5.16** was investigated. Thus, its NIS/TfOH-promoted coupling with model acceptor **5.2** resulted in the formation of trisaccharide **5.29** in 89% yield (Scheme 5.6). The coupling of disaccharide **5.16** with benzylated and benzoylated AP acceptors **5.24** and **5.13** required a NIS-free activation conditions and it was affected in the presence of MeOTf. The resulting trisaccharides

5.31 and **5.32** were obtained in 50 and 80% yield. Since these trisaccharides are equipped with the AP anomeric leaving group, their direct application to the further chain elongation can be envisaged.



Scheme 5.6 Activation of thioglycoside donor **5.16** over standard acceptor **5.2** or AP acceptors **5.24** and **5.13**

We believe that the series of experiments listed in Table 5.2 and depicted in Schemes 5.4 and 5.5, provide a convincing case of orthogonality of the AP glycosides and thioglycosides. Furthermore, this study demonstrates a promising utility of the AP building blocks in oligosaccharide synthesis. The application of the AP glycosides may stretch well beyond their initial purpose because the alkene moiety can be utilized in a variety of other modes. Similar to that of O-pentenyl²⁵ it can be temporarily deactivated toward the I⁺ activation pathway by addition of Br₂, which can be reverted as needed (active-latent strategy). The formation of adduct **5.12** indicates that under certain reaction conditions the activation of deactivated AP glycosides may result in the formation of useful series of neoglycoconjugates, and degradable oligosaccharide

mimetics. Moreover, direct conjugation of the AP moiety to biomolecules, monolayers, arrays, etc., should also be possible by executing thiol-ene chemistry³⁷ ozonolysis/reductive amination^{38,40} or other ligation protocols.^{41,42}

5.6 Conclusion

In conclusion, we investigated O-allylphenyl (AP) anomeric moiety as a new leaving group that can be activated for chemical glycosylation under a variety of conditions including Lewis acid and iodonium ion mediated reaction pathways. The two possible reaction pathways for the AP moiety activation were confirmed via the extended mechanistic study. We also demonstrated that the application of the AP moiety allows executing rapid oligosaccharide assembly via orthogonal activation concept.

5.7 Experimental

General remarks. Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F₂₅₄ (EM Science). The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at < 40 °C. CH₂Cl₂ and ClCH₂CH₂Cl were distilled from CaH₂ directly prior to application. Anhydrous DMF (EM Science) was used as is. Methanol was dried by refluxing with magnesium methoxide, distilled and stored under argon. Pyridine and acetonitrile were dried by refluxing with CaH₂ and then distilled and stored over molecular sieves (3 Å).

Molecular sieves (3 Å or 4 Å), 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.. DOWEX MONOSPHERE 650C (H) was washed three times with MeOH and stored under MeOH. Optical rotations were measured at 'Jasco P-1020' polarimeter. ¹H-n.m.r. spectra were recorded in CDCl₃ at 300 MHz, ¹³C-NMR spectra were recorded in CDCl₃ at 300 MHz (Bruker Avance) unless otherwise noted. HRMS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer.

Synthesis of glycosyl donors

2-Allylphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (B). 2-Allylphenol (1.37 mL, 10.25 mmol), BF₃-OEt₂ (1.6 mL, 12.8 mmol), and triethylamine (0.36mL, 2.56 mmol) were added to a stirring solution of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranoside (2.00 g, 5.13 mmol) in CH₂Cl₂ (40 mL). The reaction mixture was kept for 16 h at rt, then it was diluted with CH₂Cl₂ (30 mL) and washed with water (10 mL), sat. aq. NaHCO₃ (10 mL), and water (3 × 10 mL). The organic phase was separated, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane gradient elution) to afford the title compound (1.9 g, 90% yield) as white crystals. Analytical data for **B**: R_f = 0.50 (ethyl acetate - hexane, 1/5, v/v); m. p. 145-148 °C (diethyl ether-hexanes); [α]_D²³ -25.8 (c = 1.0, CHCl₃); ¹H-n.m.r.: δ, 2.02 (s, 3H, OCH₃), 2.03 (s, 3H, OCH₃), 2.04 (s, 3H, OCH₃), 2.06 (s, 3H, OCH₃), 3.23-3.38 (m, 2H, PhCH₂CH=CH₂), 3.81-3.87 (m, 1H, H-5), 4.16 (dd, 1H, J = 2.5 Hz, H-6b), 4.27 (dd, 1H, J = 5.5 Hz, H-6a), 4.95-5.05 (m, 3H, H-2, PhCH₂CH=CH₂), 5.12-5.19 (m, 1H; H-4), 5.24-5.35 (m, 2H, J_{1,2} = 8.7 Hz, H-1, H-3), 5.83-5.96 (m, 1H; PhCH₂CH=CH₂), 6.97-

7.18 (m, 4H; aromatic) ppm. ^{13}C -n.m.r.: δ , 20.7, 20.7, 20.8, 21.0, 34.0, 62.1, 68.5, 71.2, 72.1, 72.9, 99.3, 115.4, 115.9, 123.5, 127.5, 130.0, 130.5, 136.6, 154.6, 169.3, 169.5, 170.4, 170.7 ppm. HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{O}_{10}\text{Na}^+$ 487.1580, found 487.1562.

2-Allylphenyl 2,3,4,6-tetra-O-benzyl- β -D-glucopyranoside (5.1a). Compound **B** (1.00 g, 2.16 mmol) was dissolved in methanol (8 mL) and pH was adjusted (pH 9) by careful addition of a 1M solution of NaOCH_3 in MeOH (~0.1 mL). The reaction mixture was kept for 1 h at rt, then Dowex (H^+) was added until neutral pH. The resin was filtered off and rinsed with methanol (3×5 mL). The combined filtrate (~ 30 mL) was concentrated in *vacuo* and dried. The resultant solid was dissolved in DMF (14 mL) and benzyl bromide (1.41 mL, 11.82 mmol) was added. The resulting mixture was cooled to 0 °C and NaH (0.426 g, 17.74 mmol) was added portionwise. The reaction mixture was allowed to gradually warm to rt. Upon stirring for 1 h at rt, the reaction was quenched by stirring with ice water (50 mL). The organic phase was extracted with ethyl acetate/diethyl ether (1/1, v/v, 3×40 mL) and combined organic extract was washed with water (3×20 mL). The organic phase was separated, dried with MgSO_4 and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/ hexane gradient elution) to afford the title compound (1.3 g, 92%) as white crystals. Analytical data for **5.1a**: $R_f = 0.50$ (ethyl acetate - hexanes, 1/5, v/v); m. p. 94-97 °C (diethyl ether - hexanes); $[\alpha]_D^{23} +16.7$ (c = 1.0, CHCl_3); ^1H -n.m.r.: δ , 3.34-3.49 (m, 2H, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 3.54-3.55 (m, 1H, H-5), 3.60-3.76 (m, 5H, H-2, H-3, H-4, H-6a, H-6b), 4.43-4.54 (m, 2H, CH_2Ph), 4.76-4.94 (m, 4H, $2 \times \text{CH}_2\text{Ph}$), 4.94-5.00 (m, 4H, $J_{1,2} = 7.8$

Hz, H-1, PhCH₂CH=CH₂, 1/2×CH₂Ph), 5.97-6.10 (m, 1H, PhCH₂CH=CH₂), 6.94-7.28 (m, 24H, aromatic) ppm; ¹³C-n.m.r.: δ, 34.3, 69.0, 73.7, 75.2, 75.3, 75.4, 76.0, 77.4, 78.0, 82.3, 85.1, 101.5, 115.6, 116.1, 122.8, 127.6, 127.7, 127.8, 127.9 (×4), 128.0(×2), 128.1(×2), 128.2(×2), 128.5(×2), 128.6(×3), 128.7(×2), 129.8, 130.1, 136.9, 138.2, 138.3, 138.4, 138.7, 155.1 ppm; HR-FAB MS [M+Na]⁺ calcd for C₄₃H₄₄O₆Na⁺ 679.3036, found 679.3058.

2-Allylphenyl 2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside (5.1b). Compound **B** (5.40 g, 11.63 mmol) was dissolved in methanol (44 mL) and pH was adjusted (to pH 9) by careful addition of 1M solution of NaOCH₃ in MeOH (~0.2 mL). The reaction mixture was kept for 1 h at rt, then Dowex (H⁺) was added until neutral pH. The resin was filtered off and washed with methanol (3 × 5 mL). The combined filtrate was concentrated *in vacuo* and dried. The residue was dissolved in dry pyridine (70 mL), the mixture was cooled to 0 °C and benzoyl chloride (7.2 mL, 62.5 mmol) was added dropwise. The reaction mixture was allowed to gradually warm to rt. Upon stirring for 1 h at rt, the reaction was quenched by addition of methanol (5 mL). The resulting mixture was evaporated and co-evaporated with toluene (3× 10 mL) under reduced pressure. The residue was diluted with CH₂Cl₂ (20 mL) and washed with water (10 mL), sat. aq. NaHCO₃ (10 mL) and water (3×10 mL). The organic layer was separated, dried with MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the title compound (8.8 g, 90%) as white crystals. Analytical data for **5.1b**: R_f = 0.58 (ethyl acetate - hexanes, 4/10, v/v); m. p. 130-132 °C (diethyl ether - hexanes); [α]_D²³ +26.7 (c = 1, CHCl₃); ¹H-n.m.r.:

δ , 3.06 (d, 2H, $J = 6.6$ Hz, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 4.18-4.26 (m, 1H, H-5), 4.39 (dd, 1H, $J_{6a,6b} = 12.0$ Hz, H-6a), 4.54-4.69 (m, 3H, H-6b, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 5.26 (d, 1H, $J_{1,2} = 6.0$ Hz, H-1), 5.50-5.64 (m, 2H, H-4, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 5.77 (dd, 1H, $J_{2,3} = 9.0$ Hz, H-2), 5.90 (dd, 1H, $J_{3,4} = 9.5$ Hz, H-3), 6.82-7.92 (m, 24H, aromatic) ppm; ^{13}C -n.m.r.: δ , 34.0, 63.4, 69.9, 71.7, 72.8, 73.0, 99.9, 115.4, 115.7, 123.4, 128.5 ($\times 2$), 128.6 ($\times 2$), 128.7 ($\times 3$), 128.8 ($\times 2$), 128.9, 129.0, 129.3, 129.7, 129.8 ($\times 3$), 129.9 ($\times 2$), 130.0 ($\times 2$), 130.1 ($\times 2$), 130.2, 130.3, 133.4, 133.5, 133.8, 136.4, 154.8, 165.2, 165.5, 166.0, 166.2 ppm; HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{43}\text{H}_{36}\text{O}_{10}\text{Na}$ 735.2205 found 735.2194

2-Allylphenyl 2-O-benzoyl-3,4,6-tri-O-benzyl- β -D-glucopyranoside (5.1c). A mixture of 3,4,6-tri-*O*-benzyl-1,2-*O*-methoxybenzylidene- β -D-glucopyranose^[1] (0.360 g, 0.63 mmol), molecular sieves (4Å, 400 mg) and 2-allylphenol (0.84 mL, 6.34 mmol) in dry dichloromethane (3.6 mL) was stirred under argon for 10 min at rt. TMSOTf (0.03 mL, 0.16 mmol) was added, and the resulting mixture was stirred at rt for 4 h. After that the reaction mixture was filtered through Celite and filtrate was diluted with dichloromethane (30 mL) and washed with water (10 mL), sat. aq. NaHCO_3 (10 mL), and water (3×10 mL). The organic phase was separated, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane gradient elution) to afford the title compound (0.120 g, 28% yield) as a white solid. Analytical data for **5.1c**: $R_f = 0.59$ (ethyl acetate - hexanes, 3/10, v/v); $[\alpha]_D^{23} +26.4$ ($c = 1$, CHCl_3); ^1H -n.m.r.: δ , 3.31 (d, 1H, $J = 10.0$ Hz, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 3.85-4.06 (m, 5H, H-3, H-4, H-5, H-6a, H-6b), 4.71-5.01 (m, 8H, $\text{PhCH}_2\text{CH}=\text{CH}_2$, $3 \times \text{CH}_2\text{Ph}$), 5.21 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1), 5.76 (dd, 1H, $J_{2,3} = 9.0$ Hz, H-2), 5.79-5.89 (m, 1H, $\text{PhCH}_2\text{CH}=\text{CH}_2$),

7.04-8.14 (m, 24H, aromatic) ppm; ^{13}C -n.m.r.: δ , 33.98, 68.99, 73.6, 73.8, 75.3, 75.4, 75.7, 78.1, 82.9, 99.8, 115.2, 115.5, 122.9, 127.5, 127.8, 127.9, 128.0 ($\times 2$), 128.1, 128.2 ($\times 4$), 128.4 ($\times 3$), 128.5 ($\times 2$), 128.6 ($\times 2$), 128.7 ($\times 2$), 130.0 ($\times 2$), 130.1 ($\times 2$), 133.3, 136.7, 137.9, 138.0, 138.3, 155.2, 165.3 ppm; HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{43}\text{H}_{42}\text{O}_2\text{Na}$ 693.2831, found 693.2834.

2-Allylphenyl 2,3,4,6-tetra-O-acetyl- β -D-galactopyranoside (F). 2-Allylphenol (1.37 mL, 10.25 mmol), $\text{BF}_3\text{-OEt}_2$ (1.6 mL, 12.8 mmol), and triethylamine (0.36 mL, 2.56 mmol) were added to a stirring solution of 1,2,3,4,6-penta-O-acetyl- β -D-galactopyranoside (2.00 g, 5.13 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was kept for 16 h at rt, then it was diluted with CH_2Cl_2 (30 mL) and washed with water (10 mL), sat. aq. NaHCO_3 (10 mL), and water (3×10 mL). The organic phase was separated, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane gradient elution) to afford the title compound (1.8 g, 89% yield) as white crystals. Analytical data for **F**: $R_f = 0.51$ (ethyl acetate - hexane, 2/3, v/v); m. p. 98-101 (diethyl ether - hexanes); $[\alpha]_{\text{D}}^{24} -13.0$ ($c = 1.0$, CHCl_3); ^1H -n.m.r.: δ , 2.23-2.42 (m, 12H, $4 \times \text{OCH}_3$), 3.55-3.63 (m, 2H, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 4.33 (m, 1H, H-5), 4.40 (dd, 1H, $J_{6a,6b} = 11.3$ Hz, $J_{5,6a} = 6.1$ Hz, H-6a), 4.48 (dd, 1H, $J_{5,6b} = 7.2$ Hz, H-6b), 5.23 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 5.28 (t, 2H, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 5.36 (dd, 1H, $J_{3,4} = 3.4$ Hz, H-3), 5.70 (dd, 1H, H-4), 5.78 (dd, 1H, $J_{2,3} = 10.4$ Hz, H-2), 6.12-6.24 (m, 1H, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 7.10-7.29 (m, 4H; aromatic) ppm. ^{13}C -n.m.r.: δ , 20.6, 20.7, 20.8, 20.9, 33.8, 61.5, 67.0, 68.6, 70.9, 71.0, 99.6, 115.1, 115.7,

123.3, 127.4, 129.8, 130.3, 136.6, 154.6, 169.3, 170.1, 170.3, 170.5 ppm. HR-FAB MS [M+Na]⁺ calcd for C₂₃H₂₈O₁₀Na⁺ 487.1580, found 487.1573.

2-Allylphenyl 2,3,4,6-tetra-O-benzyl-β-D-galactopyranoside (5.1d). Compound **F** (2.00 g, 4.32 mmol) was dissolved in methanol (16 mL) and pH was adjusted (pH 9) by careful addition of a 1M solution of NaOCH₃ in MeOH (~0.1 mL). The reaction mixture was kept for 1 h at rt, then Dowex (H⁺) was added until neutral pH. The resin was filtered off and washed with methanol (3 × 10 mL). The combined filtrate was concentrated in *vacuo* and dried. The resultant solid was dissolved in dry DMF (24 mL) and benzyl bromide (2.4 mL, 20.27 mmol). Then the reaction mixture was cooled down to 0 °C and NaH was added (0.73 g, 30.41 mmol) portion wise. The reaction mixture was allowed to gradually warm up. Upon stirring for 1 h at rt, the reaction was quenched by stirring with ice water (50 mL). The organic phase was extracted with ethyl acetate/diethyl ether (1/1, v/v, 3 × 40 mL) and combined organic extract was washed with water (3 × 20 mL). The organic phase was separated, dried with MgSO₄ and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/ hexanes gradient elution) to afford the title compound (2.6 g, 98%) as white solid. Analytical data for **5.1d**: R_f = 0.80 (ethyl acetate - hexanes, 2/3, v/v); [α]_D²⁴ -22.3 (c = 1.0, CHCl₃); ¹H-n.m.r.: δ, 3.39-3.50 (m, 2H, PhCH₂CH=CH₂), 3.60-3.71 (m, 4H, H-3, H-4, H-6a, H-6b), 3.97 (m, 1H, H-5), 4.15 (dd, 1H, J_{2,3}=8.3 Hz, H-2), 4.43 (dd, 2H, J² = 11.6 Hz, CH₂Ph), 4.66 (d, 1H, J² = 8.4 Hz, ½ × CH₂Ph), 4.72-4.80 (s, 2H, CH₂Ph), 4.88-5.05 (m, 6H, J_{1,2} = 7.8 Hz, H-1, PhCH₂CH=CH₂, 1.5×CH₂Ph), 5.96-6.01 (m, 1H, PhCH₂CH=CH₂), 6.96-7.34 (m, 24H, aromatic) ppm; ¹³C-n.m.r.: δ, 34.2, 69.1, 73.1, 73.2, 73.3, 73.8, 74.1, 74.5, 74.7, 75.7, 79.2, 82.7, 101.8, 115.1, 115.4, 116.0, 116.2, 127.7, 127.8, 127.9, 128.1, 128.2 (×2),

128.3, 128.4, 128.5 (×2), 128.6 (×3), 128.7 (×2), 129.7, 130.0, 136.9, 138.1, 138.5, 138.6, 138.7, 155.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{43}H_{44}O_6Na^+$ 679.3036, found 679.3019.

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-glucopyranoside(5.23). Analytical data for the title compound was essentially the same as previously described.²

Thiazoliny 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-glucopyranoside(5.26). Analytical data for the title compound was essentially the same as previously described.³

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-glucopyranoside(5.28). Analytical data for the title compound was essentially the same as previously described.⁴

Tolyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-glucopyranoside(5.27). Analytical data for the title compound was essentially the same as previously described.⁵

Synthesis of glycosyl acceptors.

Methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside (5.2). Analytical data for the title compound was essentially the same as previously described.^{1,6}

Methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (5.3). Analytical data for the title compound was essentially the same as previously described.^{1,7}

Methyl 2,4,6-tri-*O*-benzyl- α -D-glucopyranoside (5.4). Analytical data for the title compound was essentially the same as previously described.^{7,8}

Methyl 3,4,6-tri-*O*-benzyl- α -D-glucopyranoside (5.5). Analytical data for the title compound was essentially the same as previously described.^{7,8}

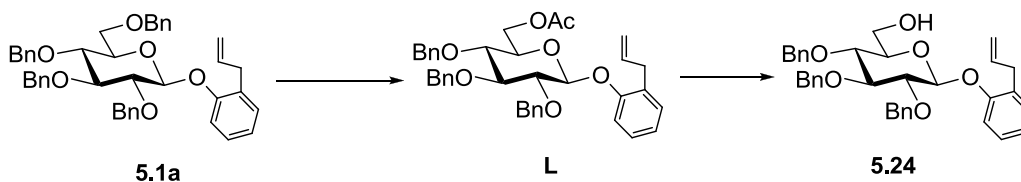
Tolyl 2,3,4-tri-*O*-benzoyl-1-thio- β -D-glucopyranoside (5.17). Analytical data for the title compound was essentially the same as previously described.⁹

Ethyl 2,3,4-tri-*O*-benzyl-1-thio- β -D-glucopyranoside (5.15). Analytical data for the title compound was essentially the same as previously described.¹⁰

Phenyl 2,3,4-tri-*O*-benzyl-1-thio- β -D-glucopyranoside (5.19). Analytical data for the title compound was essentially the same as previously described.¹¹

Phenyl 2,3,4-tri-*O*-benzoyl-1-thio- β -D-glucopyranoside (5.21). Analytical data for the title compound was essentially the same as previously described.¹²

2-Allylphenyl 2,3,4-tri-*O*-benzyl- β -D-glucopyranoside (5.24).

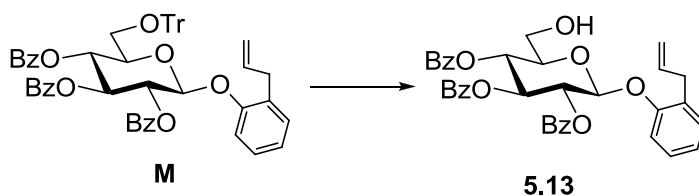


2-Allylphenyl 6-O-acetyl-2,3,4-tri-O-benzyl- β -D-glucopyranoside (L). To a stirred solution of a **5.1a** (0.1 g, 0.15 mmol) in Ac₂O/AcOH (2/1, v/v, 0.9 mL) was added freshly prepared ZnCl₂ (166 mg, 1.22 mmol) solution in Ac₂O/AcOH (2/1, v/v, 0.86 mL). The reaction mixture was stirred under argon for 4 h at rt. Upon completion, the reaction was quenched with H₂O, diluted with ethyl acetate (50 mL), and washed with water (20 mL), sat. aq. NaHCO₃ (20 mL) and water (3 x 20 mL). The organic phase was separated, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – toluene gradient elution) to afford the title compound (98 mg, 99%) as a clear form. Analytical data for **L**: R_f = 0.51 (ethyl acetate - toluene, 1/10, v/v); [α]_D²³ -5.8 (c = 1.0, CHCl₃); ¹H-n.m.r.: δ , 1.92 (s, 3H, OCH₃), 3.29-3.45 (m, 2H, PhCH₂CH=CH₂), 3.48-3.65 (m, 2H; H-4, H-5), 3.67-3.71 (m, 2H, H-2, H-3), 4.14 (dd, 1H, J_{6a,6b} = 11.8 Hz, J_{5,6a} = 5.1 Hz, H-6a), 4.24 (dd, 1H, J_{5,6b} = 1.7 Hz, H-6b), 4.51 (d, J² = 10.9 Hz, ½ CH₂Ph), 4.74-5.01 (m, 8H, H-1, PhCH₂CH=CH₂, 2.5 × CH₂Ph), 5.83-5.93 (m, 1H; PhCH₂CH=CH₂), 6.87-7.27 (m, 19H, aromatic) ppm; ¹³C-n.m.r.: 20.9, 34.2, 63.3, 73.1, 75.2, 75.3, 75.9, 82.1, 85.0, 101.3, 115.5, 116.1, 123.0, 127.5, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4 (×3), 128.5, 128.6 (×3), 128.6, 128.7 (×3), 129.9, 130.2, 136.8, 137.7, 138.2, 138.4, 154.9, 170.8 ppm; HR-FAB MS [M+Na]⁺ calcd for C₃₈H₄₀O₇Na 631.2674, found 631.2665.

2-Allylphenyl 2,3,4-tri-O-benzyl- β -D-glucopyranoside (5.24). A solution of a **L** (0.42 g, 0.69 mmol) was dissolved in methanol (3.2 mL) and pH was adjusted (pH 9) by careful addition of a 1M solution of NaOCH₃ in MeOH (~0.1 mL). The reaction mixture was kept for 1 h at rt, then Dowex (H⁺) was added until neutral pH. The resin was filtered

off and washed with methanol (3×5 mL). The combined filtrate was concentrated in *vacuo* and dried. The residue was purified by column chromatography on silica gel (ethyl acetate – hexanes gradient elution) to afford the title compound (0.270 g, 69%) as a white solid. Analytical data for **5.24**: $R_f = 0.56$ (ethyl acetate - hexanes, 2/5, v/v); $[\alpha]_D^{23} -15.1$ ($c = 1.0$, CHCl_3); $^1\text{H-n.m.r.}$: δ , 1.82 (s, 1H, OH), 3.35-3.44 (m, 2H, H-4, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 3.55-3.75 (m, 4H, $J_{2,3} = 8.7$ Hz, H-2, H-3, H-5, H-6a), 3.80 (dd, 1H, $J_{6a,6b} = 12.1$ Hz, $J_{5,6b} = 2.6$ Hz, H-6b), 4.59 (d, $J^2 = 10.9$ Hz, 1H, $\frac{1}{2}$ CH_2Ph), 4.74-4.98 (m, 7H, $\text{PhCH}_2\text{CH}=\text{CH}_2$, $2.5 \times \text{CH}_2\text{Ph}$), 5.04 (d, 1H, $J_{1,2} = 7.2$ Hz, H-1), 5.83-5.96 (m, 1H, $\text{PhCH}_2\text{CH}=\text{CH}_2$), 6.91-7.24 (m, 19H, aromatic) ppm; $^{13}\text{C-n.m.r.}$: 34.2, 62.2, 75.3, 75.5, 75.9, 82.3, 84.9, 101.1, 114.9, 116.2, 122.9, 127.7, 127.9 ($\times 3$), 128.0 ($\times 2$), 128.1 ($\times 3$), 128.3 ($\times 3$), 128.6 ($\times 3$), 128.7 ($\times 3$), 129.7, 130.4, 136.9, 138.0, 138.3, 138.6, 154.8 ppm; HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{36}\text{H}_{38}\text{O}_6\text{Na}$ 589.2668, found 589.2676.

2-Allylphenyl 2,3,4-tri-O-benzoyl- β -D-glucopyranoside (**5.13**).



2-Allylphenyl 2,3,4-tri-O-benzoyl-6-O-triphenylmethyl- β -D-glucopyranoside (**M**)

Compound **B** (1.00 g, 2.16 mmol) was dissolved in methanol (8 mL) and pH was adjusted (pH 9) by careful addition of a 1M solution of NaOCH_3 in MeOH (~ 0.1 mL). The reaction mixture was kept for 1 h at rt, then Dowex (H^+) was added until neutral pH. The resin was filtered off and rinsed with methanol (3×5 mL). The combined filtrate (~ 30 mL) was concentrated in *vacuo* and dried. The resultant solid was dissolved in pyridine

(5.3 mL), and triphenylmethyl chloride (1.9 g, 6.76 mmol) was added and the resulting reaction mixture was stirred for 16 h. After that, the reaction mixture was cooled to 0 °C and benzoyl chloride (1.6 mL, 13.5 mmol) was added dropwise. The reaction mixture was allowed to gradually warm to rt and stirred for additional 3 h at rt. The reaction was quenched by addition of methanol (10 mL), evaporated under reduced pressure and co-evaporated with toluene (3 × 20 mL). The residue was diluted with CH₂Cl₂ (20 mL) and washed with water (10 mL), sat. aq. NaHCO₃ (10 mL) and water (3×10 mL). The organic layer was separated, dried with MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexanes gradient elution) to afford the title compound (1.5 g, 86%) as a white solid. Analytical data for **M**: $R_f = 0.50$ (ethyl acetate - hexanes, 2/5, v/v); ¹H-n.m.r.: δ, 3.33 (d, 2H, J = 6.5 Hz, PhCH₂CH=CH₂), 3.43 (dd, 1H, J_{5,6a} = 2.2 Hz, H-6a), 3.52 (dd, 1H, J_{5,6b} = 6.1 Hz, J_{6a,6b} = 10.7 Hz, H-6b), 4.03-4.09 (m, 1H; H-5), 4.80-4.92 (m, 2H, PhCH₂CH=CH₂), 5.40-5.43 (d, 1H, J_{1,2} = 7.6 Hz, H-1), 5.65-5.72 (m, 1H; H-4), 5.76-5.89 (m, 1H; PhCH₂CH=CH₂), 5.93-6.01 (m, 2H, H-2, H-3), 7.09-8.04 (m, 34H; aromatic) ppm; ¹³C-n.m.r.: δ, 34.1, 60.6, 62.6, 69.6, 71.9, 73.3, 74.5, 74.6, 87.2 (×2), 100.0, 115.6, 115.7, 115.9, 123.4 (×2), 127.2, 127.6 (×5), 127.9, 128.4, 128.5, 128.7 (×6), 129.0, 129.1, 129.2, 129.4, 129.9, 129.9, 130.0 (×2), 130.1, 130.2, 133.4, 133.4, 136.6, 143.7 (×5), 155.1, 165.1 (×2), 165.3 (×2), 166.0 (×2) ppm; HR-FAB MS [M+Na]⁺ calcd for C₅₅H₄₆O₉Na 873.3072, found 873.3064

2-Allylphenyl 2,3,4-tri-O-benzoyl-β-D-glucopyranoside (5.13). To a stirred solution of **M** (1.1 g, 1.22 mmol) in CH₂Cl₂ (20 mL), water (0.2 mL) followed by trifluoroacetic acid (1.8 mL) were added until persistent yellow color obtained. The resultant mixture was

stirred at rt for 45 min, diluted with CH₂Cl₂ (20 mL), washed with water (10 mL), sat. aq. NaHCO₃ (10 mL), and water (3×10 mL). The organic layer was separated, dried with MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexanes gradient elution) to afford the title compound (0.7 g, 90%) as a white solid. Analytical data for **5.13**: R_f = 0.56 (ethyl acetate - hexanes, 2/5, v/v); [α]_D²³ +15.6 (c = 1.0, CHCl₃); ¹H-n.m.r.: δ, 3.13 (t, J = 6.2 Hz, 1H, OH), 3.35 (d, 2H, J = 6.5 Hz, PhCH₂CH=CH₂), 3.87-4.02 (m, 2H, H-6a, H-6b), 4.08-4.13 (m, 1H, H-5), 4.89 (m, 2H, PhCH₂CH=CH₂), 5.57 (d, 1H, J_{1,2} = 7.9 Hz, H-1), 5.73 (dd, 1H, J_{3,4} = 9.7 Hz, H-4), 5.77-5.90 (m, 1H; PhCH₂CH=CH₂), 5.99 (dd, 1H, J_{2,3} = 9.8 Hz, H-2), 6.20 (dd, 1H, J_{3,4} = 9.7 Hz, H-3), 7.08-7.56 (m, 13H, aromatic), 7.95-8.09 (m, 6H, aromatic) ppm; ¹³C-n.m.r.: 33.9, 61.6, 69.6, 71.7, 72.9, 75.1, 77.6, 99.6, 114.9, 115.7, 123.3, 127.6, 128.5 (×3), 128.7 (×3), 128.9 (×2), 129.3, 129.9 (×2), 129.9 (×2), 130.1 (×2), 130.4, 133.5 (x2), 133.9, 136.5, 154.7, 165.2, 165.9, 166.1 ppm; HR-FAB MS [M+Na]⁺ calcd for C₃₆H₃₂O₉Na 631.1944, found 631.1937

Synthesis of glycosides

Typical MeOTf-promoted glycosylation procedure (Method A). A mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3Å, 300 mg) in 1,2-dichloroethane (1.4 mL) was stirred under argon for 1 h. MeOTf (0.33 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Tables), the solid was filtered off and the residue was rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 20% NaHCO₃ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO₄ and

concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate- hexane gradient elution) to afford the corresponding oligosaccharide.

