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New Methods and Strategies for Orthogonal Oligosaccharide Synthesis

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NEW METHODS AND STRATEGIES FOR ORTHOGONAL OLIGOSACCHARIDE SYNTHESIS

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ABSTRACT

New Methods and Strategies for Orthogonal Oligosaccharide Synthesis

Although scientists have been able to isolate certain classes of naturally occurring carbohydrates, the overall availability of pure natural isolates remains inadequate. As a result, chemical synthesis has been employed to access complex carbohydrates. Unfortunately, traditional oligosaccharide synthesis often requires laborious protecting-group manipulations that results in lower yields. Expeditious strategies effectively shorten the task of oligosaccharide assembly by minimizing the need for protecting-group manipulations between glycosylation steps, or even purification of the intermediates. Additionally, prediction of the stereoselective outcome of the coupling reaction between two sugar units is a major obstacle facing carbohydrate chemists. It is well known that 1,2-*trans* (**β**) glycosides can be easily obtained with the assistance of a neighboring participating group at C-2, typically an acyl moiety such as *O*-acetyl or *O*-benzoyl. In order to achieve 1,2-*cis* (**α**) glycosides, a glycosyl donor bearing a non-participating group at C-2 (e.g., *O*-benzyl, or azido) needs to be employed. Unfortunately, these reactions often proceed *via* S_N1 mechanism and result in poor stereoselectivity.

Presented herein is the investigation into the use of *S*-benzimidazolyl (SBiz) glycosides as building blocks for oligosaccharide synthesis. It has been determined that the SBiz leaving group can be manipulated to tune the reactivity of the building block. This reactivity of the leaving group can be significantly enhanced (or reduced) toward selective activation by the use of an N-protecting group on the imidazole ring. This, in turn, allows executing oligosaccharide assembly via the very effective active-latent concept and orthogonal activation-based strategies.

Addressing the issue of stereocontrol of glycosylations, we report the use of silver(I) perchlorate ($AgClO_4$) as a powerful promoter toward assembling 1,2-*cis* glycosides. In this study, $AgClO_4$ is employed to promote glycosyl thioimidates as well as thioglycosides. Furthermore, we have investigated the use of various silver salts, such as $AgBF_4$, $AgPF_6$, AgOTf, and $AgClO_4$ in the coupling reaction. Surprisingly, although the series of promoters all contain silver, their counter ions vastly affect the stereoselectivity of the product. $AgClO_4$ was determined to induce a higher **α** to **β** ratio and in some cases this is a ten-fold increase.

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Finally, I want to thank my wife Jolene and son Chase for their unwavering love and support during the highs and lows of my doctoral studies, I love you both more than you will ever imagine! WE DID IT!

List of Abbreviations

Å ..... Angstrom

Ac ..... Acetyl

$AgBF_4$ ..... Silver tetrafluoroborate

$AgClO_4$ ..... Silver perchlorate

AgOTf ..... Silver trifluoromethanesulfonate

$AgPF_6$ ..... Silver hexafluorophosphate

$Bi(OTf)_3$ ..... Bismuth trifluoromethanesulfonate

Bn ..... Benzyl

Bz ..... Benzoyl

$BF_3(OEt)_2$ ..... Boron trifluoride etherate

Bu_4NBr ..... Tetrabutylammonium bromide

$Cu(OTf)_2$ ..... Copper trifluoromethanesulfonate

d ..... Doublet

DCE 1,2-Dichloroethane

DCM ..... Methylene chloride

dd ..... Doublet of doublets

DMF ..... *N*,*N*-Dimethylformamide

DMTST ..... Dimethyl(methylthio)sulfonium trifluoromethanesulfonate

Et ..... Ethyl

EtOAc ..... Ethyl acetate

Et_2O ..... Diethyl ether

Gal ..... Galactose

Glc ..... Glucose

h ..... Hour(s)

HR-FAB MS ..... High Resolution Fast Atom Bombardment mass spectrum

HSEt .....*S*-Ethyl

HSPh .....*S*-Phenyl

Hz ..... Hertz

IDCP ..... Iodonium dicollidine perchlorate

KOH ..... Potassium hydroxide

m ..... Multiplet

Man ..... Mannose

min ..... Minute

m/z ..... Mass to charge ratio

Me ..... Methyl

MeOTf..... Methyl trifluoromethanesulfonate

MeI ..... Methyl iodide

MeCN ..... Acetonitrile

MeOH ..... Methanol

MS ..... Molecular sieves

NaOH ..... Sodium hydroxide

NaOMe ..... Sodium methoxide

NIS ..... *N*-Iodosuccinimide

NMR ..... Nuclear magnetic resonance

Pent ..... Pentenoyl

Ph ..... Phenyl

pMB ..... *para*-Methoxybenzyl

ppm ..... Parts per million

R_f ..... Retention factor

rt ..... Room temperature

SBaz ..... *S*-Benzothiazolyl

SBox ..... *S*-Benzoxazolyl

SBiz ..... *S*-Benzimidazolyl

SNea ..... *O*-Methyl phenylcarbamothioate

STaz ..... *S*-Thiazolinyl

s ..... Singlet

t ..... Triplet

TBDMS ..... *tert*-Butyldimethylsilyl

TBAF ..... Tetra-*n*-butyl ammonium fluoride

TfOH ..... Trifluoromethanesulfonic (triflic) acid

TLC ..... Thin layer chromatography

TMSOTf ..... Trimethylsilyl trifluoromethanesulfonate

Troc 2,2,2-Trichloroethoxycarbonyl

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Chapter 1

Glycosyl thioimidates as versatile building blocks for organic synthesis

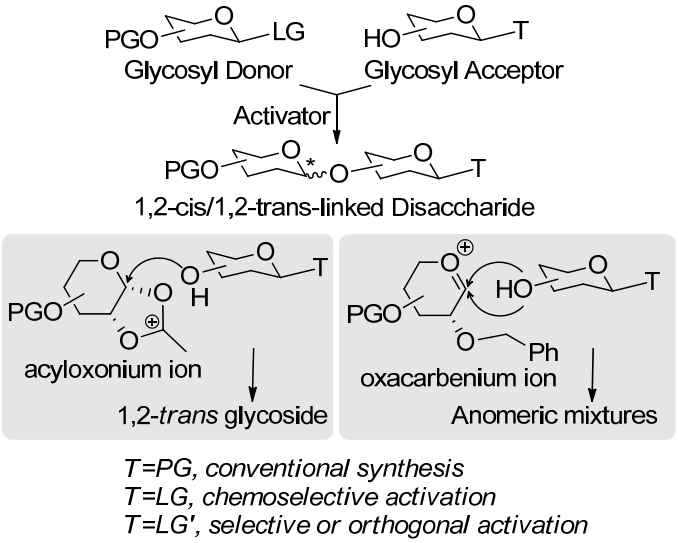
1.1 Introduction

Carbohydrates are the most abundant biomolecules on the planet, having long been known exclusively as a biochemical energy source. Recently, researchers have become increasingly aware of the role carbohydrates play aside from energy supply and storage. Carbohydrates are involved in a wide range of biological processes such as fertilization, anti-inflammation, immunoresponse, joint lubrication, cell growth, antigenic determination, etc.[1] They also have a sizable contribution into harmful processes such as bacterial and viral infections, development of tumors, metastasis, tissue rejection, and congenital disorders.[2] Because many of these cellular processes are directly associated with pathogenesis of deadly diseases including AIDS, cancer, pneumonia, septicemia, hepatitis and malaria, scientific efforts in the field of modern glycosciences have expanded.[3] While scientists have been able to successfully isolate certain classes of natural carbohydrates, the availability of appreciable quantities of these pure natural isolates is still inadequate to address the challenges offered by modern glycosciences. For this reason, chemical and enzymatic syntheses of complex carbohydrates have been employed to gain access to large quantities of both natural compounds and mimetics thereof. Even with significant advancements, controlled chemical synthesis of complex carbohydrates remains difficult. Hence, further development of methods and strategies for oligosaccharide and glycoconjugate synthesis remains a demanding area of research.

The majority of the biologically and therapeutically active carbohydrates are oligosaccharides or complex glycoconjugates (glycolipids, glycoproteins, etc.) in which monomeric sugar units are joined via *O*-glycosidic bonds. This linkage is formed by a glycosylation reaction, most commonly a promoter-assisted nucleophilic displacement of

a leaving group (LG) of the glycosyl donor with a hydroxyl moiety of the glycosyl acceptor (Scheme 1.1).[4] Other functional groups on both the donor and acceptor are temporarily masked with protecting groups (PG, T). Since the new glycosidic linkage creates a chirality center, particular care has to be taken with regards to the stereoselectivity.

Scheme 1.1. The outline of a typical glycosylation reaction.



This represents a major challenge in comparison to the synthesis of the intermonomeric linkages in other natural biopolymers, proteins and nucleosides. Although mechanistic studies of the glycosylation reaction are still scarce, certain conventions have already been established.[5] For instance, 1,2-*trans*-linked glycosides are often stereoselectively obtained from 2-*O*-acylated glycosyl donors, as these reactions proceed via an acyloxonium intermediate (Scheme 1.1).[6] In the case of ether-type (2-*O*-benzyl) non-participating substituents, the glycosylation proceeds via the flattened oxacarbenium ion that often leads to anomeric mixtures. Although 1,2-*cis* glycosides (for D-gluco/galacto

series) are favored by the anomeric effect, the stereoselectivity is often low, which makes their synthesis a notable challenge.[7,8] In spite of significant progress, chemical *O*-glycosylation remains among the top challenges of modern synthetic chemistry due to the requirement to achieve complete stereocontrol and the necessity to suppress side reactions.

Aside from glycosyl donor structure, a number of factors can influence the stereoselective outcome of the glycosylation reaction such as structure of glycosyl donor or acceptor, solvent, temperature, and many others. Occasionally, the nature of a leaving group may also have an influence on the anomeric stereoselectivity, and these observations led to the development of a large number of different classes of glycosyl donors.[4] Early methods developed by Fischer[9] and Koenigs and Knorr[10] had been the main driving forces in the area of carbohydrate chemistry until the 1970s through the early 1980s, when the traditional approach to glycosylation was revolutionized by the development of a series of new leaving groups. The new generation of glycosyl donors included *S*-phenyl glycosides by Ferrier,[11] Nicolaou,[12] Garegg,[13] and others,[14] cyanoethylidene derivatives by Kochetkov,[15] *O*-imidates by Sinay[16] and Schmidt,[17] *S*-benzothiazolyl derivatives (SBaz) by Mukaiyama,[18] *S*-pyridyl and *S*-pyrimidin-2-yl derivatives by Hanessian[19] and Woodward,[20] and fluorides by Mukaiyama[21] among others. The fate of these methods for chemical glycosylation is very different. While the development of trichloroacetimidates,[22] thioglycosides,[23] and fluorides[24] has produced general glycosylation methodologies, glycosyl thioimidates, broadly defined as compounds equipped with S-C=N leaving groups, had been long out shadowed by other glycosyl donors that offered more promise for further development.

For many years, glycosyl thioimidates have been viewed as an insignificant variation of the thioglycoside glycosidation methodology. Because of this, glycosyl thioimidates received very little attention, in part due to marginal stability toward protecting group manipulations. Over the last decade, the thioimidate method has evolved into a very robust methodology for glycosylation.[25,26] Particularly with the introduction of novel *S*-benzoxazolyl (SBox) and *S*-thiazolinyl (STaz) leaving groups, it has become apparent that thioimidates can withstand many reaction conditions associated with protecting group manipulations.[27,28] In addition, these thioimidates are easily accessible from a variety of simple precursors, can be glycosidated under a range of different, and often unique, reaction conditions. Likewise, they are able to provide superior stereoselectivity and can be selectively activated in the presence of other types of leaving groups. These listed factors are important traits for both glycoside and oligosaccharide synthesis and all are rarely found in one class of a leaving group.

Stereoselectivity is particularly important in light of the fact that a single-step glycosylation is only one challenge researchers working on oligosaccharide synthesis face wherein additional protecting and/or leaving group manipulations between each glycosylation step are required. Resultantly, the synthesis becomes increasingly inefficient which is particularly evident at the advanced stages of the assembly[29,30] and often leads to a dramatic drop in yield, and as a consequence, the availability of oligosaccharides. Further study of glycosyl thioimidates allowed for the design of novel strategies for the synthesis of oligosaccharides including the temporary deactivation concept,[31,32] the inverse armed-disarmed strategy,[33] STICS: surface-tethered iterative carbohydrate synthesis,[34] and the thioimidate-only orthogonal strategy.[35] It also helped to

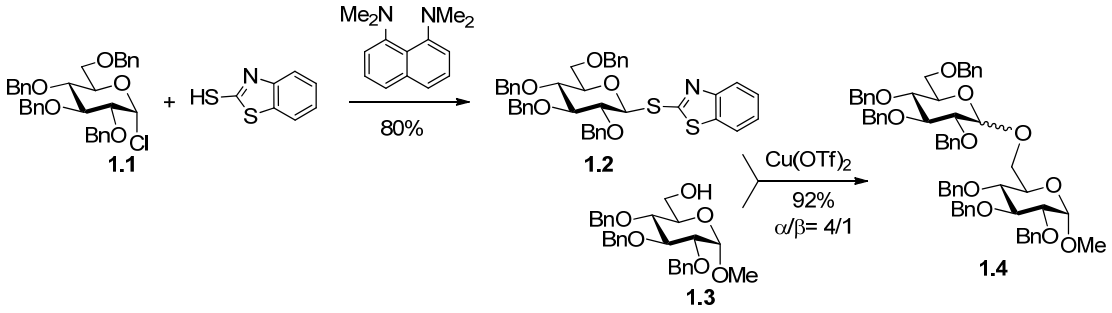
uncover the *O*-2/*O*-5 cooperative effect in glycosylation that allows for superarming and superdisarming of building blocks by simple alteration of protecting group pattern,[36-39] and to perform basic mechanistic aspects of glycosylation,[33,40] the most common but least understood reaction in glycochemistry.[4] Very recently, *S*-benzimidazolyl (SBiz) building blocks promises to become a new versatile platform for active-latent oligosaccharide synthesis.[41] In addition, a number of medicinally relevant oligosaccharides and glycoconjugates have been obtained using the thioimidate approach.[32,42-47] The remainder of this chapter discusses major aspects of the synthesis and glycosidation of SBaz, SBox, STaz, and SBiz thioimidates and the roles in which they fit into modern strategies for expeditious oligosaccharide synthesis. Emphasis has been placed on methods, strategies, and phenomena that have been discovered thanks to unique structural features and reactivity pattern of glycosyl thioimidates.

1.2 *S*-Benzothiazolyl (SBaz) derivatives

Per-acetylated *S*-benzothiazolyl (SBaz) glycosides were first synthesized in 73% yield by Zinner from acetobromoglucose and mercury(II) salt of 2-mercaptobenzothiazole (HSBaz) in the presence of sodium.[48] Mukaiyama was the first to report glycosidation of a glycosyl donor equipped with SBaz leaving group.[18] For this study, the glycosyl donor **1.2** was prepared from per-benzylated chloride **1.1** and HSBaz in the presence of 1,8-bis(dimethylamino)naphthalene in 80% yield (Scheme 1.2). Glycosylation studies were performed in the presence of $Cu(OTf)_2$ with various acceptors in diethyl ether and in most cases glycosylations proceeded with high yields and good stereoselectivity. For example, the reaction of **1.2** with glycosyl acceptor **1.3** in the

presence of $Cu(OTf)_2$ resulted in the formation of disaccharide **1.4** in an excellent yield of 92% as an anomeric mixture (α/β = 4/1).

Scheme 1.2. *S*-Benzothiazolyl approach to glycoside synthesis reported by Mukaiyama.[18]

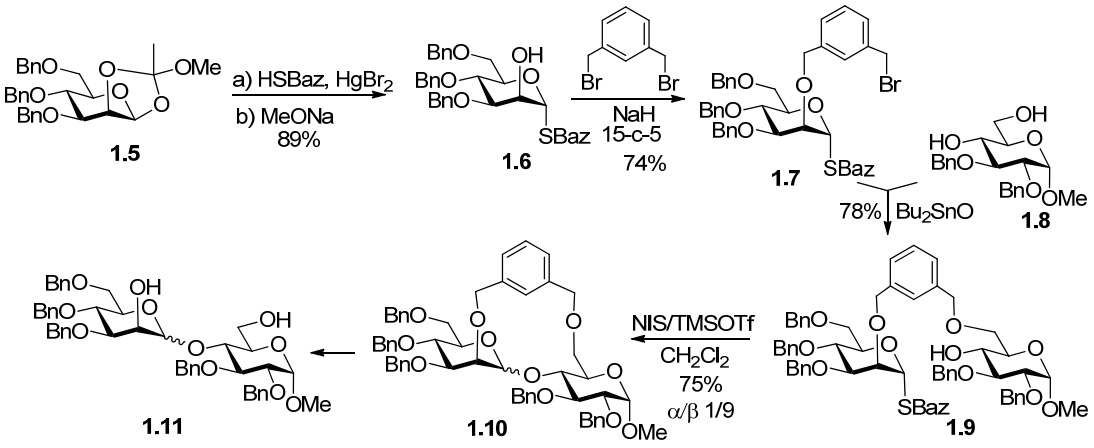


A number of general modifications and ultimately improvements to this approach have emerged. Various precursors and reaction conditions have been investigated. For instance, Szeja reported the synthesis of **1.2** from the hemiacetal derivative, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose under phase-transfer conditions in the presence of TsCl and Bu_4NCl in benzene/50% aq. NaOH.[49] Compound **1.2** was isolated in 95% yield as a mixture of anomers (α/β = 1/3). Likewise, SBaz mannofuranoside and xylopyranoside were obtained as anomeric mixtures in 92 and 81% yield, respectively.[49] Schmidt et al. reported the synthesis of SBaz mannoside **1.6** by opening 1,2-orthoester **1.5** in the presence of $HgBr_2$ (Scheme 1.3).[50] Bogusiak reported the synthesis of SBaz furanosides of the L-arabino, D-ribo, and D-xylo series from the reducing sugars and HSBaz in the presence of diphenyl phosphoryl chloride [$(PhO)_2P(=O)Cl$] under phase transfer conditions.[51] Ferrieres and Plusquellec described the synthesis of per-acetylated SBaz galactofuranosides from the corresponding β-pentaacetate in the presence of BF_3-Et_2O in 83% yield as an anomeric mixture.[52,53] The obtained thioimidates were then deprotected

and applied in anomeric phosphorylation. A number of acylated SBaz and analogous 5-methoxy-SBaz derivatives of D-gluco, D-galacto, and D-ribofurano series have been reported by Khodair et al.[54] While the syntheses of hexoses were accomplished from acetobromosugar and the corresponding sodium thiolates in MeCN, the synthesis of thioribofuranoside derivative was achieved from the corresponding tetraacetate and trimethylsilylated thiols in the presence of TMSOTf.[54] The synthesis of a range of differently protected SBaz derivatives from the corresponding glycosyl bromides and KSBaz in acetone has also been reported.[55]

The glycosylation studies of SBaz derivatives have also been significantly expanded. For instance, Gama et al. reported the glycosidation of **1.2** by using methyl iodide as an activator in several solvents under high pressure.[56] It was found that high pressure-assisted glycosidation of **1.2** provided the corresponding disaccharides with an improved stereoselectivity compared to that reported by Mukaiyama.[18] For example, coupling of **1.2** with **1.3** in dichloromethane at 1.3 GPa produced **1.4** in 71% yield as a mixture of anomers (α/β = 7/1). SBaz mannoside **1.6** was employed in the elegant intramolecular glycosylation (molecular clamp) approach involving *m*-xylylene as a rigid spacer (Scheme 1.3).[50] For this purpose, the free hydroxyl of **1.6** was reacted with α,α'-dibromoxylene resulting in the intermediate **1.7**, which was subsequently linked to acceptor **1.8**. The resulting compound **1.9** was subjected to NIS/TMSOTf-promoted intramolecular condensation to afford disaccharide **1.10** in 75% yield with high β-manno stereoselectivity (α/β = 1/9).