Typical TMSOTf-promoted glycosylation procedure (Method B). A mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 150 mg) in 1,2-dichloroethane (1.6 mL) was stirred under argon for 1 h. TMSOTf (0.22 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Tables), the solid was filtered off and the residue was rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 20% NaHCO₃ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate- hexane gradient elution) to afford the corresponding oligosaccharide.

Typical NIS/TfOH-promoted glycosylation procedure (Method C). A mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 150 mg) in 1,2-dichloroethane (1.6 mL) was stirred under argon for 1 h. NIS (0.22 mmol) and TfOH (0.022 mmol) was added and the reaction mixture was monitored by TLC. Upon completion, the mixture was diluted with CH₂Cl₂, the solid was filtered off, and the residue was rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 10% Na₂S₂O₃ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate- hexane gradient elution) to afford the corresponding oligosaccharide.

Typical NIS/TMSOTf-promoted glycosylation procedure (Method D). A mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 150 mg) in 1,2-dichloroethane (1.6 mL) was stirred under argon for 1 h. NIS (0.22 mmol) and TMSOTf (0.022 mmol) was added and the reaction mixture was monitored by TLC. Upon completion, the mixture was diluted with CH₂Cl₂, the solid was filtered off, and the residue was rinsed successively with CH₂Cl₂. The combined filtrate (30 mL) was washed with 10% Na₂S₂O₃ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate - hexane gradient elution) to afford the corresponding oligosaccharide.

Methyl 6-O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (5.6a). Analytical data for the title compound was essentially the same as previously described.¹³

Methyl 6-O-(2,3,4,6-tetra-O-benzoyl- β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (5.6b). Analytical data for the title compound was essentially the same as previously described.¹³

Methyl 6-O-(2-O-benzoyl-3,4,6-tri-O-benzyl- β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (5.6c). Analytical data for the title compound was essentially the same as previously described.¹⁴

Methyl 4-O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-2,3,6-tri-O-benzyl- α -D-glucopyranoside (5.7a). Analytical data for the title compound was essentially the same as previously described.¹³

Methyl 3-O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-2,4,6-tri-O-benzyl- α -D-glucopyranoside (5.8a). Analytical data for the title compound was essentially the same as previously described.¹⁵

Methyl 2-O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-3,4,6-tri-O-benzyl- α -D-glucopyranoside (5.9a). Analytical data for the title compound was essentially the same as previously described.¹⁶

Methyl 2-O-(2,3,4,6-tetra-O-benzyl-D-galactopyranosyl)-3,4,6-tri-O-benzyl- α -D-glucopyranoside (5.9d). The title compound was obtained as a clear film from **5.1d** and **5.5** by Method C in 80% yield ($\alpha/\beta = 3.0/1$). Selected analytical data for α -**5.9d**: ¹H n.m.r.: δ , 3.91 (dd, 1H, $J_{2,3} = 2.7$ Hz, H-2), 4.02 (dd, 1H, $J_{2',3'} = 9.6$ Hz, H'-2), 4.93 (d, 1H, $J_{1,2} = 3.4$ Hz, H-1), 4.97 (d, 1H, $J_{1',2'} = 3.5$ Hz, H'-1) ppm; ¹³C n.m.r.: δ , 94.9 (C-1), 96.7 (C'-1) ppm. HR-FAB MS $[M+Na]^+$ calcd for C₆₂H₆₆O₁₁Na⁺ 1009.4503, found 1009.4510.

Methyl 3-O-(2,3,4,6-tetra-O-benzyl-D-galactopyranosyl)-2,4,6-tri-O-benzyl- α -D-glucopyranoside (5.8d). Analytical data for the title compound was essentially the same as previously described.¹⁷

Methyl 4-O-(2,3,4,6-tetra-O-benzyl-D-galactopyranosyl)-2,3,6-tri-O-benzyl- α -D-glucopyranoside (5.7d). Analytical data for the title compound was essentially the same as previously described.¹⁸

Methyl 6-O-(2,3,4,6-tetra-O-benzyl-D-galactopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (5.6d). Analytical data for the title compound was essentially the same as previously described.¹⁹

Methyl 2-O-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)-3,4,6-tri-O-benzyl- α -D-glucopyranoside (5.9b). Analytical data for the title compound was essentially the same as previously described.¹⁶

Ethyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl-1-thio- β -D-glucopyranoside (5.16) Analytical data for the title compound was essentially the same as previously described.²

Phenyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl-1-thio- β -D-glucopyranoside (5.22). Analytical data for the title compound was essentially the same as previously described.¹⁶

2-[3-iodo-2-(methyl 2,3,4-tri-O-benzyl- α -D-glucopyranosid-6-yl)propyl]oxyphenyl 2,3,4,6-tetra-O-benzyl- β -D-glucopyranoside (5.12). The title compound was isolated as

a by-product from the synthesis of **5.6a** from **5.1a** and **5.2** by Method B in 15% yield. Selected analytical data for **5.12**: ^1H -n.m.r.: δ 3.74 (dd, 1H, $J_{2,3'} = 7.9$ Hz, H'-2), 4.53 (d, $J_{1,2} = 4.1$ Hz, H-1), 5.02 (d, 1H, $J_{1',2'} = 8.0$ Hz, H'-1) ppm; ^{13}C -n.m.r.: δ , 10.6, 35.9, 55.3, 68.0, 68.8, 70.4, 73.5, 73.6, 73.7, 74.8, 75.2, 75.3, 75.4, 75.5, 75.8, 75.9, 77.4, 77.8, 77.9, 79.4, 79.9, 80.1, 82.2, 82.3, 82.4, 85.1, 85.2, 98.2, 101.8, 115.8, 122.8, 122.9, 127.1, 127.6, 127.7, 127.8, 127.9 ($\times 2$), 128.0 ($\times 2$), 128.1 ($\times 2$), 128.1 ($\times 2$), 128.2 ($\times 2$), 128.3, 128.4 ($\times 2$), 128.5 ($\times 2$), 128.6 ($\times 4$), 128.7 ($\times 4$), 128.9, 129.2, 132.2, 138.1, 138.2, 138.3, 138.4, 138.5, 138.6, 138.7, 138.8, 155.5 ppm; HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{71}\text{H}_{75}\text{IO}_{12}\text{Na}^+$ 1269.4201, found 1269.4214.

Tolyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzoyl-1-thio- β -D-glucopyranoside (5.18). The title compound was obtained as a clear film from **5.6** and **5.15** by Method A in 75% yield ($\alpha/\beta = 2.4/1$). Selected analytical data for α -**5.18**: ^1H n.m.r.: δ , 4.67 (d, 1H, $J_{1',2'} = 3.7$ Hz, H'-1), 4.85 (d, 1H, $J_{1,2} = 9.3$ Hz, H-1) ppm. ^{13}C -n.m.r.: δ , 86.1 (C-1), 97.6 (C'-1) ppm. Selected analytical data for β -**5.18**: ^1H n.m.r.: δ , 4.52 (d, 1H, $J_{1',2'} = 10.8$ Hz, H'-1) ppm. ^{13}C -n.m.r.: δ , 87.2 (C-1), 103.9 (C'-1) ppm. HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{68}\text{H}_{64}\text{O}_{13}\text{SNa}^+$ 1143.3965, found 1143.3970.

2-Allylphenyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- β -D-glucopyranoside (5.25). The title compound was obtained as a clear film from donors **5.24**, **5.27-5.29** and acceptor **5.24** by Method A in 82-90% yield. Selected analytical data for α -**5.25**: ^1H n.m.r.: δ , 4.37 (d, 1H, $J_{1',2'} = 2.7$ Hz, H'-1) ppm; ^{13}C -n.m.r.: δ , 97.6 (C-1), 100.6 (C'-1) ppm; Selected analytical data for β -**5.25**: ^1H n.m.r.: δ , 4.34 (d, 1H, $J_{1',2'} =$

5.6 Hz, H¹-1) ppm; ¹³C-n.m.r.: ¹³C-n.m.r.: δ, 101.6 (C-1), 104.2 (C'-1) ppm; HR-FAB MS [M+Na]⁺ calcd for C₇₀H₇₂O₁₁Na⁺ 1111.5057, found 1111.4980.

2-Allylphenyl 6-O-(2,3,4,6-tri-O-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-O-benzoyl-β-D-glucopyranoside (5.14). The title compound was obtained as a clear film from **5.1a** and **5.13** by Method B in 78% yield (α/β = 1.0/1). Selected analytical data for α-**5.14**: ¹H n.m.r.: δ, 4.58 (d, 1H, J_{1,2'} = 4.6 Hz, H¹-1), 5.28 (d, J_{1,2} = 7.8 Hz, H-1) ppm. ¹³C-n.m.r.: δ, 80.4 (C-1), 98.4 (C'-1) ppm; Selected analytical data for β-**5.14**: ¹H n.m.r.: δ, 4.42 (d, 1H, J_{1',2'} = 11.0 Hz, H¹-1) ppm; ¹³C-n.m.r.: δ, 82.2 (C-1), 100.1 (C'-1) ppm; HR-FAB MS [M+Na]⁺ calcd for C₇₀H₆₈O₁₄Na⁺ 1155.4609, found 1155.4623.

Phenyl 6-O-(2,3,4,6-tri-O-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranoside (5.20). The title compound was obtained as clear film from **5.1a** and **5.19** by Method B in 90% yield (α/β = 1.0/1). Selected analytical data for α-**5.20**: ¹H n.m.r.: δ, 3.95 (t, 1H, J_{2,3} = 9.0 Hz, H-3), 4.57 (d, 1H, J_{1,2} = 9.3 Hz, H-1), 5.00 (d, 1H, J_{1',2'} = 3.5 Hz, H¹-1), ppm. ¹³C-n.m.r.: δ, 89.2 (C-1), 96.6 (C'-1) ppm. Selected analytical data for β-**5.20**: ¹H n.m.r.: δ, 4.37 (d, 1H, J_{1',2'} = 7.8 Hz, H¹-1), ¹³C-n.m.r.: δ, 95.2 (C-1), 103.4 (C'-1) ppm. HR-FAB MS [M+Na]⁺ calcd for C₆₇H₆₈O₁₀SNa⁺ 1087.4433, found 1087.4406.

Methyl O-(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)-(1→6)-O-(2,3,4-tri-O-benzyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-glucopyranoside (5.29).

Analytical data for the title compound was essentially the same as previously described.^[20]

2-Allylphenyl O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-O-(2,3,4-tri-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-2,3,4-tri-O-benzyl- β -D-glucopyranoside

(5.31). The title compound was obtained as colorless syrup from **5.16** and **5.25** by method A in 50% yield. Selected analytical data for β -**5.32**: ^1H n.m.r.: δ , 4.37 (d, 1H, $J_{1,2} = 12.4$ Hz, H'-1), 4.47 (d, 1H, $J_{1'',2''} = 2.5$ Hz, H''-1), 4.99 (d, 1H, $J_{1,2} = 6.9$ Hz, H-1) ppm; ^{13}C -n.m.r.: δ , 98.2 (C-1), 102.0 (C'-1), 103.8 (C''-1) ppm; HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{97}\text{H}_{100}\text{O}_{16}\text{Na}^+$ 1543.6909, found 1543.6936.

2-Allylphenyl O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-O-(2,3,4-tri-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-2,3,4-tri-O-benzoyl- β -D-glucopyranoside

(5.32). The title compound was obtained as colorless syrup from **5.16** and **5.13** by method A in 80% yield. Selected analytical data for α -**5.32**: ^1H n.m.r.: δ , 4.67 (d, 1H, $J_{1,2} = 3.2$ Hz, H'-1), 4.90 (d, 1H, $J_{1'',2''} = 2.5$ Hz, H''-1) ppm; ^{13}C -n.m.r.: δ , 97.4 (C-1), 97.5 (C'-1), 97.6 (C''-1) ppm; Selected analytical data for β -**5.32**: 5.27 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1) ppm; ^{13}C -n.m.r.: δ , 99.7 (C-1), 99.8 (C'-1), 103.8 (C''-1) ppm; HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{97}\text{H}_{94}\text{O}_{19}\text{Na}^+$ 1585.7729, found 1585.7762.

Phenyl O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-O-(2,3,4-tri-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-2,3,4-tri-O-benzoyl-1-thio- β -D-glucopyranoside

(5.30). The title compound was obtained as clear film from **5.26** and **5.21** by method B in

90% yield. Selected analytical data for **5.30**: Selected analytical data for α -**5.30**: ^1H n.m.r.: δ , 4.69 (d, 1H, $J_{1,2'} = 3.1$ Hz, H'-1), 4.96 (d, 1H, $J_{1'',2''} = 2.3$ Hz, H''-1) ppm; ^{13}C -n.m.r.: δ , 97.4 (C-1), 97.5 (C'-1), 97.6 (C''-1) ppm; Selected analytical data for β -**5.30**: 5.27 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1) ppm; ^{13}C -n.m.r.: δ , 99.7 (C-1), 99.8 (C'-1), 103.8 (C''-1) ppm; HR-FAB MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{94}\text{H}_{90}\text{O}_{18}\text{SNa}^+$ 1561.5745, found 1561.5731.

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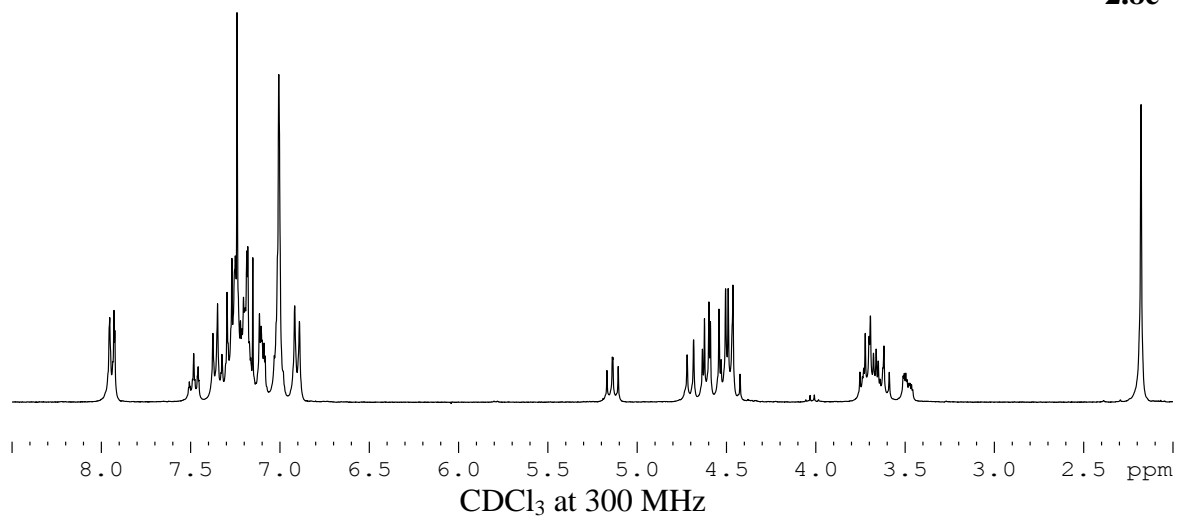
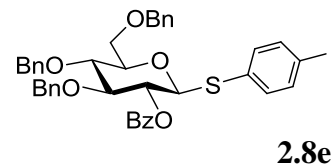
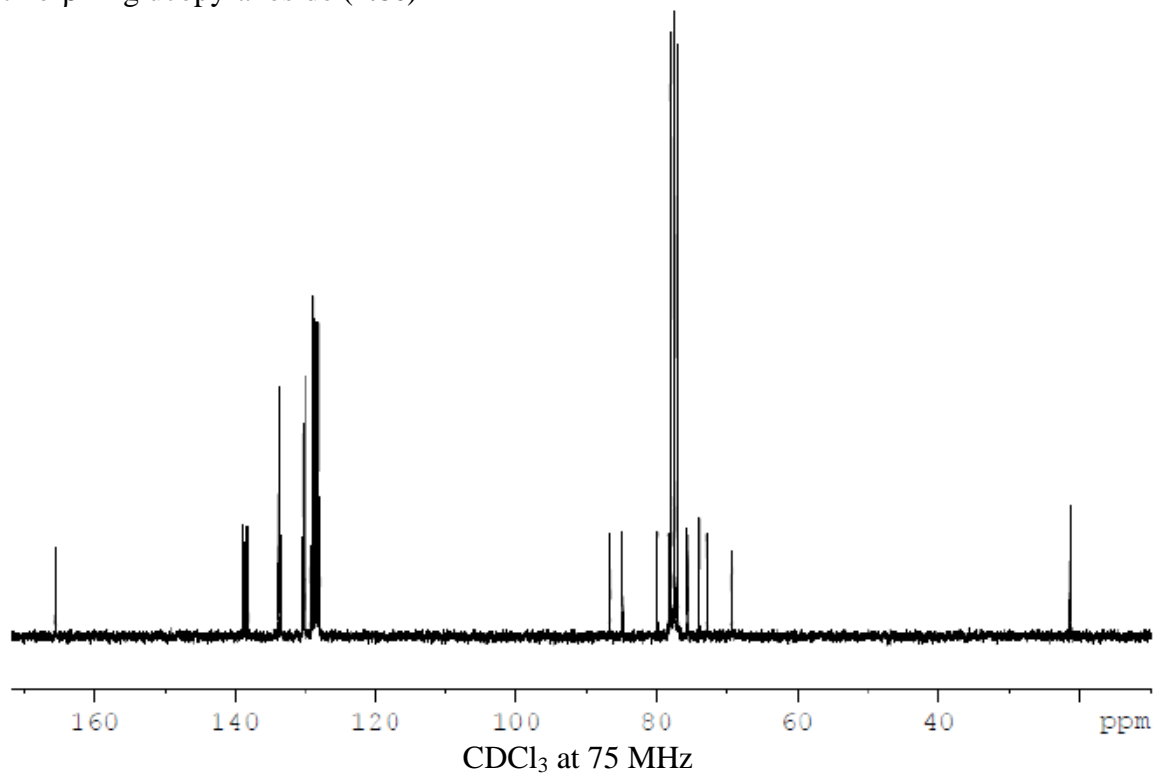
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CHAPTER 6

Appendix

Selected NMR spectral data

Figure A-1: ¹H NMR spectrum of *p*-Methylphenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.8e**)Figure A-2 ¹³C-NMR spectrum of *p*-Methylphenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.8e**)

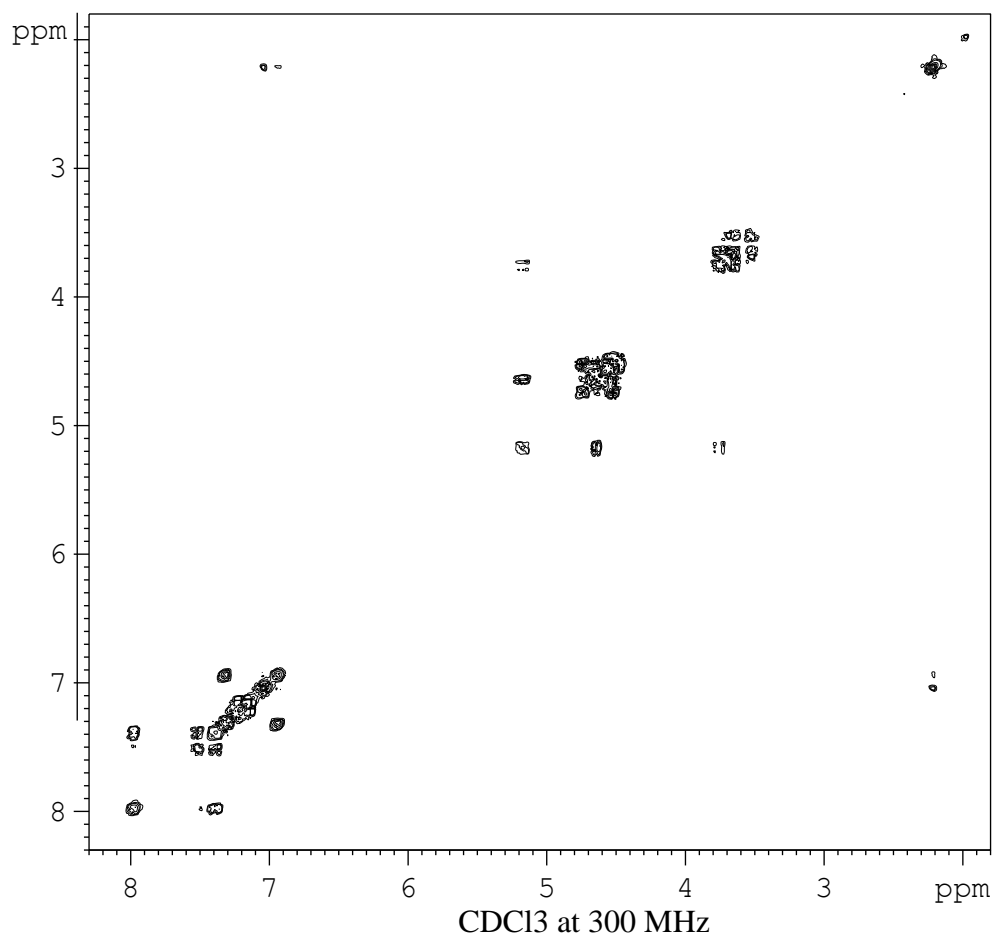
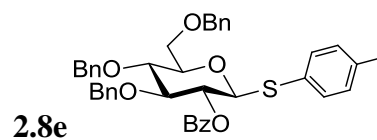


Figure A-3: 2-D-NMR COSY spectrum of *p*-Methylphenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio- β -D-glucopyranoside (**2.8e**)

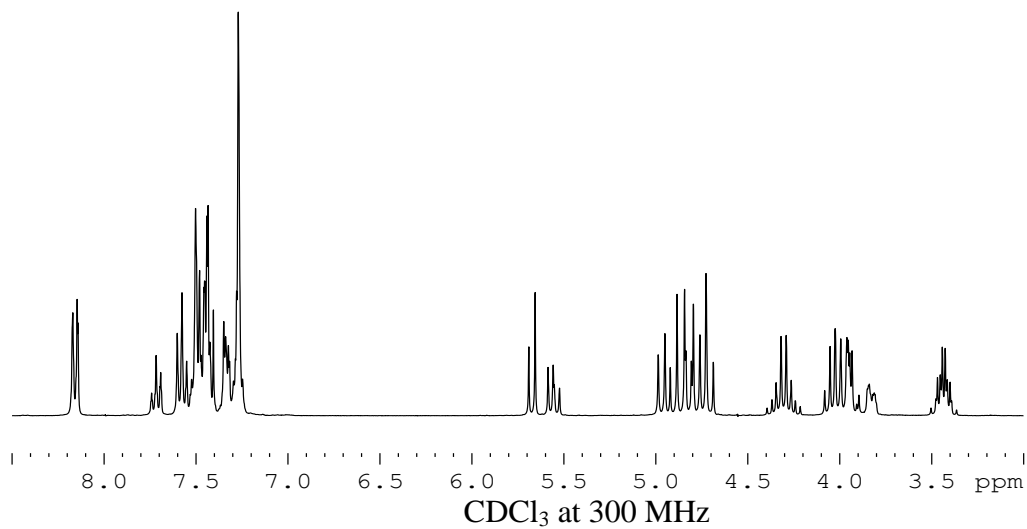
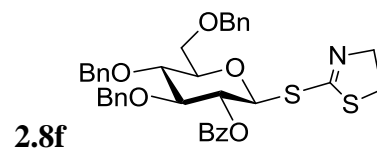


Figure A-4: ¹H NMR spectrum of Thiazolinyll 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.8f**)

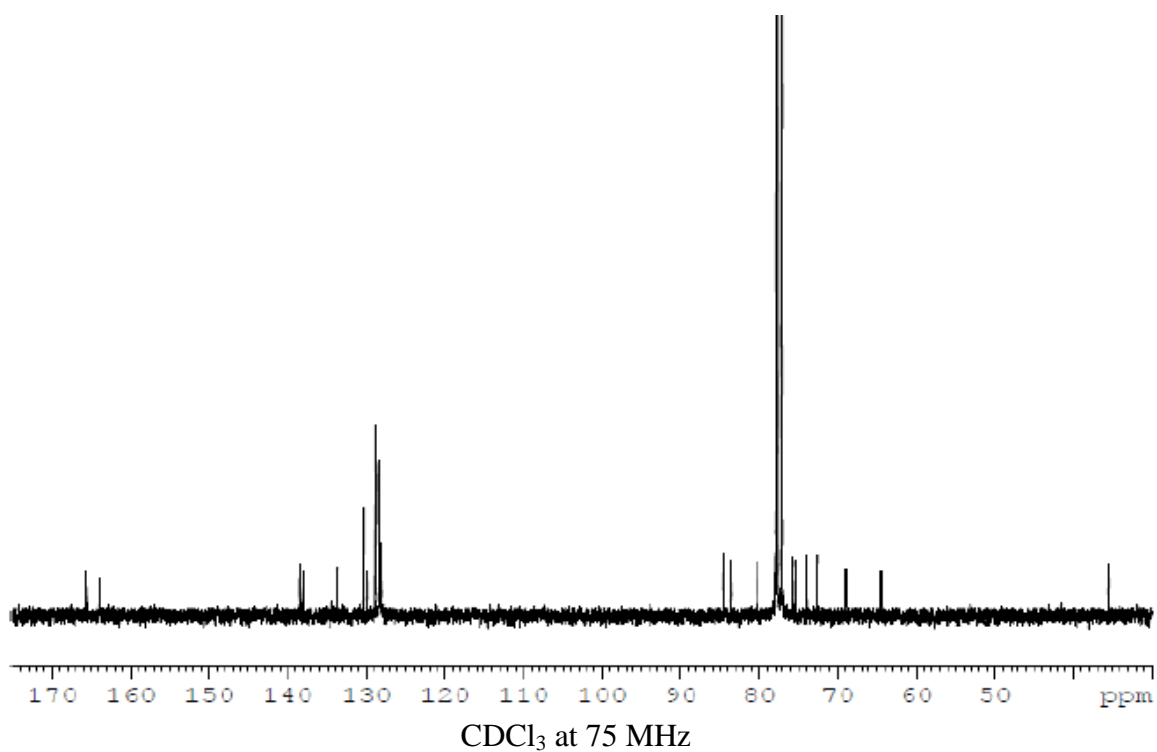


Figure A-5: ¹³C NMR spectrum of Thiazolinyll 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.8f**)

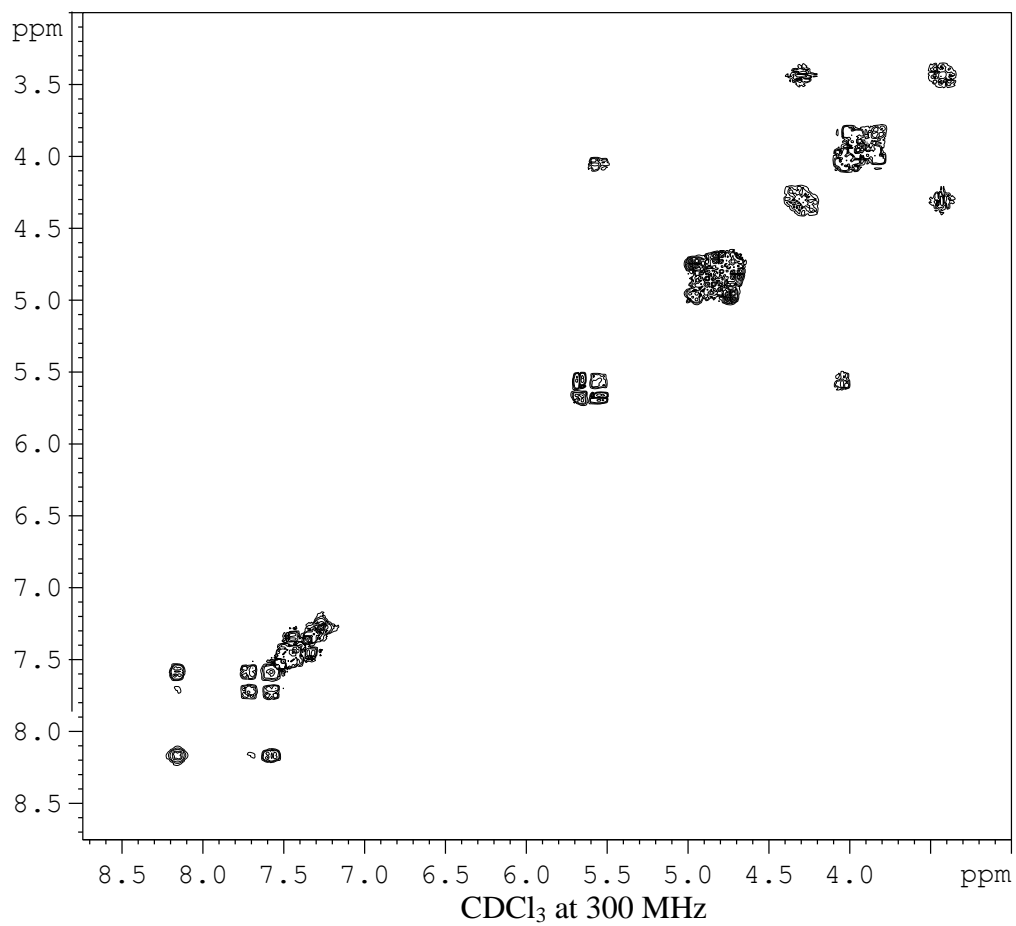
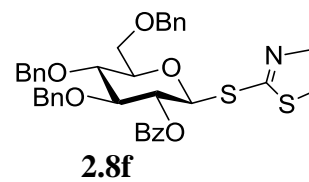


Figure A-6: 2-D NMR COSY spectrum of Thiazolanyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio- β -D-glucopyranoside (**2.8f**)

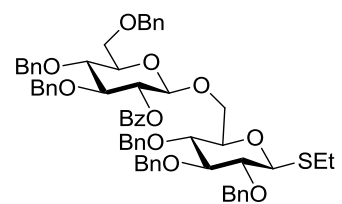
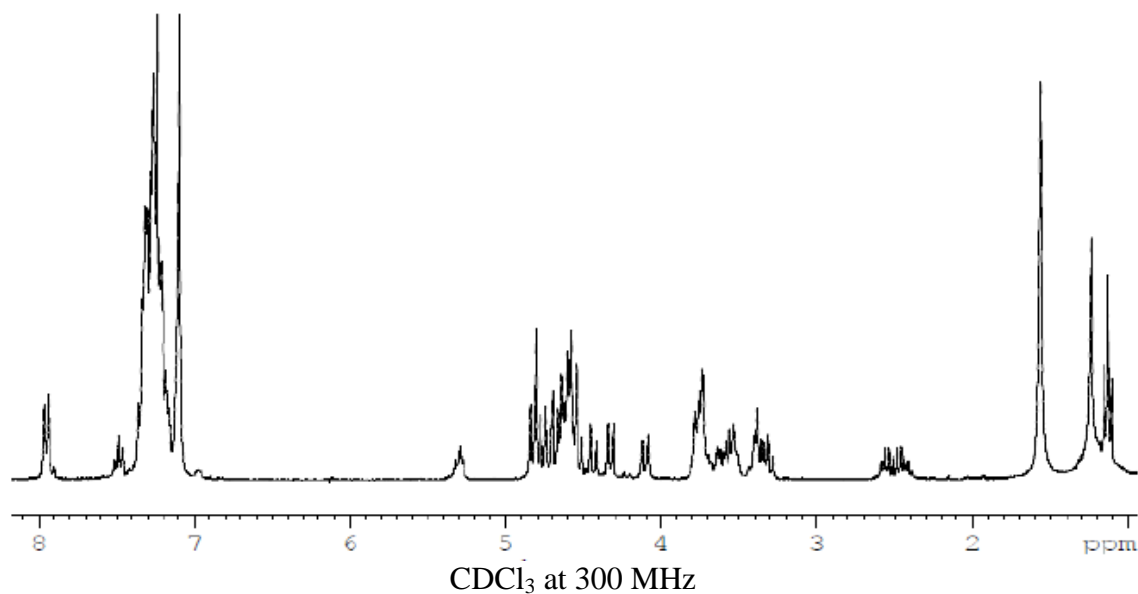
**2.13**

Figure A-7: ¹H NMR spectrum of Ethyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.13**)

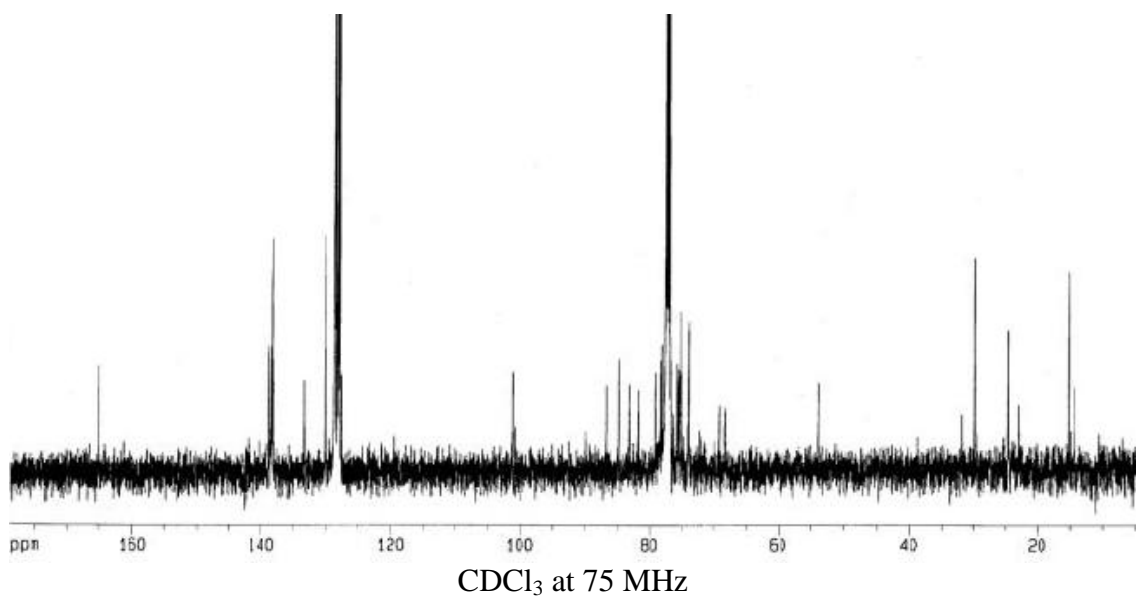


Figure A-8: ¹³C NMR spectrum of Ethyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.13**)

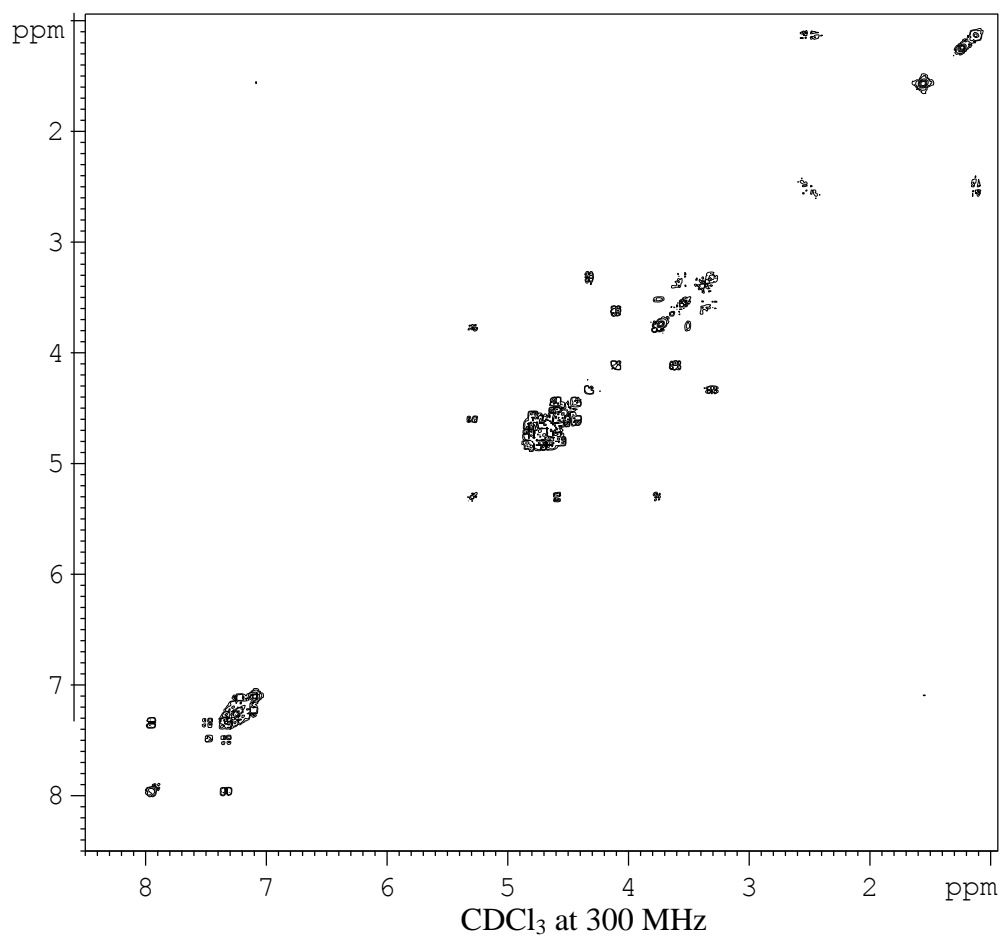
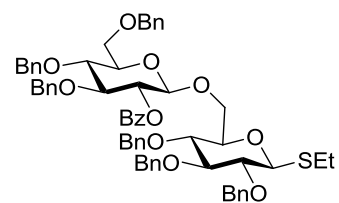


Figure A-9: 2-D NMR COSY spectrum of Ethyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-glucopyranosyl)-(1 \rightarrow 6)-2,3,4-tri-*O*-benzyl-1-thio- β -D-glucopyranoside (**2.13**)

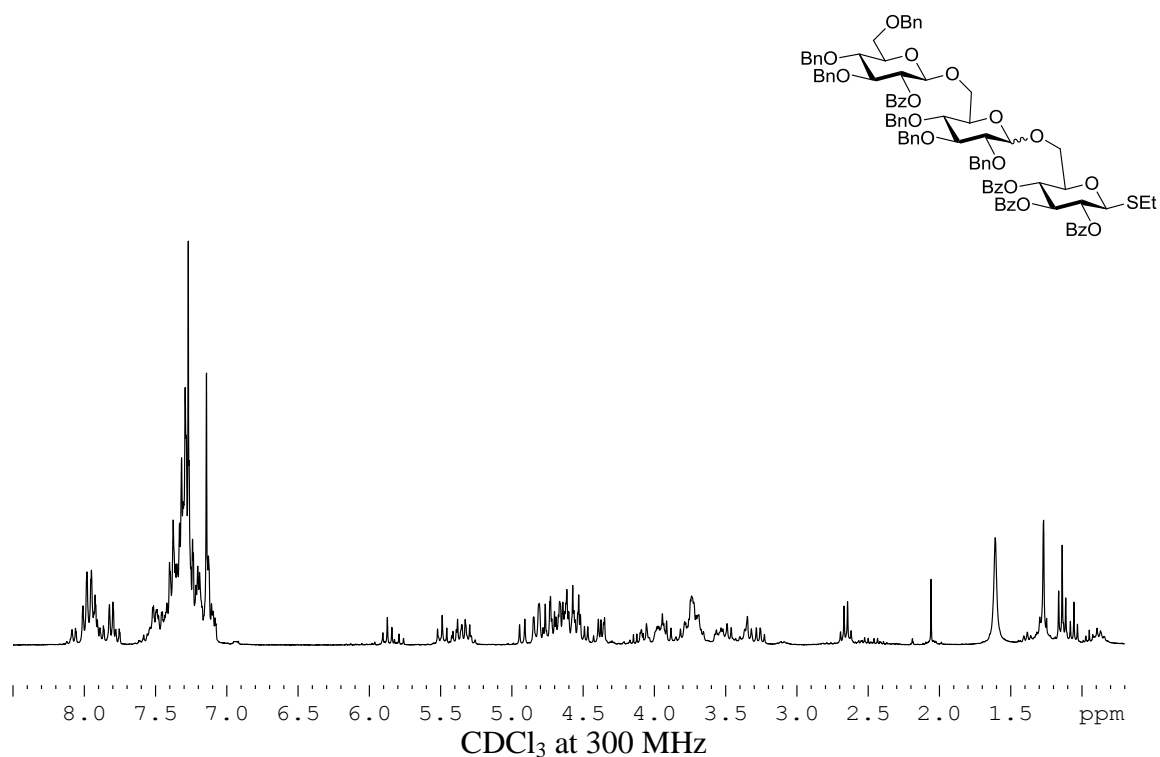


Figure A-10: ¹H NMR spectrum of Ethyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.15**)

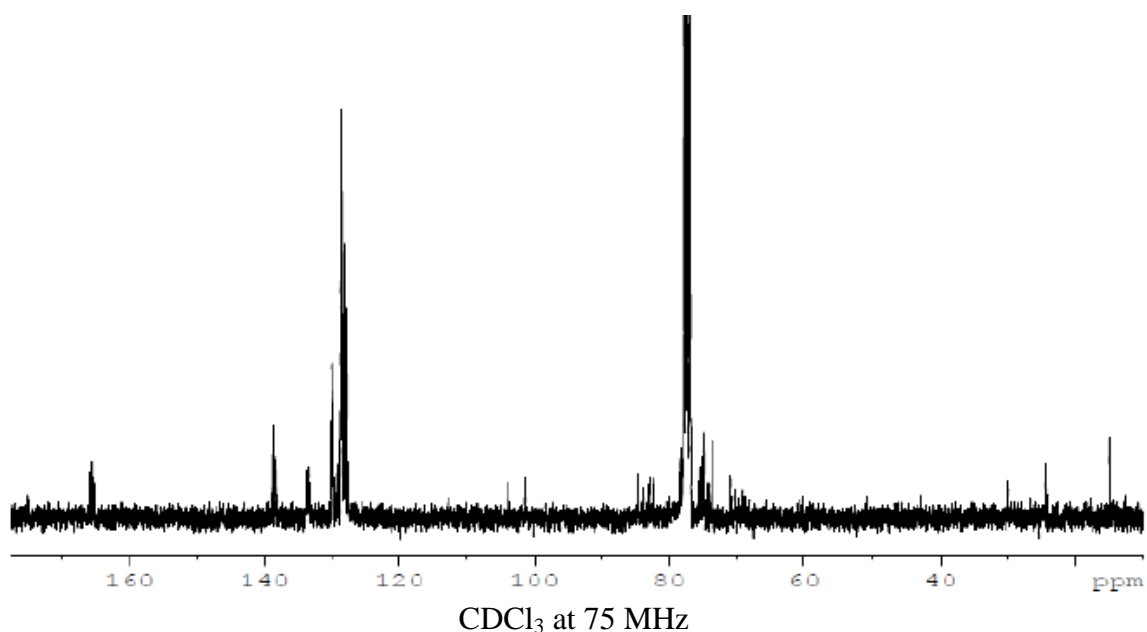


Figure A-11: ¹³C NMR spectrum of Ethyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.15**)

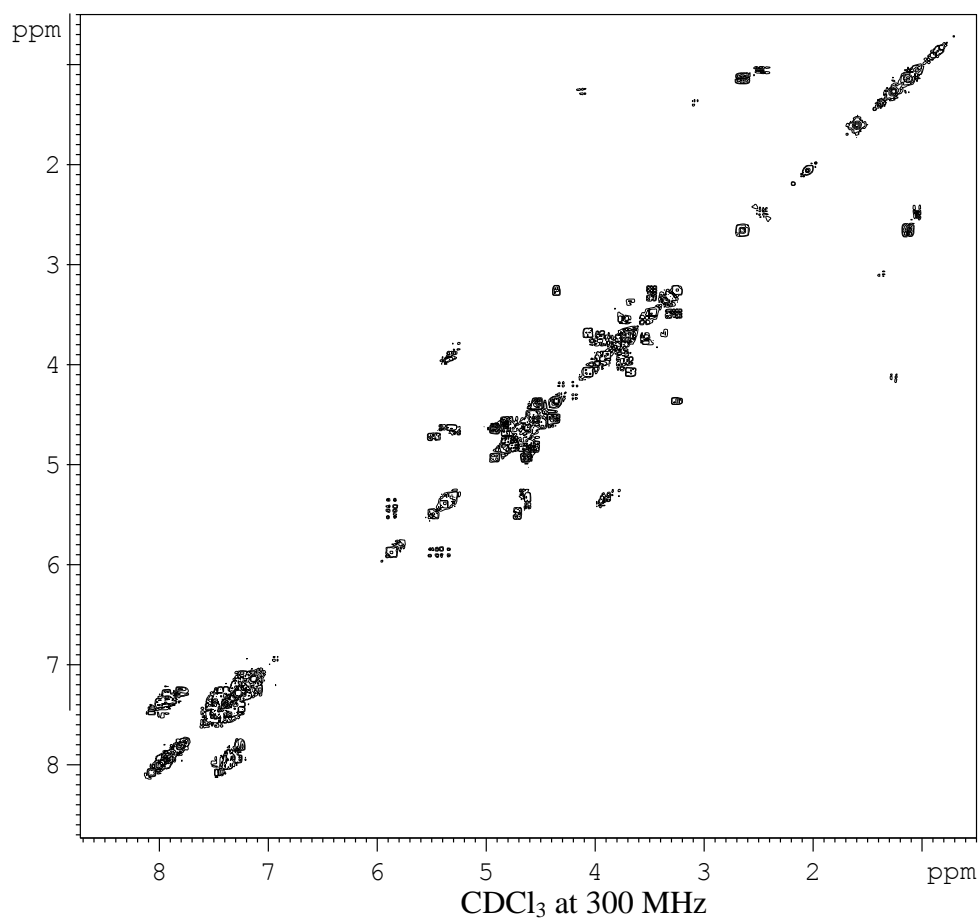
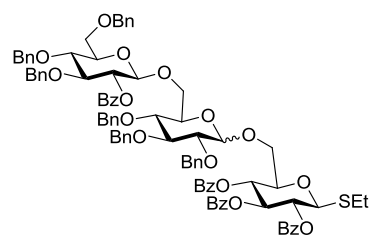


Figure A-12: ^1H NMR spectrum of Ethyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-glucopyranosyl)-(1 \rightarrow 6)-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyl)-(1 \rightarrow 6)-2,3,4-tri-*O*-benzoyl-1-thio- β -D-glucopyranoside (**2.15**)

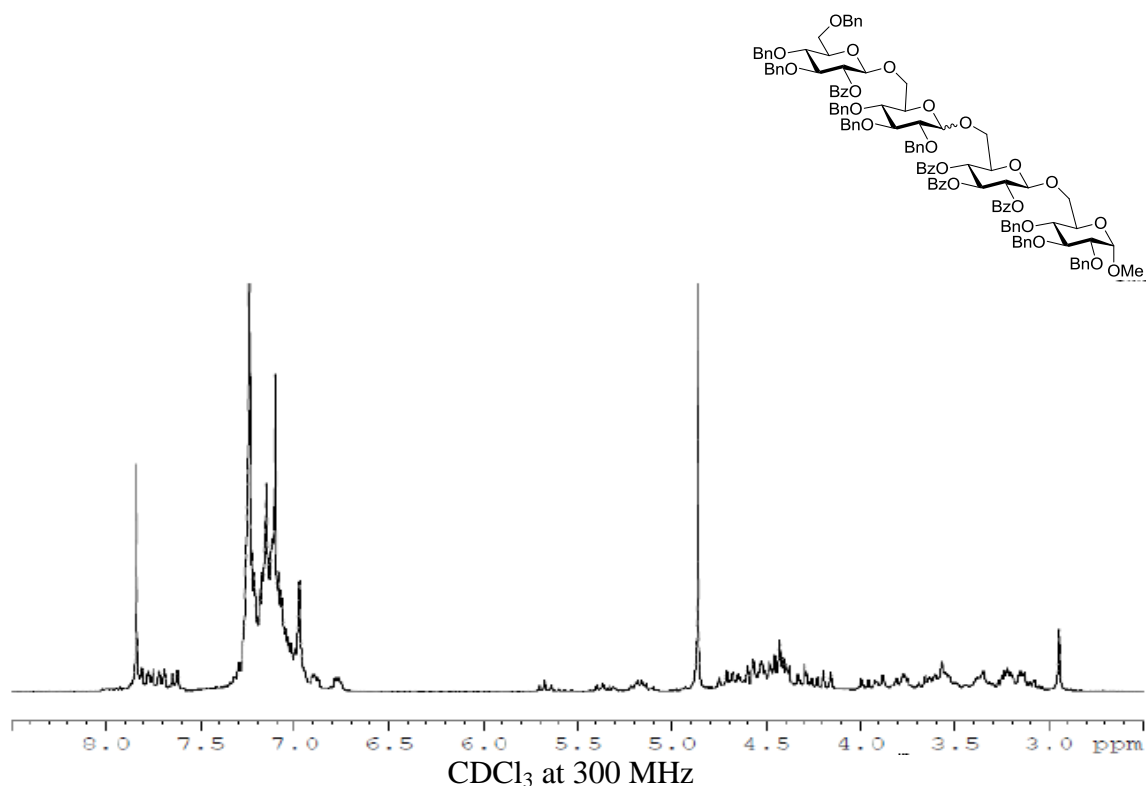


Figure A-13: ¹H NMR spectrum of Methyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2.16**).

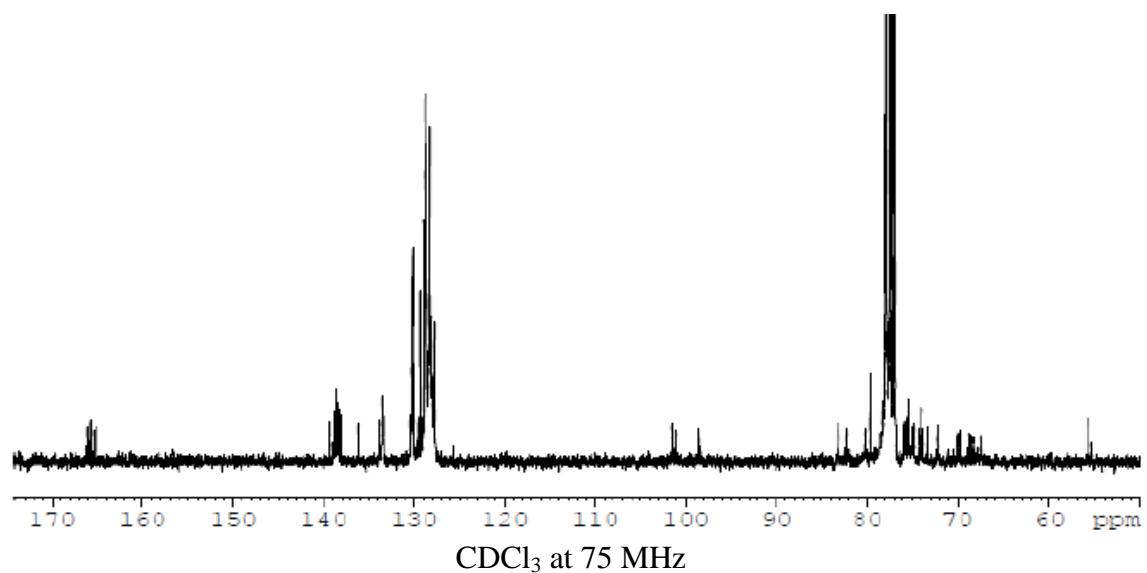


Figure A-14: ¹³C NMR spectrum of Methyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2.16**).

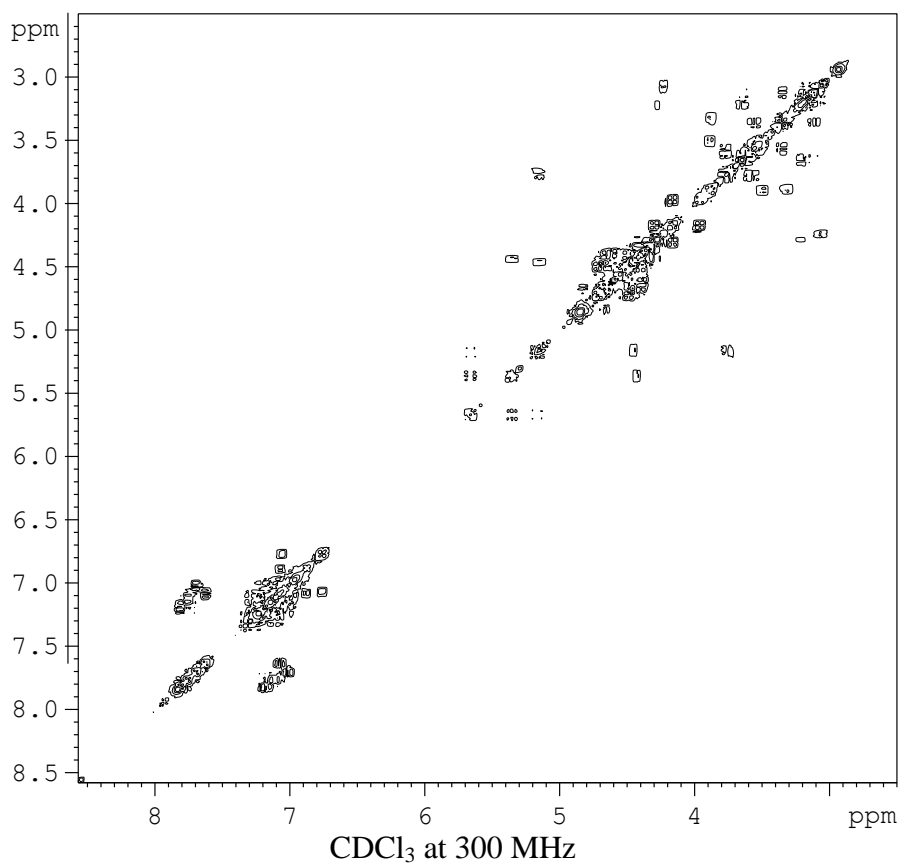
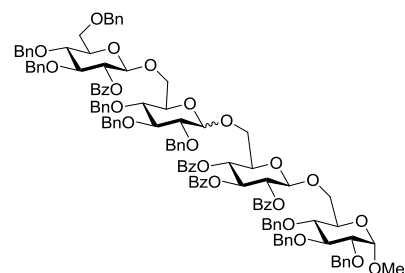


Figure A-15: 2-D NMR COSY spectrum of Methyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2.16**).

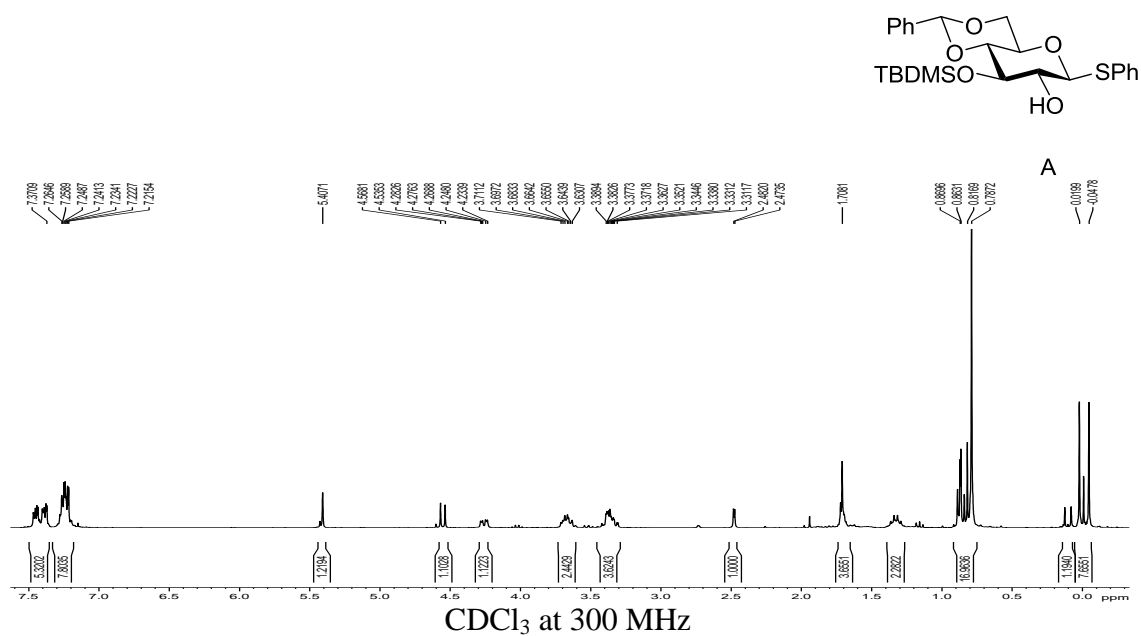


Figure A-16: ¹H NMR spectrum of Phenyl 3-O-tert-butyl dimethylsilyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside (A)

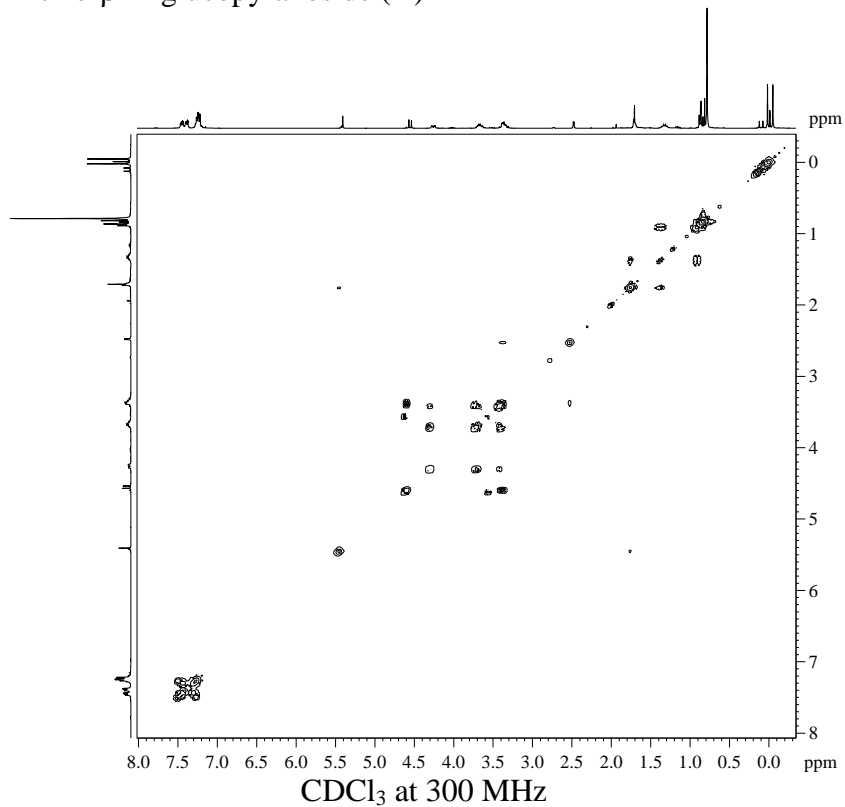


Figure A-17: 2-D NMR COSY spectrum of Phenyl 3-O-tert-butyl dimethylsilyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside (A)

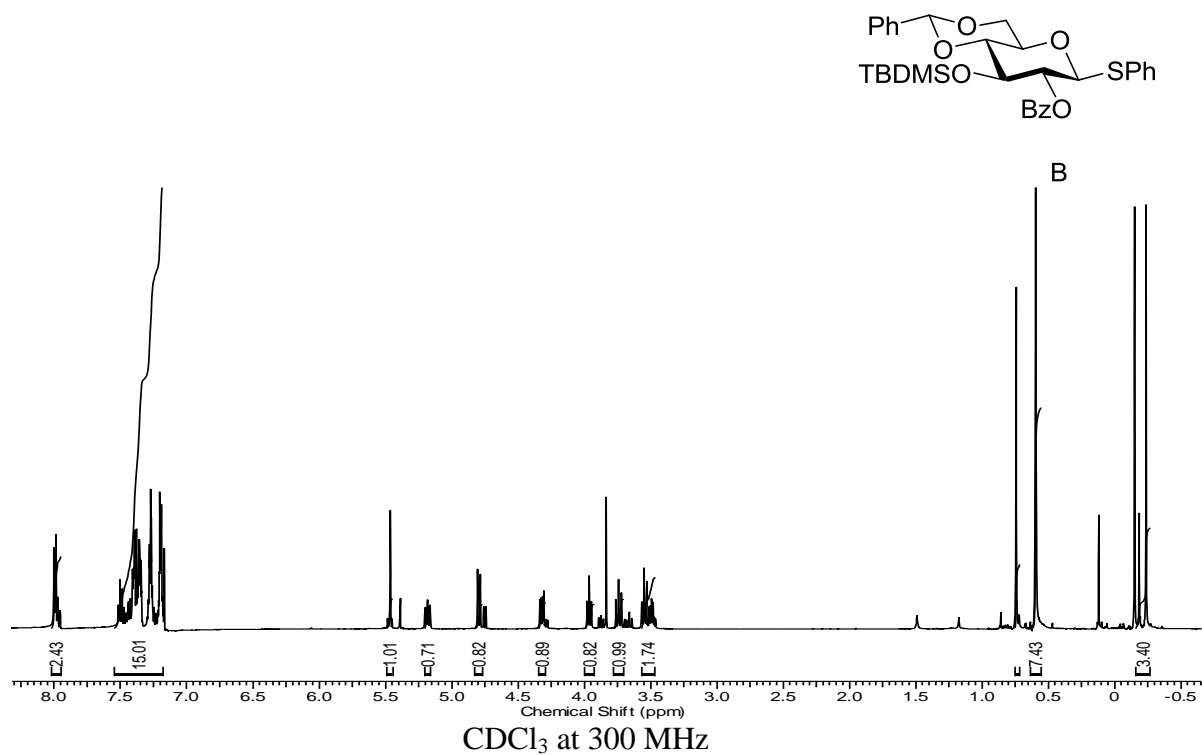


Figure A-18: ¹H NMR spectrum of Phenyl 2-*O*-benzoyl-3-*O*-tert-butyldimethylsilyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (B)

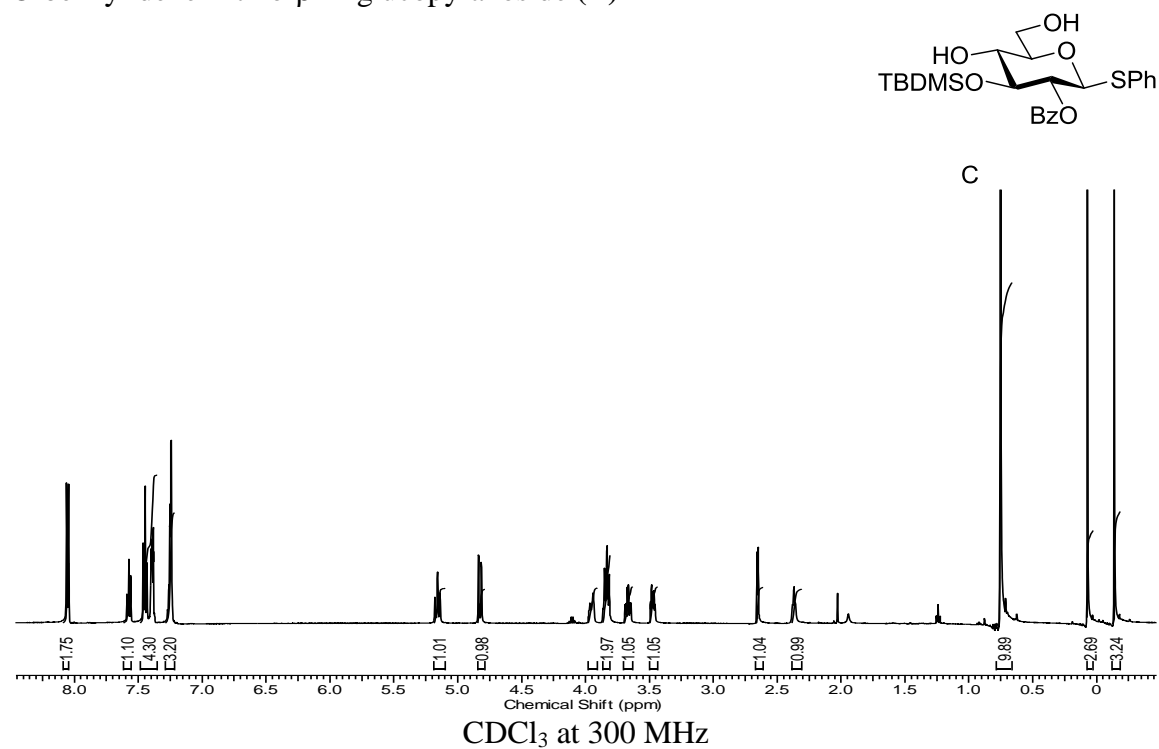


Figure A-19: 2-D NMR COSY spectrum of Phenyl 2-*O*-Benzoyl-3-*O*-tert-butyldimethylsilyl-1-thio-β-D-glucopyranoside (C).