Scheme 1.3. Intramolecular β-mannosylation using SBaz methodology.[50]

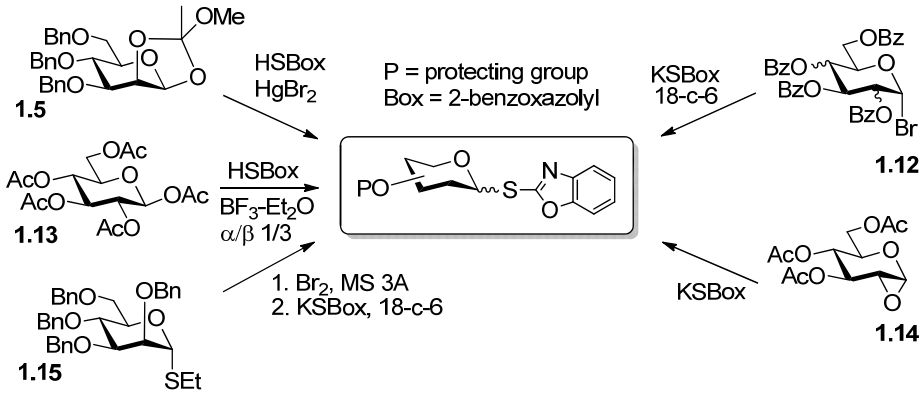


It was determined that AgOTf or NIS/TfOH can serve as suitable activators for *S*-benzothiazolyl furanosides.[51] As an example, AgOTf-promoted glycosylation of diacetone galactose acceptor (6-OH) with glycosyl donors of the L-arabino, D-ribo, and D-xylo series in toluene afforded the corresponding disaccharides in 75% (α/β = 4/3), 98% (α/β = 7/2), and 70% (α/β = 3/10) yield, respectively. It was also reported that the SBaz leaving group can be activated very rapidly for glycosylation in the presence of $AgBF_4$ and is applicable to selective activation over other types of leaving group involving *S*-alkyl and *O*-pentenyl glycosides.[55] It was also observed that the SBaz leaving group can be activated in the presence of MeOTf, but not in the presence of weaker alkylating reagents, which created a basis for selective activation of STaz donors with benzyl bromide or methyl iodide in the presence of glycosyl acceptors equipped with the SBaz anomeric group.[35]

1.3 *S*-Benzoxazolyl (SBox) derivatives

Per-acetylated SBox derivatives were first synthesized by Zinner from acetobromoglucose and 2-mercaptobenzoxazole (HSBox) in the presence of sodium.[57,58] Schmidt's group had achieved the synthesis of SBox mannosides via orthoester **1.5** with HSBox and $HgBr_2$ (Scheme 1.4).[50] Shortly thereafter, it was reported the synthesis of SBox glycosyl donors of the D-gluco, D-galacto, and D-manno series from the corresponding anomeric bromides **1.12** and KSBox in the presence of 18-crown-6.[59] Alternatively, glycosyl bromides can react directly with HSBox in the presence of K_2CO_3 in acetone.[28] In addition, SBox glycosides were obtained from anomeric acetates (e.g., **1.13**), thioglycosides **1.15**, or 1,2-anhydro sugars **1.14** (Scheme 1.4).[40] The introduction of the SBox moiety is completely stereoselective, except for the BF_3-Et_2O-promoted introduction from anomeric acetate **1.13** that results in the formation of anomeric mixtures of 1,2-*cis* and 1,2-*trans* SBox glycosides (α/β = 1/3).[59]

Scheme 1.4. Synthesis of SBox glycosides.



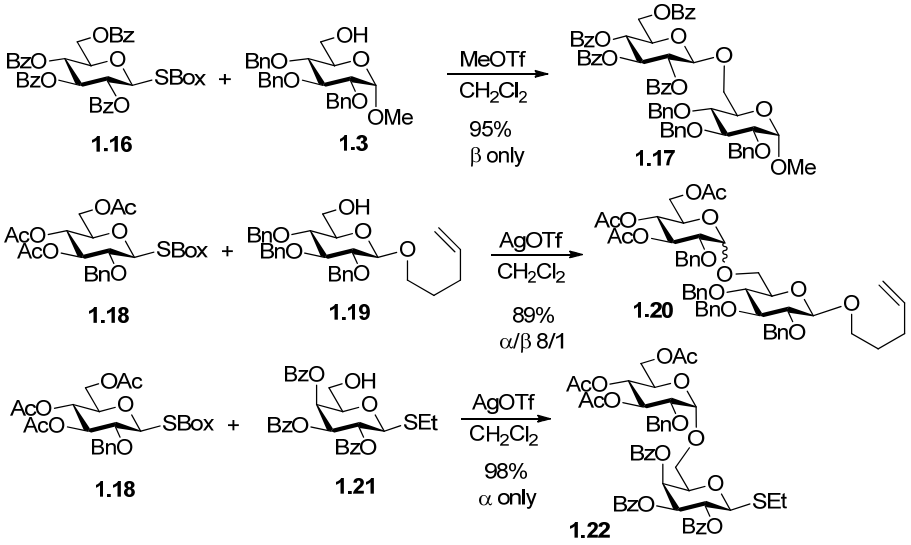
Schmidt and co-workers reported the application of the SBox glycosides to indirect β-mannosylations, in which a glycosyl donor and a glycosyl acceptor were

tethered by a rigid spacer.[50] The resulting disaccharide was obtained in 78% yield (α/β = 1/10). Demchenko et al. reported the use of SBox derivatives as glycosyl donors for the synthesis of 1,2-cis glycosides of D-gluco and D-galacto,[28] as well as 1,2-*trans* glycosides of the D-gluco, D-galacto, and D-manno series.[59] These studies showed that the SBox leaving group can be activated using a broad range of promoters including AgOTf, $Cu(OTf)_2$, $Bi(OTf)_3$, $AgBF_4$, NIS/TfOH, TMSOTf, MeOTf, etc. and enabled the stereoselective synthesis of 1,2-*trans* and 1,2-*cis* glycosides. For example, the glycosidation of SBox glycosyl donor **1.16** with acceptor **1.3** in the presence of MeOTf in dichloroethane afforded **1.17** in 95% yield (Scheme 1.5). In attempts to improve the stereoselectivity of mannosylation, SBox glycosyl donors bearing remote protecting groups *p*-methoxybenzoyl or *N,N*-diethyl thiocarbamoyl at C-4 were investigated.[60]

Since the SBox moiety can be activated in the presence of AgOTf or $Cu(OTf)_2$, conditions that fail to activate the alkyl/aryl thioglycosides, selective activation of SBox over a range of other leaving groups has been investigated. For example, the SBox donor **1.18** could be selectively activated over *O*-pentenyl **1.19** or *S*-ethyl acceptor **1.21** to give the corresponding disaccharides **1.20** or **1.22**, respectively, in high yields (98-99%) and stereoselectivities (Scheme 1.5).[28] Because the resulting disaccharides already bear a suitable leaving group at the anomeric center, no additional protecting/anomeric group manipulations are required for the continuation of the coupling sequence. This is very beneficial as chain elongation can be conducted in a stepwise manner (vide infra).[61] De Meo reported the application of the SBox approach to stereoselective α-sialylation and to the efficient synthesis of a GM3 analog.[62] In this synthesis, selective activation of the SBox moiety of the sialyl donor over the *S*-ethyl moiety of the galactosyl acceptor was

achieved in the presence of AgOTf. The obtained disaccharide was used in subsequent coupling directly to afford the desired GM3 trisaccharide sequence in good overall yield. A similar activation principle was also employed in a high output one-pot synthesis.[63]

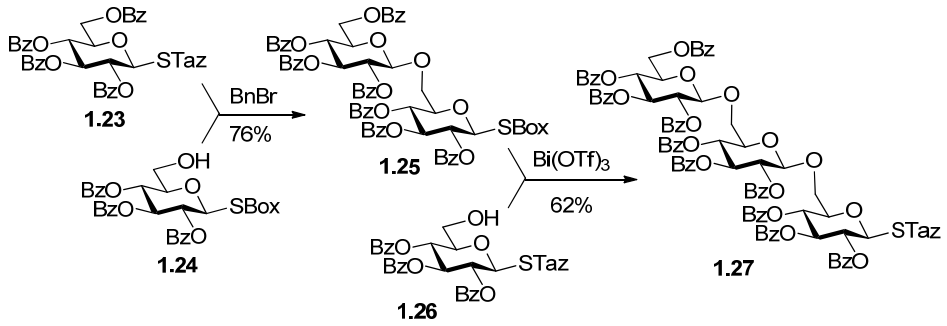
Scheme 1.5. SBox glycosides in stereoselective glycoside synthesis.



SBox glycosides also showed promising orthogonal combinations with glycosyl alkoxyimidates[64] and STaz glycosides.[35] The orthogonality with other thioimidates is a unique feature of this methodology because conventional orthogonal activation[65,66] requires two different classes of leaving groups, whereas here both leaving groups are of the same class. The key to this methodology is the choice of activator. In the case of STaz, activation an alkylation agent is used and SBox activation is carried out with $Bi(OTf)_3$ (Scheme 1.6).[35] Herein, STaz glycosyl donor **1.23** and SBox acceptor **1.24** are coupled in the presence of benzyl bromide. In the subsequent step, disaccharide **1.25** is activated with $Bi(OTf)_3$ and reacted with STaz acceptor **1.26** producing trisaccharide **1.27** in 62% yield. This methodology was largely based on extended mechanistic work, which

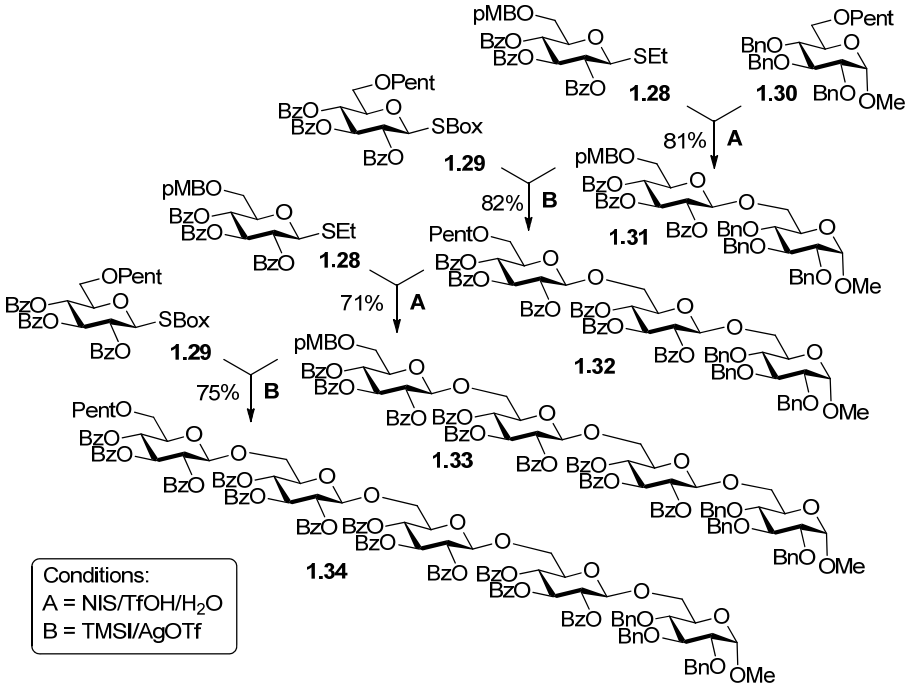
demonstrated that STaz glycosides are activated via the heterocyclic nitrogen atom (remote activation), whereas SBox glycosides are activated via exocyclic/anomeric sulfur (direct activation).[35,40]

Scheme 1.6. Orthogonal activation of STaz and SBox leaving groups.[35]



As a directional modification of the traditional orthogonal approach based on the orthogonality of leaving groups, a reverse approach was reported wherein a protecting group-based chain elongation was conducted. This strategy, termed reverse orthogonal, takes advantage of orthogonal stability of protecting groups along with simultaneous activation of the applicable anomeric leaving group.[67] Glycosyl donors employed were SEt glycosides with 6-*O*-*p*-methoxybenzyl (pMB) protection **1.28** and SBox glycosides with 6-*O*-pentenoyl (Pent) protection **1.29**. The first disaccharide was obtained from **1.28** and **1.30** in 81% yield using NIS/TfOH/H_2O. Disaccharide **1.31** was then glycosylated with SBox donor **1.29** equipped with an *O*-pentenoyl group. The resulting trisaccharide **1.32** was obtained in 82% yield and then reacted with **1.28** to afford tetrasaccharide **1.33** in 71% yield. Finally, tetrasaccharide **1.33** was coupled with **1.29** and the resulting pentasaccharide **1.34** was isolated in 75% yield.

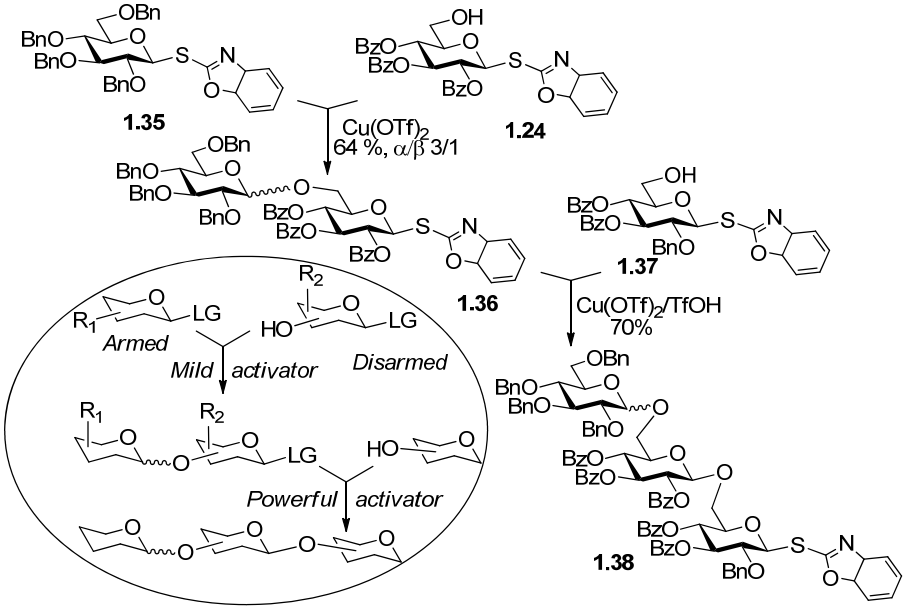
Scheme 1.7. Four-step synthesis of pentasaccharide **1.34** via the reverse orthogonal strategy.[67]



Another general concept for oligosaccharide synthesis makes 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 (PG_1, PG_2, Scheme 1.8).[68] Usually, the protecting groups in both reaction components and careful selection of mild reaction conditions have to be taken into consideration to allow for direct chemoselective activation of the armed glycosyl donor over the disarmed glycosyl acceptor. Many classes of leaving groups can be activated accordingly, and SBox is no exception. For instance, armed donor **1.35** could be chemoselectively activated over the disarmed acceptor **1.24**. This activation was effected in the presence of $Cu(OTf)_2$ and resulted in chemoselective formation of disaccharide **1.36** in 64%. Further study of chemoselective activation of SBox glycosides revealed other reactivity levels

gor differently protected building blocks. Thus, it was demonstrated that disarmed disaccharide **1.36** could be further chemoselectively activated over superdisarmed building block **1.37**. This activation was achieved in the presence of $Cu(OTf)_2$/TfOH to produce trisaccharide **1.38** in 70% yield.[36] This finding was somewhat surprising because it was anticipated that reactivity of building block such as **1.37** 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[69] for building blocks of the L-rhamnose series.

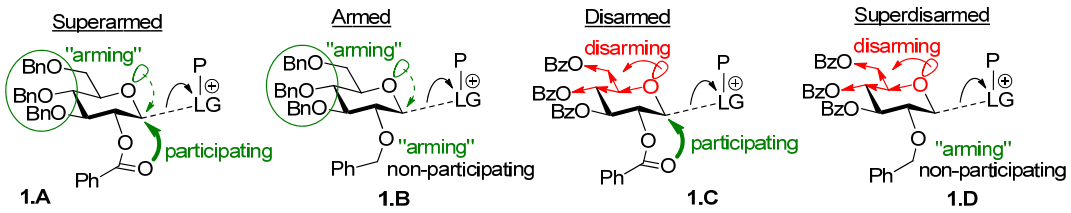
Scheme 1.8. Expansion of the armed-disarmed strategy to superdisarmed building blocks.[68]



The observed reactivity pattern was rationalized by the occurrence of the so-called "*O*-2/*O*-5 Cooperative Effect".[36] 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. If electron withdrawing protecting groups are placed near the *O*-5 ring oxygen (at C-4 and C-6, as in the disarmed donors **1.C** or **1.D** in Figure 1.1), 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 the formation of an acyloxonium ion intermediate, like in disarmed glycosyl donor **1.C**, may become increasingly important. Crich et al.[70] emphasized that the anchimeric assistance was particular to the 1,2-*trans* orientation of the 2-*O*-acyl and 1-SBox leaving group. If no source of secondary stabilization is available, as in case of 2-*O*-benzyl substituent in **1.D**, this combination will give rise to the overall "superdisarming" protecting group pattern.

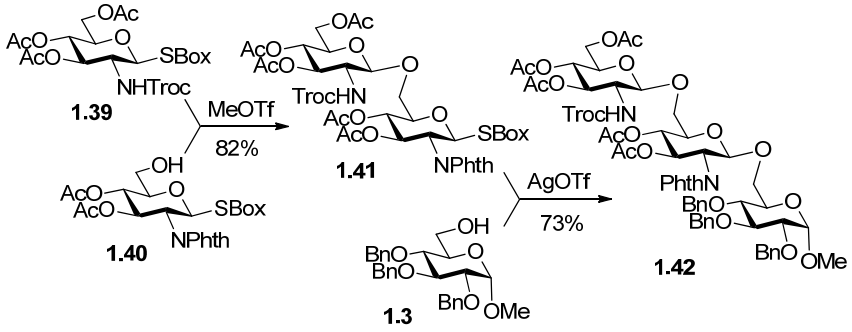
Figure 1.1. *O*2/*O*5 cooperative effect in glycosylation.



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 and these glycosyl donors proved to be even more reactive (superarmed) than their armed per-benzylated counterparts.[37,38] This observed reactivity pattern was also rationalized by the occurrence of the "*O*-2/*O*-5 Cooperative Effect" (see donor **1.A** depicted in Figure 1.1).[36] Furthermore, this concept was found to be universal and applicable to glycosidations of *O*-pentenyl, *S*-ethyl, *S*-phenyl, *S*-tolyl and STaz building blocks.[71]

In attempts to employ the SBox moiety with 2-amino-2-deoxy glycoside donors, it was observed that 2-*N*-trichloroethoxycarbonyl (Troc) derivatives are significantly more reactive than their 2-*N*-phthaloyl counterparts in MeOTf-promoted glycosylations.[72] This modified armed-disarmed approach allowed for an efficient chemical synthesis of 1,2-*trans*-linked oligosaccharides (Scheme 1.9). Taking advantage of the reactivity differences, the 2-*N*-Phth-protected glycosyl acceptor **1.40** was glycosylated with 2-*N*-Troc-protected glycosyl donor **1.39** in the presence of MeOTf, producing disaccharide **1.41** in 82% yield. Then, with AgOTf activation, the disaccharide was coupled with acceptor **1.3** affording trisaccharide **1.42** in 73% yield.

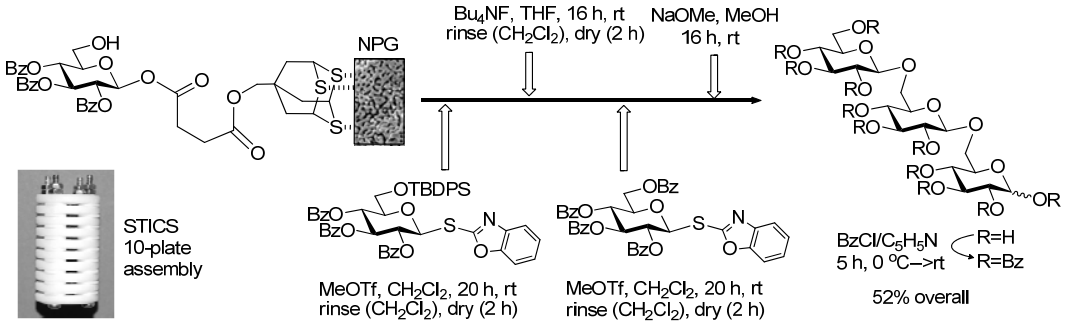
Scheme 1.9. Chemoselective synthesis of 2-amino-2-deoxy SBox glycosides.[72]



It was also demonstrated that SBox-equipped building blocks can be used in both glycosyl acceptor and glycosyl donor bound approaches using polymer supports (Merrifield's resin or Tentagel).[73] As an extension of this study, a novel approach to solid supported synthesis termed surface-tethered iterative carbohydrate synthesis (STICS) was developed.[34] This methodology employs nanoporous gold (NPG) plates as the support to which the glycosyl acceptor is anchored via a thiol linker (Scheme 1.10).