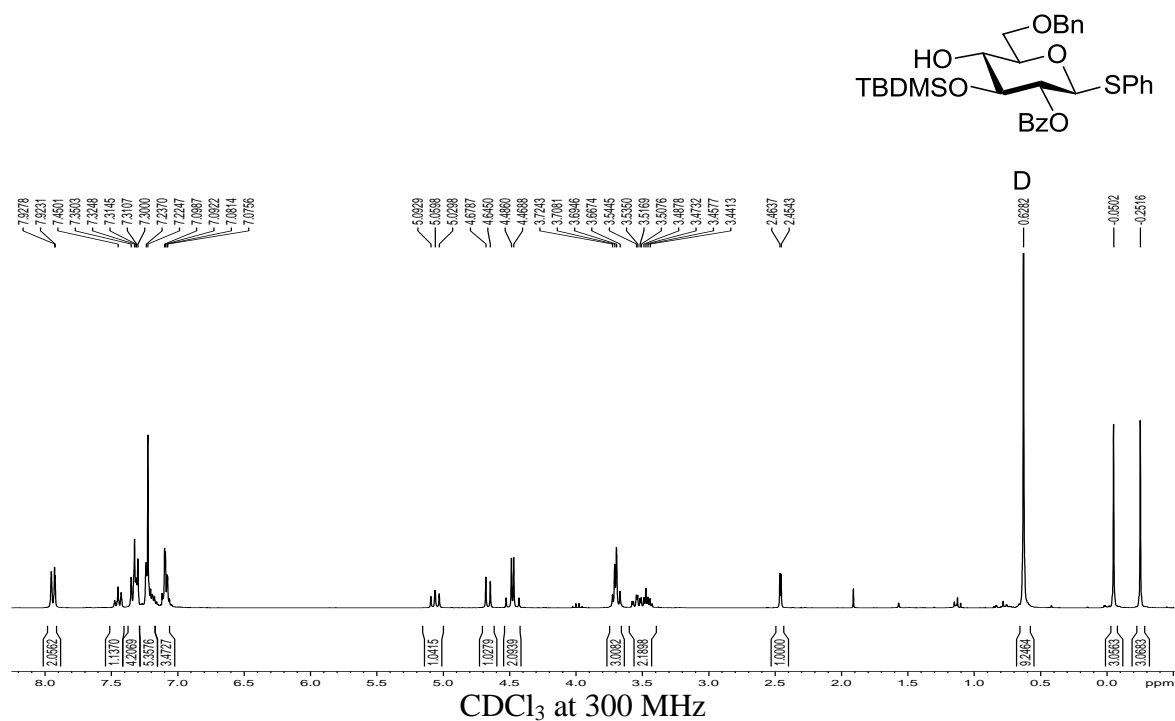


Figure A-20: ¹H NMR spectrum of Phenyl 2-*O*-Benzoyl-6-*O*-Benzyl-3-*O*-tert-butylidimethylsilyl-1-thio-β-D-glucopyranoside (**D**)

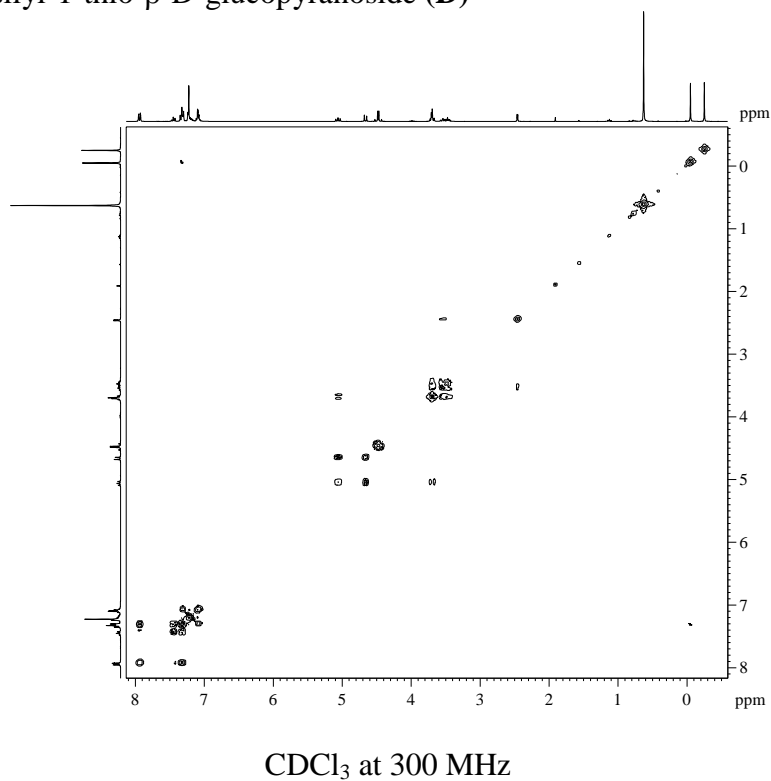


Figure A-21: 2-D NMR COSY spectrum of Phenyl 2-*O*-Benzoyl-6-*O*-Benzyl-3-*O*-tert-butylidimethylsilyl-1-thio-β-D-glucopyranoside (**D**)

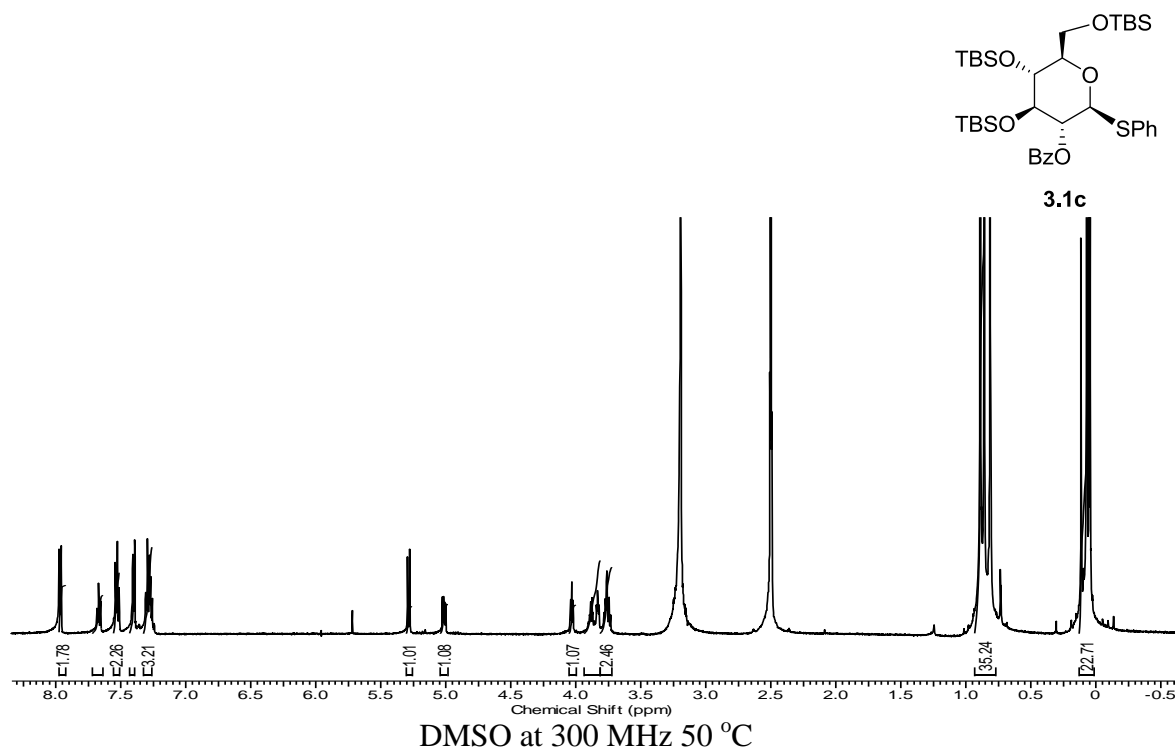


Figure A-22: ^1H NMR spectrum of Phenyl 2-*O*-benzoyl-3,4,6-tri-*O*-tert-butylidimethylsilyl-1-thio- β -D-glucopyranoside (**3.1c**)

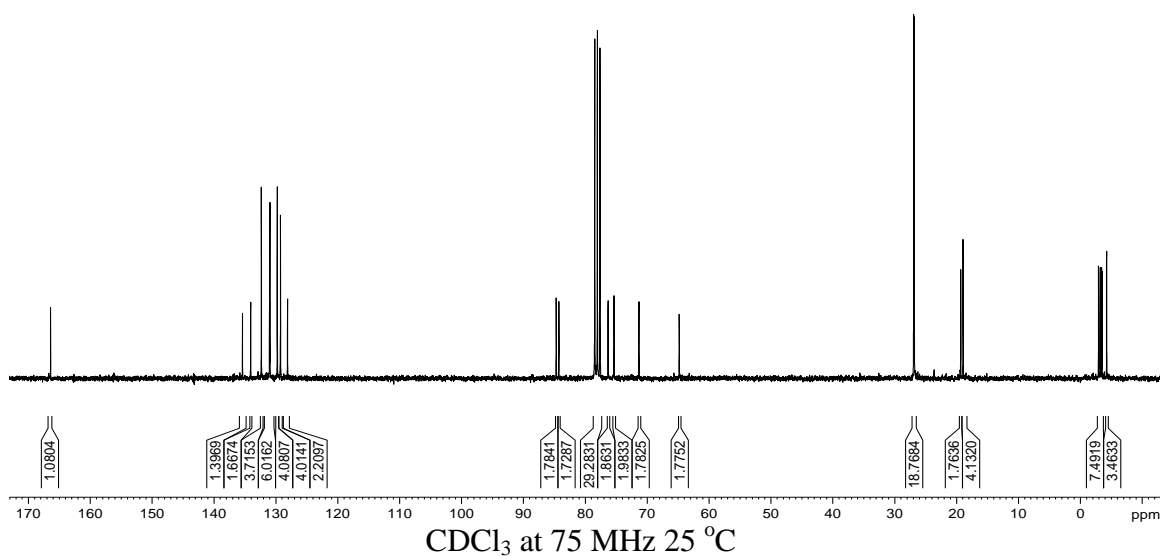


Figure A-23: ^{13}C NMR spectrum of Phenyl 2-*O*-Benzoyl-3,4,6-tri-*O*-tert-butylidimethylsilyl-1-thio- β -D-glucopyranoside (**3.1c**)

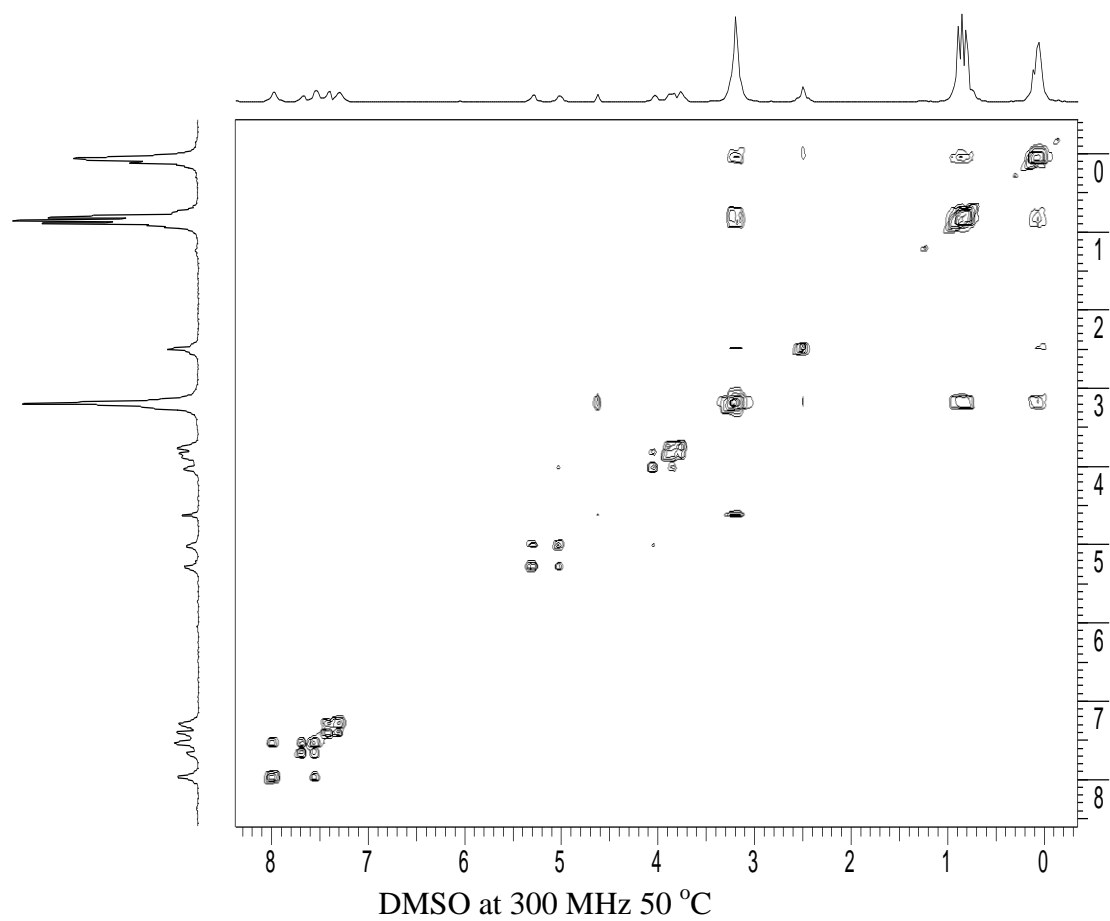
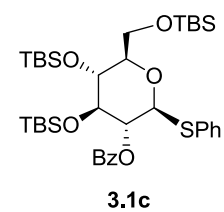


Figure A-24: 2-D NMR COSY spectrum of Phenyl 2-*O*-benzoyl-3,4,6-tri-*O*-tert-butylsilyl-1-thio-β-D-glucopyranoside (**3.1c**)

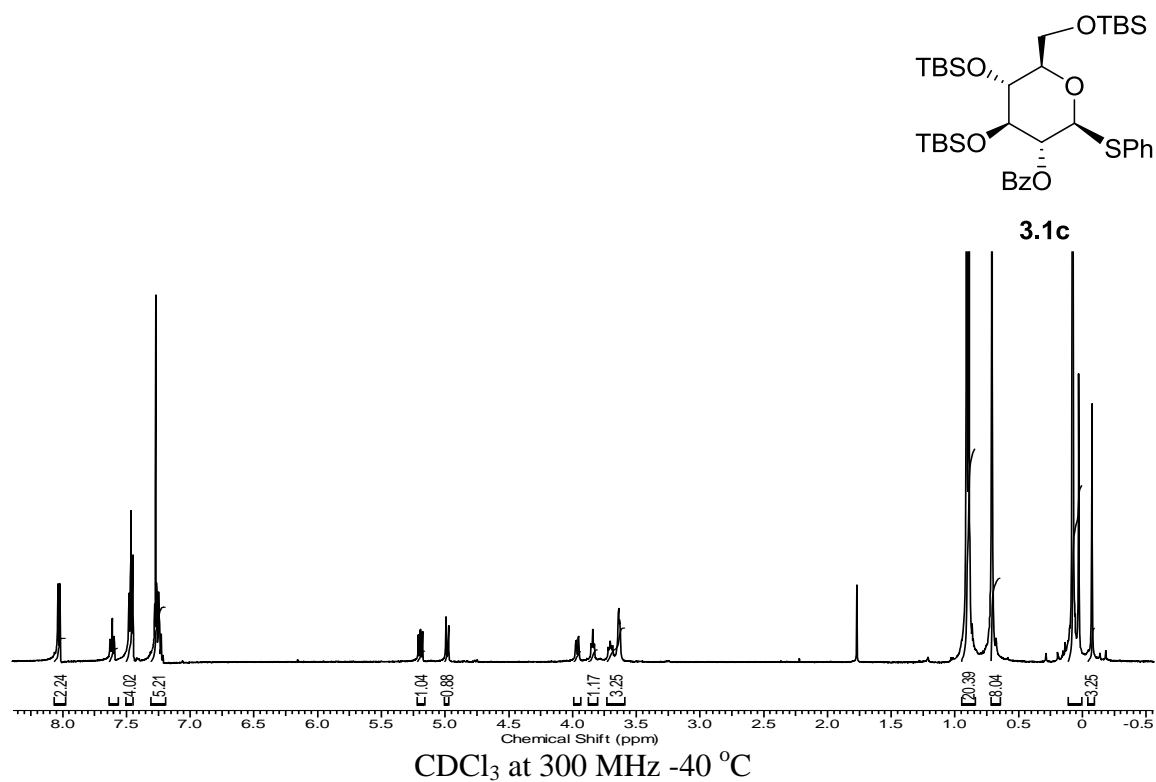


Figure A-25: ¹H NMR spectrum of Phenyl 2-*O*-Benzoyl-3,4,6-tri-*O*-tert-butyl-dimethylsilyl-1-thio-β-D-glucopyranoside (**3.1c**)

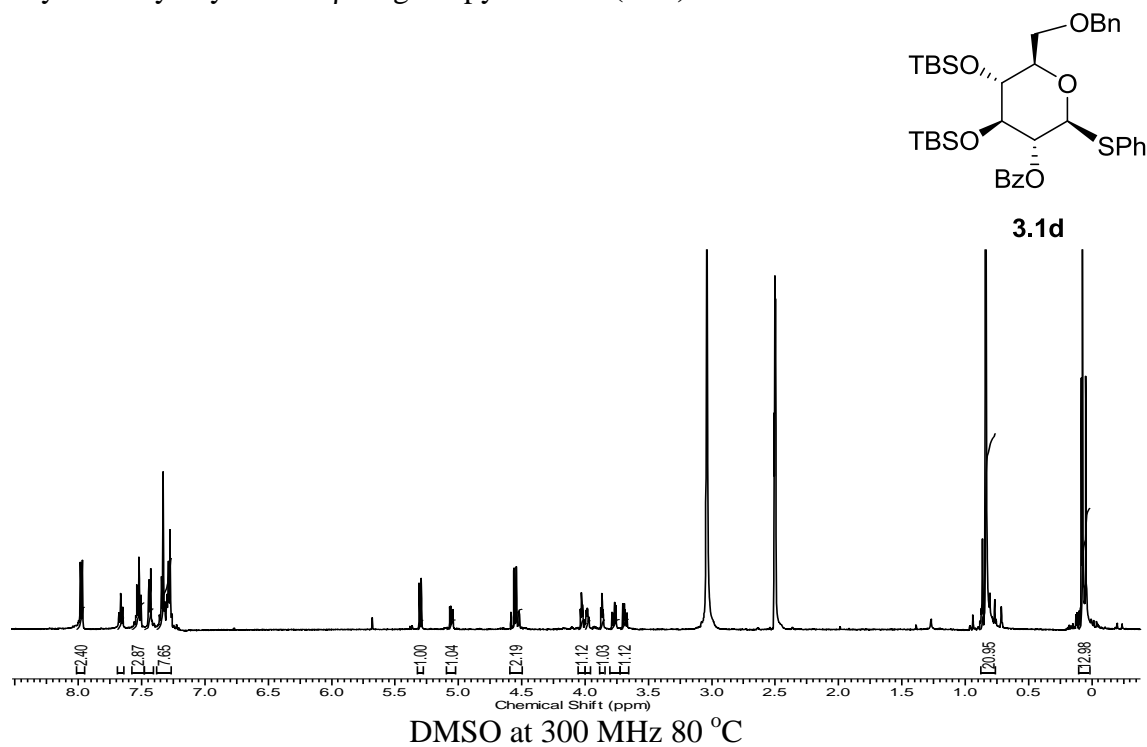


Figure A-26: ¹H NMR spectrum of Phenyl 2-*O*-benzoyl-6-*O*-benzyl-3,4-di-*O*-tert-butyl-dimethylsilyl-1-thio-β-D-glucopyranoside (**3.1d**)

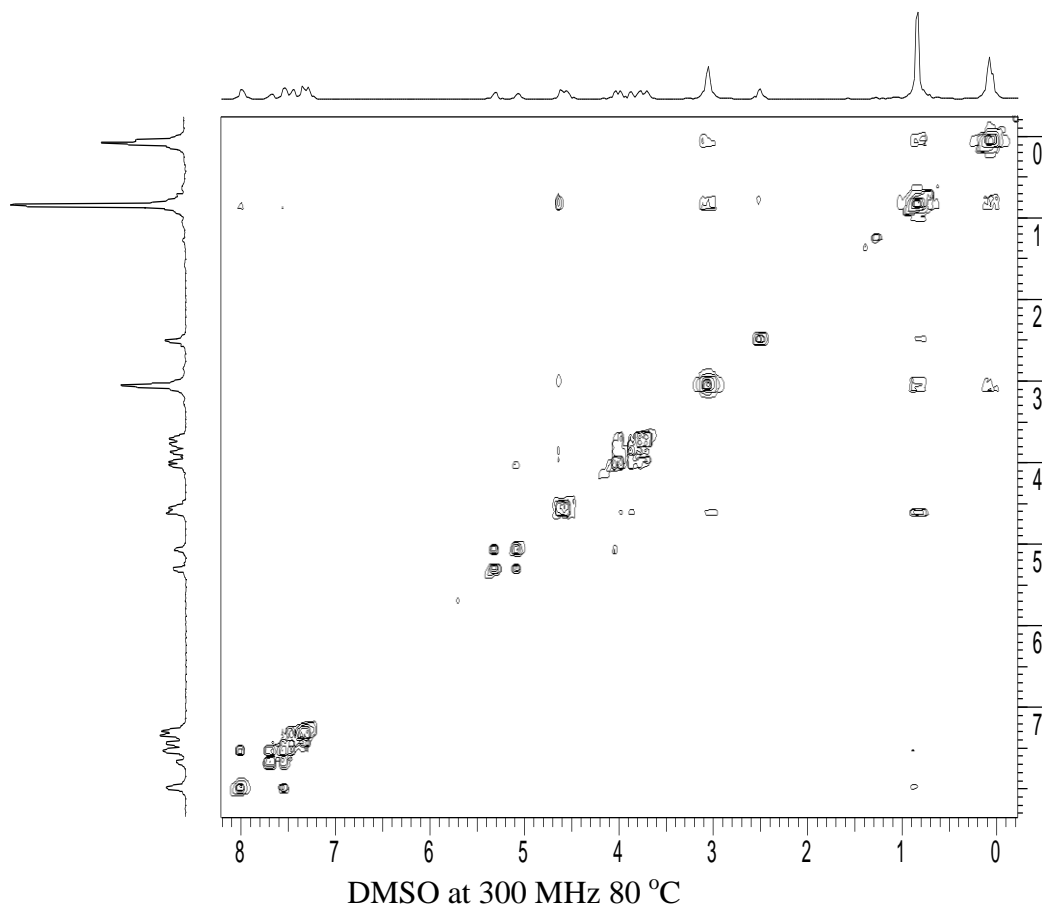
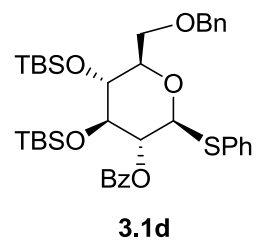


Figure A-27: 2-D NMR COSY spectrum of Phenyl 2-*O*-benzoyl-6-*O*-benzyl-3,4,-di-*O*-tert-butylidimethylsilyl-1-thio-β-D-glucopyranoside (**3.1d**)

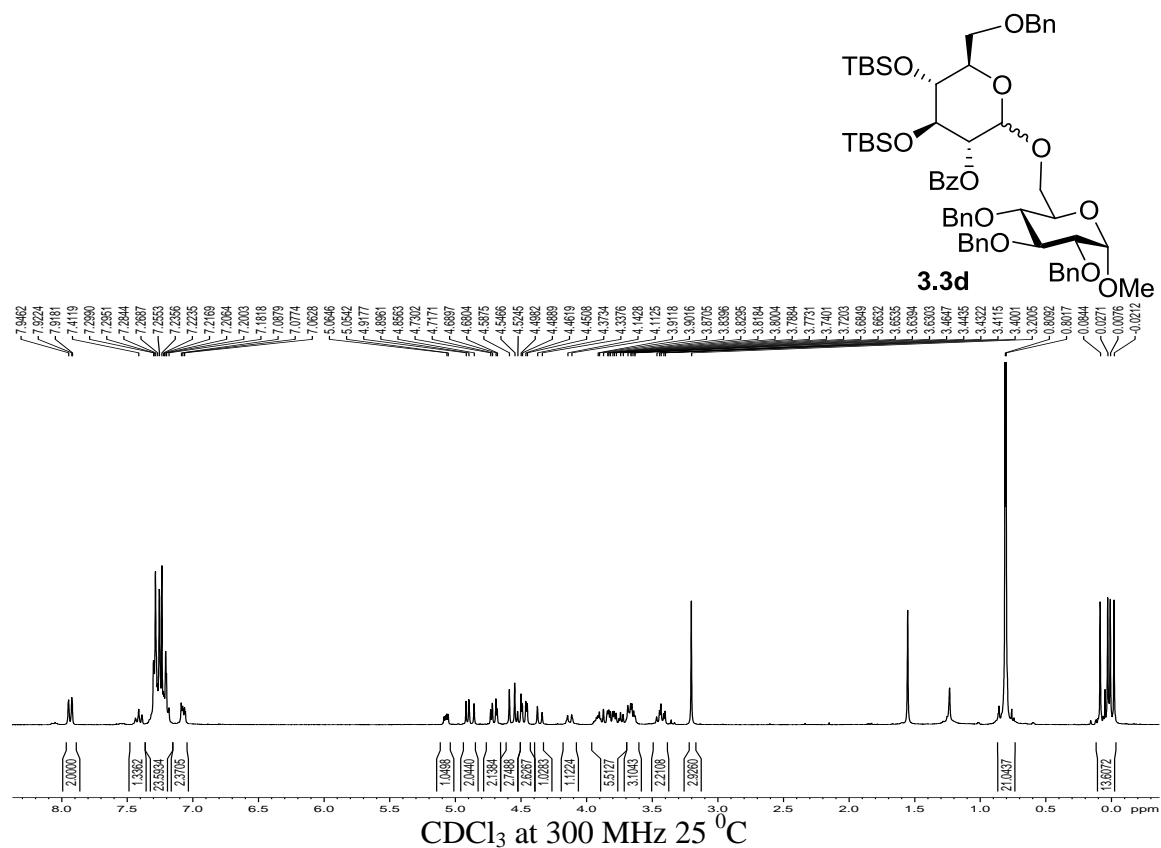


Figure A-28: ^1H NMR spectrum of Methyl 6-O-(2-O-benzoyl-6-O-benzyl-3,4-di-O-tert-butylidimethylsilyl- β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (**3.3d**).

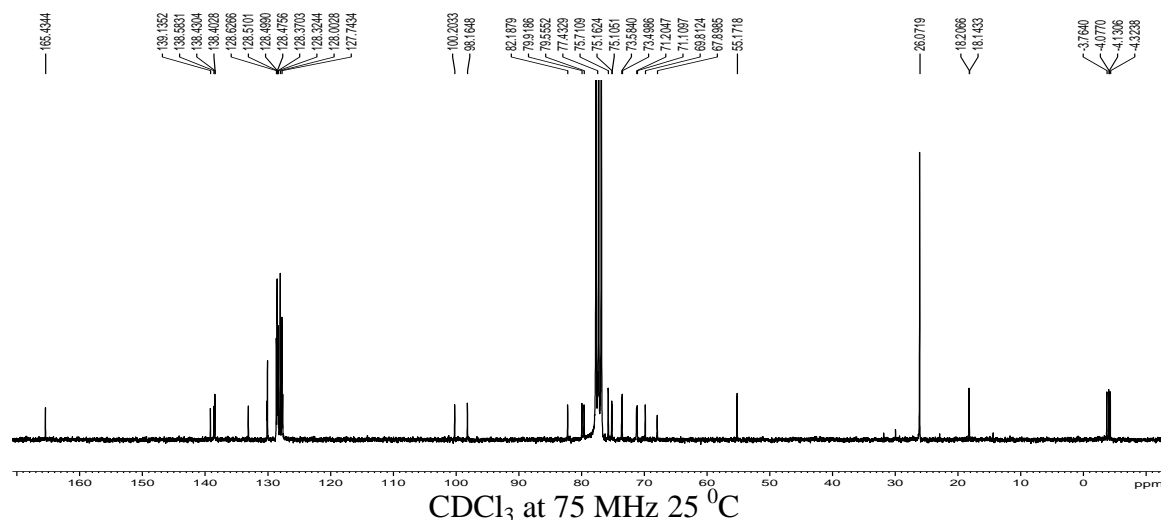


Figure A-29: ^{13}C NMR spectrum of Methyl 6-O-(2-O-benzoyl-6-O-benzyl-3,4-di-O-tert-butylidimethylsilyl- β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (**3.3d**).

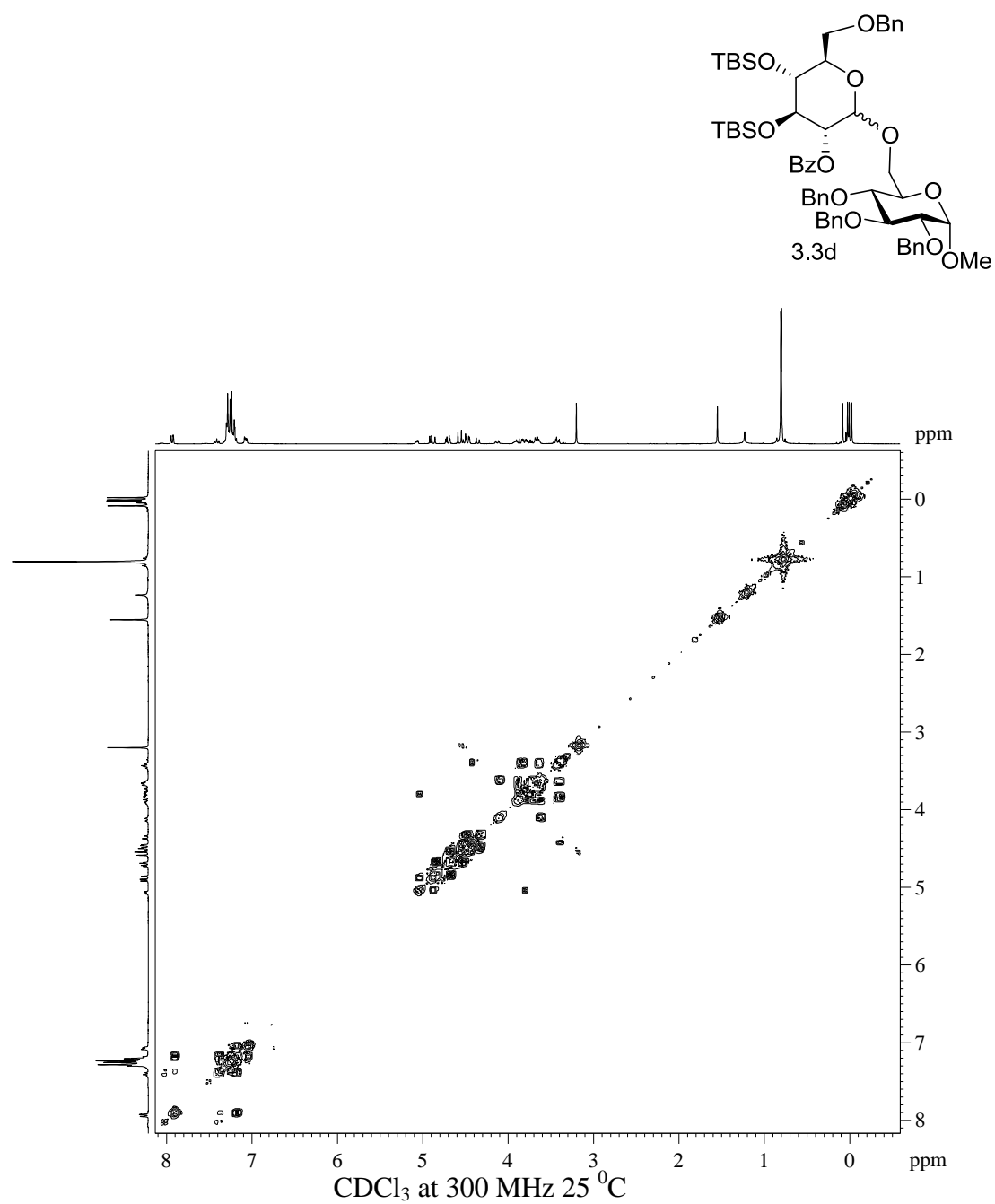


Figure A-30: 2-D NMR COSY spectrum of Methyl 6-O-(2-O-benzoyl-6-O-benzyl-3,4-di-O-tert-butyldimethylsilyl- β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (**3.3d**).

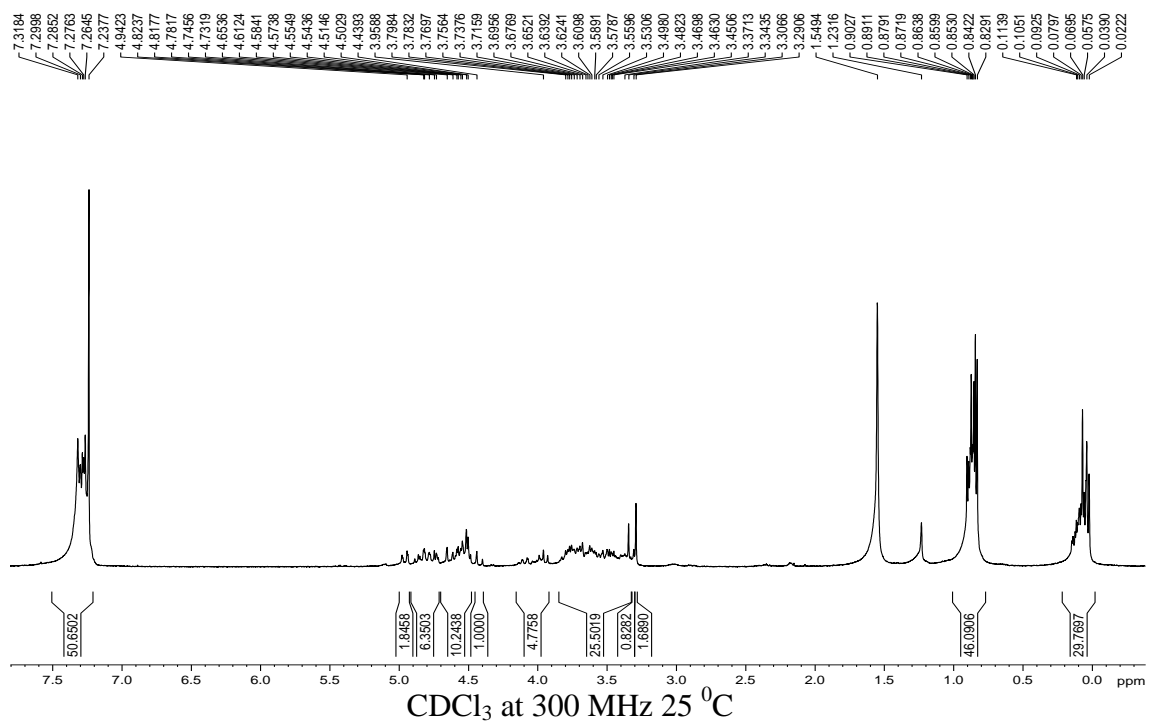
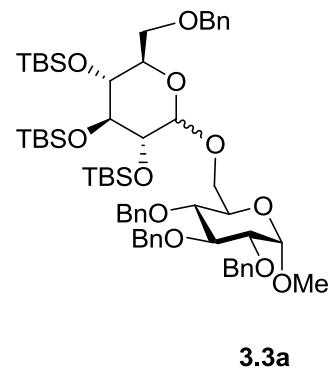


Figure A-31: ¹H NMR spectrum of Methyl 6-O-(6-O-benzyl-2,3,4-tri-O-tert-butylsilyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (**3.3a**).

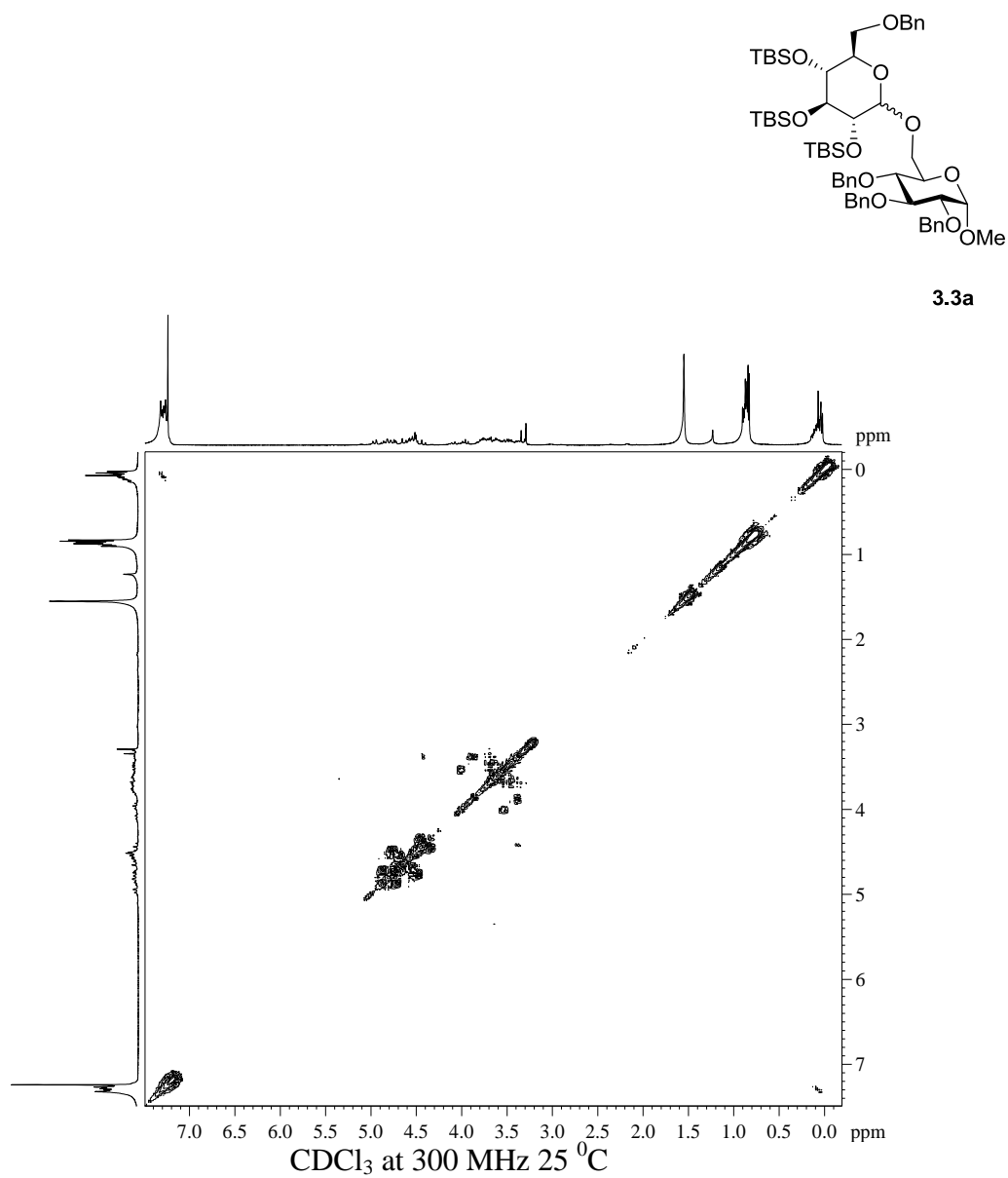


Figure A-32: 2-D NMR COSY spectrum of Methyl 6-O-(6-O-benzyl-2,3,4-tri-O-tert-butyl dimethylsilyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (**3.3a**).

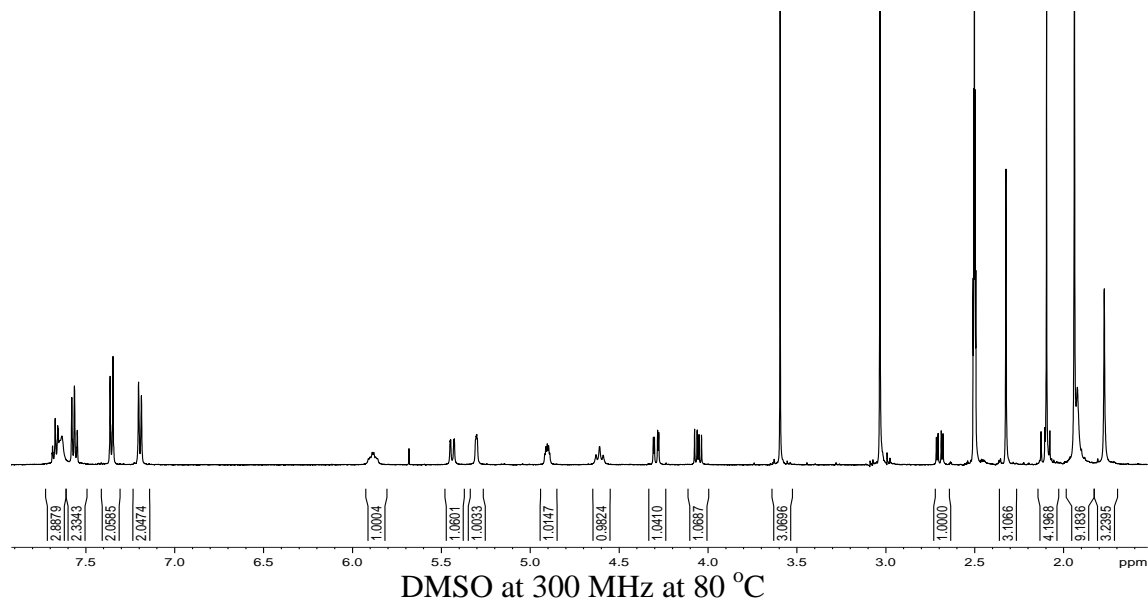
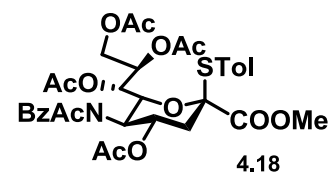


Figure A-33: ^1H NMR spectrum of Methyl (*p*-methylphenyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-ulosyranoside)onate (**4.18**).

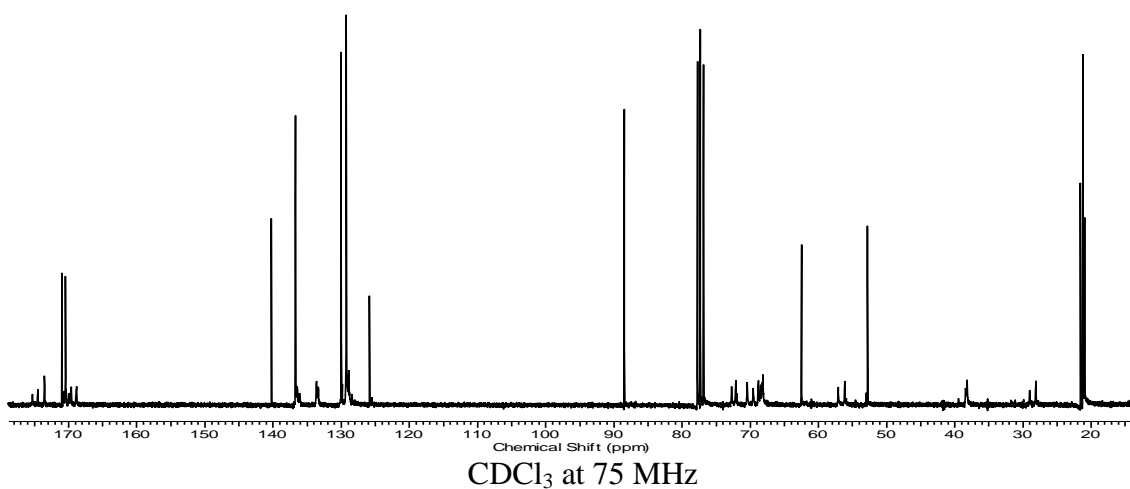


Figure A-34: ^{13}C NMR spectrum of Methyl (*p*-methylphenyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-ulosyranoside)onate (**4.18**).

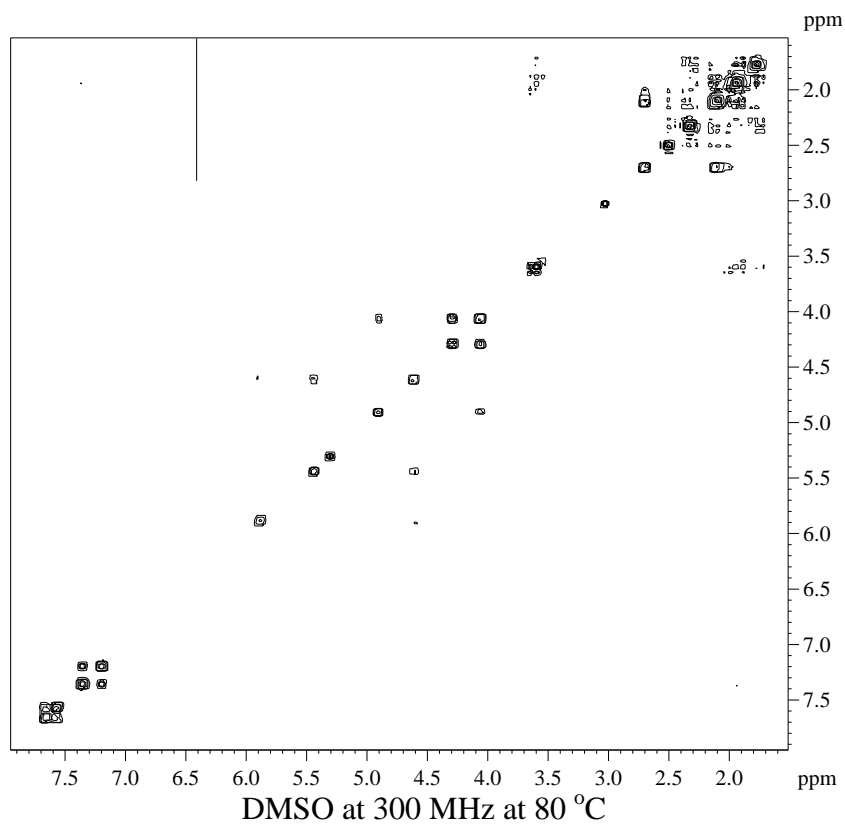
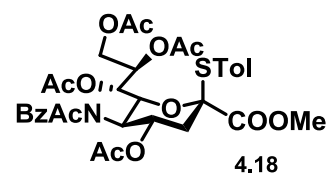


Figure A-35: 2-D NMR COSY spectrum of Methyl (*p*-methylphenyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero- β -D-galactono-2-ulopyranoside)onate (**4.18**).

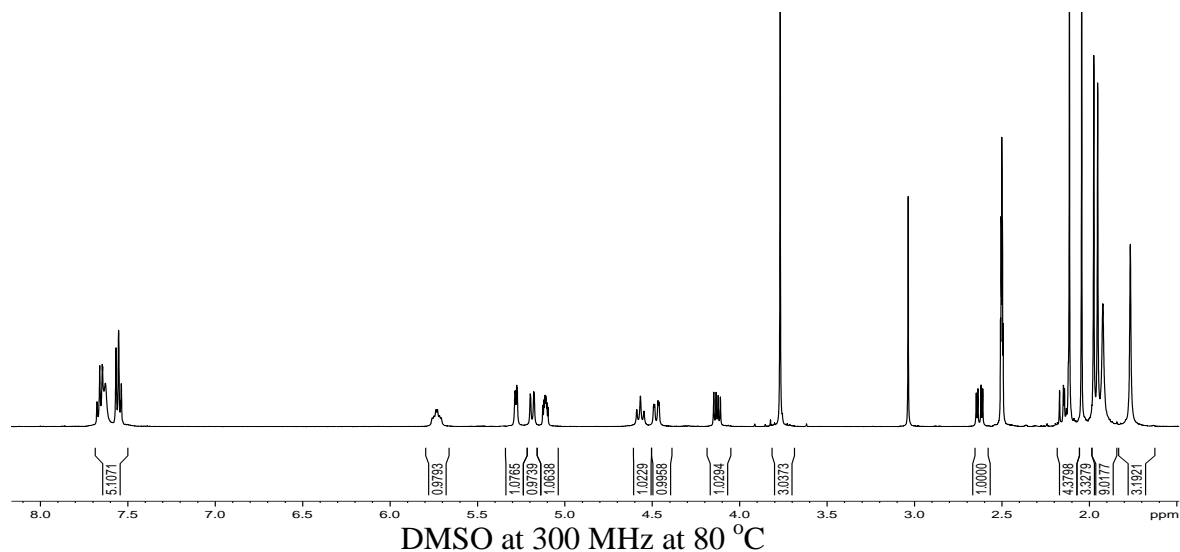
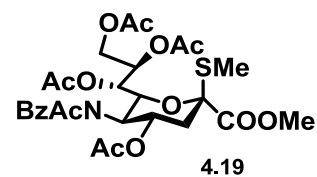


Figure A-36: ^1H NMR spectrum of Methyl (methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-ulopyranoside)onate (**4.19**).

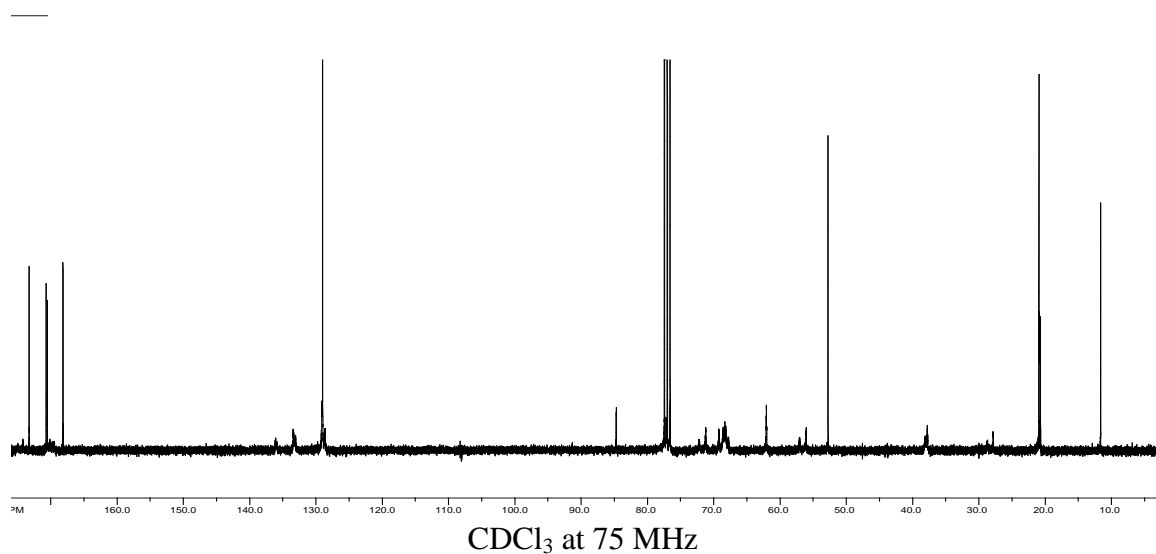


Figure A-37: ^{13}C NMR spectrum of Methyl (methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-ulopyranoside)onate (**4.19**).

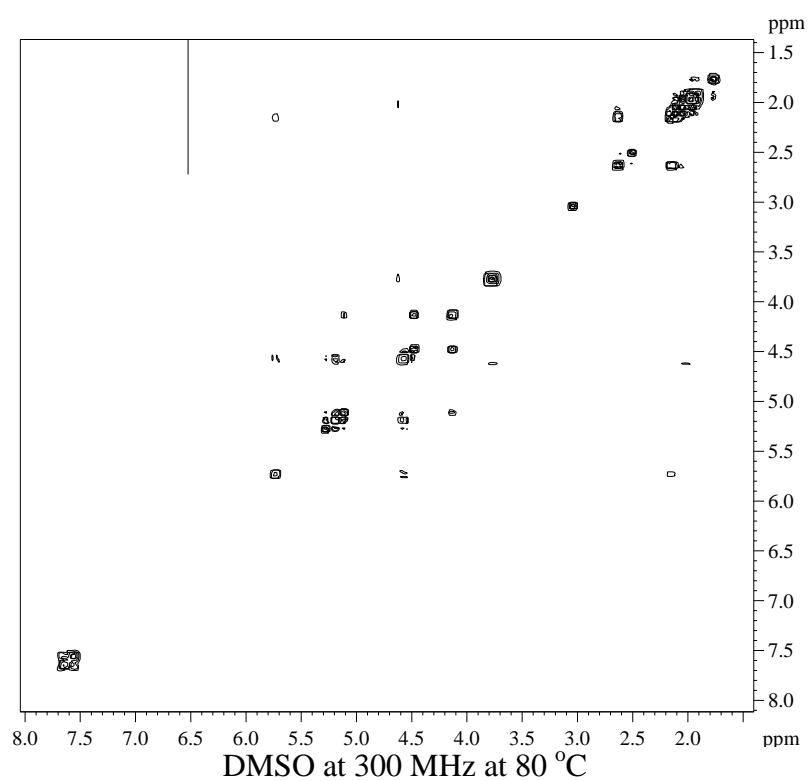
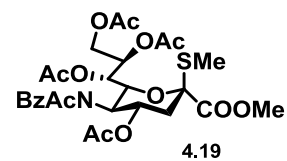


Figure A-38: ^1H NMR spectrum of Methyl (methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-ulopyranoside)onate (**4.19**).

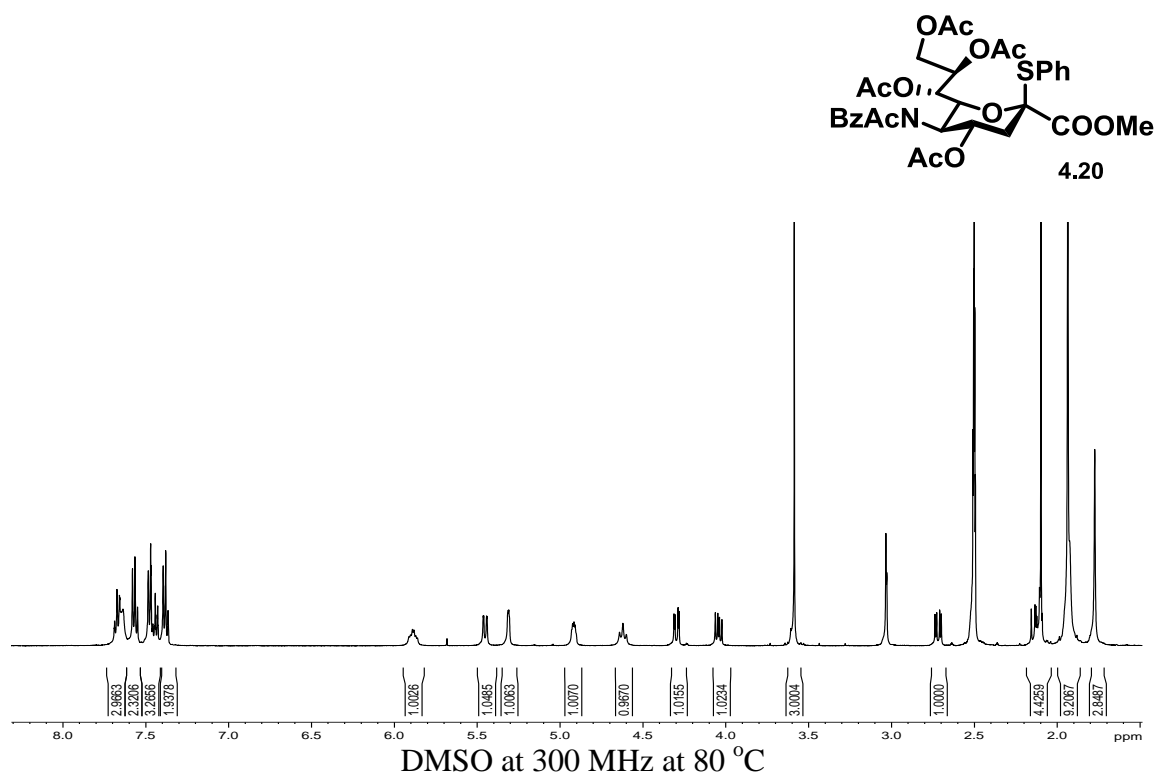


Figure A-39: ¹H NMR spectrum of Methyl (phenyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero-β-D-galacto-non-2-ulopyranoside)onate (4.20).

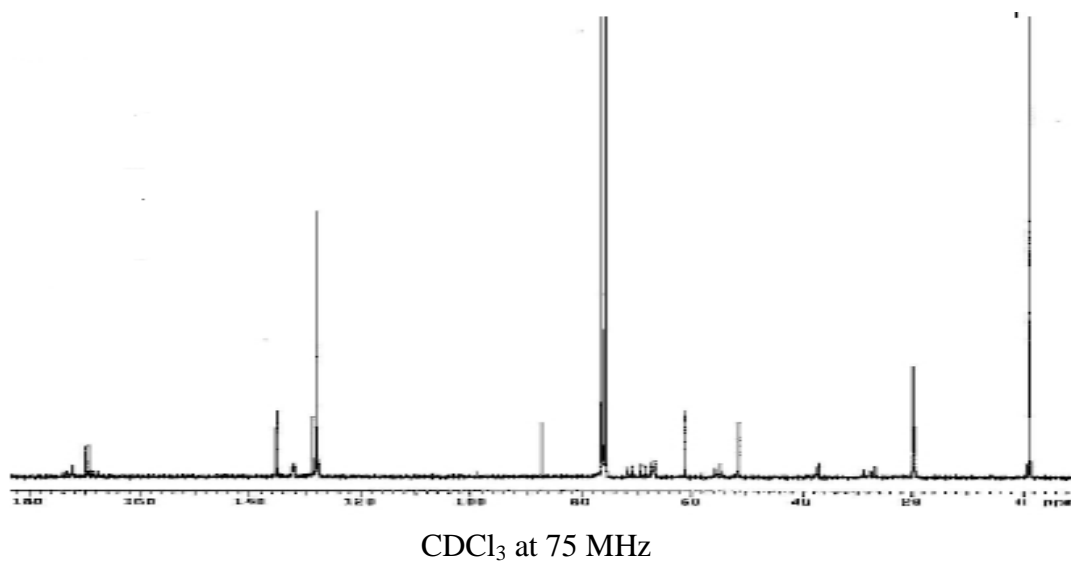


Figure A-40: ¹³C NMR spectrum of Methyl (phenyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero-β-D-galacto-non-2-ulopyranoside)onate (4.20).