The process involves the coupling of the 6-*O*-TBDPS-protected glycosyl donor with the anchored acceptor using MeOTf. The tethered disaccharide was then desilylated and subsequently coupled with per-benzoylated SBox donor, cleaved from the NPG, and benzoylated for characterization yielding the trisaccharide in 52% overall on a 7-10 mg scale utilizing ten 8 x 8 x 0.2 mm NPG plates assembled in a shelved Teflon mini reactor.

Scheme 1.10. STICS approach to solid-supported synthesis of oligosaccharides.[34]

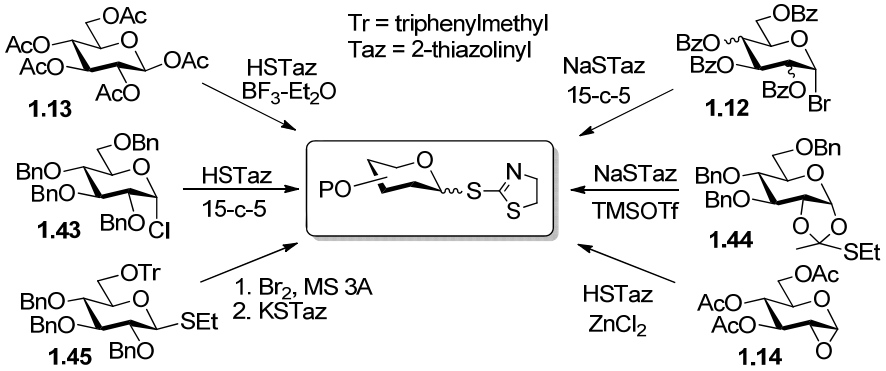


1.4 *S*-Thiazolinyl (STaz) derivatives

The synthesis of per-acetylated STaz glucopyranosides from acetobromoglucose and 2-mercaptothiazoline (HSTaz) in the presence of DIPEA or directly from glucose pentaacetate **1.13** and HSTaz in the presence of BF_3-Et_2O in 64 and 69% yield respectively, was first reported by Descotes et al. (Scheme 1.11).[74] Ferrieres and Plusquellec described the synthesis of per-acetylated thiazolinyl galactofuranosides from β-D-galactofuranose pentaacetate in the presence of BF_3-Et_2O in 53% yield.[52,53] Demchenko et al. reported the synthesis of benzoylated STaz glycosides from the corresponding anomeric bromides **1.12** and NaSTaz or KSTaz in the presence of a crown ether (Scheme 1.11).[27] In these syntheses, the STaz glycosides of the D-gluco, D-galacto, and D-manno series were isolated in 60, 90, and 70% yield, respectively. Subsequently,

it was determined that direct conversion of the anomeric acetates into STaz glycosides is by far more efficient for the D-gluco and D-galacto series in comparison to the synthesis from glycosyl bromides. Thus, the target compounds were obtained in 91 and 85%, respectively.[27] Lower yields resulted when glycosyl halide donors were employed in the synthesis of STaz glycosides, which was due to two side reactions, *N*-glycosylation and β-elimination. Formation of by-products, *N*-linked "Taz" and 1,2-anhydro derivatives, are probably due to the ambient reactivity of HSTaz and its relatively high basicity. Nevertheless, the STaz glycosides were obtained from anomeric chlorides **1.43**,[27] thioglycosides (e.g., **1.45**),[31] 1,2-anhydro sugars **1.14**,[74] or 1,2-orthoesters **1.44** (Scheme 1.11).[33] The formation of 1,2-*trans* STaz glycosides were found in complete stereoselectivity.

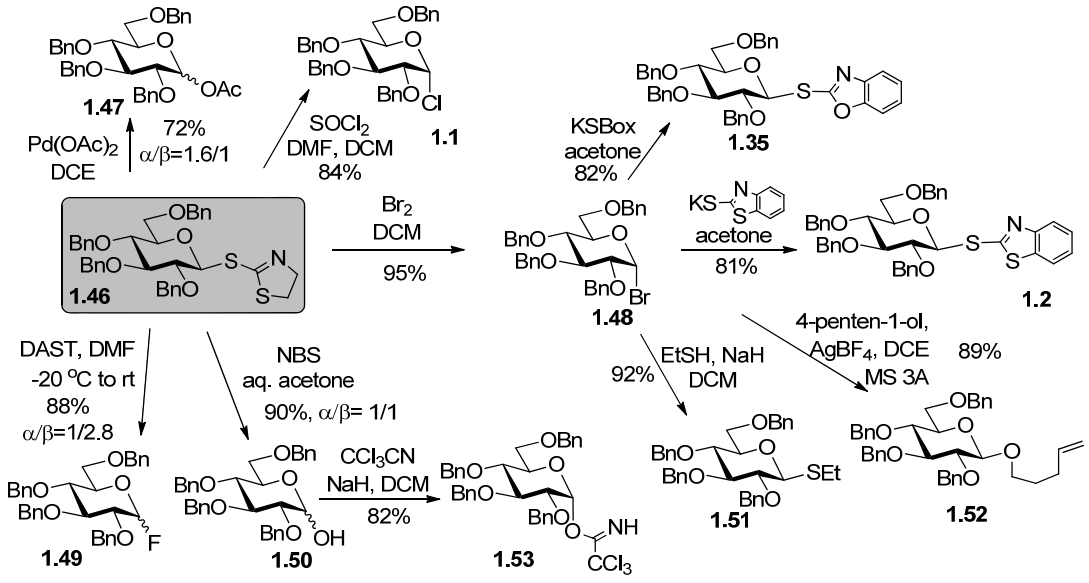
Scheme 1.11. Synthesis of STaz glycosides.



The STaz moiety was found to be stable toward common protecting group manipulations involving basic and acidic conditions; this including acetylation, benzylation, acetal formation and cleavage, among others.[31] Moreover, in comparative hydrolytic stability studies, STaz glycosides exhibited even more stability than their 1-*S*-

ethyl and 1-*S*-phenyl counterparts in the presence of NBS or NIS/TfOH.[27,75] Studies were conducted to determine whether thiazolinyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **1.46** could serve as a common precursor toward the synthesis of an array of glycosyl donors.[55] It was found that the STaz glycoside **1.46** can be directly converted into the following glycosyl donors: acetate **1.47**, chloride **1.1**, bromide **1.48**, fluoride **1.49**, and hemiacetal **1.50** in excellent yields (84–95%, Scheme 1.12). Moreover, glycosyl bromide **1.48** was then used as a precursor for subsequent synthetic steps to obtain benzoxazolyl, benzothiazolyl, and ethyl thioglycosides (**1.35**, **1.2**, and **1.51**), as well as *n*-pentenyl glycoside 1.**52**, all with exclusive β-stereoselectivity. The hemiacetal derivative **1.50** was converted into the corresponding glycosyl trichloroacetimidate **1.53**.

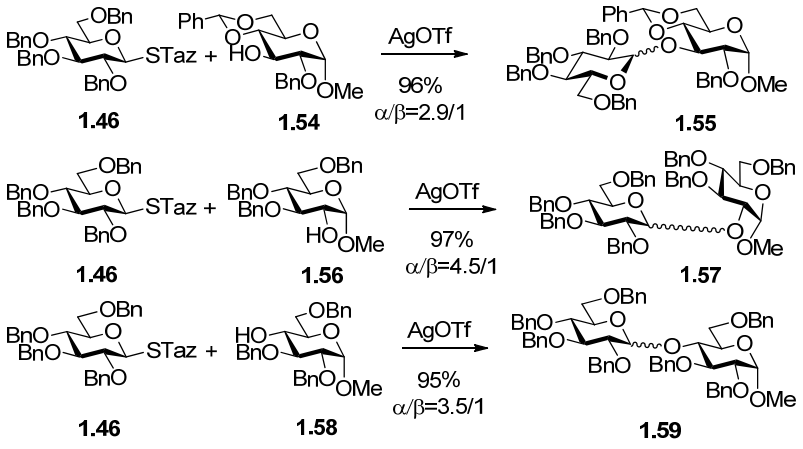
Scheme 1.12. Versatile synthesis of other glycosyl donors from STaz precursor **1.46**.[55]



Investigation into the properties of the STaz glycosyl donor brought about the development of a general methodology for 1,2-*cis* and 1,2-*trans* glycosylation. Early

studies by Descotes and co-workers involved the displacement of the STaz functionality of per-acetylated derivatives of the D-gluco series using MeOH in the presence of $HgNO_3$.[74] Further investigation into the glycosylation protocol toward disaccharide and oligosaccharide synthesis was reported by Demchenko et al. Activators such as AgOTf, MeOTf, NIS/TfOH, benzyl bromide, methyl iodide, $AgBF_4$ and $Cu(OTf)_2$ have been found to be suitable for efficient STaz activation for glycosylation.[27] STaz glycosyl donors were shown to react smoothly with common glycosyl acceptors. As shown in Scheme 1.13, STaz donor **1.46** was coupled with acceptors **1.54**, **1.56**, and **1.58** in the presence of AgOTf to afford disaccharides **1.55** in 96% yield (α/β = 2.9/1), **1.57** in 97% yield (α/β = 4.5/1), and **1.58** in 95% yield (α/β = 3.5/1), respectively. De Meo et al. reported application of the STaz approach to stereoselective α-sialylation.[62]

Scheme 1.13. Activation of STaz glycosyl donors.



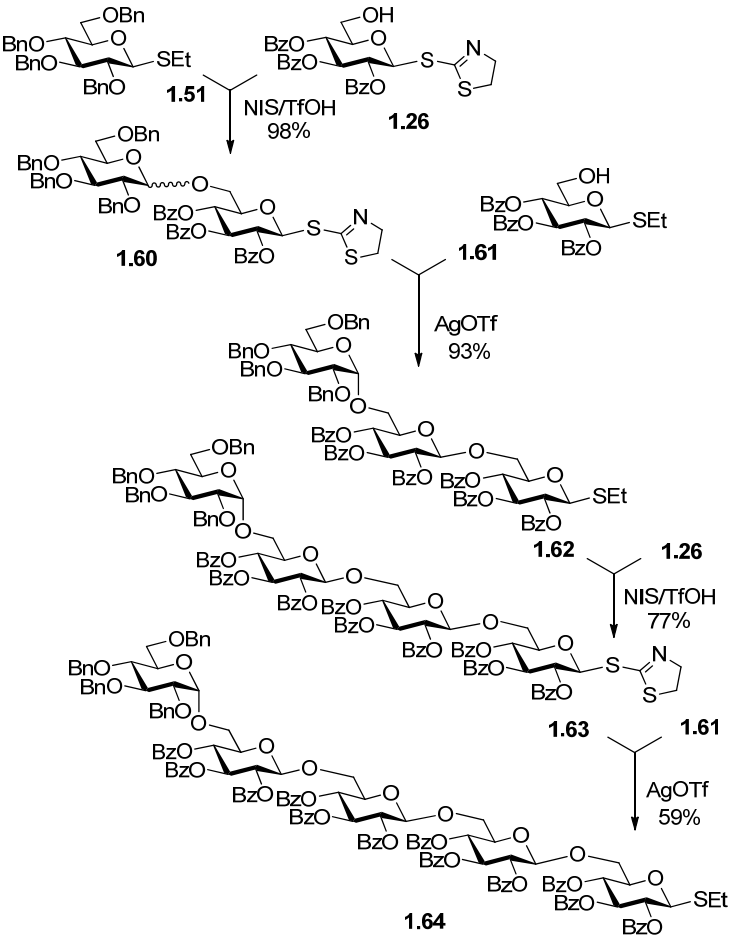
The applicability of the STaz method to selective glycosylation strategies for expeditious oligosaccharide synthesis was also evaluated.[27] As aforementioned, the STaz leaving group remains inert in the presence of NIS in combination with *catalytic* amount

of TfOH, which are common conditions for alkyl/aryl thioglycoside activation. This finding led to the development of a promising combination of orthogonal leaving groups, wherein STaz is activated selectively with AgOTf, whereas ethyl thioglycoside is activated with NIS and catalytic amount of TfOH.[27] This concept was applied to the synthesis of pentasaccharide **1.64**, as depicted in Scheme 1.14.[76] The thioglycoside donor **1.51** was first activated over the STaz acceptor **1.26** in the presence of NIS/cat. TfOH. The resulting disaccharide **1.60**, isolated in 98% yield, was in turn activated over thioglycoside acceptor **1.61** with AgOTf to give trisaccharide **1.62** in 93% yield. The sequence was then reiterated as follows. Thioglycoside donor **1.62** was activated over STaz acceptor **1.26** in the presence of NIS/cat. TfOH. The resulting tetrasaccharide **1.63** was selectively activated over thioglycoside acceptor **1.61** in the presence of AgOTf to give pentasaccharide **1.64** in 59% yield. It should be noted that NIS and *stoichiometric* TfOH are capable of effective activation of the STaz leaving group.[27]

The selective activation methodology was further applied in a five-step synthesis of a hexasaccharide, wherein two classes of glycosyl thioimidates, STaz and SBox, were used as building blocks (Scheme 1.15).[77] First, the thiocyanate glycoside donor **1.65** was activated with $Cu(OTf)_2$ over STaz acceptor **1.26** in 89% yield. Subsequently, disaccharide **1.66** was coupled with SBox glycosyl donor **1.24** in the presence of benzyl bromide to achieve the trisaccharide **1.67** in 67% yield. The latter was coupled with fluoride acceptor **1.68** in the presence of MeOTf to produce tetrasaccharide **1.69** in 87% yield. Tetrasaccharide **1.69** was then reacted with SEt acceptor **1.70** in the presence of $AgClO_4/Cp_2ZrCl_2$ to afford the pentasaccharide **1.71** in 84% yield. Lastly, the coupling

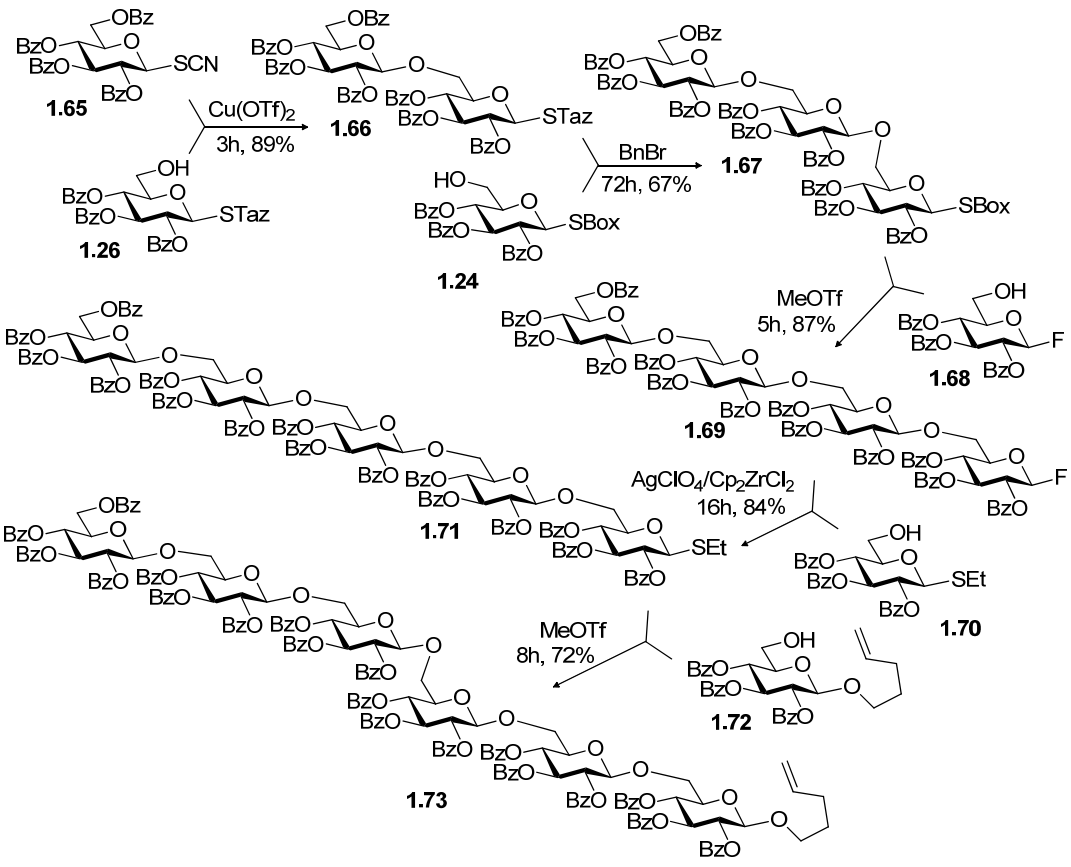
of *O*-pentenyl acceptor **1.72** with the pentasaccharide **1.71** using MeOTf as an activator produced hexasaccharide **1.73** in 72% yield.

Scheme 1.14. Orthogonality of the STaz and SEt glycosides. [76]



The selective activation principle was found beneficial for the synthesis of oligosaccharides of *Streptococcus pneumoniae* serotypes 6A, 6B, and 6C, as well as mimetics thereof for the development of synthetic vaccine components,[43,45,46] and for the synthesis of a tumor associated glycosphingolipid SSEA-3 analog.[47]

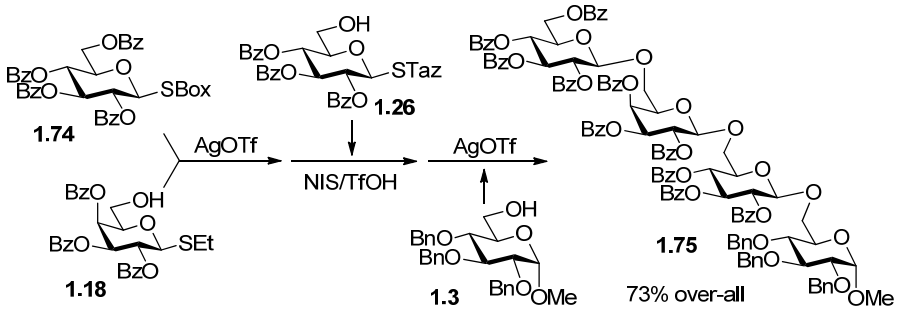
Scheme 1.15. Synthesis of hexasaccharide **1.73** via five-step sequential selective activation.[77]



One-pot glycosylation methods, whereby a few sequential glycosylation steps are executed in one reaction vessel, are of further advantage because there is no need for purification of the intermediates. Many different leaving groups and methods fit into this general concept[61] and thioimidate-based one-pot glycosylation procedures have also emerged.[55,78] For instance, SBox glycoside **1.74** was activated over SEt acceptor **1.18** with AgOTf (Scheme 1.16).[78] Upon completion of the coupling, NIS and catalytic amounts of TfOH were added to the reaction mixture along with the STaz glycosyl acceptor **1.26**. In the final step, glycosyl acceptor **1.3** and AgOTf were added in order to glycosidate the STaz moiety of the trisaccharide intermediate. Upon completion of the

one-pot sequence and purification by column chromatography, the tetrasaccharide **1.75** was isolated in 73% yield over three steps.[78]

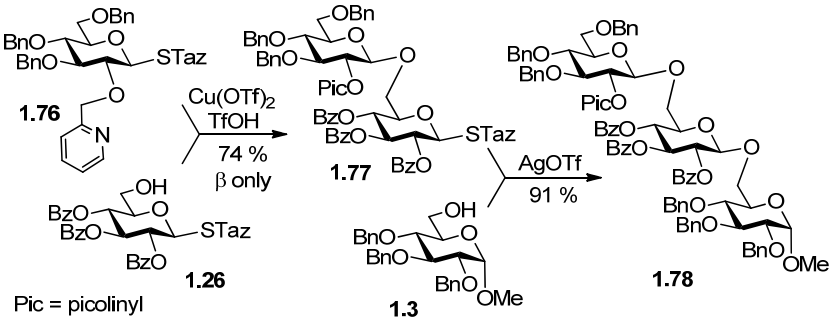
Scheme 1.16. Thioimidate-based one-pot oligosaccharide synthesis. [78]