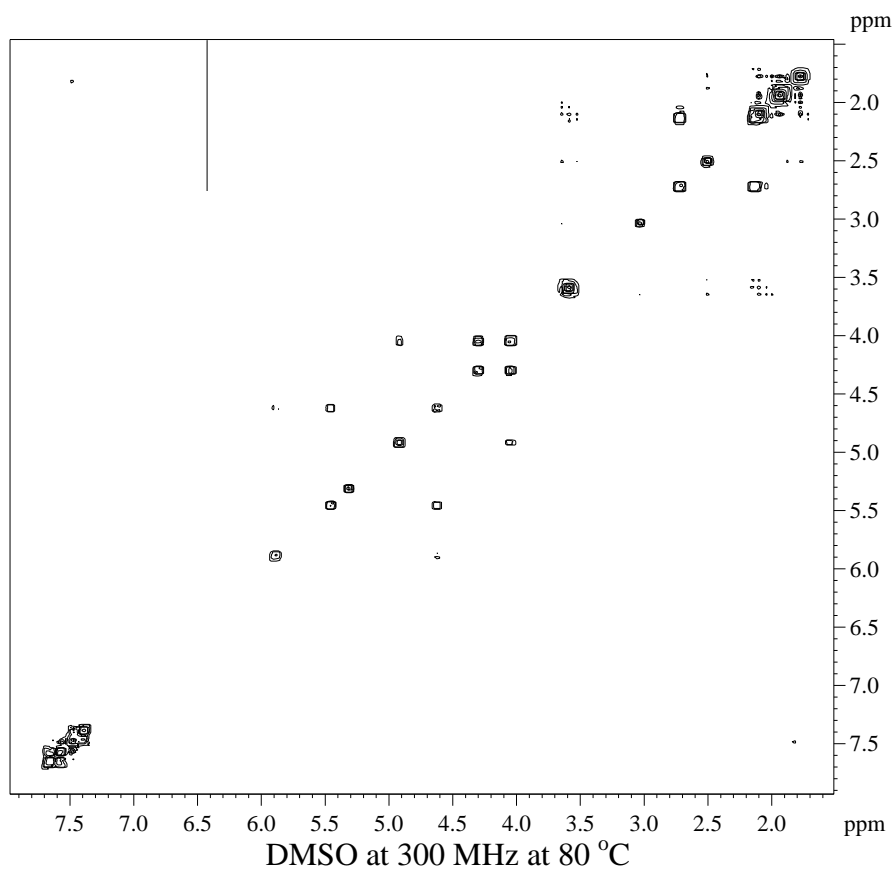
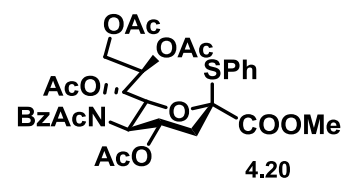


Figure A-41: ^1H NMR spectrum of Methyl (phenyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-ulopyranoside)onate (4.20).

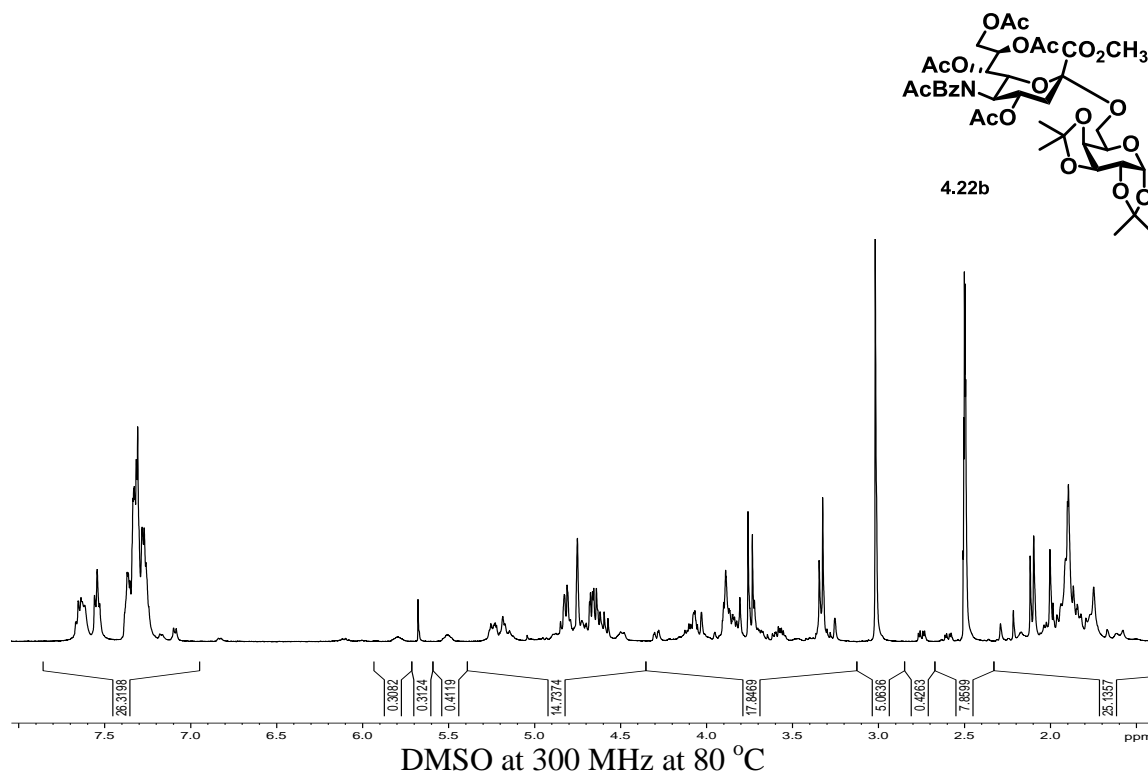


Figure A-42: ¹H NMR spectrum of O-(Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→6)-1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (**4.22b**).

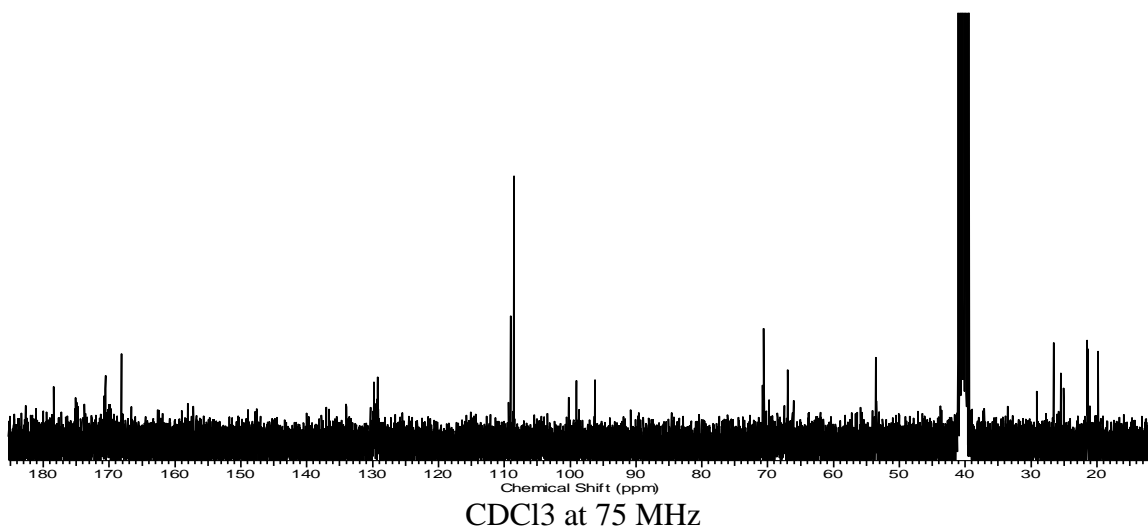


Figure A-43: ¹³C NMR spectrum of O-(Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→6)-1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (**4.22b**).

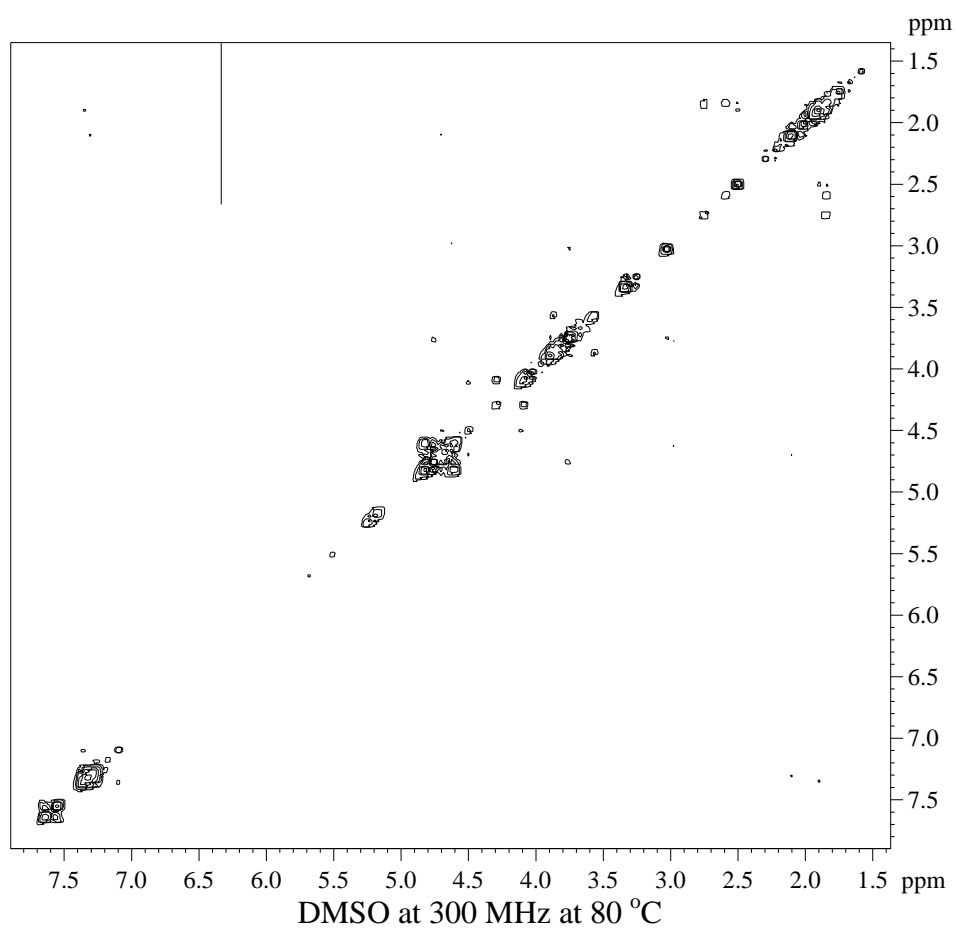
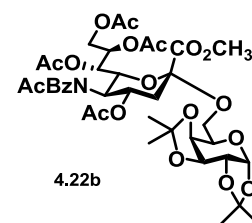


Figure A-44: 2D-NMR COSY spectrum of O-(Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylate)-(2→6)-1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (**4.22b**).

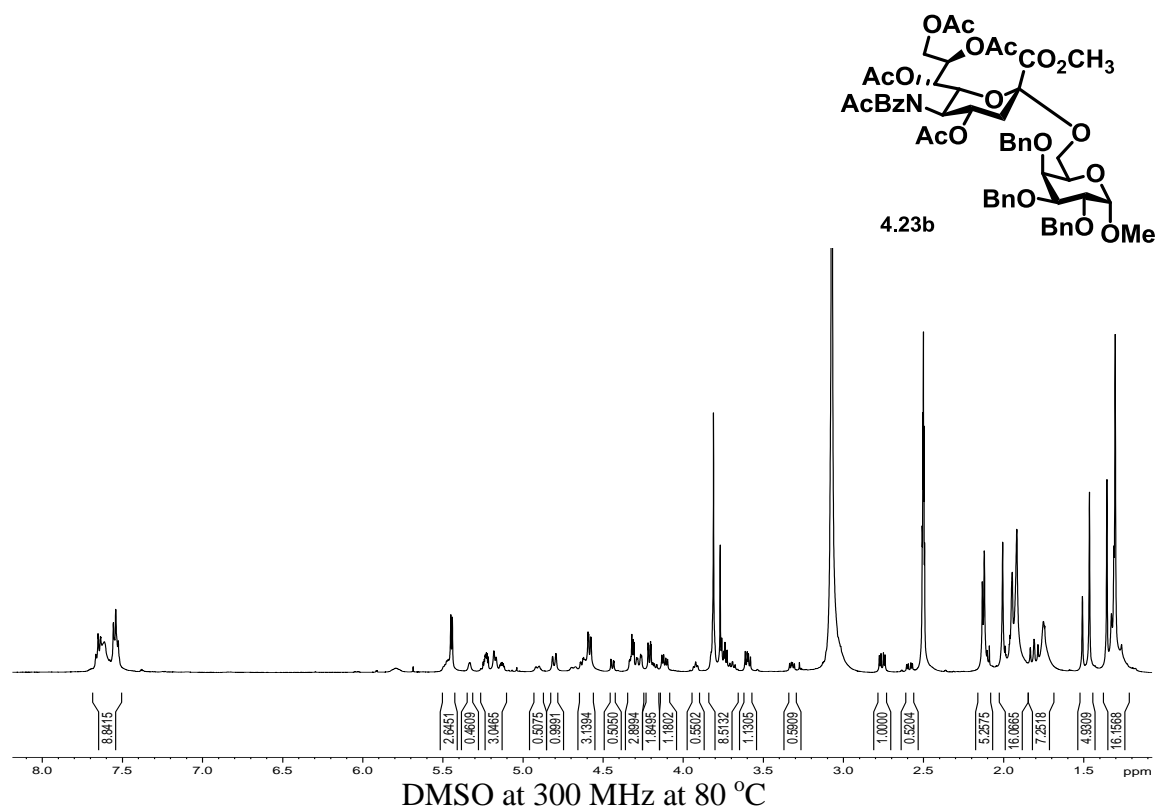


Figure A-45: ¹H NMR spectrum of Methyl O-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→6)-2,3,4-tri-O-benzyl-α-D-galactopyranoside (**4.23b**).

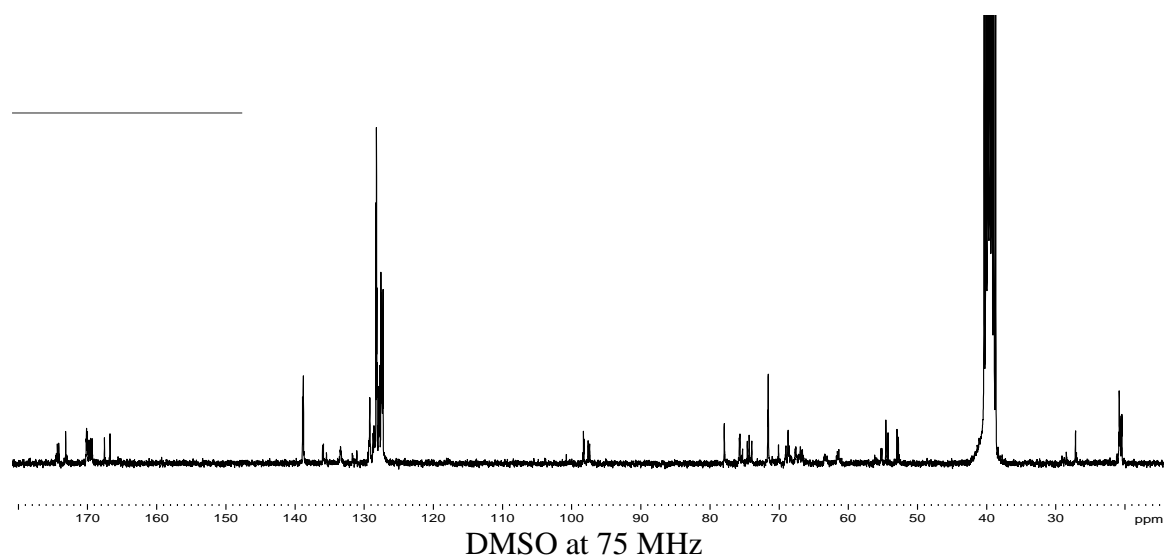


Figure A-46: ¹³C NMR spectrum of Methyl O-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2→6)-2,3,4-tri-O-benzyl-α-D-galactopyranoside (**4.23b**).

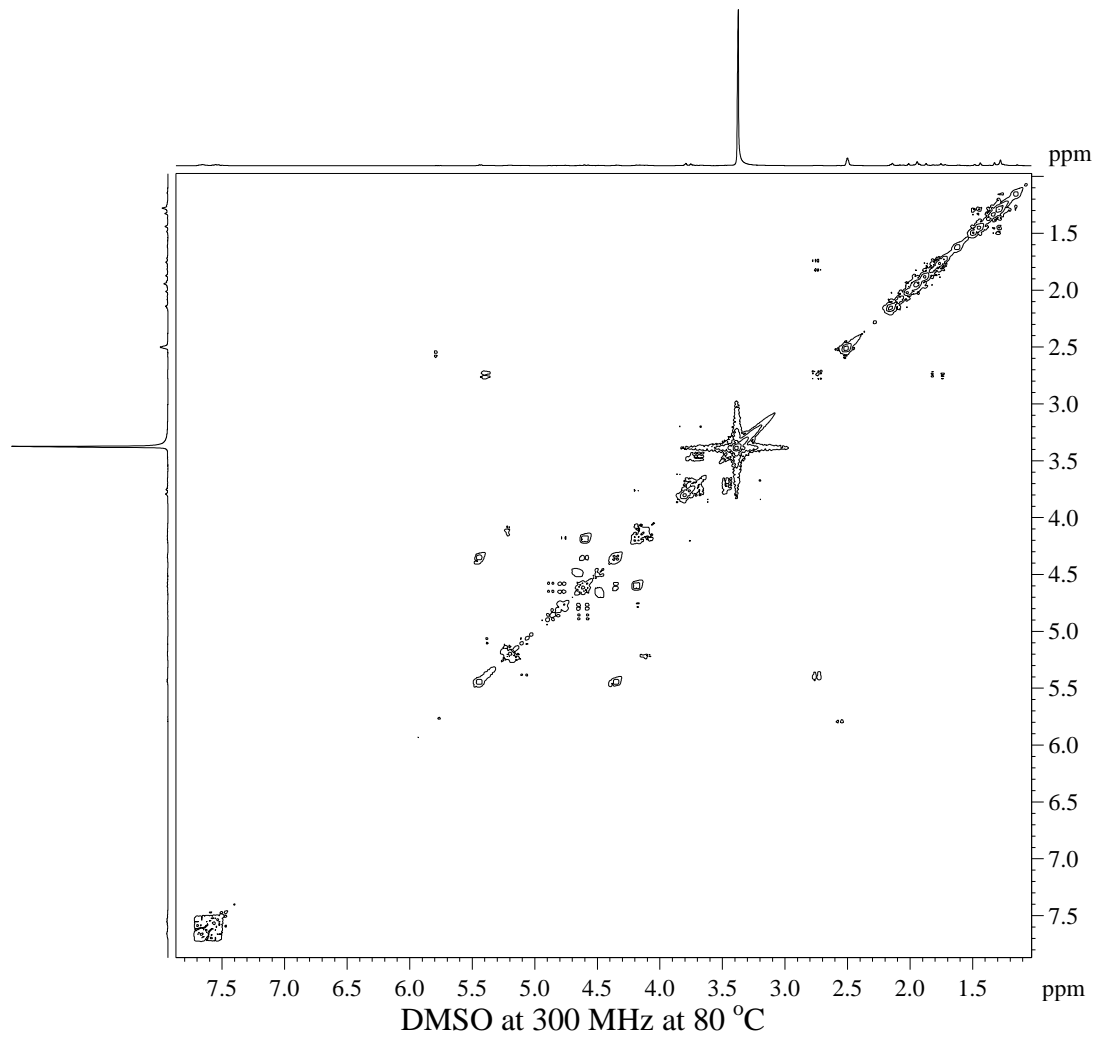
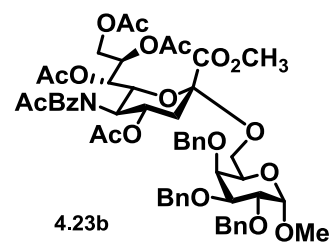


Figure A-47: ^1H NMR spectrum of Methyl O-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-5-N-benzoyl-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranosylonate)-(2 \rightarrow 6)-2,3,4-tri-O-benzyl- α -D-galactopyranoside (**4.23b**).

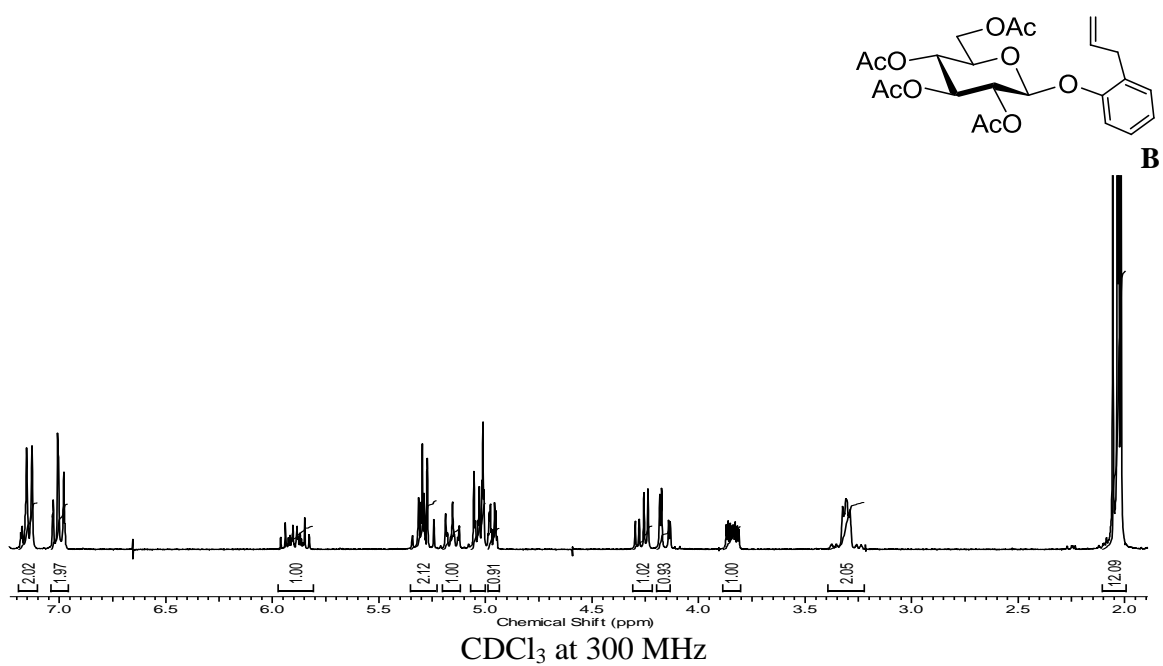


Figure A-50: ¹H NMR spectrum of 2-Allylphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (B)

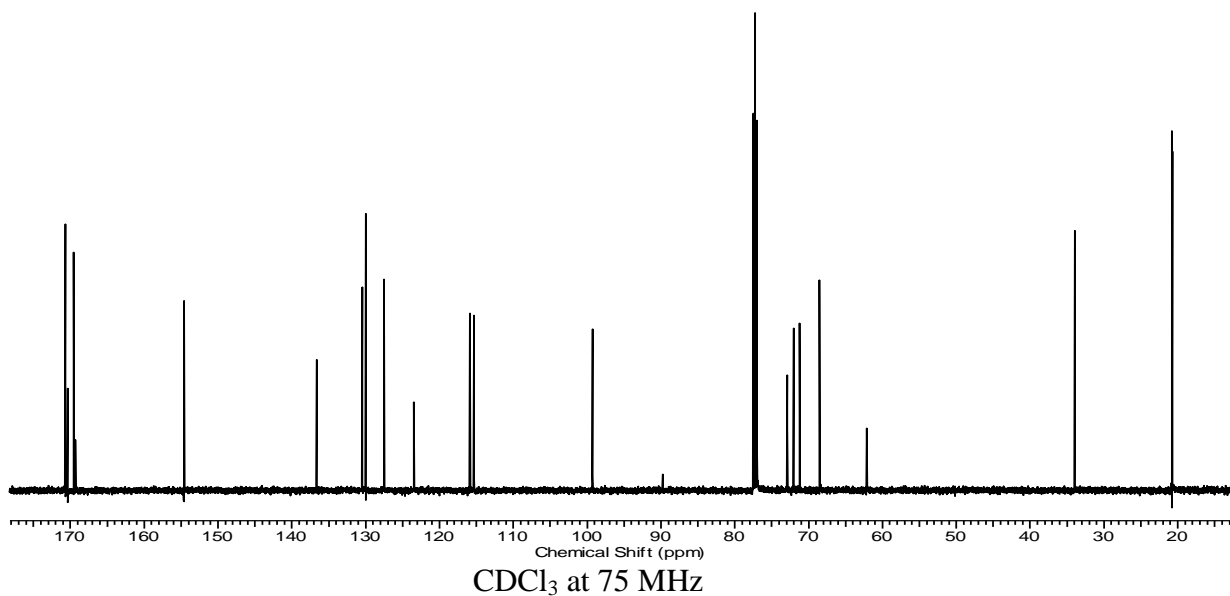


Figure A-51: ¹³C NMR spectrum of 2-Allylphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (B)

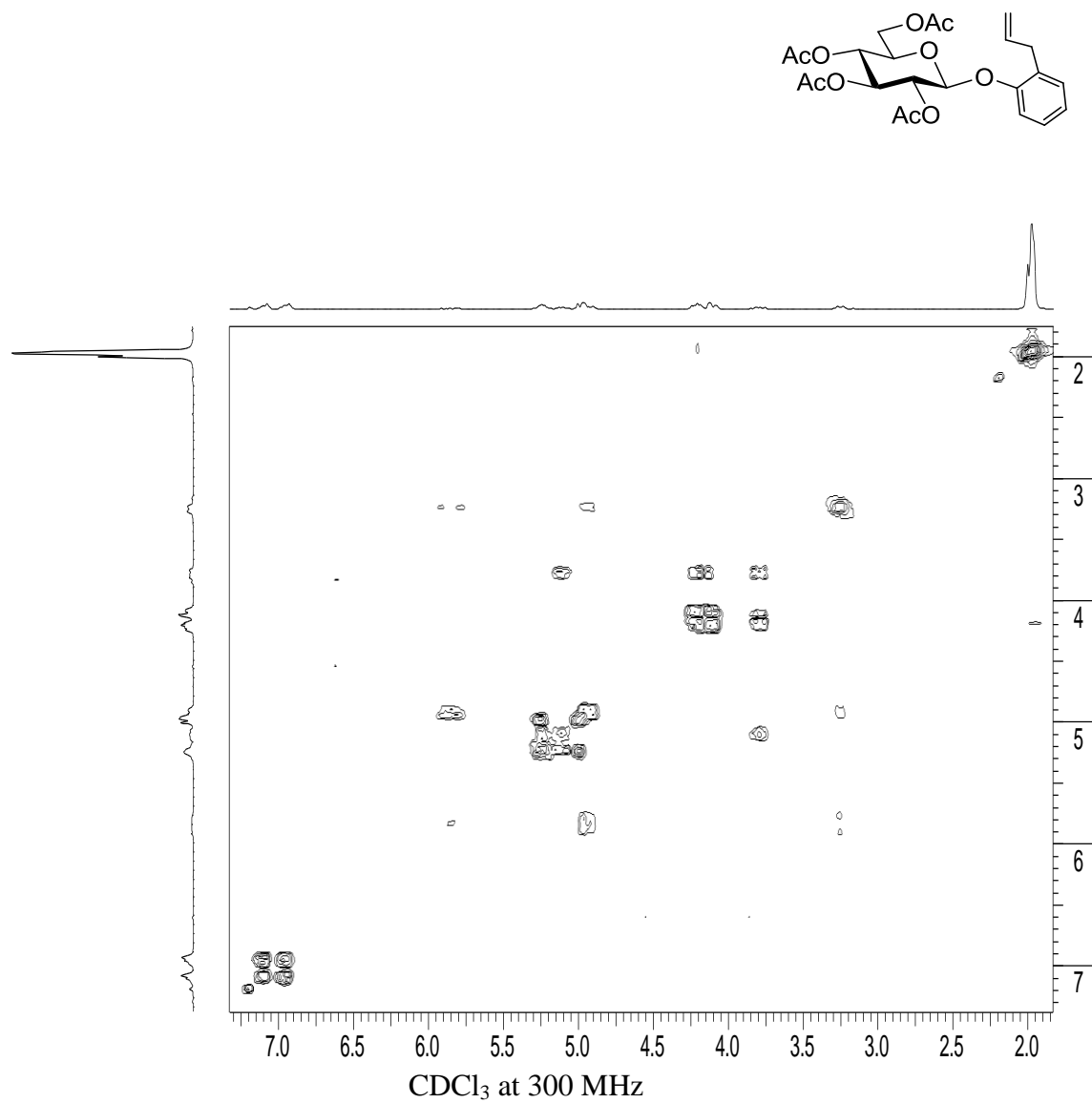


Figure A-52: 2-D NMR COSY spectrum of 2-Allylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (**B**)

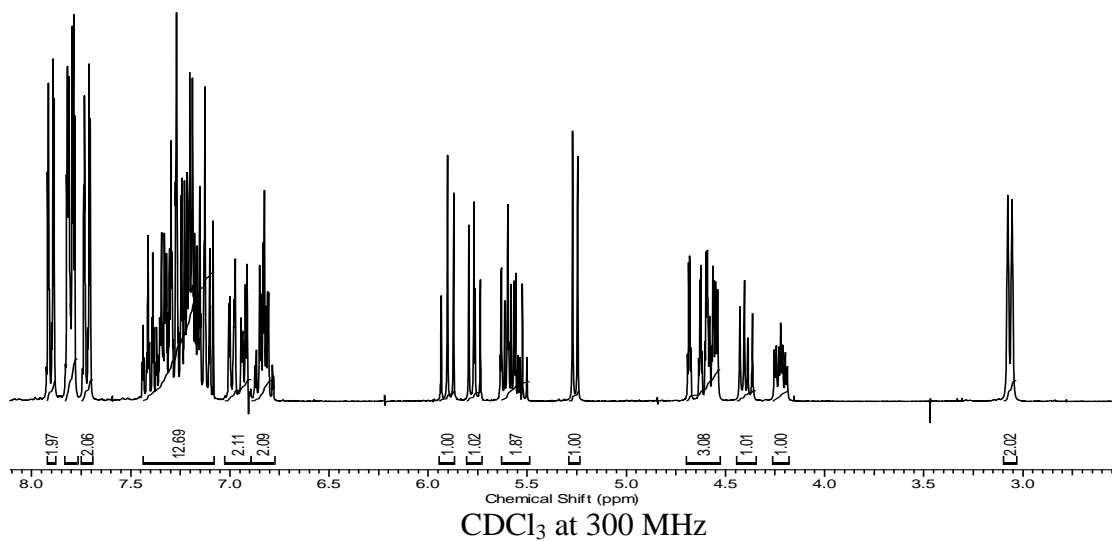
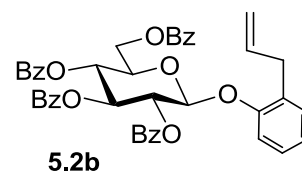


Figure A-53: ¹H NMR spectrum of 2-Allylphenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (**5.1b**).