Additionally, the armed and disarmed properties of differently protected STaz glycosides were evaluated in the context of chemoselective oligosaccharide synthesis. It was determined that STaz glycosides follow the general concept of the armed-disarmed[79] approach. The activated (benzylated) STaz derivatives could be promoted over electronically disarmed (acylated) STaz glycosyl acceptors in the presence of either AgOTf or $Cu(OTf)_2$.[33] The scope of this methodology was expanded by the invention of a novel arming participating group, which expanded chemoselective activation principle to the synthesis of *trans-trans* sequenced oligosaccharides.[33] Thus, it was observed that when 2-*O*-picolinyl protected glycosyl donor **1.76** was activated, the corresponding disaccharides were obtained with exclusive β-stereoselectivity. Extended mechanistic study demonstrated that these reactions proceed via the formal intermediacy of the α-pyridinium salt intermediate that can be stereoselectively opened to provide β-linked products. This finding gave rise to the development of a new strategy for oligosaccharide

synthesis termed "inverse armed-disarmed strategy."[33] When STaz donor **1.76** was activated over the disarmed acceptor **1.26**, disaccharide **1.77** was obtained in 74% yield with complete 1,2-*trans* stereoselectivity (Scheme 1.17). This is the inverse outcome in comparison to the classical armed-disarmed approach resulting in 1,2-*cis* bond formation in the first step (*vide supra*, see Scheme 1.8). Subsequent activation of **1.77** with AgOTf yielded the *trans*-*trans*-linked trisaccharide **1.78** in 91% yield.[80]

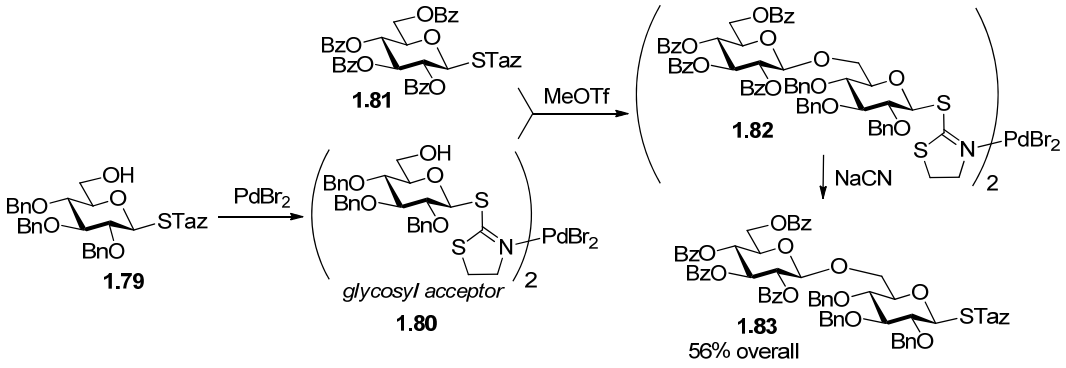
Scheme 1.17. Chemoselective activation of STaz glycosides.[33]



An interesting observation that STaz glycosides can participate in stable non-ionizing transition metal complexes led to the development of a temporary deactivation concept.[31] The outline of this strategy that involves the temporary disarming of a leaving group by external deactivation of its active sites is depicted in Scheme 1.18. Thus, the deactivation of the would-be-armed glycosyl acceptor **1.79** was accomplished by coordinating its STaz functionality into a stable, non-ionizing metal complex with $PdBr_2$ **1.80**. This allowed for the activation of the "free" STaz moiety of the disarmed glycosyl donor **1.81** over the temporarily deactivated (capped) STaz moiety of the complexed acceptor **1.80** in the presence of MeOTf. Upon glycosylation, disaccharide **1.82** was

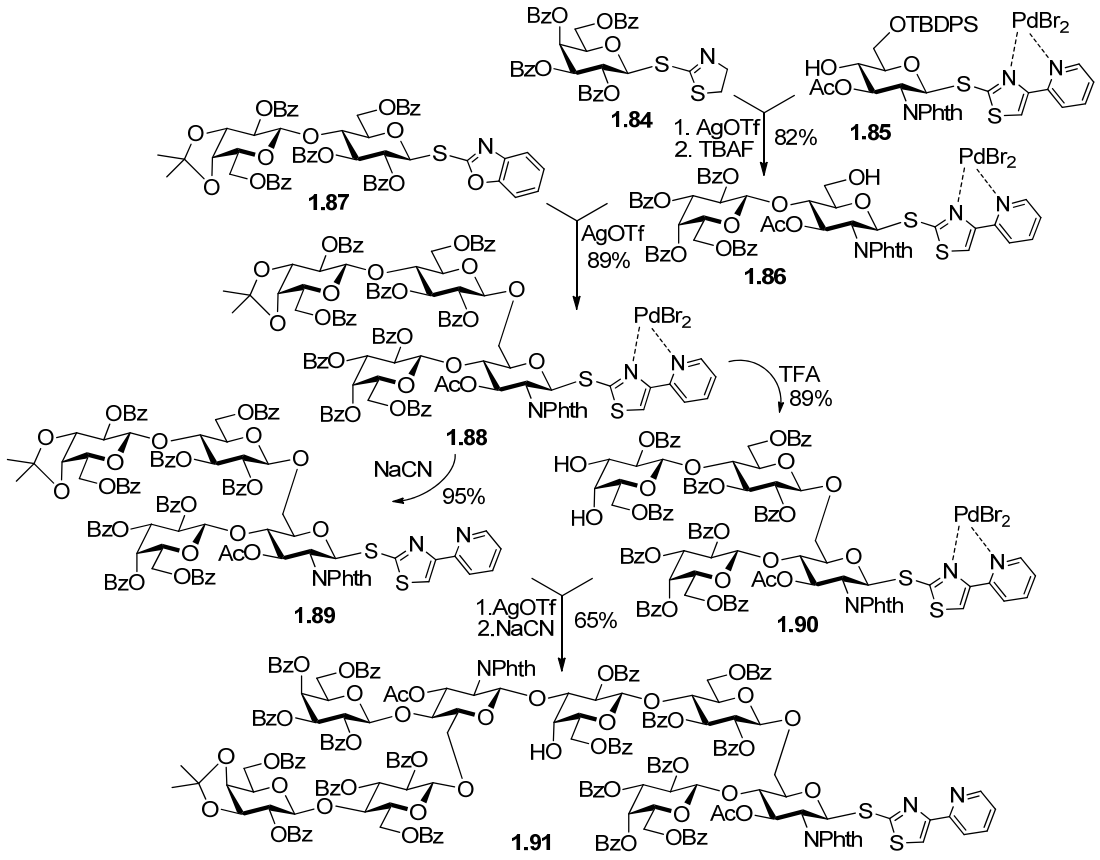
released from the complex by treatment with NaCN yielding a "free" disaccharide **1.83**, which could be used in subsequent transformations.

Scheme 1.18. Temporary deactivation concept.[31]



The temporary deactivation concept was further expanded by the development of a new generation of leaving groups capable of bidentate bonding, and therefore a more stable complexation mode with the deactivating reagent $PdBr_2$. This approach was applied to the synthesis of medicinally relevant oligosaccharides of *Streptococcus pneumoniae* serotype 14 (Scheme 1.19).[32] STaz donor **1.84** was reacted with the complexed 4-(pyridin-2-yl)thiazole-2-yl thioglycoside acceptor **1.85** in the presence of AgOTf followed by desilylation with TBAF to provide the disaccharide acceptor **1.86**. The latter was then coupled with SBox lactose donor **1.87** to afford the pneumococcal tetrasaccharide repeating unit **1.88**. For the subsequent convergent elongation, one portion of tetrasaccharide **1.88** was treated with NaCN to afford thiazolyl donor **1.89**, whereas another portion of **1.88** was treated with 10% TFA to afford complexed glycosyl acceptor **1.90**. The coupling of **1.89** and **1.90** followed by decomplexation under the standard reaction conditions afforded octasaccharide **1.91**.[32]

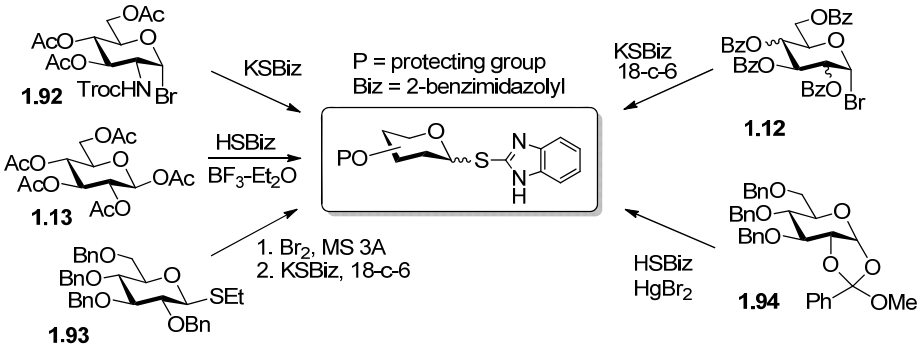
Scheme 1.19. Synthesis of *Streptococcus pneumonia* serotype 14.[32]



1.5 *S*-Benzimidazolyl (SBiz) derivatives

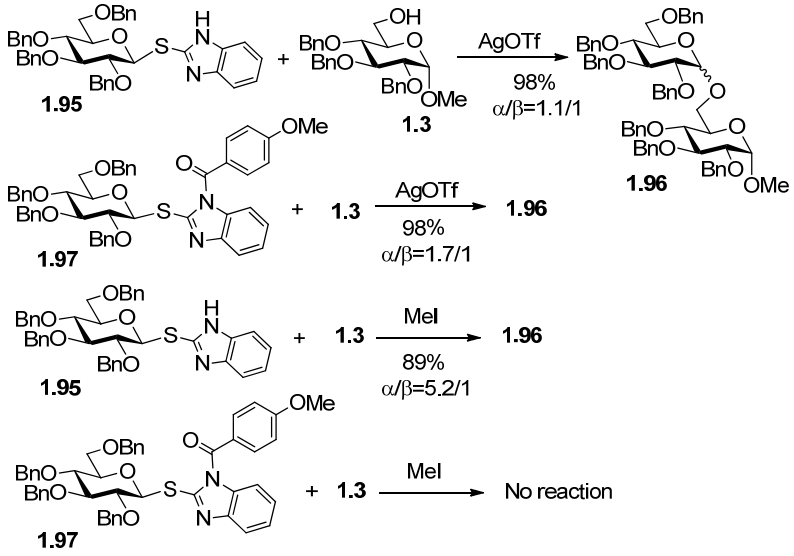
Per-acetylated SBiz glycosides were first reported by Zinner.[81] The SBiz moiety was then investigated as a leaving group for phosphorylation of unprotected glycosyl donors.[52,53] More recently the use of the SBiz moiety as a new platform for active-latent-like glycosylations was reported.[41] For this study, the synthesis SBiz glycosyl donors of the D-gluco and D-galacto series **1.12**, as well as the 2-amino-2-deoxy-D-gluco series **1.92** was accomplished from the corresponding anomeric bromides and potassium salt of HSBiz (KSBiz). The synthesis of SBiz building blocks from the anomeric acetate **1.13**, thioglycoside **1.93**, and 1,2-orthoester **1.94** were also reported (Scheme 1.20).[41]

Scheme 1.20. Synthesis of SBiz glycosides.



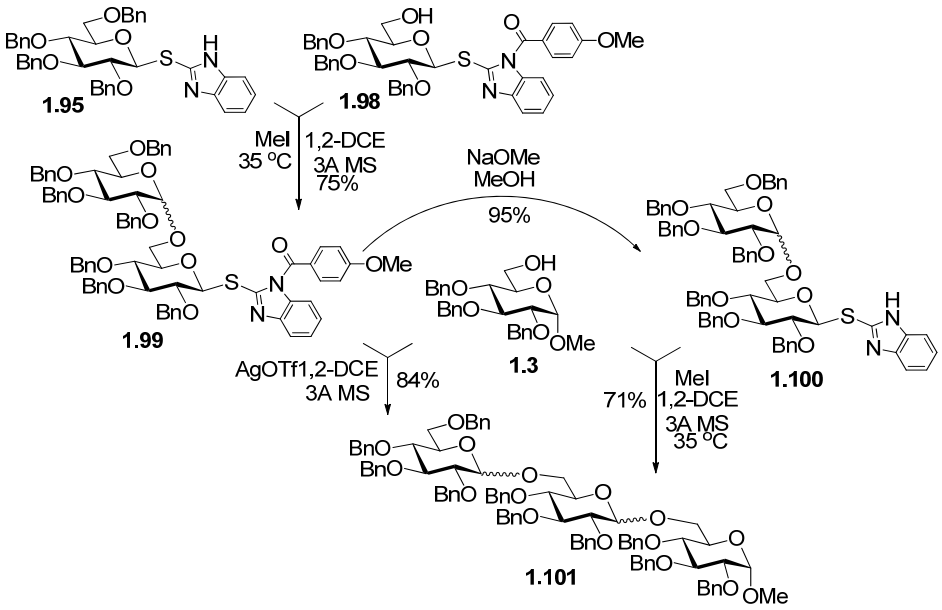
It was determined that activation of the SBiz leaving group can be readily achieved with the use of AgOTf, $Cu(OTf)_2$, and DMTST. For example, the SBiz glycosyl donor **1.95** was coupled with glycosyl acceptor **1.3** in the presence of AgOTf to produce disaccharide **1.96** in 98% yield (Scheme 1.21). Similarly, the activation of the *N*-anisoylated derivative of SBiz (SBizAn) **1.97**, obtained by simple acylation of **1.95**, could be also achieved with AgOTf. Thus, disaccharide **1.96** was obtained in 98% yield. Alkylating reagents, such as methyl iodide, benzyl bromide and allyl bromide are also able to promote SBiz leaving group departure (Scheme 1.21). For instance, the reaction between SBiz glycosyl donor **1.95** and acceptor **1.3** in the presence of methyl iodide produced disaccharide **1.96** in 89% yield. Further investigation of the alkylation activation pathway led to the discovery that when the SBiz moiety is *N*-anisoylated, its reactivity in the presence of methyl iodide was essentially turned off. As an example, in the attempt to react SBiz donor **1.97** with acceptor **1.3** using methyl iodide, no product **1.96** was found.

Scheme 1.21. Comparison of reactivity between SBiz glycoside **1.95** and its *N*-anisoylated counterpart **1.97**.[41]



This differential reactivity of the SBiz vs. SBizAn moieties enabled active-latent-like oligosaccharide synthesis, a strategy pioneered by Roy et al.[82,83] In ordinance with this methodology, the active SBiz donor **1.95** was glycosidated with the latent SBizAn acceptor **1.98** in the presence of methyl iodide to afford disaccharide **1.99** in 75% yield. After subsequent deprotection of the anisoyl group, using NaOMe, the resulting active disaccharide **1.100** was coupled with acceptor **1.3**, methyl iodide promoted, in 71% yield. Since both SBiz and SBizAn donors are activated smoothly in the presence of AgOTf, further activation of the SBizAn disaccharide **1.99** can be also conducted to afford trisaccharide **1.101** directly. An extended mechanistic study led to a conclusion that the deactivation effect of *N*-anisoyl moiety in **1.98** is an electronic effect similar to that described for the classical disarming effect in glycosylation.[79] Herein, the disarming is achieved by acylation of the leaving group, not by introducing the neighboring acyl substituents in the sugar moiety.

Scheme 1.22. Selective activation of the SBiz over SBizAn moieties.



1.6 Conclusion

Glycosyl thioimidates represent a broad class of leaving groups used in carbohydrate syntheses. While the discussion of these compounds was very limited, it should be noted that generalization of synthesis, reactivity and application should be avoided. Thioimidates can be prepared from a broad range of precursors including acetates, halides, anhydrosugars, hemiacetals, orthoesters, thioglycosides. Single step activation of thioimidates for glycosylation is typically a simple and fast process that leads to disaccharides in very high yields and often with superior stereoselectivities. Due to the polyfunctional character of the thioimidoyl leaving group, the activation can be achieved via a variety of modes such as with AgOTf, $Cu(OTf)_2$, NIS/TfOH, TfOH, MeOTf, $Bi(OTf)_3$, $AgBF_4$ and with alkylating reagents such as benzyl bromide, methyl iodide and allyl bromide. This ultimately allows for fine tuning of the activation conditions. The high stability of glycosyl thioimidates compared with other glycosyl

donors permits their use for the temporary protection of the anomeric center of the glycosyl acceptor. Consequently, thioimidates fit into many existing strategies for oligosaccharide assembly and conceptually new approaches and methods can be develops with them.

1.7 References

(1) Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Bertozzi, C. R.; Stanley, P.; Hart, G. W.; Etzler, M. E.: *Essentials of Glycobiology*; Second ed.; CSH Laboratory Press: New York, 2009.

(2) Cipolla, L.; Arajo, A. C.; Bini, D.; Gabrielli, L.; Russo, L.; Shaikh, N.: Discovery and design of carbohydrate-based therapeutics. *Expert Opin. Drug Discovery* **2010**, *5*, 721-737.

(3) Seeberger, P. H.; Werz, D. B.: Synthesis and medical applications of oligosaccharides. *Nature* **2007**, *446*, 1046-1051.

(4) *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

(5) Mydock, L. K.; Demchenko, A. V.: Mechanism of chemical O-glycosylation: from early studies to recent discoveries. *Org. Biomol. Chem.* **2010**, *8*, 497-510.

(6) Goodman, L.: Neighboring-group participation in sugars. *Adv. Carbohydr. Chem. Biochem.* **1967**, *22*, 109-175.

(7) Demchenko, A. V.: Stereoselective chemical 1,2-cis O-glycosylation: from "Sugar Ray" to modern techniques of the 21st century. *Synlett* **2003**, 1225-1240.

(8) Demchenko, A. V.: 1,2-cis O-Glycosylation: methods, strategies, principles. *Curr. Org. Chem.* **2003**, *7*, 35-79.

(9) Fischer, E.: Über die Glucoside der Alkohole. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2400-2412.

(10) Koenigs, W.; Knorr, E.: Über einige Derivate des Traubenzuckers und der Galactose. *Ber. Deutsch. Chem. Ges.* **1901**, *34*, 957-981.

(11) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N.: A potentially versatile synthesis of glycosides. *Carbohydr. Res.* **1973**, *27*, 55-61.

(12) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P.: A mild and general method for the synthesis of O-glycosides. *J. Am. Chem. Soc.* **1983**, *105*, 2430-2434.

(13) Garegg, P. J.; Henrichson, C.; Norberg, T.: A reinvestigation of glycosidation reactions using 1-thioglycosides as glycosyl donors and thiophilic cations as promoters. *Carbohydr. Res.* **1983**, *116*, 162-165.

(14) Oscarson, S.: General synthetic methods: Reactions at the anomeric center: S-glycosylation. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin - Heidelberg - New York, 2001; Vol. 1; pp 643-671.

(15) Bochkov, A. F.; Kochetkov, N. K.: A new approach for the synthesis of oligosaccharides. *Carbohydr. Res.* **1975**, *39*, 355-357.

(16) Pougny, J. R.; Jacquinet, J. C.; Nassr, M.; Duchet, D.; Milat, M. L.; Sinay, P.: A novel synthesis of 1,2-cis-disaccharides. *J. Am. Chem. Soc.* **1977**, *99*, 6762-6763.

(17) Schmidt, R. R.; Michel, J.: Facile synthesis of α- and β-O-glycosyl imidates; Preparation of glycosides and disaccharides. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731-732.

(18) Mukaiyama, T.; Nakatsuka, T.; Shoda, S. I.: An efficient glucosylation of alcohol using 1-thioglucoside derivative. *Chem. Lett.* **1979**, 487-490.

(19) Hanessian, S.; Bacquet, C.; Lehong, N.: Chemistry of the glycosidic linkage. Exceptionally fast and efficient formation of glycosides by remote activation. *Carbohydr. Res.* **1980**, *80*, c17-c22.

(20) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.: Asymmetric total synthesis of erythromycin. 3. Total synthesis of erythromycin. *J. Am. Chem. Soc.* **1981**, *103*, 3215-3217.

(21) Mukaiyama, T.; Murai, Y.; Shoda, S.-i.: An efficient method for glucosylation of hydroxy compounds using glucopyranosyl fluoride. *Chem. Lett.* **1981**, 431-432.

(22) Zhu, X.; Schmidt, R. R.: Glycoside synthesis from 1-oxygen-substituted glycosyl imidates. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 143-185.

(23) Zhong, W.; Boons, G.-J.: Glycoside synthesis from 1-sulfur/selenium-substituted derivatives: thioglycosides in oligosaccharide synthesis. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 261-303.

(24) Shoda, S.-i.: Glycoside synthesis from anomeric halides: glycosyl fluorides. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 29-59.

(25) Pornsuriyasak, P.; Kamat, M. N.; Demchenko, A. V.: Glycosyl thioimidates as versatile glycosyl donors for stereoselective glycosylation and convergent oligosaccharide synthesis. *ACS Symp. Ser.* **2007**, *960*, 165-189.