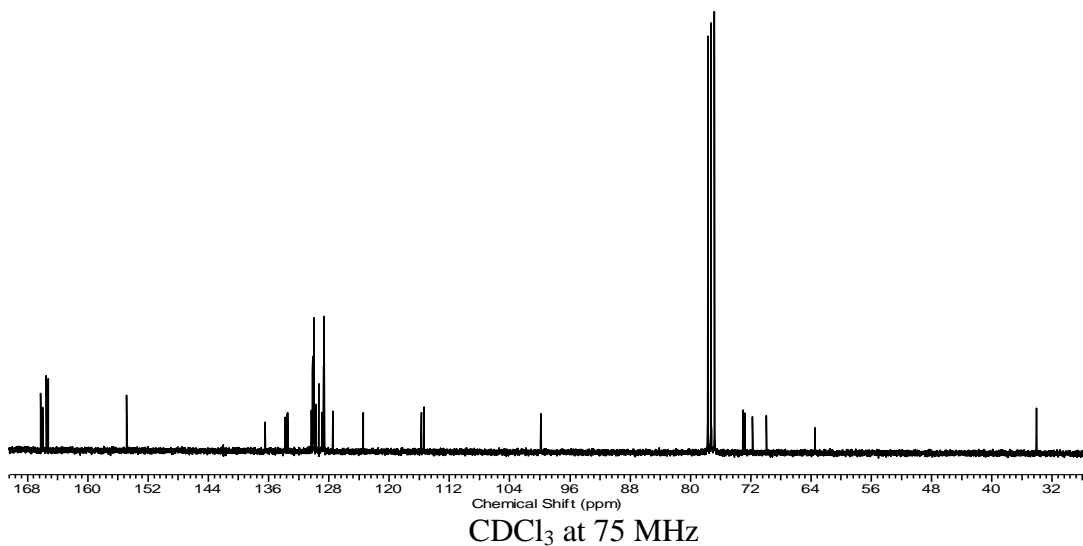


Figure A-54: ¹³C NMR spectrum of 2-Allylphenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (**5.1b**).

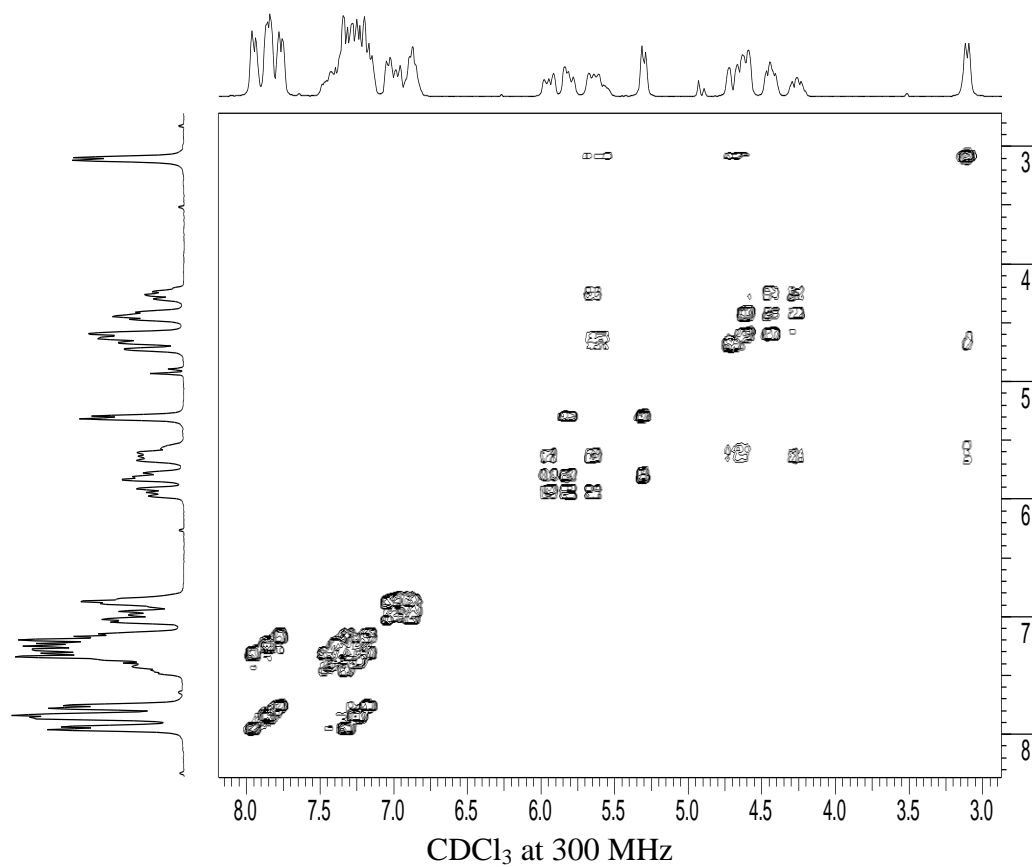
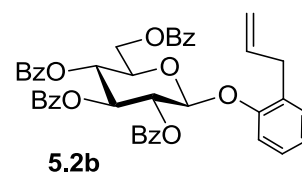


Figure A-55: 2-D NMR COSY spectrum of 2-Allylphenyl 2,3,4,6-tetra-*O*-benzoyl- β -D-glucopyranoside (**5.1b**).

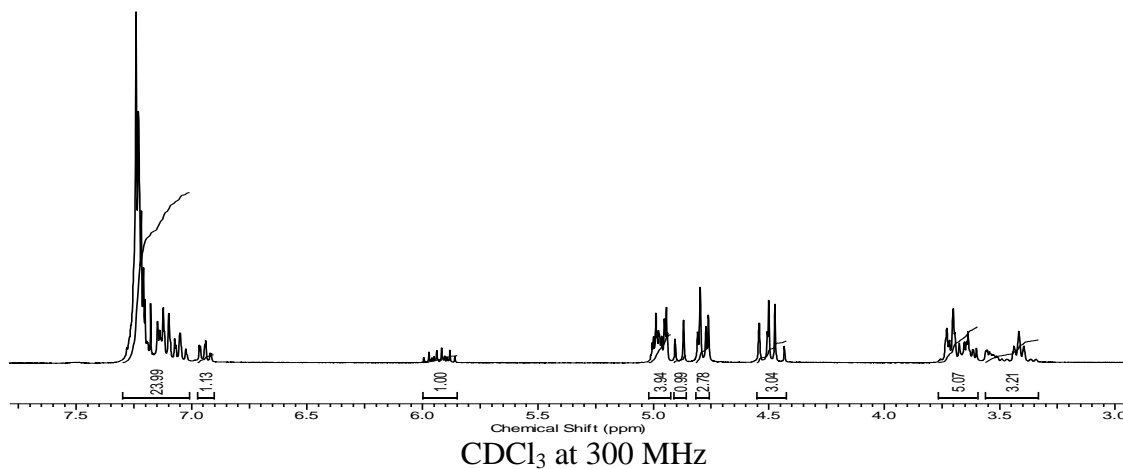
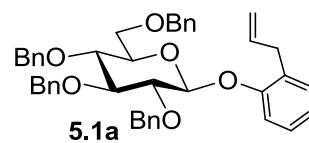


Figure A-56: ¹H NMR spectrum of 2-Allylphenyl 2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside (**5.1a**).

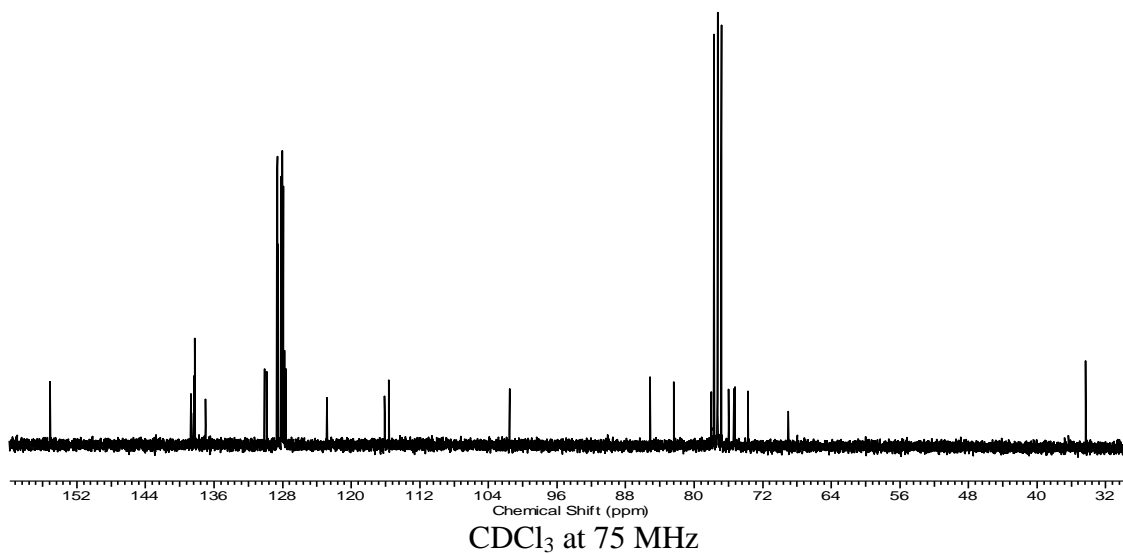


Figure A-57: ¹³C NMR spectrum of 2-Allylphenyl 2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside (**5.1a**).

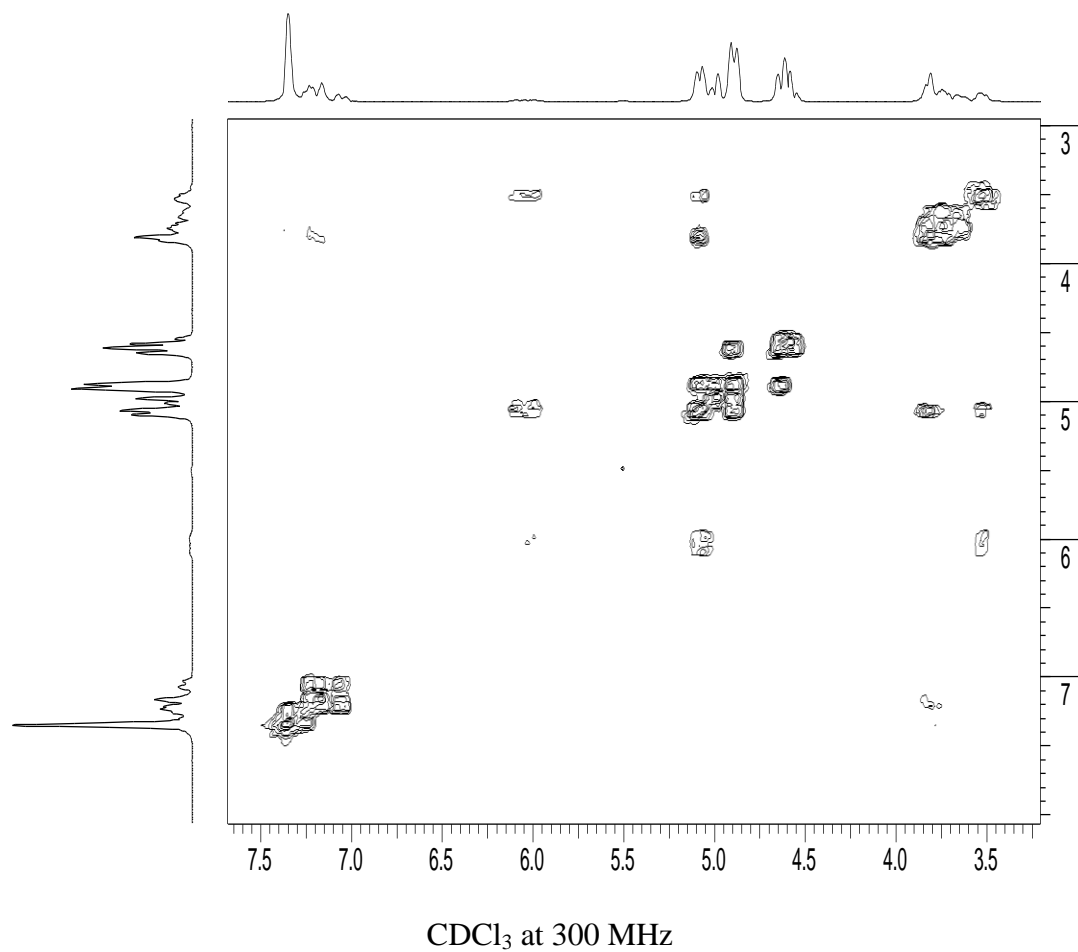
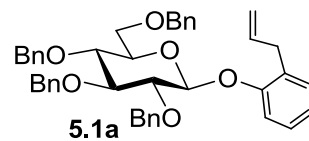


Figure A-58: 2-D NMR COSY spectrum of 2-Allylphenyl 2,3,4,6-tetra-O-benzyl- β -D-glucopyranoside (**5.1a**).

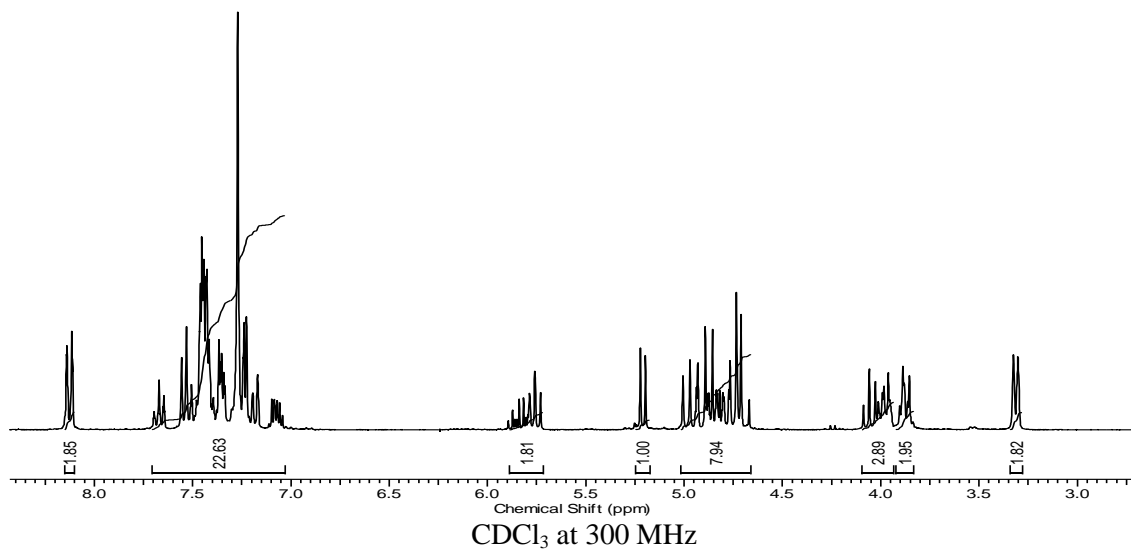
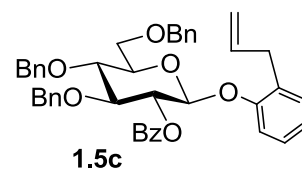


Figure A-59: ¹H NMR spectrum of 2-Allylphenyl 2-O-benzoyl-3,4,6-tri-O-benzyl-β-D-glucopyranoside (**5.1c**).

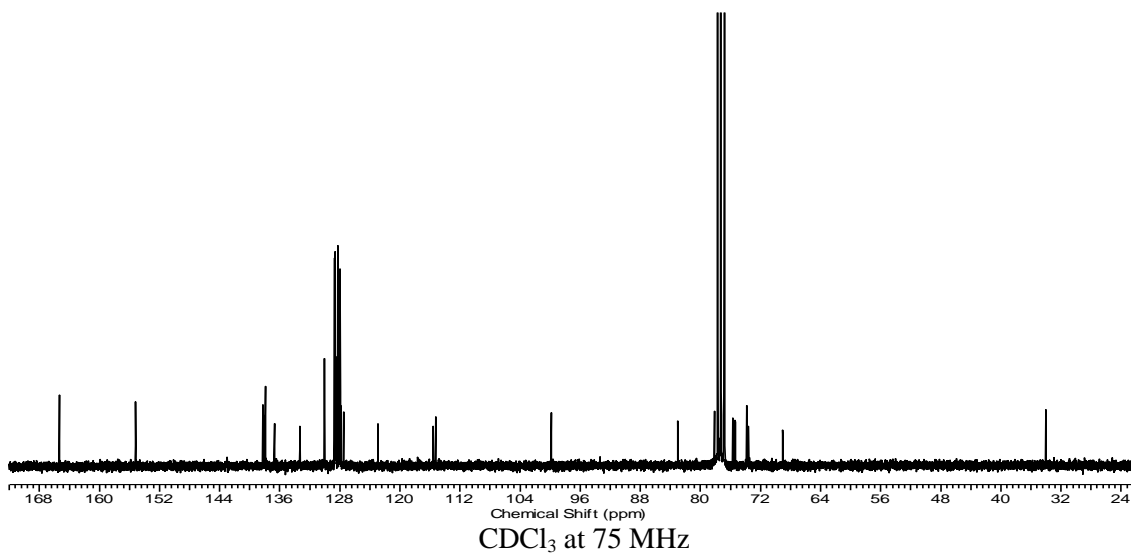


Figure A-60: ¹³C NMR spectrum of 2-Allylphenyl 2-O-benzoyl-3,4,6-tri-O-benzyl-β-D-glucopyranoside (**5.1c**).

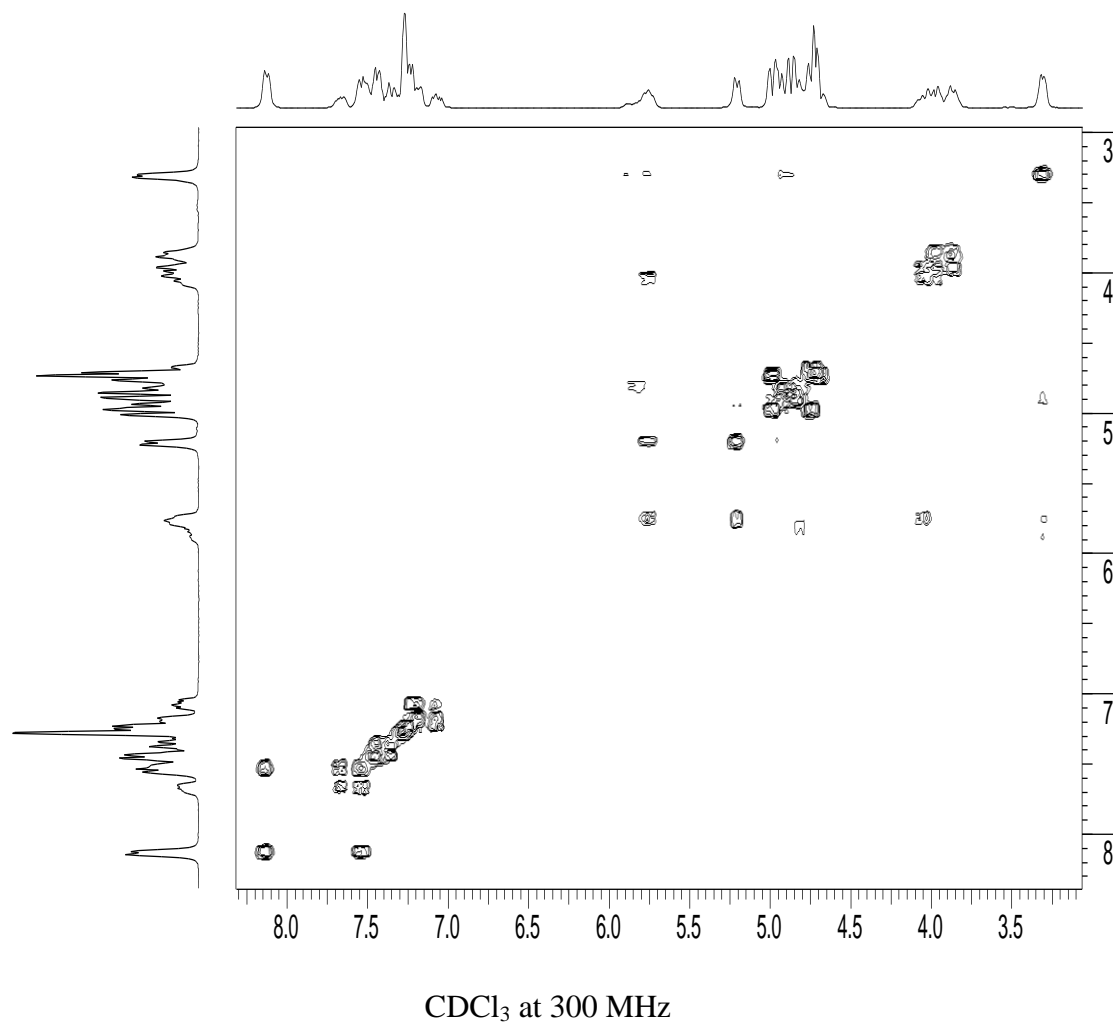
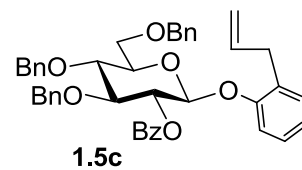


Figure A-61: ¹H NMR spectrum of 2-Allylphenyl 2-O-benzoyl-3,4,6-tri-O-benzyl-β-D-glucopyranoside (**5.1c**).

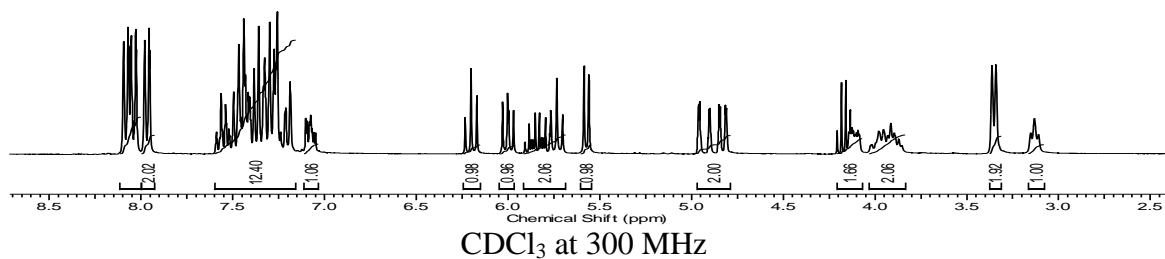
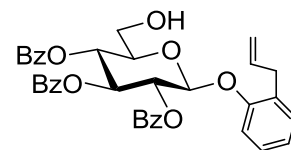


Figure A-62: ^1H NMR spectrum of 2-Allylphenyl 2,3,4-tri-O-benzoyl- β -D-glucopyranoside (**5.13**).

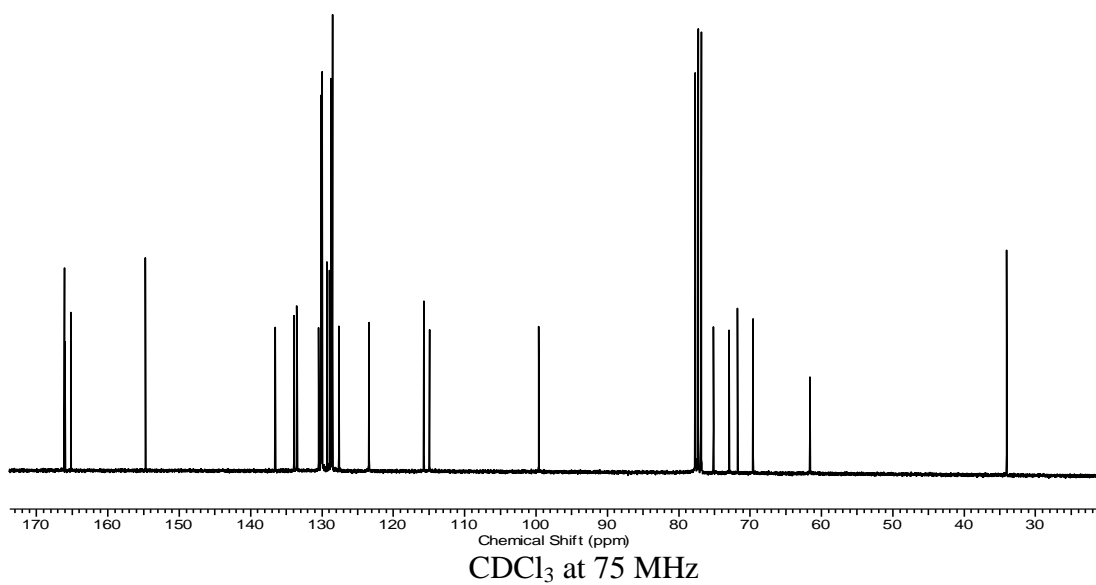


Figure A-63: ^{13}C NMR spectrum of 2-Allylphenyl 2,3,4-tri-O-benzoyl- β -D-glucopyranoside (**5.13**).

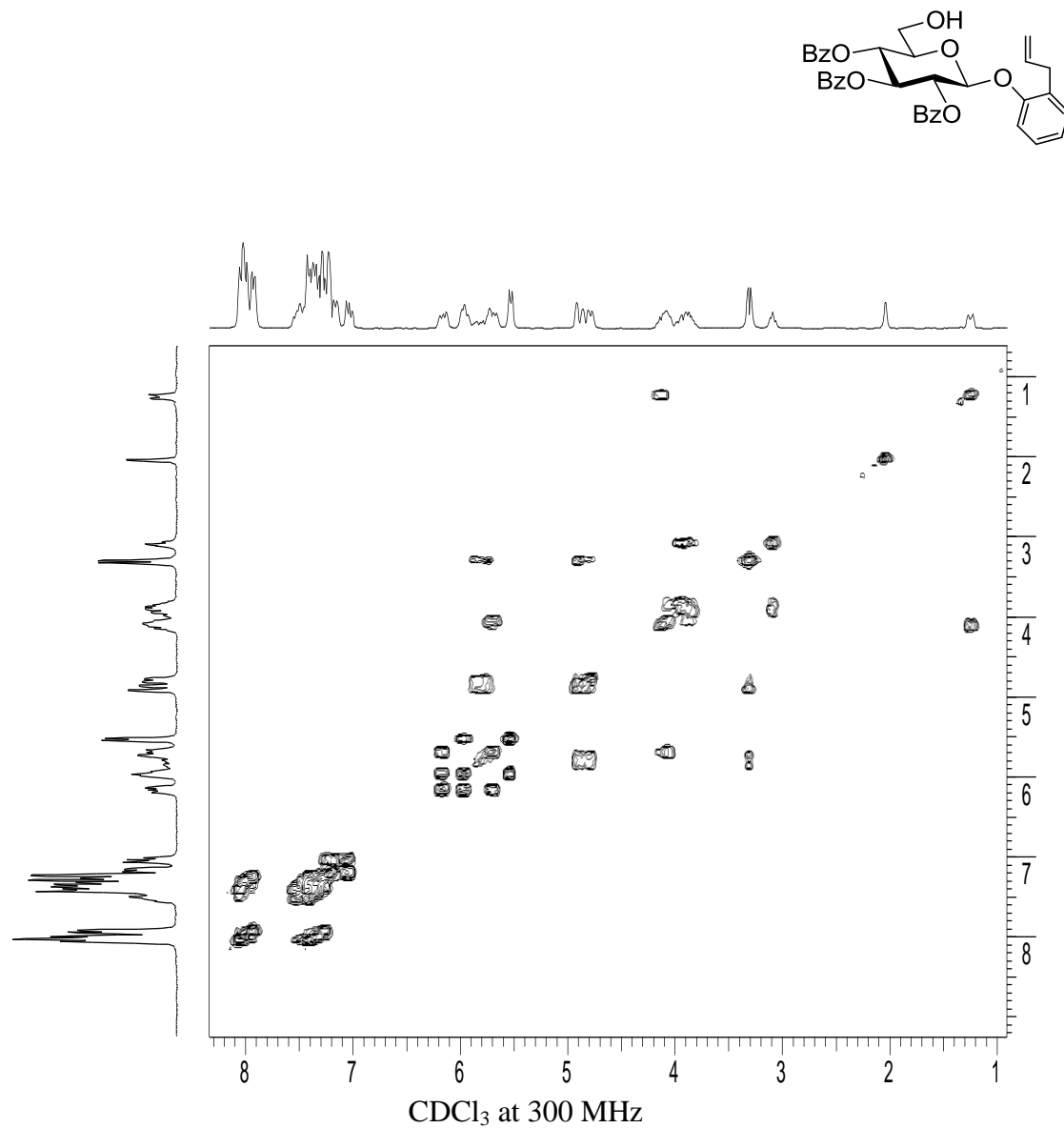


Figure A-64: 2-D NMR COSY spectrum of 2-Allylphenyl 2,3,4-tri-O-benzoyl-β-D-glucopyranoside (**5.13**).

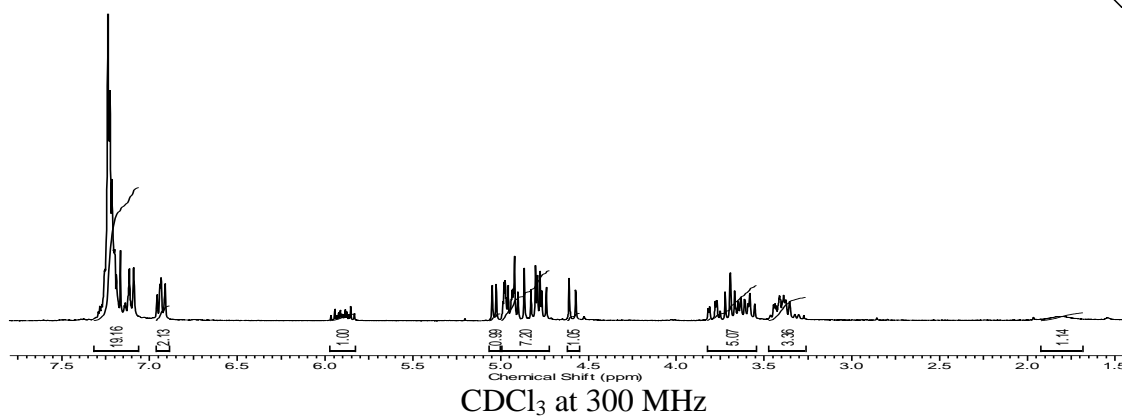
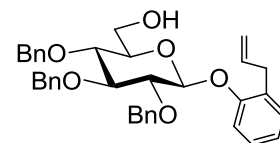


Figure A-65: ^1H NMR spectrum of 2-Allylphenyl 2,3,4-tri-O-benzyl- β -D-glucopyranoside (**5.24**).