(26) Szeja, W.; Grynkiewicz, G.: Xanthates, thioimidates and other thio derivatives. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinhein, Germany, 2008; pp 329-361.

(27) Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N.: Potent, versatile, and stable: thiazolyl thioglycosides as glycosyl donors. *Angew. Chem. Int. Ed.* **2004**, *43*, 3069-3072.

(28) Demchenko, A. V.; Malysheva, N. N.; De Meo, C.: S-Benzoxazolyl (SBox) glycosides as novel, versatile glycosyl donors for stereoselective 1,2-cis glycosylation. *Org. Lett.* **2003**, *5*, 455-458.

(29) Demchenko, A. V.: Strategic approach to the chemical synthesis of oligosaccharides. *Lett. Org. Chem.* **2005**, *2*, 580-589.

(30) Smoot, J. T.; Demchenko, A. V.: Oligosaccharide synthesis: from conventional methods to modern expeditious strategies. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 161-250.

(31) Pornsuriyasak, P.; Gangadharmath, U. B.; Rath, N. P.; Demchenko, A. V.: A novel strategy for oligosaccharide synthesis via temporarily deactivated S-thiazolyl glycosides as glycosyl acceptors. *Org. Lett.* **2004**, *6*, 4515-4518.

(32) Pornsuriyasak, P.; Rath, N. P.; Demchenko, A. V.: 4-(Pyridin-2-yl)thiazol-2-yl thioglycosides as bidentate ligands for oligosaccharide synthesis via temporary deactivation. *Chem. Commun.* **2008**, 5633-5635.

(33) Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V.: Development of an arming participating group for stereoselective glycosylation and chemoselective oligosaccharide synthesis. *Angew. Chem. Int. Ed.* **2005**, *44*, 7123-7126.

(34) Pornsuriyasak, P.; Ranade, S. C.; Li, A.; Parlato, M. C.; Sims, C. R.; Shulga, O. V.; Stine, K. J.; Demchenko, A. V.: STICS: surface-tethered iterative carbohydrate synthesis. *Chem. Commun.* **2009**, 1834-1836.

(35) Kaeothip, S.; Pornsuriyasak, P.; Rath, N. P.; Demchenko, A. V.: Unexpected orthogonality of S-benzoxazolyl and S-thiazolinyl derivatives: application to expeditious oligosaccharide assembly. *Org. Lett.* **2009**, *11*, 799-802.

(36) Kamat, M. N.; Demchenko, A. V.: Revisiting the armed-disarmed concept rationale: chemoselective activation of the S-benzoxazolyl glycosides in oligosaccharide synthesis. *Org. Lett.* **2005**, *7*, 3215-3218.

(37) Mydock, L. K.; Demchenko, A. V.: Superarming the S-benzoxazolyl glycosyl donors by simple 2-O-benzoyl-3,4,6-tri-O-benzyl protection. *Org. Lett.* **2008**, *10*, 2103-2106.

(38) Mydock, L. K.; Demchenko, A. V.: Application of the superarmed glycosyl donor to chemoselective oligosaccharide synthesis. *Org. Lett.* **2008**, *10*, 2107-2110.

(39) Kamkhachorn, T.; Parameswar, A. R.; Demchenko, A. V.: Comparison of the armed/disarmed building blocks of the D-gluco and D-glucosamino series in the

context of chemoselective oligosaccharide synthesis. *Org. Lett.* **2010**, *12* 3078-3081.

(40) Kamat, M. N.; Rath, N. P.; Demchenko, A. V.: Versatile synthesis and mechanism of activation of S-benzoxazolyl glycosides. *J. Org. Chem.* **2007**, *72*, 6938-6946.

(41) Hasty, S. J.; Kleine, M. A.; Demchenko, A. V.: S-Benzimidazolyl glycosides as a platform for oligosaccharide synthesis by an active-latent strategy *Angew. Chem. Int. Ed.* **2011**, *50*, 4197-4201.

(42) Park, S.; Parameswar, A. R.; Demchenko, A. V.; Nahm, M. H.: Identification of a simple chemical structure associated with protective human antibodies against multiple pneumococcal serogroups. *Infect. Immun.* **2009**, *77*, 3374-3379.

(43) Parameswar, A. R.; Park, I. H.; Saksena, R.; Kovac, P.; Nahm, M. H.; Demchenko, A. V.: Synthesis, conjugation, and immunological evaluation of the serogroup 6 pneumococcal oligosaccharides. *Chembiochem : a European journal of chemical biology* **2009**, *10*, 2893-2899.

(44) Shulga, O. V.; Zhou, D.; Demchenko, A. V.; Stine, K. J.: Detection of free prostate specific antigen (fPSA) on a nanoporous gold platform. *The Analyst* **2008**, *133*, 319-322.

(45) Parameswar, A. R.; Hasty, S. J.; Demchenko, A. V.: Synthesis of spacer-containing analogs of serogroup 6 pneumococcal oligosaccharides. *Carbohydr. Res.* **2008**, *343*, 1707-1717.

(46) Parameswar, A. R.; Pornsuriyasak, P.; Lubanowski, N. A.; Demchenko, A. V.: Efficient stereoselective synthesis of oligosaccharides of *Streptococcus*

pneumoniae serotypes 6A and 6B containing multiple 1,2-cis glycosidic linkages. *Tetrahedron* **2007**, *63*, 10083-10091.

(47) Pornsuriyasak, P.; Demchenko, A. V.: Synthesis of cancer-associated glycoantigens: stage-specific embryonic antigen 3 (SSEA-3). *Carbohydr. Res.* **2006**, *341*, 1458-1466

(48) Zinner, H.; Peseke, K.: Benzazoles. XIX. Benzothiazolethione glycosides. *Chem. Ber.* **1965**, *98*, 3508-3514.

(49) Bogusiak, J.; Szeja, W.: An efficient synthesis of benzothiazole derivatives under phase-transfer conditions. *Chem. Lett.* **1988**, 1975-1976.

(50) Abdel-Rahman, A. A. H.; El Ashry, E. S. H.; Schmidt, R. R.: Efficient intramolecular b-mannoside formation using m-xylylene and isophtaloyl derivatives as rigid spacer. *Carbohydr. Res.* **2002**, *337*, 195-206.

(51) Bogusiak, J.: 2-benzothiazolyl 1-thiofuranosides - synthesis and application. *Lett. Org. Chem.* **2005**, *2*, 271-273.

(52) Ferrieres, V.; Blanchard, S.; Fischer, D.; Plusquellec, D.: A novel synthesis of D-galactofuranosyl, D-glucofuranosyl and D-mannofuranosyl 1-phosphates based on remote activation of new and free hexofuranosyl donors. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3515-3518.

(53) Euzen, R.; Ferrieres, V.; Plusquellec, D.: General one-step synthesis of free hexofuranosyl 1-phosphates using unprotected 1-thioimidoyl hexofuranosides. *J. Org. Chem.* **2005**, *70*, 847-855.

(54) Khodair, A. I.; Al-Masoudi, N. A.; Gesson, J. P.: A new approach to the synthesis of benzothiazole, benzoxazole, and pyridine nucleosides as potential antitumor agents. *Nucleosides, Nucleotides & Nucleic Acids* **2003**, *22*, 2061-2076.

(55) Kaeothip, S.; Pornsuriyasak, P.; Demchenko, A. V.: Silver(I) tetrafluoroborate as a potent promoter for chemical glycosylation. *Tetrahedron Lett.* **2008**, *49*, 1542-1545.

(56) Gama, Y.; Yasumoto, M.: A highly stereoselective synthesis of a-glucosides from 1-thioglucoside derivative under high pressure. *Chem. Lett.* **1993**, *2*, 319-322.

(57) Zinner, H.; Pfeifer, M.: Benzoxazoles. XVIII. Glycosides of benzoxazolethione. *Ber.* **1963**, *96*, 432-437.

(58) Zinner, H.; Peseke, K.: Benzoxazoles. XX. Reaction of benzoxazolethione salts and tetra-O-acetyl-a-D-glucopyranosyl bromide. *Chem. Ber.* **1965**, *98*, 3515-3519.

(59) Demchenko, A. V.; Kamat, M. N.; De Meo, C.: S-Benzoxazolyl (SBox) glycosides in oligosaccharide synthesis: novel glycosylation approach to the synthesis of β-D-glucosides, β-D-galactosides, and α-D-mannosides. *Synlett* **2003**, 1287-1290.

(60) De Meo, C.; Kamat, M. N.; Demchenko, A. V.: Remote participation-assisted synthesis of β-mannosides. *Eur. J. Org. Chem.* **2005**, 706-711.

(61) Parameswar, A. R.; Demchenko, A. V.: One-pot oligosaccharide synthesis. In *Progress in the synthesis of complex carbohydrate chains of plant and microbial polysaccharides*; Nifantiev, N. E., Ed.; Transworld Res. Network: Kerala, 2009; pp 463-488.

(62) De Meo, C.; Parker, O.: Thioimidoyl approach to the synthesis of α-sialosides. *Tetrahedron: Asymmetry* **2005**, *16*, 303-307.

(63) Wang, C. C.; Lee, J. C.; Luo, S. Y.; Kulkarni, S. S.; Huang, Y. W.; Lee, C. C.; Chang, K. L.; Hung, S. C.: Regioselective one-pot protection of carbohydrates. *Nature* **2007**, *446*, 896-899.

(64) Ranade, S. C.; Kaeothip, S.; Demchenko, A. V.: Glycosyl alkoxythioimidates as complementary building blocks for chemical glycosylation. *Org. Lett.* **2010**, *12*, 5628-5631.

(65) Kanie, O.; Ito, Y.; Ogawa, T.: Orthogonal glycosylation strategy in oligosaccharide synthesis. *J. Am. Chem. Soc.* **1994**, *116*, 12073-12074.

(66) Kaeothip, S.; Demchenko, A. V.: Expeditious oligosaccharide synthesis via selective and orthogonal activation. *Carbohydr. Res.* **2011**, *346*, 1371-1388.

(67) Fujikawa, K.; Vijaya Ganesh, N.; Tan, Y. H.; Stine, K. J.; Demchenko, A. V.: Reverse orthogonal approach to oligosaccharide synthesis. *Chem. Commun.* **2011**, 10602-10604.

(68) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B.: "Armed" and "disarmed" n-pentenyl glycosides in saccharide couplings leading to oligosaccharides. *J. Am. Chem. Soc.* **1988**, *110*, 5583-5584.

(69) Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L.: Tuning glycoside reactivity: new tool for efficient oligosaccharides synthesis. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51-65.

(70) Crich, D.; Li, M.: Revisiting the armed-disarmed concept: The importance of anomeric configuration in the activation of S-benzoxazolyl glycosides. *Org. Lett.* **2007**, *9*, 4115-4118.

(71) 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.

(72) Bongat, A. F. G.; Kamat, M. N.; Demchenko, A. V.: Chemoselective synthesis of oligosaccharides of 2-deoxy-2-aminosugars. *J. Org. Chem.* **2007**, *72*, 1480-1483.

(73) Parlato, M. C.; Kamat, M. N.; Wang, H.; Stine, K. J.; Demchenko, A. V.: Application of glycosyl thioimidates in solid-phase oligosaccharide synthesis. *J. Org. Chem.* **2008**, *73*, 1716-1725.

(74) Cottier, L.; Descotes, G.; Kudelska, W.: Synthesis of saturated and unsaturated thioglycosides. *C. R. Acad. Sci. Ser. 2* **1992**, *314*, 657-660.

(75) Ramakrishnan, A.; Pornsuriyasak, P.; Demchenko, A. V.: Synthesis, glycosidation, and hydrolytic stability of novel glycosyl thioimidates. *J. Carbohydr. Chem.* **2005**, *24*, 649-663.

(76) Pornsuriyasak, P.; Demchenko, A. V.: S-Thiazolinyl (STaz) glycosides as versatile building blocks for convergent selective, chemoselective, and orthogonal oligosaccharide synthesis. *Chem. Eur. J.* **2006**, *12*, 6630-6646.

(77) Kaeothip, S.; Demchenko, A. V.: On orthogonal and selective activation of glycosyl thioimidates and thioglycosides: application to oligosaccharide assembly. *J. Org. Chem.* **2011**, *76*, 7388-7398.

(78) Pornsuriyasak, P.; Demchenko, A. V.: Glycosyl thioimidates in a highly convergent one-pot strategy for oligosaccharide synthesis. *Tetrahedron: Asymmetry* **2005**, *16*, 433-439.

(79) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H.: Armed/disarmed effects in glycosyl donors: rationalization and sidetracking. *J. Org. Chem.* **1990**, *55*, 6068-6070.

(80) Smoot, J. T.; Demchenko, A. V.: How the arming participating moieties can broaden the scope of chemoselective oligosaccharide synthesis by allowing the inverse armed-disarmed approach *J. Org. Chem.* **2008**, *73*, 8838-8850.

(81) Zinner, H.; Peseke, K.: Benzazoles. XXV. Glucosidation of benzimidazolethione. *J. Prakt. Chem.* **1969**, *3011*, 997-1012.

(82) Roy, R.; Andersson, F. O.; Letellier, M.: "Active" and "latent" thioglycosyl donors in oligosaccharide synthesis. Application to the synthesis of α-sialosides. *Tetrahedron Lett.* **1992**, *33*, 6053-6056.

(83) Cao, S.; Hernandez-Mateo, F.; Roy, R.: Scope and applications of "active and latent" thioglycosyl donors. Part 4. *J. Carbohydr. Chem.* **1998**, *17*, 609-631.

Chapter 2

S-Benzimidazolyl (SBiz) glycosides as a new platform for expeditious oligosaccharide synthesis via active-latent strategy

2.1 Introduction

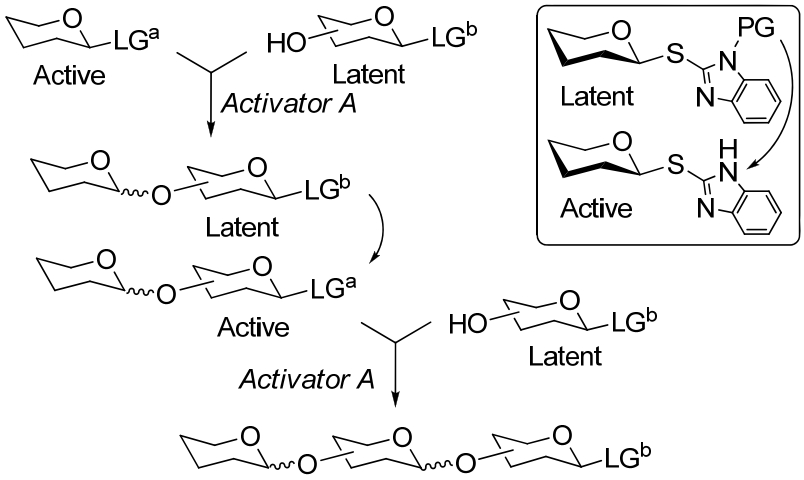
The involvement of complex carbohydrates in a wide variety of disease-related cellular processes has given this class of natural compounds tremendous appeal for their diagnostic and therapeutic potential.[1] While scientists have been able to successfully isolate certain classes of natural carbohydrates, the availability of pure natural isolates is still inadequate to address the challenges offered by modern glycosciences. As a consequence, chemical glycosylation has become a viable means to obtain both natural complex carbohydrates and unnatural analogs thereof.[2-4] Unfortunately, chemical synthesis of oligosaccharides of even moderate complexity still remains a considerable challenge, and many more complex structures are not available at all. Consequently, the development of efficient strategies for the oligosaccharide and glycoconjugates synthesis stands out as a demanding area of research.[5]

As a part of the on-going research effort in our laboratory to develop versatile methods for chemical glycosylation and expeditious oligosaccharide synthesis, we became interested in glycosyl thioimidates, glycosyl donors equipped with $SCR_1=NR_2$ leaving group. Among a variety of thioimidates studied by us and others,[6,7] *S*-benzoxazolyl (SBox)[8] and *S*-thiazolinyl (STaz)[9] moieties were found to be excellent building blocks for oligosaccharide synthesis. We determined that the SBox and STaz glycosides fit into existing progressive strategies for oligosaccharide synthesis, such as selective (including one-pot[10-12] and solid phase synthesis),[13-15] chemoselective (armed-disarmed),[16-18] and orthogonal[19-22] approaches. In addition, the glycosyl thioimidates led us to the development of conceptually new strategies for oligosaccharide synthesis: the inverse armed-disarmed strategy,[23,24] the temporary deactivation concept,[25,26] the *O*-2/*O*-5 cooperative effect (superarmed and

superdisarmed glycosyl donors),[17,27-29] coordination-assisted glycosylation,[30] and Surface-Tethered Iterative Carbohydrate Synthesis (STICS).[31]

At the core of the study presented here is the development of a new method for chemical glycosylation and expeditious oligosaccharide synthesis based on S-benzimidazolyl (SBiz) glycosides. The SBiz moiety was previously investigated as a leaving group for phosphorylation of unprotected glycosyl donors.[32,33] We envisaged that the SBiz moiety may be also compatible with a very attractive active-latent concept pioneered by Roy,[34] Fraser-Reid,[16] Boons[35] and more recently further advanced by Kim[36,37] and others.[38-40] According to this concept, an active (reactive) leaving group (LG_a) is selectively activated over its latent (unreactive) counterpart (LG_b, Scheme 2.1). Subsequently, the latent LG_b of the formed disaccharide is converted into an active LG_a.

Scheme 2.1. Outline of the active-latent strategy and the SBiz leaving group explored in this work.



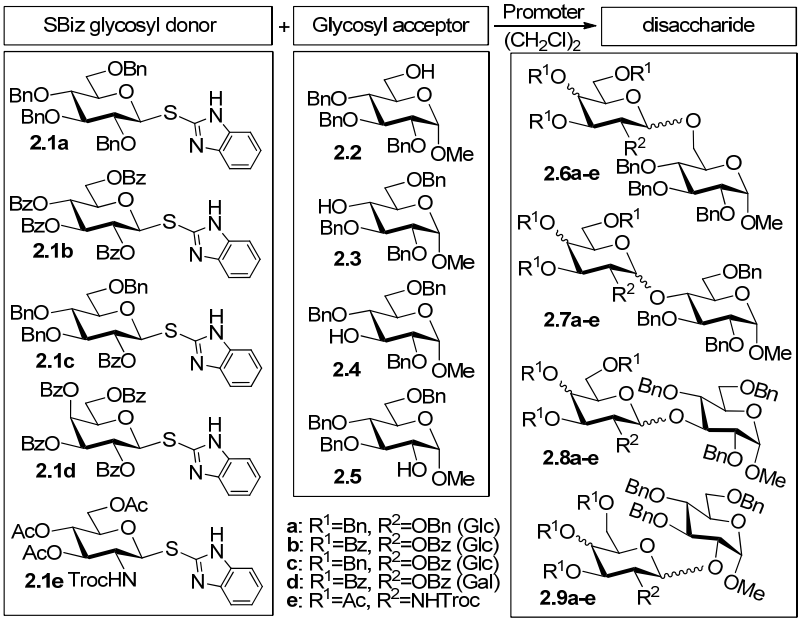
This modification does not involve substitution at the anomeric center as in the two-step activation strategy;[5] rather it is achieved by a modification of the leaving group,

usually at a remote position. We assumed that in case of the SBiz glycosides, deactivation of the leaving group could be achieved by placing an easily removable protecting group at the nitrogen atom of the imidazolium ring. The active SBiz leaving group can be then regenerated by simple deprotection as needed.

2.2 Results and Discussion

To pursue this concept we obtained a range of differently protected SBiz glucosides including per-benzylated **2.1a**, per-benzoylated **2.1b**, and derivative **2.1c** equipped with the superarming protecting group pattern.[28] We also obtained the SBiz donor of the D-galacto **2.1d** and 2-amino-2-deoxy-D-gluco series **2.1e**. With glycosyl donors **2.1a-e** in hand, we began evaluating their applicability to chemical glycosidation with standard glycosyl acceptors **2.2**-**2.5**.[41] Encouragingly, reaction of glycosyl donor **2.1a** with the primary glycosyl acceptor **2.2** in the presence of silver(I) triflate was completed in 15 min and provided the corresponding disaccharide **2.6a** in 98% yield (Table 2.1, Entry 1). Copper(II) triflate is a significantly milder promoter for thioimidates, and although a significantly lower reaction rate was observed (60 h), **2.6a** was isolated in an excellent yield of 93% (Entry 2). Subsequently, we demonstrated that the SBiz moiety can be efficiently activated under alkylation conditions at elevated temperature, similarly to that of STaz glycosides.[22] No significant difference between AllBr, BnBr, or MeI-promoted glycosidations of **2.1a** was detected, and **2.6a** was obtained in 84-90% yield (Entry 3). We noticed a significantly improved α-stereoselectivity (up to 5.3/1 with AllBr) in comparison to that of the metal-assisted glycosylations. Glycosylation of the secondary glycosyl acceptors **2.3-2.5** was also proven feasible in the presence of AgOTf, and the corresponding disaccharides **2.7a-2.9a** were obtained in 81-95% yield (Entries 4-6).