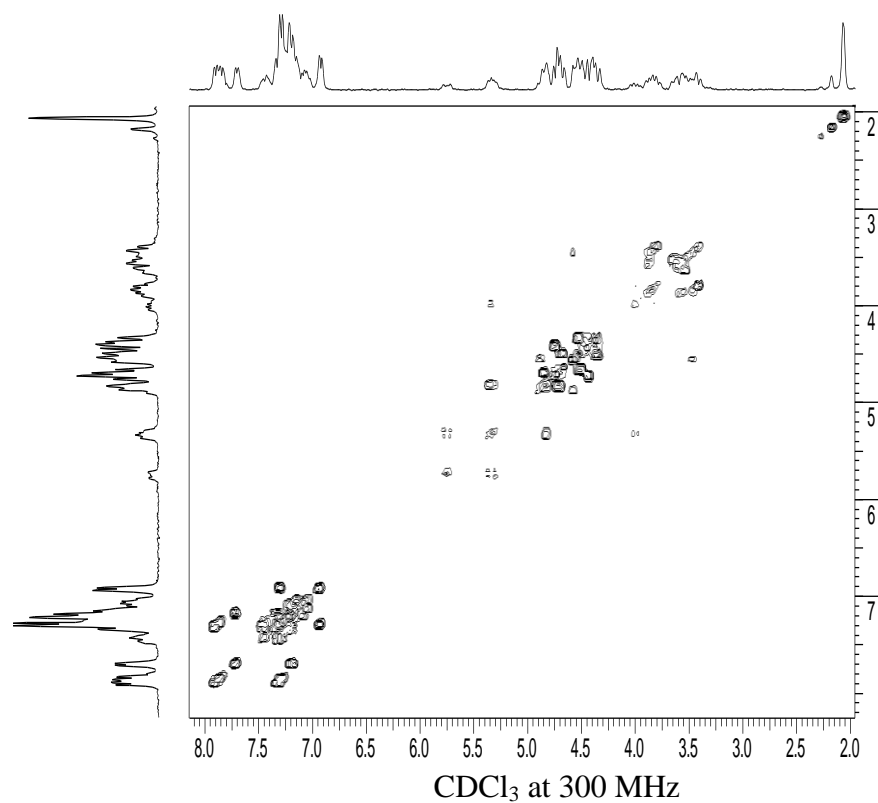


Figure A-66: 2-D NMR COSY spectrum of 2-Allylphenyl 2,3,4-tri-O-benzyl- β -D-glucopyranoside (**5.24**).

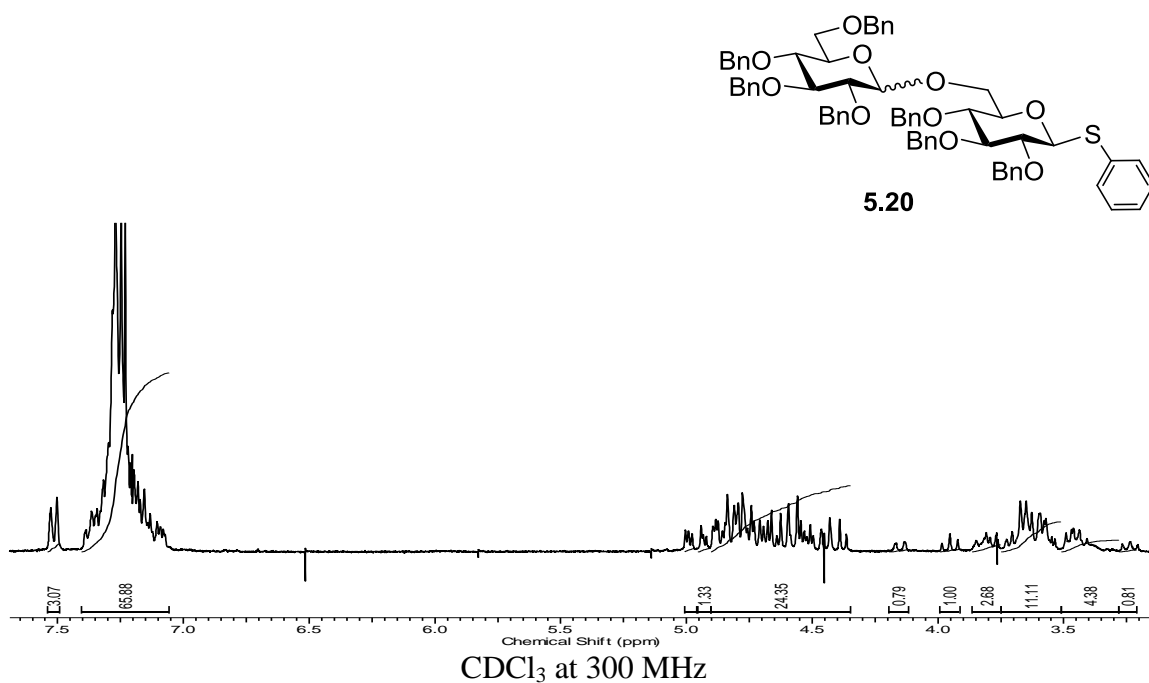


Figure A-67: ^1H NMR spectrum of Phenyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl-1-thio- β -D-glucopyranoside (**5.20**).

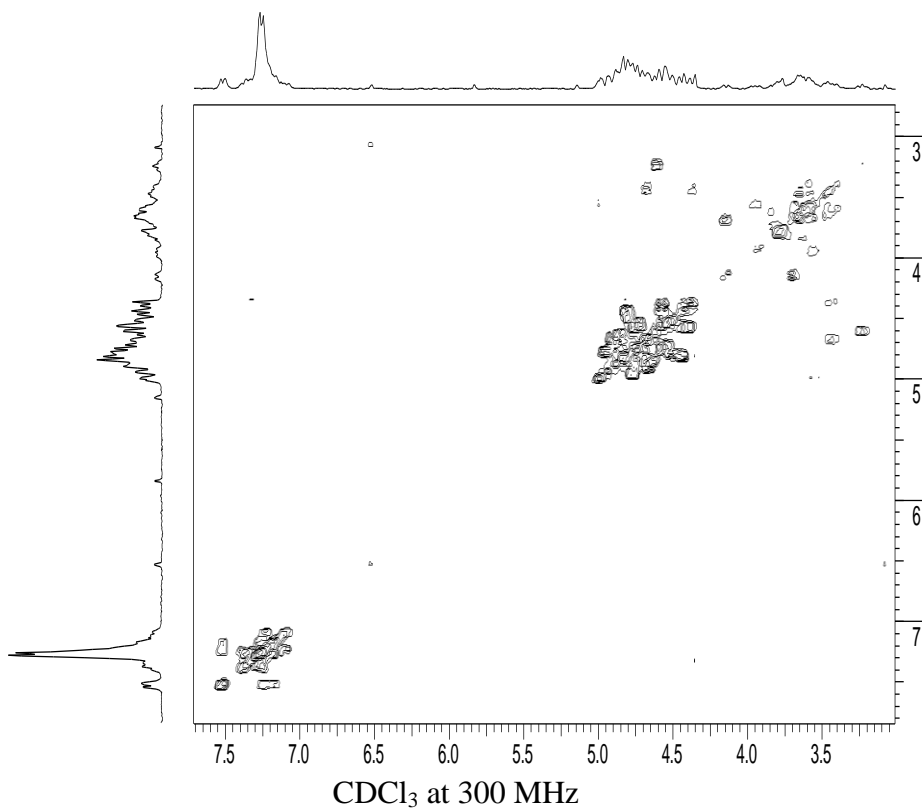


Figure A-68: 2-D NMR COSY spectrum of Phenyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl-1-thio- β -D-glucopyranoside (**5.20**).

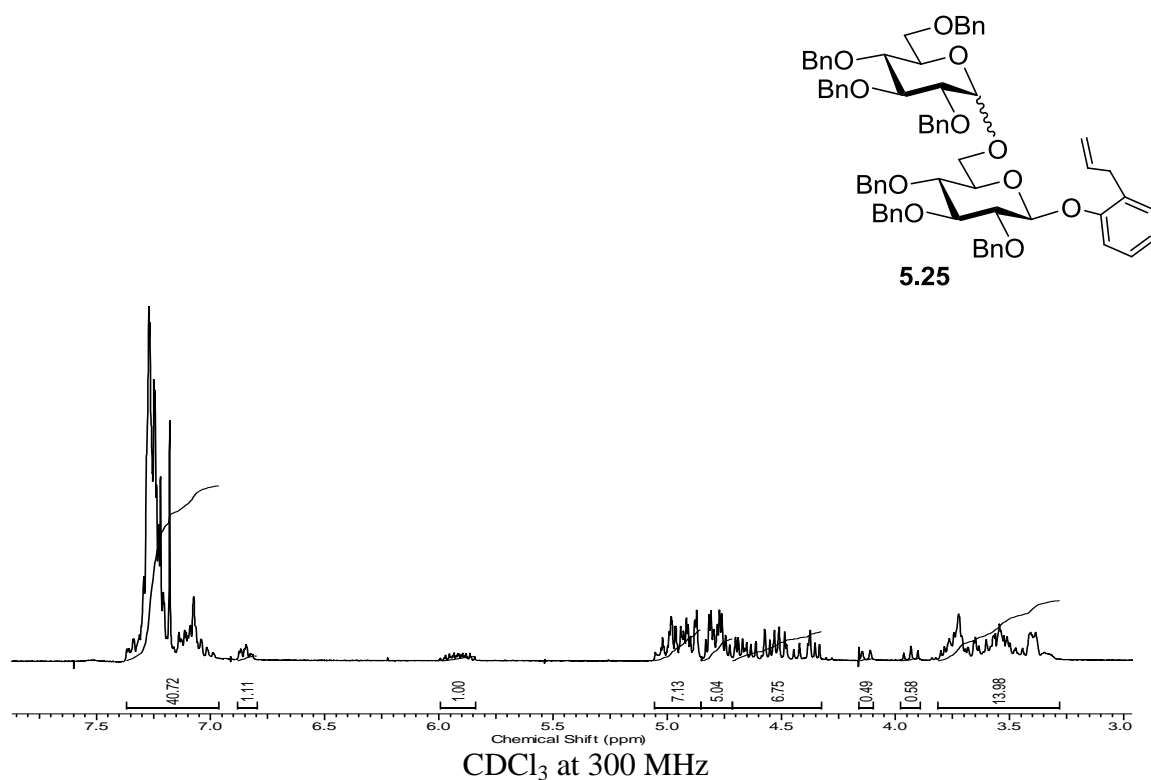


Figure A-69: ^1H NMR spectrum of 2-Allylphenyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- β -D-glucopyranoside (**5.25**).

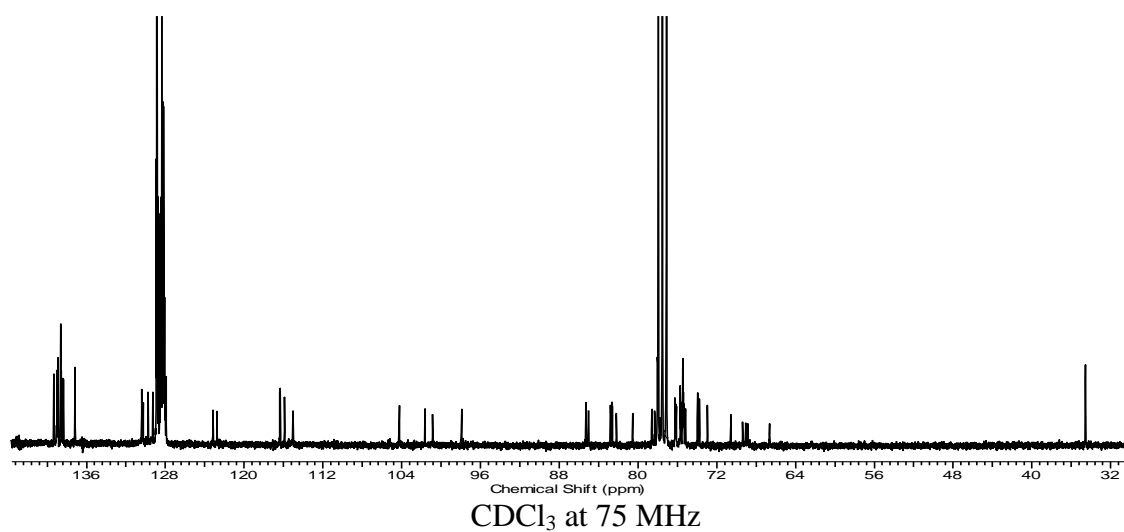


Figure A-70: ^{13}C NMR spectrum of 2-Allylphenyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- β -D-glucopyranoside (**5.25**).

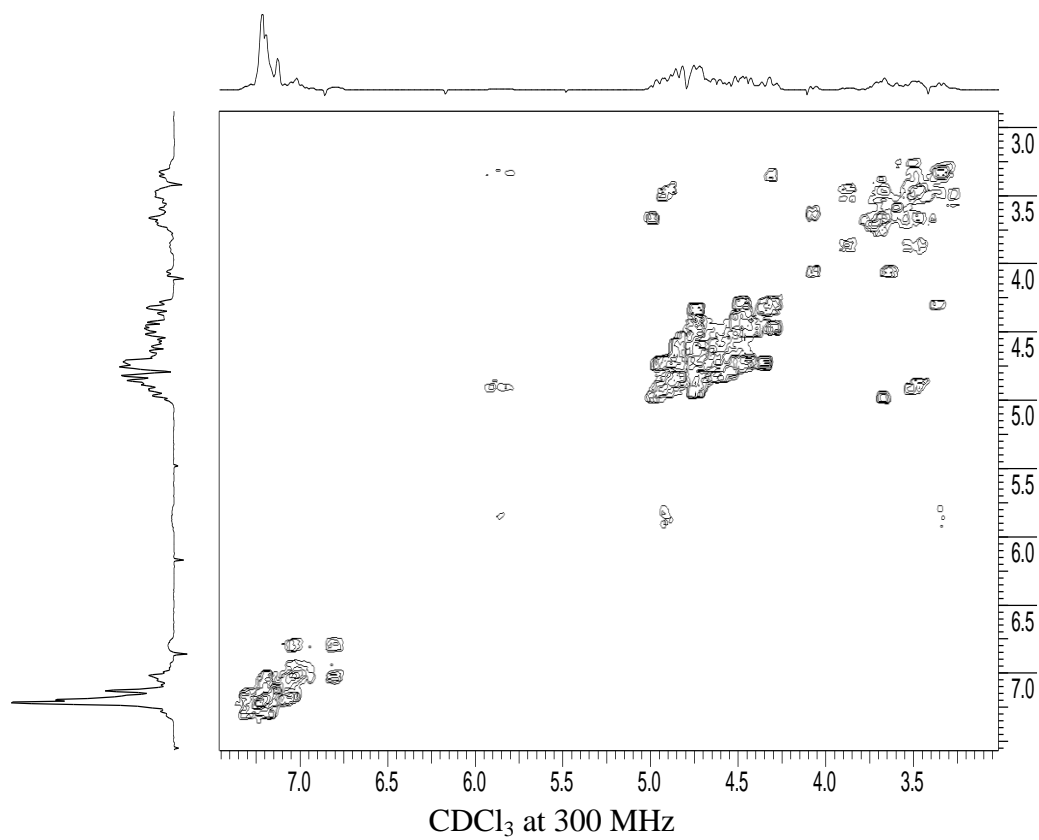
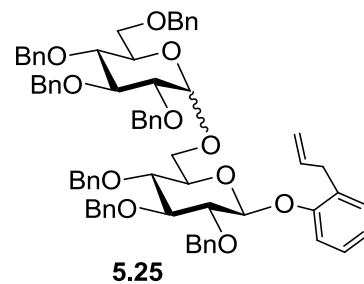


Figure A-71: 2-D NMR COSY spectrum of 2-Allylphenyl 6-O-(2,3,4,6-tri-O-benzyl- α / β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- β -D-glucopyranoside (**5.25**).

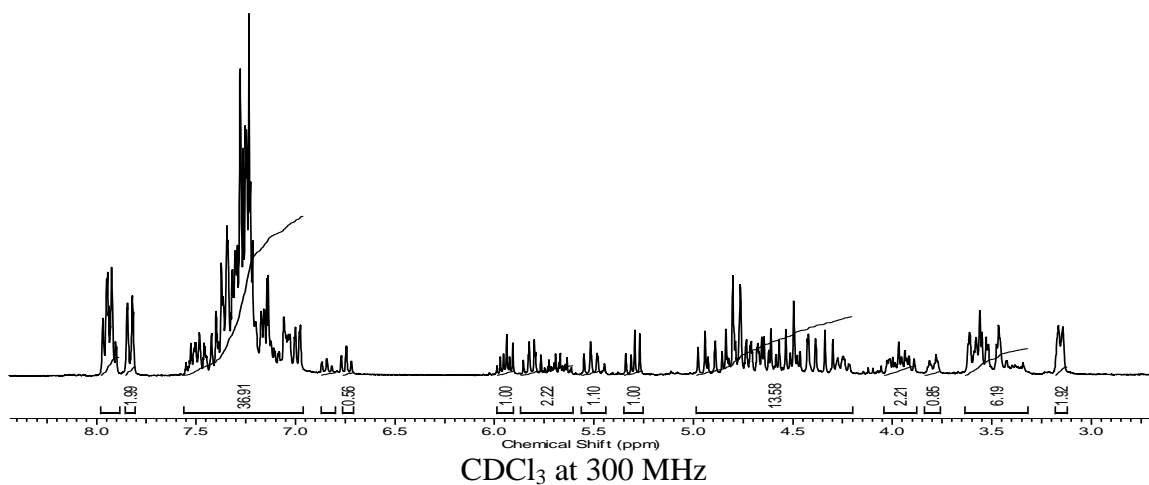
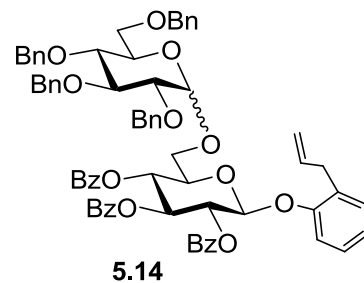


Figure A-72: ¹H NMR spectrum of 2-Allylphenyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzoyl- β -D-glucopyranoside (**5.14**).

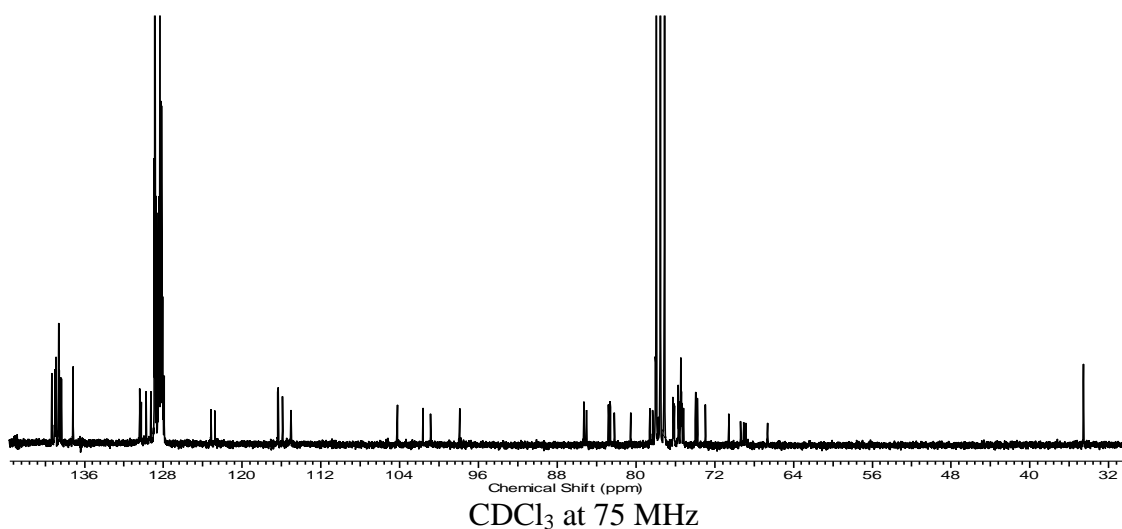


Figure A-73: ¹³C NMR spectrum of 2-Allylphenyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzoyl- β -D-glucopyranoside (**5.14**).

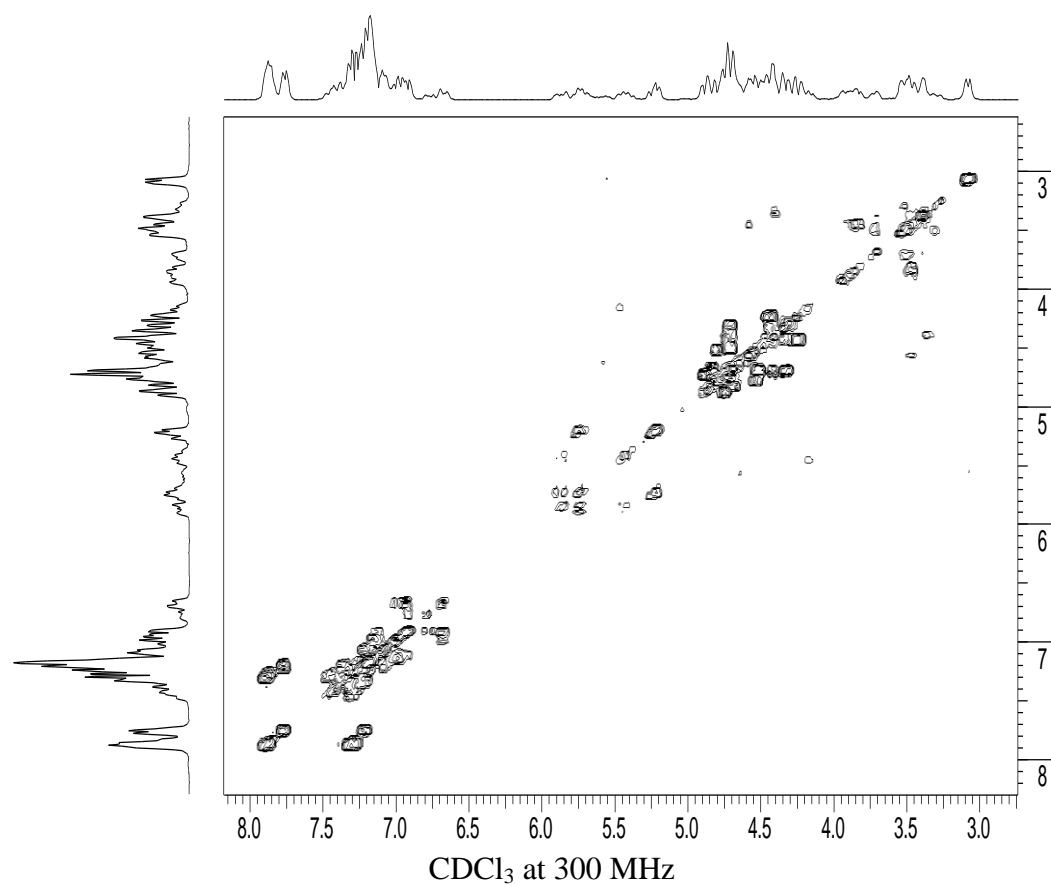
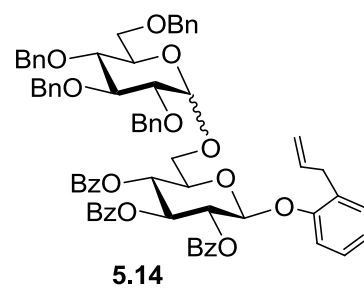


Figure A-74: 2-D NMR COSY spectrum of 2-Allylphenyl 6-O-(2,3,4,6-tri-O-benzyl- α/β -D-glucopyranosyl)-2,3,4-tri-O-benzoyl- β -D-glucopyranoside (**5.14**).

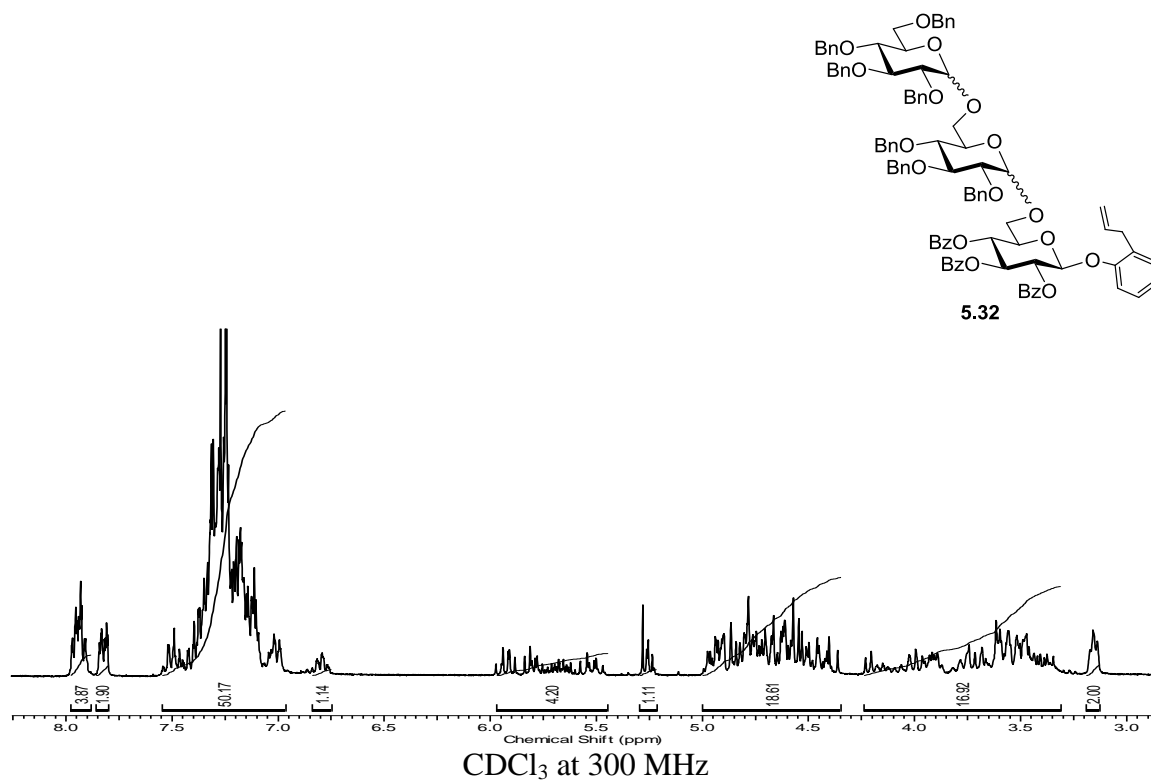


Figure A-75: ^1H NMR spectrum of 2-Allylphenyl O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-O-(2,3,4-tri-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-2,3,4-tri-O-benzoyl- β -D-glucopyranoside (**5.32**).

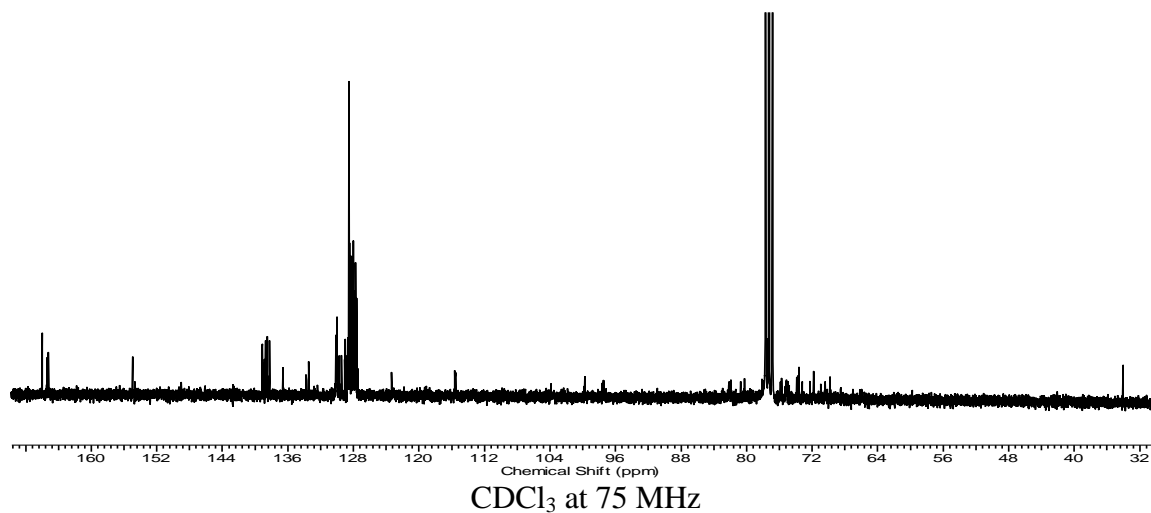


Figure A-76: ^{13}C NMR spectrum of 2-Allylphenyl O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-O-(2,3,4-tri-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-2,3,4-tri-O-benzoyl- β -D-glucopyranoside (**5.32**).

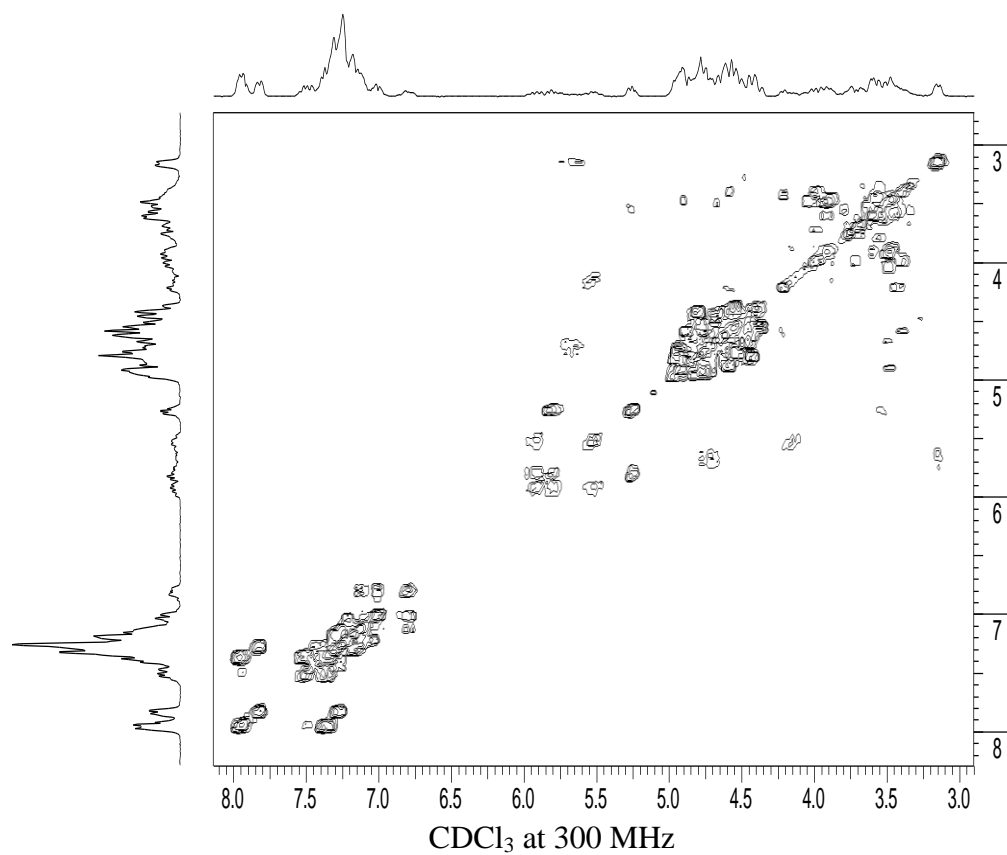
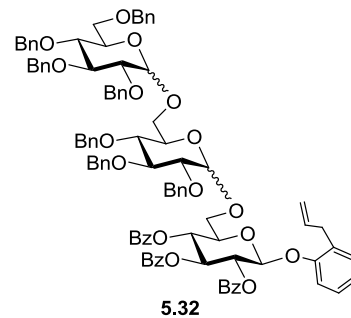


Figure A-77: 2-D NMR COSY spectrum of 2-Allylphenyl O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-O-(2,3,4-tri-O-benzyl- α/β -D-glucopyranosyl)-(1 \rightarrow 6)-2,3,4-tri-O-benzoyl- β -D-glucopyranoside (**5.32**).