Table 2.1. Glycosidation of SBiz glycosyl donors **2.1a-e** with glycosyl acceptors **2.2-2.5**.



entry	donor + acceptor	Promoter[a]	time	Product	yield, α/β ratio
1	**2.1a** + **2.2**	AgOTf	15 min	**2.6a**	98%, 1.1/1
2	**2.1a** + **2.2**	$Cu(OTf)_2$	60 h	**2.6a**	93%, 1.3/1
3	**2.1a** + **2.2**	AllBr, BnBr, MeI (55 °C)[b]	12 h	**2.6a**	84-90%, 3.3-5.3/1
4	**2.1a** + **2.3**	AgOTf	15 min	**2.7a**	81%, 1.8/1
5	**2.1a** + **2.4**	AgOTf	15 min	**2.8a**	91%, 1.3/1
6	**2.1a** + **2.5**	AgOTf	15 min	**2.9a**	95%, 1.6/1
7	**2.1b** + **2.2**	AgOTf	2 h	**2.6b**	86%, β only
8	**2.1b** + **2.2**	$Cu(OTf)_2$	144 h	**2.6b**	83%, β only
9	**2.1b** + **2.2**	AllBr, BnBr, MeI (55 °C)	120 h	no reaction	
10	**2.1b** + **2.3**	AgOTf	45 min	**2.7b**	94%, β only
11	**2.1b** + **2.4**	AgOTf	2 h	**2.8b**	87%, β only
12	**2.1b** + **2.5**	AgOTf	2 h	**2.9b**	84%, β only
13	**2.1c** + **2.2**	AgOTf	<5 min	**2.6c**	98%, β only
14	**2.1c** + **2.2**	$Cu(OTf)_2$	2 h	**2.6c**	93%, β only
15	**2.1c** + **2.3**	AgOTf	<5 min	**2.7c**	84%, β only
16	**2.1c** + **2.4**	AgOTf	<5 min	**2.8c**	90%, β only
17	**2.1c** + **2.5**	AgOTf	<5 min	**2.9c**	88%, β only
18	**2.1d** + **2.2**	AgOTf	2 h	**2.6d**	97%, β only
19	**2.1d** + **2.3**	AgOTf	2 h	**2.7d**	94%, β only
20	**2.1d** + **2.4**	AgOTf	3 h	**2.8d**	89%, β only
21	**2.1d** + **2.5**	AgOTf	3.5 h	**2.9d**	89%, β only

22	**2.1e** + **2.2**	AgOTf	30 min	**2.6e**	94%, β only
23	**2.1e** + **2.3**	AgOTf	30 min	**2.7e**	92%, β only
24	**2.1e** + **2.4**	AgOTf	30 min	**2.8e**	86%, β only
25	**2.1e** + **2.5**	AgOTf	30 min	**2.9e**	92%, β only

[a] performed in the presence of molecular sieves 3 Å at rt, unless noted otherwise; [b] reaction at rt was much more sluggish

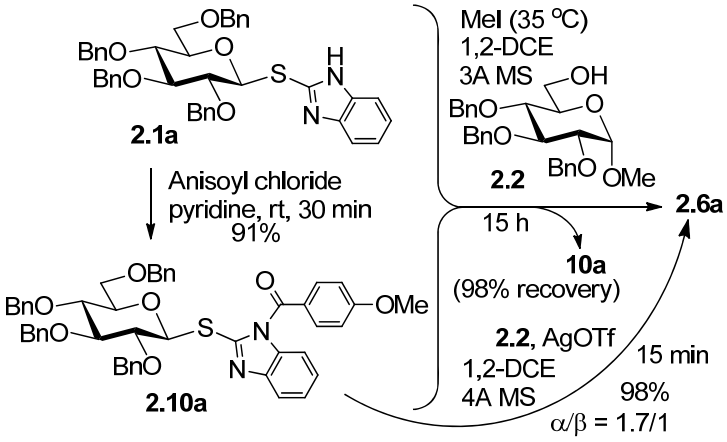
Having investigated the reactivity of per-benzylated (armed) glycosyl donor **2.1a**, we turned our attention to testing its per-benzoylated (disarmed) counterpart **2.1b**. As anticipated, the reactivity of **2.1b** was significantly lower than that of **2.1a**, and only AgOTf-promoted glycosidations were proven to be of preparative value. The desired disaccharides **2.6b-2.9b** were isolated in 84-94% yield (Entries 7, 10-12). Copper(II) triflate–promoted glycosidation was very slow (144 h, Entry 8) while alkyl halide-promoted reactions did not proceed at all (Entry 9). These results suggest that the SBiz glycosides can be applied in accordance with the classic armed-disarmed strategy.[42] In order to develop a more flexible route to the synthesis of 1,2-*trans* glycosides, we also investigated SBiz glycosyl donor **2.1c**, bearing the superarming protecting group pattern.[28] As expected, AgOTf-promoted glycosidation produced disaccharides **2.6c-2.9c** almost instantaneously in 84-98% yield (Entries 13, 15-17). Also in the presence of $Cu(OTf)_2$, the reaction rate was significantly higher than that observed with either the armed glycosyl donor **2.1a** or its disarmed counterpart **2.1b** (2 h, 93%, Entry 14).

In order to broaden the scope of this glycosylation investigation, we tested its applicability to the synthesis of D-galactosides and 2-amino-2-deoxyglucosides, highly important and abundant sugar series.[43-45] Glycosidation of the SBiz galactose donor **2.1d** with glycosyl acceptors **2.2-2.5** in the presence of AgOTf proceeded smoothly and the corresponding disaccharides **6d-9d** were obtained in 89-97% yield (Entries 18-21). Also glycosidation of *N*-(2,2,2-trichloroethoxy) carbamoyl (*N*-Troc)

protected glycosyl donor **1e** with acceptors **2.2-2.5** in the presence of AgOTf was successfully accomplished. The resulting disaccharides **2.6e-2.9e** were isolated in 86-94% yields (Entries 22-25).

Having investigated the applicability of the SBiz glycosides for chemical glycosylation, we next investigated the effects that *N*-substitution may have on the reactivity of the leaving group. For this purpose, we investigated a variety of *N*-acyl substituents (acetyl, haloacetyls, benzoyl, substituted benzoyls), and the highest yielding results were achieved with the *N*-anisoylated SBiz building block **2.10a** obtained from **2.1a** by reaction with anisoyl chloride in the presence of pyridine (Scheme 2.2). As projected, no product was formed in glycosidations of **2.10a** under alkylation conditions (up to 120 h at 55 ^{o}C).

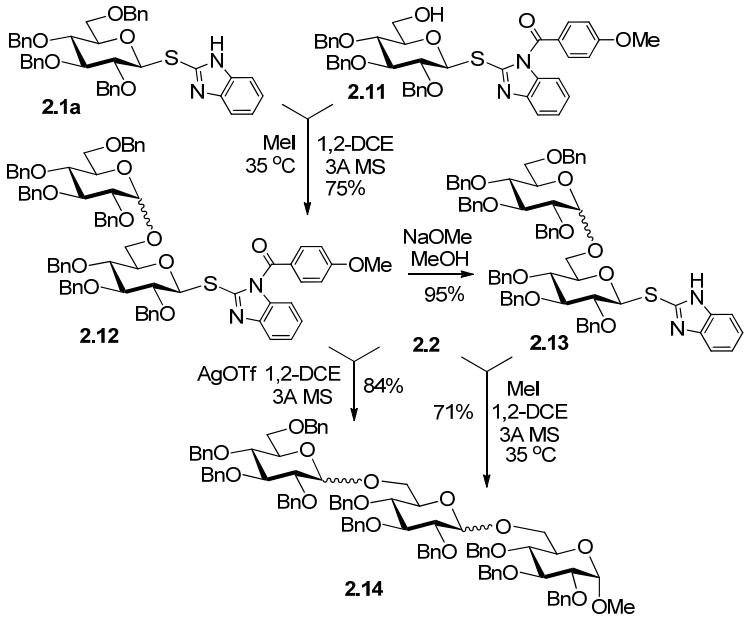
Scheme 2.2. Synthesis and glycosidation of *N*-anisoylated SBiz glycosyl donor **2.10a**; competition experiment with SBiz donor **2.1a**.



In addition, competitive glycosylation wherein two glycosyl donors (**2.1a** and **2.10a**) were allowed to compete for glycosyl acceptor **2.2** allowed differentiating the reactivities of SBiz and anisoylated SBiz leaving groups. Thus, the competition experiment in the presence of MeI allowed for nearly complete recovery of the

unreacted **2.10a** (98%), while only traces of **2.1a** (2%) were remaining. Less expectedly, AgOTf-promoted activation of the *N*-anisoylated glycosyl donor **2.10a** was as efficient as that of its SBiz counterpart **2.1a** and disaccharide **2.6a** was rapidly produced (15 min) in 98% yield.

Scheme 2.3. Activation of SBiz donor **2.1a** over *N*-anisoylated SBiz acceptor **2.11** in the active-latent fashion.

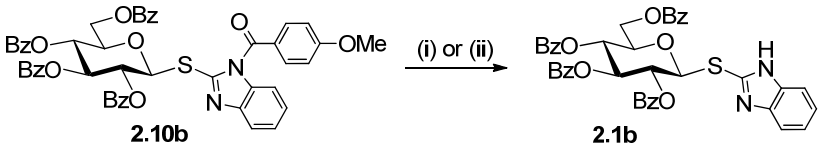


With these promising results, we next investigated whether SBiz donor **2.1a** could be selectively activated in the presence of the *N*-anisoylated SBiz acceptor: this represents the key step for executing the SBiz-based active-latent concept. For this purpose we obtained glycosyl acceptor **2.11** (see experimental). Very encouragingly, MeI-promoted glycosylation between building blocks **2.1a** and **2.11** produced the expected latent disaccharide **2.12** in 75% yield (α/β = 1/1.8, Scheme 2.3). After that, the *N*-anisoyl group was removed by the treatment with NaOMe in MeOH yielding the active disaccharide **2.13** which was subsequently activated with MeI to afford

trisaccharide **2.14** in 71% yield. This two-step SBiz activation sequence mimics the traditional active-latent concept.[5]

It should be noted that although the removal of *N*-anisoyl moiety in **2.12** with NaOMe/MeOH is suitable for the synthesis of benzylated building blocks, it would represent a hurdle if the application of the active-latent methodology were attempted with acylated compounds. To broaden the scope of this transformation, we investigated other reaction conditions that would not trigger concomitant *O*-deacylation. As depicted in Scheme 2.4, we discovered that *N*-anisoyl in *O*-benzoylated compound **2.10b** can be effectively removed in the presence of guanidine in MeOH or, alternatively, TBAF in THF. No competitive *O*-benzoyl group removal was detected under these reaction conditions and the desired SBiz donor **2.1b** was obtained quantitatively. In this context, we anticipate that other acyl groups, e.g., 2-(azidomethyl)benzoyl,[46] 3-(2′-benzyloxyphenyl)-3,3-dimethylpropanoate,[47] or (2-nitrophenyl)acetyl,[48] which can be reductively cleaved in the presence of conventional *O*-acyl substituents (benzoyl), are expected to be suitable for the purpose of the temporary *N*-acylation.

Scheme 2.4. Removal of *N*-anisoyl in the presence of *O*-benzoyl group.



2.10b **2.1b**

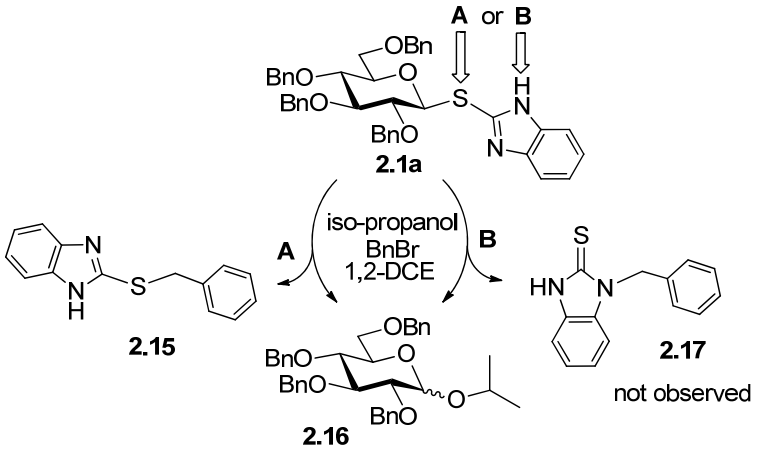
Conditions	Time	Yield of 2.1b
(i) 0.5 M Guanidine/MeOH (0.5 equiv.) in CH_2Cl_2/MeOH (9/1, v/v) at rt	5 min	Quant
(ii) 1 M TBAF/THF (2 equiv.) in THF at rt	3 h	Quant

Since the *N*-protected latent SBiz moiety can be activated with a stronger promoter (Scheme 2.2), we also pursued this pathway. AgOTf-promoted activation of latent disaccharide **2.12** lead to trisaccharide **2.14** in 84% yield (Scheme 2.3). By exploring this two-way activation approach we showed that the SBiz moiety serves as a suitable new platform for the active-latent like activations, but also allows for the direct activation of the latent *N*-acylated leaving group using a stronger promoter.

What remained unknown is why alkylating reagents are able to activate SBiz but not its *N*-anisoylated counterpart. Based on the anticipation that the SBiz is activated by the direct activation pathway A (Scheme 2.5) via the anomeric sulfur, as in *S*-alkyl/aryl[49] or SBox glycosides,[22,50] one possible explanation is the electronic effect. It is possible that upon *N*-anisoylation the sulfur atom in compound **2.10a** will become too weak a nucleophile to displace the halogen atom of the alkylating reagent. Alternatively, the activation of the SBiz may also take place via the nitrogen atom of the imidazole ring representing the remote activation pathway B, as in *S*-pyridyl[51,52] or STaz[22] derivatives. In this case, the effect of the *N*-anisoyl group is steric as it will block the N-activation site of the SBiz moiety. To differentiate between the two possible reaction pathways we set up a model experiment wherein SBiz donor **2.1a** reacted with isopropanol in the presence of BnBr (Scheme 2.5). Upon completion of the reaction, judged by the disappearance of **2.1a** and formation of **2.16** (TLC),[53] we separated and analyzed all components of the reaction mixture. 2-Benzylsulfanyl-1*H*-benzimidazole **2.15**[54,55] was isolated and its identity was proven by spectral and X-ray methods, whereas no trace of its *N*-benzylated counterpart **2.17**[56,57] was detected. The result of this study indicates that activation of SBiz under alkylation conditions takes place via the sulfur atom similarly to that found previously for SBox glycosides.[22,50] Therefore, we conclude that the deactivating effect of the *N*-anisoyl moiety in **2.10a** is

electronic. However, whether this effect is due to simple electron-withdrawal or distortion of the aromaticity of the imidazole ring is yet to be determined. What differs this disarming effect from the well-documented disarming effect in glycosylation[42] is that herein the disarming is achieved by acylation of the leaving group, not by introducing the neighboring acyl substituents in the sugar moiety.

Scheme 2.5. Direct pathway A vs. remote pathway B for SBiz activation.



2.3 Conclusion

In conclusion, we investigated *S*-benzimidazolyl (SBiz) anomeric moiety as a new leaving group that can be activated for chemical glycosylation under a variety of conditions including metal-assisted and alkylation pathways. Differentiation between the two possible reaction pathways for the SBiz moiety activation was achieved via an extended mechanistic study. We also demonstrated that the application of the substituted SBiz moiety allows executing rapid oligosaccharide assembly via active/latent and armed/disarmed-like concepts.

2.4 Experimental Section

General remarks

Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). 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 ^{o}C. CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled from CaH_2 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 CaH_2 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. DOWEX MONOSPHERE 650C (H) was washed three times with MeOH and stored under MeOH. Optical rotations were measured using a 'Jasco P-1020' polarimeter. ^{1}H-NMR. spectra were recorded in $CDCl_3$ at 300 MHz, ^{13}C-NMR spectra were recorded in $CDCl_3$ at 75 MHz (Bruker Avance) unless otherwise noted. HRMS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer.

Synthesis of 2-benzimidazolethione, potassium salt ("KSBiz").

Anhydrous K_2CO_3 (0.93 g, 6.7 mmol) was added to a stirred solution of 2-mercaptobenzoxazole (1.0 g, 6.7 mmol) in dry acetone (7 mL). The reaction mixture was refluxed for 3 h at 60 ^{o}C, acetone was then evaporated off and the residue was dried *in vacuo*.

Synthesis of glycosyl donors

Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (2.1a). The solution of ethyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside[58] (2.19 g, 3.75 mmol) and activated molecular sieves (3 Å, 1.88 g) in CH_2Cl_2 (56 mL) was stirred under argon for 1 h at rt. Freshly prepared solution of Br_2 in CH_2Cl_2 (36 mL, 1/165, v/v) was then added and the reaction mixture was stirred for 5 min at rt. After that, the solid was filtered-off and the filtrate was concentrated *in vacuo* at rt. Crude residue was dissolved in dry MeCN (80 mL) and KSBiz (1.76 g, 9.36 mmol) and 18-crown-6 (0.20 g, 0.75 mmol) was added. The resulting reaction mixture was stirred under argon for 16 h at rt. After that, the solid was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (200 mL) and washed successively with 10% aq. NaOH (20 mL), water (3 x 20 mL). The organic layer was separated, dried with $MgSO_4$, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford title compound (1.85 g, 73 %) as an off-white foam. Analytical data for **2.1a**: R_f = 0.54 (ethyl acetate/toluene, 3/17, v/v); $[\alpha]_D^{28}$ -28.7 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.45 (dd, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 3.58-3.82 (m, 5H, H-3, 4, 5, 6a, 6b), 4.57 (dd, 2H, ^2J = 11.5 Hz, CH_2Ph), 4.64 (dd, 2H, ^2J = 11.1 Hz, CH_2Ph), 4.76 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.76 (dd, 2H, ^2J = 10.0 Hz, CH_2Ph), 4.82 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 6.38 – 7.38 (m, 25H, aromatic, NH) ppm; ^{13}C-n.m.r.: δ, 68.8, 74.0, 75.3, 75.8, 76.0, 77.2, 78.3, 80.9, 84.1, 86.0, 122.5, 127.9 (x3), 128.1 (x4), 128.4, 128.5 (x3), 128.6 (x10), 128.9 (x3), 129.0, 137.4, 137.5, 137.7, 138.1, 146.5 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{41}H_{41}N_2O_5S$ 673.2736, found 673.2732.

Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (2.1b) was obtained from 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide[59] in 56% as an off-white foam as described in the synthesis of compound **2.1a**. Analytical data for **2.1b**: R_f = 0.47 (ethyl acetate/toluene, 3/17, v/v); $[\alpha]_D^{27}$ +15.7 (c = 1, $CHCl_3$); ^{1}H-n.m.r.: δ, 4.21 (m, 1H, $J_{5,6a}$ = 4.7 Hz, $J_{5,6b}$ = 2.6 Hz, H-5), 4.43 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.85 (dd, 1H, H-6b), 5.45 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 5.60 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 5.71 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.96 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 7.12-8.08 (m, 24H, aromatic), 10.28 (s, 1H, NH) ppm; ^{13}C-n.m.r.: δ, 62.6, 69.0, 71.0, 73.9, 83.9, 119.6, 123.7, 128.4 , 128.5 (x3), 128.6 (x3), 128.7 (x6), 128.8 (x3), 129.2, 129.5, 129.9 (x2), 130.1 (x3), 130.2 (x2), 133.6, 133.7, 133.8, 133.9, 144.0, 165.3, 165.6, 165.8, 167.1 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{41}H_{33}N_2O_9S$ 729.1907, found 729.1919.

Benzimidazol-2-yl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2.1c) was obtained by a procedure similar to those previously reported.[23,60,61] A mixture of 3,4,6-tri-*O*-benzyl-1,2-*O*-methoxybenzylidene-α-D-glucopyranose[62] (1.2 g, 2.05 mmol) and molecular sieves (3Å, 300 mg) in dry acetonitrile (20 mL) was stirred under argon for 1 h at rt. 2-Mercaptobenzimidazole (0.768 g, 5.11 mmol) and mercuric(II) bromide (0.074 g, 0.205 mmol) were added, and the resulting mixture was heated at reflux for 6 h. After that, the solid was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (200 mL) and washed successively with 10% aq. NaOH (20 mL), water (3 x 20 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–toluene gradient elution) to afford the title compound (1.21 g, 86% yield) as a white foam. Analytical

data for **2.1c**: R_f = 0.46 (ethyl acetate/toluene, 3/17, v/v); $[\alpha]_D^{27}$ +26.1 (c = 1, $CHCl_3$); ^{1}H-n.m.r: δ, 3.48 (dd, 1H, $J_{6a,6b}$ = 9.8 Hz, H-6a), 3.56 (dd, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 3.61-3.72 (m, 2H, H-5, 6b), 3.81 (dd, 1H, $J_{3,4}$ = 8.8 Hz, H-3), 4.48 (s, 2H, CH_2Ph), 4.58 (dd, 2H, ^2J = 11.1, CH_2Ph), 4.60 (dd, 2H, ^2J = 10.9, CH_2Ph), 4.92 (d, 1H, $J_{1,2}$ = 10.1 Hz, H-1), 5.30 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 6.82-7.91 (m, 24H, aromatic) ppm; ^{13}C-n.m.r.: δ, 69.5, 72.7, 74.2, 75.4, 75.9, 78.0, 79.1, 83.7, 84.1, 128.1, 128.2 (x3), 128.4 (x4), 128.5, 128.6 (x3), 128.7 (x6), 128.8 (x3), 129.0 (x2), 129.3, 130.2 (x2), 133.7, 137.4, 137.5, 137.6, 146.4, 165.6 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{41}H_{38}N_2O_6SNa$ 709.2348, found 709.2326.

Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (2.1d) was obtained from 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide[59] in 82% as a white foam as described in the synthesis of compound **2.1a**. Analytical data for **2.1d**: R_f = 0.50 (ethyl acetate/toluene, 1/5, v/v); $[\alpha]_D^{25}$ +23.7 (c = 1, $CHCl_3$); ^{1}H-n.m.r.: δ, 4.39-4.49 (m, 2 H, H-6a, 6b) , 4.76 (m, 1H, H-5), 5.35 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 5.66 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 5.87 (dd, 1H, H-2), 6.02 (d, 1H, H-4), 7.13-7.99 (m, 24H, aromatic), 10.50 (s, 1H, NH) ppm; ^{13}C-n.m.r.: δ, 63.0, 68.6, 72.6, 76.3, 77.4, 83.8, 111.0, 119.9, 122.7, 123.7, 128.5 (x2), 128.6 (x2), 128.7 (x5), 128.8, 128.9 (x2), 129.4, 129.9 (x2), 130.0 (x3), 130.2 (x2), 133.6, 133.7, 133.8 (x2), 135.2, 143.6, 143.8, 165.5, 165.6, 165.8, 166.8 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{41}H_{33}N_2O_9S$ 729.1907, found 729.1895.

Benzimidazol-2-yl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxy) carbamoyl-1-thio-β-D-glucopyranoside (2.1e) was obtained from 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxy)carbamoyl-α-D-glucopyranosyl bromide[63] in 53%

as a white amorphous solid as described in the synthesis of compound **2.1a**. Analytical data for **2.1e**: R_f = 0.50 (ethyl acetate/toluene, 1/1, v/v); $[\alpha]_D^{25}$ -6.8 (c = 1, $CHCl_3$); ^{1}H-n.m.r.: δ, 2.00, 2.03, 2.06 (3s, 9H, 3 x $COCH_3$), 3.69-3.82 (m, 2H, H-2, 5), 4.14 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.34 (dd, 1H, H-6b), 4.70 (dd, 2H, ^2J = 12.1 Hz, CH_2CCl$_3$), 5.02 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.24 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 5.40 (dd, 1H, $J_{3,4}$ = 9.9 Hz, H-3), 6.26 (d, 1H, NH), 7.11-7.32 (m, 4H, aromatic) ppm; ^{13}C-n.m.r.: δ, 20.8 (x2), 20.9, 55.9, 62.0, 68.5, 73.1, 74.7, 76.9, 83.9, 95.4, 111.0, 119.3, 122.9, 123.9, 135.1, 143.3, 144.2, 154.9, 169.7, 170.7, 171.5 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{22}H_{25}Cl_3N_3O_9S$ 612.0377, found 612.0381.

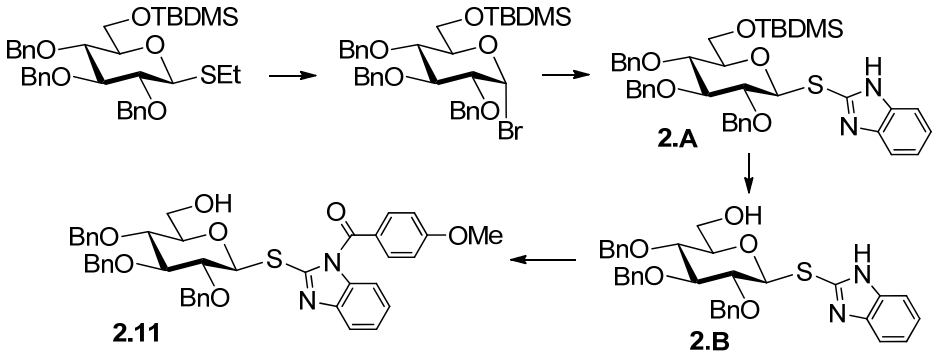
(*N*-Anisoyl)benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (2.10a). Anisoyl chloride (0.58 mL, 4.29 mmol) was added dropwise to a stirring solution of **2.1a** (0.962 g, 1.4 mmol) in pyridine (10 mL). The resulting reaction mixture was stirred under argon for 15 min at rt. After that, the volatiles were removed *in vacuo* and the residue was co-evaporated with toluene (3 x 10 mL). The residue was diluted with CH_2Cl_2 (~200 mL), and washed with water (20 mL), 1N aq. HCl (20 mL), water (20 mL), sat. aq. $NaHCO_3$ (2 x 20 mL), and water (3 x 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 – toluene gradient elution) to afford the title compound (1.05 g, 91%) as an off-white foam. Analytical data for **2.10a**: R_f = 0.50 (ethyl acetate/toluene, 1/9, v/v); $[\alpha]_D^{27}$ +119.5 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.66 (dd, 1H, $J_{2,3}$ = 8.67 Hz, H-2), 3.70 - 3.87 (m, 5H, 3 , 4, 5, 6a, 6b), 3.88 (s, 3H, OCH_3), 4.54 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.71 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 4.87 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 4.88 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 5.83 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 6.89-7.71 (m, 28H, aromatic); ^{13}C-n.m.r.:

δ, 55.8, 68.8, 73.5, 75.1, 75.5, 75.9, 77.9, 79.6, 81.2, 85.1, 86.9, 113.4, 114.4 (x3), 119.3, 123.4, 124.2, 124.9, 127.7, 127.9 (x3), 128.0 (x7), 128.5 (x3), 128.6 (x4), 129.2, 132.8 (x2), 134.7, 138.1, 138.3 (x2), 138.6, 143.9, 151.8, 164.5, 167.3 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{49}H_{47}N_2O_7S$ 807.3104, found 807.3081.

(*N*-Anisoyl)benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (2.10b) was obtained from **2.2b** as an off-white foam in 92%, as described in the synthesis of compound **2.10a**. Analytical data for **2.10b**: R_f = 0.54 (ethyl acetate/toluene, 1/9, v/v); $[\alpha]_D^{27}$ +73.1 (c = 1, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.83 (s, 3H, OCH_3), 4.41-4.61 (m, 3H, H-5, 6a, 6b), 5.71 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 5.73 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 6.09 (dd,1H, $J_{3,4}$ = 9.4 Hz, H-3), 6.44 (dd, 1H, $J_{1,2}$ = 10.6 Hz , H-1), 6.79-7.94 (m, 28H, aromatic) ppm; ^{13}C-n.m.r.: δ, 55.8, 63.5, 69.7, 70.7, 74.5, 77.0, 83.4, 113.5, 114.4 (x2), 119.1, 123.5, 124.4 (x2), 125.5, 128.4 (x3), 128.5 (x3), 128.6 (x2), 128.9, 129.0, 129.2, 129.8, 129.9 (x2), 130.0 (x2), 130.1 (x2), 130.2 (x2), 132.8, 133.1, 133.5 (x2), 133.7,134.7, 143.8, 151.2, 164.6, 165.2, 165.4, 165.9, 166.3, 167.0 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{49}H_{38}N_2O_{11}SH^+$ 863.2275, found 863.2266.

Synthesis of glycosyl acceptors.

(*N*-Anisoyl)benzimidazol-2-yl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2.11).



Benzimidazol-2-yl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (2.A) was obtained from 2,3,4-tri-O-benzoyl-6-O-*tert*-butyldimethylsilyl-β-D-glucopyranosyl bromide[64] as a clear film in 53%, as described in the synthesis of compound **2.1a**: R_f = 0.41 (ethyl acetate/toluene, 1/9, v/v); $[\alpha]_D^{27}$ -35.7 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 0.10 (s, 6H, $2CH_3$), 0.91(s, 9H, $C(CH_3)_3$), 3.47 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 3.47 (m, 1H, $J_{5,6a}$ = 4.3 Hz, $J_{5,6b}$ = 1.9 Hz, H-5), 3.62 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.70 (dd, 1H, $J_{4,5}$ = 8.7 Hz, H-4), 3.83 (dd, 1H, $J_{6a,6b}$ = 11.3 Hz, H-6a), 3.93 (dd, 1H, H-6b), 4.73 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 4.76 (dd, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.78 (dd, 2H, ^2J = 10.0 Hz, CH_2Ph), 4.81 (dd, 2H, ^2J = 9.6 Hz, CH_2Ph), 7.15-7.59 (m, 22H, NH, aromatic) ppm; ^{13}C-n.m.r.: δ, -4.8, -4.7, 18.9, 26.3 (x3), 62.6, 75.3, 75.9, 76.2, 77.1, 80.8, 81.2, 84.9, 86.6, 123.0, 128.0 (x4), 128.1 (x4), 128.2, 128.3, 128.7 (x4), 128.8 (x6), 137.6, 138.1, 138.2, 146.6 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{40}H_{48}N_2O_5SSiNa$ 729.2945, found 719.2937.

Benzimidazol-2-yl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (2.B). To a stirred solution of **2.A** (1.134 g, 1.63 mmol) in THF (10 mL) was added TBAF (2.12 mL, 2.12 mmol). The reaction mixture was stirred under argon for 3 h at rt. Upon completion, the reaction was diluted with CH_2Cl_2 (200 mL), and washed with water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and water (3 x 20 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-toluene gradient elution) to afford the title compound (0.778 g, 92 %) as a white solid. Analytical data for **2.B**: R_f = 0.59 (ethyl acetate/toluene, 2/5, v/v); $[\alpha]_D^{27}$ -24.5 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.03 (br. s, 1H, OH), 3.48 (dd, 1H, $J_{2,3}$ = 8.9 Hz, H-2), 3.51 (m, 1H, $J_{5,6a}$ = 4.5, $J_{5,6b}$ = 1.7 Hz, H-5), 3.58 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 3.70 (dd, 1H, $J_{3,4}$ = 8.7, H-3), 3.73 (dd, 1H, $J_{6a,6b}$

= 11.1, H-6a), 3.96 (dd, 1H, H-6b), 4.72 (dd, 2H, ^2J = 11.1 Hz, CH_2Ph), 4.80 (dd, 2H, ^2J = 10.3 Hz, CH_2Ph), 4.81 (dd, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.86 (dd, 2H, ^2J = 11.0 Hz, CH_2Ph), 7.15-7.72 (m, 20H, aromatic), 10.66 (s, 1H, NH) ppm ; ^{13}C-n.m.r.: δ, 61.2, 75.2, 75.7, 76.0, 80.1, 81.2, 84.7, 86.3, 122.9, 127.9 (x4), 128.2 (x5), 128.6 (x9), 128.7 (x3), 137.6, 137.9, 138.3, 146.4 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{34}H_{35}N_2O_5S$ 583.2267, found 583.2264.

(*N*-Anisoyl)benzimidazol-2-yl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2.11). To a stirred solution of **2.B** (1.033 g, 1.77 mmol) in pyridine (10 mL) was added dropwise TMS chloride (3.4 mL, 26.6 mmol). The reaction mixture was stirred under argon for 1 h at rt. Then, dropwise was added anisoyl chloride (0.571 mL, 3.55 mmol) and stirred for an additional 1h at rt. After that, the volatiles were removed *in vacuo* and the residue was co-evaporated with toluene (3 x 10 mL). The residue was then diluted with CH_2Cl_2 (~200 mL), and washed with water (20 mL), 1N HCl (20 mL), water (20 mL), sat. aq. $NaHCO_3$ (2 x 20 mL), and water (3 x 20 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-toluene gradient elution) to afford the title compound (1.128 g, 89 %) as a white solid. Analytical data for **2.7**: R_f = 0.44 (ethyl acetate/toluene, 1/4, v/v); $[\alpha]_D^{27}$ -5.0 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.59-3.94 (m, 9H, H-2, 3, 4, 5, 6a, 6b, OCH_3), 4.78 (dd, 2H, ^2J = 11.0 Hz, CH_2Ph), 4.82 (dd, 2H, ^2J = 10.6 Hz, CH_2Ph), 4.91 (dd, 2H, ^2J = 11.8 Hz, CH_2Ph), 5.64 (d, 1H, $J_{1,2}$=10.2 Hz, H-1), 6.93-7.75 (m, 24H, aromatic) ppm; ^{13}C-n.m.r.: δ, 55.8, 62.1, 75.2, 75.6, 76.0, 77.8, 80.0, 81.0, 84.8, 86.7, 113.3, 114.4, 119.4, 123.6, 124.3, 124.8, 127.9 (x2), 128.0 (x2), 128.1 (x3), 128.2 (x3), 128.5 (x2), 128.6

(x3), 128.7 (x2), 132.9, 134.6, 137.9, 138.1, 138.5, 143.8, 151.1, 164.6, 167.4 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{42}H_{41}N_2O_7S$ 717.2629, found 717.2631.

Synthesis of glycosides

Typical AgOTf-promoted glycosylation procedure (Method A). A mixture of glycosyl donor (0.045 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (3Å, 125 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. AgOTf (0.090 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Table 2.1), the solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~15 mL) was washed with 1% NaOH (5.0 mL) and water (3 x 5.0 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-toluene gradient elution) to afford the corresponding oligosaccharide.

Typical $Cu(OTf)_2$-promoted glycosylation procedure (Method B). A mixture of glycosyl donor (0.045 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (4Å, 125 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. $Cu(OTf)_2$ (0.045 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Table 2.1), the solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~15 mL) was washed with 1% NaOH (5.0 mL) and water (3 x 5.0 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-toluene gradient elution) to afford the corresponding disaccharide.

Typical alkyl halide-promoted glycosylation procedure (Method C). A mixture of glycosyl donor (0.045 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (4Å, 125 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. Alkyl halide (0.027 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Table 2.1), the solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~15 mL) was washed with 1% NaOH (5.0 mL) and water (3 x 5.0 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-toluene gradient elution) to afford the corresponding disaccharide.

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (2.8d) was synthesized by method A from glycosyl donor **2.1d** (50 mg, 0.069 mmol) and glycosyl acceptor **2.4** (21 mg, 0.046 mmol) in 89% (42 mg) yield. Analytical data for **2.8d**: R_f = 0.45 (ethyl acetate/toluene, 1/5, v/v); $[\alpha]_D^{25}$ +10.5 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.24 (s, 1H, OCH_3), 3.35 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.53-3.71 (m, 3H, H-5, 6a, 6b), 3.61 (dd, 1H, $J_{4,5}$ = 8.7 Hz, H-4), 4.26-4.39 (m, 2H, H-5', 6b'), 4.29 (d, 1H, $J_{1,2}$ = 3.4, H-1), 4.39 (dd, 2H, ^2J = 12.2 Hz, CH_2Ph), 4.44 (dd, 1H, $J_{3,4}$ = 8.5 Hz, H-3), 4.51 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.53-3.59 (m, 1H, H-6a'), 4.91 (dd, 2H, ^2J = 10.6 Hz, CH_2Ph), 5.49 (d, 1H, $J_{1',2'}$ = 7.9Hz, H-1'), 5.66 (dd, 1H, $J_{3',4'}$ = 3.4 Hz, H-3'), 5.86 (dd, 1H, $J_{2',3'}$ = 10.6 Hz, H-2'), 5.98 (d, 1H, $J_{4',5'}$ = 3.3 Hz, H-4'), 7.04-8.03 (m, 35H, aromatic) ppm; ^{13}C-n.m.r.: δ, 55.2, 61.7, 68.3, 68.6, 69.8, 70.8, 71.1, 71.9, 73.7, 74.0, 75.1, 75.5, 77.4, 78.8, 81.0, 98.0, 101.2, 127.8, 127.9, 128.0 (x2), 128.2 (x6), 128.4 (x4), 128.5 (x2), 128.6 (x3), 128.7 (x4), 129.0, 129.2, 129.6, 129.7, 129.9 (x2), 130.0 (x3), 130.1 (x2), 133.3, 133.4, 133.5, 138.1,

138.8, 165.5, 165.6, 165.8, 166.1 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{62}H_{58}O_{15}SNa$ 1065.3673, found 1065.3644.

Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (2.9d) was synthesized by method A from glycosyl donor **2.1d** (50 mg, 0.069 mmol) and glycosyl acceptor **5** (21 mg, 0.046 mmol) in 89% (43 mg) yield. Analytical data for **2.9d**: R_f = 0.48 (ethyl acetate/toluene, 1/5, v/v); $[\alpha]_D^{25}$ +92.4 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.40 (s, 1H, OCH_3), 3.61 (dd, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 3.66-3.78 (m, 3H, H-5, 6a, 6b), 3.82 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 3.95 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 4.29-4.35 (m, 1H, H-5'), 4.42-4.48 (m, 1H, H-6b'), 4.48 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 4.53 (dd, 2H, ^2J = 12.2 Hz, CH_2Ph), 4.55-4.60 (m, 1H, H-6a'), 4.53-3.59 (m, 1H, H-6a'), 4.56 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 5.07 (d, 1H, $J_{1,2}$ = 3.4, H-1), 5.13 (d, 1H, $J_{1',2'}$ = 8.1Hz, H-1'), 5.56 (dd, 1H, $J_{3',4'}$ = 3.4 Hz, H-3'), 5.96 (dd, 1H, $J_{2',3'}$ = 8.1 Hz, H-2'), 5.98 (d, 1H, $J_{4',5'}$ = 3.4 Hz, H-4'), 6.92-8.12 (m, 35H, aromatic) ppm, ^{13}C-n.m.r.: δ, 55.6, 62.4, 68.4, 68.7, 69.9, 70.2, 71.7, 72.3, 73.7, 75.1, 75.4, 77.4, 77.9, 81.1, 82.4, 99.7, 103.0, 127.3 (x3), 127.7, 127.9, 128.0 (x2), 128.2 (x2), 128.4 (x6), 128.6 (x2), 128.7 (x2), 128.8 (x2), 129.1, 129.2, 129.4, 129.8 (x2), 129.9 (x2), 130.0 (x2), 130.3 (x2), 133.2, 133.4, 133.5, 133.8, 138.2, 138.3, 138.7, 165.3, 165.7, 165.8, 166.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{62}H_{58}O_{15}SNa$ 1065.3673, found 1065.3690.

***N*-Anisoylbenzimidazol-2-yl 6-*O*-(2,3,4,6-tri-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (2.12).** A mixture of glycosyl donor **2.1a** (0.142 g, 0.212 mmol), glycosyl acceptor **2.11** (0.101 g, 0.141 mmol), and freshly activated molecular sieves (3Å, 426 mg), in 1,2-dichloroethane (4 mL) was stirred

under argon for 1h. After that, methyl iodide (1.272 mmol) was added, and the reaction mixture was monitored by TLC. Upon disappearance of the glycosyl acceptor, the solid was filtered off and the filtrate was diluted with CH_2Cl_2 (60 mL), washed with sat. aq. $NaHCO_3$ (20 mL) and water (3 x 20 mL). The organic layer was separated, dried with $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel to afford the title compound (0.131 g, 75%, α/β = 1/1.8) as a clear film. Selected analytical data for α-**2.8**: ^{1}H-n.m.r.: δ, 5.14 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H'-1), 5.77 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1) ppm; ^{13}C-n.m.r.: δ, 86.7 (C-1), 97.1 (C'-1) ppm; Selected analytical data for β-**2.8**: ^{1}H n.m.r.: δ, 5.87 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1) ppm; ^{13}C-n.m.r.: δ, 86.9 (C-1), 103.6 (C'-1) ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{68}H_{68}N_2O_{10}SNa^+$ 1127.4492, found 1127.4475.

2-Benzimidazolyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (2.13). To a stirred solution of a **2.8** (0.044 g, 0.035 mmol) in CH_2Cl_2/MeOH (2 mL, 1/1, v/v) was added NaOMe until pH ~8. The reaction mixture was stirred under argon for 1 h at rt. After that, the reaction was neutralized with Dowex. The solid was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (~30 mL), washed with sat. aq. $NaHCO_3$ (10 mL) and water (3 x 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-toluene gradient elution) to afford the title compound (0.037 g, 95 %) as a clear film. Selected analytical data for α-**2.9**: ^{13}C-n.m.r.: δ, 86.5 (C-1), 97.9 (C'-1) ppm; (β anomer): ^{13}C-n.m.r.: δ, 86.2 (C-1), 104.9 (C'-1) ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{68}H_{68}N_2O_{10}SNa$ 1127.4492, found 1127.4475.

Procedure for competitive glycosylation

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (2.6a). A mixture of glycosyl donor **2.1a** (0.045 mmol), glycosyl donor **2.10a** (0.045 mmol), glycosyl acceptor **2.2** (0.041 mmol), and freshly activated molecular sieves (3Å, 130 mg), in 1,2-dichloroethane (1.5 mL) was stirred under argon for 1h. After that, methyl iodide (0.135 mmol) was added, and the reaction mixture was monitored by TLC. Upon disappearance of the glycosyl acceptor, the solid was filtered off and the filtrate was diluted with CH_2Cl_2 (30 mL), washed with sat. aq. $NaHCO_3$ (10 mL) and water (3 x 10 mL). The organic layer was separated, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel.

2.5 References

(1) Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Bertozzi, C. R.; Stanley, P.; Hart, G. W.; Etzler, M. E.: *Essentials of Glycobiology*; Second ed.; CSH Laboratory Press: New York, 2009.

(2) Demchenko, A. V.: General aspects of the glycosidic bond formation. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 1-27.

(3) Zhu, X.; Schmidt, R. R.: New principles for glycoside-bond formation. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934.

(4) Boltje, T. J.; Buskas, T.; Boons, G. J.: Opportunities and challenges in synthetic oligosaccharide and glycoconjugate research. *Nature Chemistry* **2009**, *1*, 611-622.

(5) Smoot, J. T.; Demchenko, A. V.: Oligosaccharide synthesis: from conventional methods to modern expeditious strategies. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 161-250.

(6) Ramakrishnan, A.; Pornsuriyasak, P.; Demchenko, A. V.: Synthesis, glycosidation, and hydrolytic stability of novel glycosyl thioimidates. *J. Carbohydr. Chem.* **2005**, *24*, 649-663.

(7) Szeja, W.; Grynkiewicz, G.: Xanthates, thioimidates and other thio derivatives. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinhein, Germany, 2008; pp 329-361.

(8) Demchenko, A. V.; Malysheva, N. N.; De Meo, C.: S-Benzoxazolyl (SBox) glycosides as novel, versatile glycosyl donors for stereoselective 1,2-cis glycosylation. *Org. Lett.* **2003**, *5*, 455-458.

(9) Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N.: Potent, versatile, and stable: thiazolyl thioglycosides as glycosyl donors. *Angew. Chem. Int. Ed.* **2004**, *43*, 3069-3072.

(10) Wang, Y.; Ye, X. S.; Zhang, L. H.: Oligosaccharide assembly by one-pot multi-step strategy. *Org. Biomol. Chem.* **2007**, *5*, 2189-2200.

(11) Pornsuriyasak, P.; Demchenko, A. V.: Glycosyl thioimidates in a highly convergent one-pot strategy for oligosaccharide synthesis. *Tetrahedron: Asymmetry* **2005**, *16*, 433-439.

(12) Parameswar, A. R.; Demchenko, A. V.: One-pot oligosaccharide synthesis. In *Progress in the synthesis of complex carbohydrate chains of plant and microbial polysaccharides*; Nifantiev, N. E., Ed.; Transworld Res. Network: Kerala, 2009; pp 463-488.

(13) Seeberger, P. H.; Haase, W. C.: Solid-phase oligosaccharide synthesis and combinatorial carbohydrate libraries. *Chem. Rev.* **2000**, *100*, 4349-4393.

(14) Schmidt, R. R.; Jonke, S.; Liu, K.: New Aspects of Glycoside Bond Formation: Solid-Phase Oligosaccharide Synthesis In *ACS Symp. Ser. (Frontiers in Modern Carbohydrate Chemistry)* Demchenko, A. V., Ed.; Oxford Univ. Press, 2007; Vol. 960; pp 209-237.

(15) Parlato, M. C.; Kamat, M. N.; Wang, H.; Stine, K. J.; Demchenko, A. V.: Application of glycosyl thioimidates in solid-phase oligosaccharide synthesis. *J. Org. Chem.* **2008**, *73*, 1716-1725.

(16) Fraser-Reid, B.; Udodong, U. E.; Wu, Z. F.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R.: n-Pentenyl glycosides in organic chemistry: a contemporary example of serendipity. *Synlett* **1992**, 927-942 and references therein.

(17) Kamat, M. N.; Demchenko, A. V.: Revisiting the armed-disarmed concept rationale: chemoselective activation of the S-benzoxazolyl glycosides in oligosaccharide synthesis. *Org. Lett.* **2005**, *7*, 3215-3218.

(18) Bongat, A. F. G.; Kamat, M. N.; Demchenko, A. V.: Chemoselective synthesis of oligosaccharides of 2-deoxy-2-aminosugars. *J. Org. Chem.* **2007**, *72*, 1480-1483.

(19) Kanie, O.; Ito, Y.; Ogawa, T.: Orthogonal glycosylation strategy in oligosaccharide synthesis. *J. Am. Chem. Soc.* **1994**, *116*, 12073-12074.

(20) Pornsuriyasak, P.; Demchenko, A. V.: S-Thiazolinyl (STaz) glycosides as versatile building blocks for convergent selective, chemoselective, and orthogonal oligosaccharide synthesis. *Chem. Eur. J.* **2006**, *12*, 6630-6646.

(21) Vidadala, S. R.; Thadke, S. A.; Hotha, S.: Orthogonal activation of propagyl and n-pentenyl glycosides and 1,2-orthoesters. *J. Org. Chem.* **2009**, *74*, 9233-9236.

(22) Kaeothip, S.; Pornsuriyasak, P.; Rath, N. P.; Demchenko, A. V.: Unexpected orthogonality of S-benzoxazolyl and S-thiazolinyl derivatives: application to expeditious oligosaccharide assembly. *Org. Lett.* **2009**, *11*, 799-802.

(23) Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V.: Development of an arming participating group for stereoselective glycosylation and chemoselective oligosaccharide synthesis. *Angew. Chem. Int. Ed.* **2005**, *44*, 7123-7126.

(24) Smoot, J. T.; Demchenko, A. V.: How the arming participating moieties can broaden the scope of chemoselective oligosaccharide synthesis by allowing the inverse armed-disarmed approach *J. Org. Chem.* **2008**, *73*, 8838-8850.

(25) Pornsuriyasak, P.; Gangadharmath, U. B.; Rath, N. P.; Demchenko, A. V.: A novel strategy for oligosaccharide synthesis via temporarily deactivated S-thiazolyl glycosides as glycosyl acceptors. *Org. Lett.* **2004**, *6*, 4515-4518.

(26) Pornsuriyasak, P.; Rath, N. P.; Demchenko, A. V.: 4-(Pyridin-2-yl)thiazol-2-yl thioglycosides as bidentate ligands for oligosaccharide synthesis via temporary deactivation. *Chem. Commun.* **2008**, 5633-5635.

(27) Mydock, L. K.; Demchenko, A. V.: Application of the superarmed glycosyl donor to chemoselective oligosaccharide synthesis. *Org. Lett.* **2008**, *10*, 2107-2110.

(28) Mydock, L. K.; Demchenko, A. V.: Superarming the S-benzoxazolyl glycosyl donors by simple 2-O-benzoyl-3,4,6-tri-O-benzyl protection. *Org. Lett.* **2008**, *10*, 2103-2106.

(29) 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.

(30) Pornsuriyasak, P.; Vetter, C.; Kaeothip, S.; Kovermann, M.; Balbach, J.; Steinborn, D.; Demchenko, A. V.: Coordination chemistry approach to the long-standing challenge of anomeric stereoselectivity. *Chem. Commun.* **2009**, 6379-6381.

(31) Pornsuriyasak, P.; Ranade, S. C.; Li, A.; Parlato, M. C.; Sims, C. R.; Shulga, O. V.; Stine, K. J.; Demchenko, A. V.: STICS: surface-tethered iterative carbohydrate synthesis. *Chem. Commun.* **2009**, 1834-1836.

(32) Ferrieres, V.; Blanchard, S.; Fischer, D.; Plusquellec, D.: A novel synthesis of D-galactofuranosyl, D-glucofuranosyl and D-mannofuranosyl 1-phosphates based on remote activation of new and free hexofuranosyl donors. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3515-3518.

(33) Euzen, R.; Ferrieres, V.; Plusquellec, D.: General one-step synthesis of free hexofuranosyl 1-phosphates using unprotected 1-thioimidoyl hexofuranosides. *J. Org. Chem.* **2005**, *70*, 847-855.

(34) Roy, R.; Andersson, F. O.; Letellier, M.: "Active" and "latent" thioglycosyl donors in oligosaccharide synthesis. Application to the synthesis of α-sialosides. *Tetrahedron Lett.* **1992**, *33*, 6053-6056.

(35) Boons, G. J.; Isles, S.: Vinyl glycosides in oligosaccharide synthesis. Part 1: A new latent-active glycosylation strategy. *Tetrahedron Lett.* **1994**, *35*, 3593-3596.

(36) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J.: 2-(Hydroxycarbonyl)benzyl glycosides: a novel type of glycosyl donors for

highly efficient β-mannopyranosylation and oligosaccharide synthesis by latent-active glycosylation. *J. Am. Chem. Soc.* **2001**, *123*, 8477-8481.

(37) Kim, K.-S.; Jeon, H.-B.: Anomeric transglycosylation. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 185-223.

(38) Hinklin, R. J.; Kiessling, L. L.: Glycosyl sulfonylcarbamates: new glycosyl donor with tunable reactivity. *J. Am. Chem. Soc.* **2001**, *123*, 3379-3380.

(39) Huang, L.; Wang, Z.; Huang, X.: One-pot oligosaccharide synthesis: reactivity tuning by post-synthetic modification of aglycone. *Chem. Commun.* **2004**, 1960-1961.

(40) Wang, P.; Haldar, P.; Wang, Y.; Hu, H.: Simple glycosylation reaction of allyl glycosides. *J. Org. Chem.* **2007**, *72*, 5870-5873.

(41) Ranade, S. C.; Kaeothip, S.; Demchenko, A. V.: Glycosyl alkoxythioimidates as complementary building blocks for chemical glycosylation. *Org. Lett.* **2010**, *12*, 5628-5631.

(42) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H.: Armed/disarmed effects in glycosyl donors: rationalization and sidetracking. *J. Org. Chem.* **1990**, *55*, 6068-6070.

(43) Varki, A.: Biological roles of oligosaccharides: all of the theories are correct. *Glycobiology* **1993**, *3*, 97-130.

(44) Bongat, A. F. G.; Demchenko, A. V.: Recent trends in the synthesis of O-glycosides of 2-amino-2-deoxysugars. *Carbohydr. Res.* **2007**, *342*, 374-406.

(45) Robyt, J. E.: General principles: General occurrence of carbohydrates. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K.,

Thiem, J., Eds.; Springer: Berlin - Heidelberg - New York, 2001; Vol. 1; pp 75-114.

(46) Xu, J.; Guo, Z.: (2-Azidomethyl)phenylacetyl as a new, reductively cleavable protecting group for hydroxyl groups in carbohydrate synthesis. *Carbohydr. Res.* **2002**, *337*, 87-91 and references therein.

(47) Crich, D.; Cai, F.: Stereocontrolled glycoside and glycosyl ester synthesis. Neighboring group participation and hydrogenolysis of 3-(2′-benzyloxyphenyl)-3,3-dimethylpropanoates. *Org. Lett.* **2007**, *9*, 1613-1615.

(48) Daragics, K.; Fügedi, P.: (2-Nitrophenyl)acetyl: A new, selectively removable hydroxyl protecting group. *Org. Lett.* **2010**, *12*, 2076-2079.

(49) Zhong, W.; Boons, G.-J.: Glycoside synthesis from 1-sulfur/selenium-substituted derivatives: thioglycosides in oligosaccharide synthesis. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 261-303.

(50) Kamat, M. N.; Rath, N. P.; Demchenko, A. V.: Versatile synthesis and mechanism of activation of S-benzoxazolyl glycosides. *J. Org. Chem.* **2007**, *72*, 6938-6946.

(51) Hanessian, S.; Bacquet, C.; Lehong, N.: Chemistry of the glycosidic linkage. Exceptionally fast and efficient formation of glycosides by remote activation. *Carbohydr. Res.* **1980**, *80*, c17-c22.

(52) Mereyala, H. B.; Reddy, G. V.: Stereoselective synthesis of α-linked saccharides by use of per O-benzylated 2-pyridyl 1-thio hexopyranosides as glycosyl donors and methyl-iodide as an activator. *Tetrahedron* **1991**, *47*, 6435-6448.

(53) Briner, K.; Vasella, A.: Glycosylidene carbenes a new approach to glycoside synthesis. Part 1. Preparation of glycosylidene-derived diaziridines and diazirines. *Helv. Chim. Acta* **1989**, *72*, 1371-1382.

(54) Kumar, R. V.; Gopal, K. R.; Kumar, K. V. S. R. S.: Facile synthesis and antimicrobial properties of 2-(substituted-benzylsulfanyl)-1H-benzimidazoles. *J. Heterocycl. Chem.* **2005**, *42*, 1405-1408.

(55) Yavo, E. A.; Kakou-Yao, R.; Coulibaly, S.; Abou, A.; Tenon, A. J.: 2-Benzylsulfanyl-1H-benzimidazole *Acta Cryst., Sec. E* **2007**, *E63*, o4551.

(56) Lee, T. R.; Kim, K.: A facile one pot synthesis of 1-alkylbenzimidazoline-2-thiones. *J. Heterocycl. Chem.* **1989**, *26*, 747-751.

(57) Kruse, L. I.; Kaiser, C.; DeWolf, W. E.; Finkelstein, J. A.; Frazee, J. S.; Hilbert, E. L.; Ross, S. T.; Flaim, K. E.; Sawyer, J. L.: Some benzyl-substituted imidazoles, triazoles, tetrazoles, pyridinethiones, and structural relatives as multisubstrate inhibitors of dopamine β-hydroxylase. 4. Structure-activity relationships at the copper binding site *J. Med. Chem.* **1990**, *33*, 781-789.

(58) Andersson, F.; Fugedi, P.; Garegg, P. J.; Nashed, M.: Synthesis of 1,2-cis-linked glycosides using dimethyl(methylthio)sulfonium triflate as promoter and thioglycosides as glycosyl donors. *Tetrahedron Lett.* **1986**, *27*, 3919-3922.

(59) Lemieux, R. U.: Acylglycosyl halides. Tetra-O-benzoyl-α-D-glucopyranosyl bromide. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolform, M. L., Eds.; Academic Press Inc.: New York and London, 1963; Vol. 2; pp 226-228.

(60) Abdel-Rahman, A. A. H.; El Ashry, E. S. H.; Schmidt, R. R.: Efficient intramolecular b-mannoside formation using m-xylylene and isophtaloyl derivatives as rigid spacer. *Carbohydr. Res.* **2002**, *337*, 195-206.

(61) Beignet, J.; Tiernan, J.; Woo, C. H.; Benson, M. K.; Cox, L. R.: *J. Org. Chem.* **2004**, *69*, 6341-6356.

(62) Ekborg, G.; Glaudemans, C. P. J.: p-(Trifluoroacetamido)phenyl 2-acetamido-2-deoxy-4-O-β-D-mannopyranosyl-β-D-glucopyranoside. *Carbohydr. Res.* **1984**, *129*, 287-292.

(63) Boullanger, P.; Jouineau, M.; Bouammali, B.; Lafont, D.; Descotes, G.: The use of N-alkoxycarbonyl derivatives of 2-amino-2-deoxy-D-glucose as donors in glycosylation reactions. *Carbohydr. Res.* **1990**, *202*, 151-164.

(64) Khan, A. T.; Ghosh, S.; Choudhury, L. H.: A simple and useful synthetic protocol for selective deprotection of tert-butyldimethylsilyl (TBS) ethers. *Eur. J. Org. Chem.* **2004**, 2198-2204.

Chapter 3

Expanding upon the *S*-Benzimidazolyl (SBiz) platform for expeditious oligosaccharide synthesis: active-latent, armed-disarmed, selective and orthogonal activations

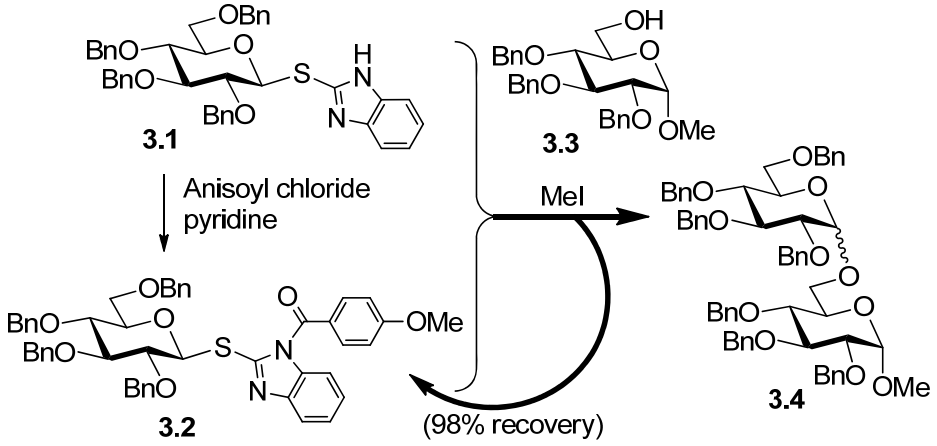
3.1 Introduction

The involvement of complex carbohydrates in a wide variety of disease-related cellular processes has given this class of natural compounds tremendous diagnostic and therapeutic potential.[1] Certain classes of natural carbohydrates can be isolated, but in the most general sense, the availability of complex carbohydrates is still inadequate to address the challenges offered by modern glycosciences. Chemical and enzymatic synthesis glycosylation have become viable means to obtain both natural carbohydrates and unnatural analogs thereof.[2-4] Nevertheless, chemical synthesis of oligosaccharides of even moderate complexity still remains a considerable challenge, and many more complex structures are not yet available at all. Because of this, the development of new effective methods for chemical and enzymatic glycosylation, as well as efficient strategies for the oligosaccharide and glycoconjugates synthesis stand out as timely and demanding areas of research in chemical, biological and medical sciences.[5]

As a part of the ongoing research effort in our laboratory to develop versatile building blocks for chemical glycosylation and expeditious oligosaccharide synthesis, we have been studying glycosyl thioimidates which are glycosyl donors equipped with $SCR_1{=}NR_2$ leaving group. Among a variety of leaving groups studied by us and others,[6,7] we determined that *S*-benzimidazolyl (SBiz) glycosides offer a new class of potent glycosyl donors.[8] We also demonstrated that SBiz glycosides offer a very effective new platform for an attractive active-latent concept for expeditious oligosaccharide synthesis pioneered by Roy,[9] Fraser-Reid,[10] Boons,[11] and more recently further advanced by Kim[12,13] and others.[14-16] As described in Chapter 2, we have acquired a convincing set of experimental data showing that MeI can activate only

glycosyl donor **3.1** equipped with unprotected SBiz (HSBiz) leaving group. In the direct competition experiment, we have clearly shown that the *N*-anisoylated SBiz (AnSBiz) donor **3.2** remains intact and can be recovered nearly quantitatively (98%, Scheme 3.1).[8]

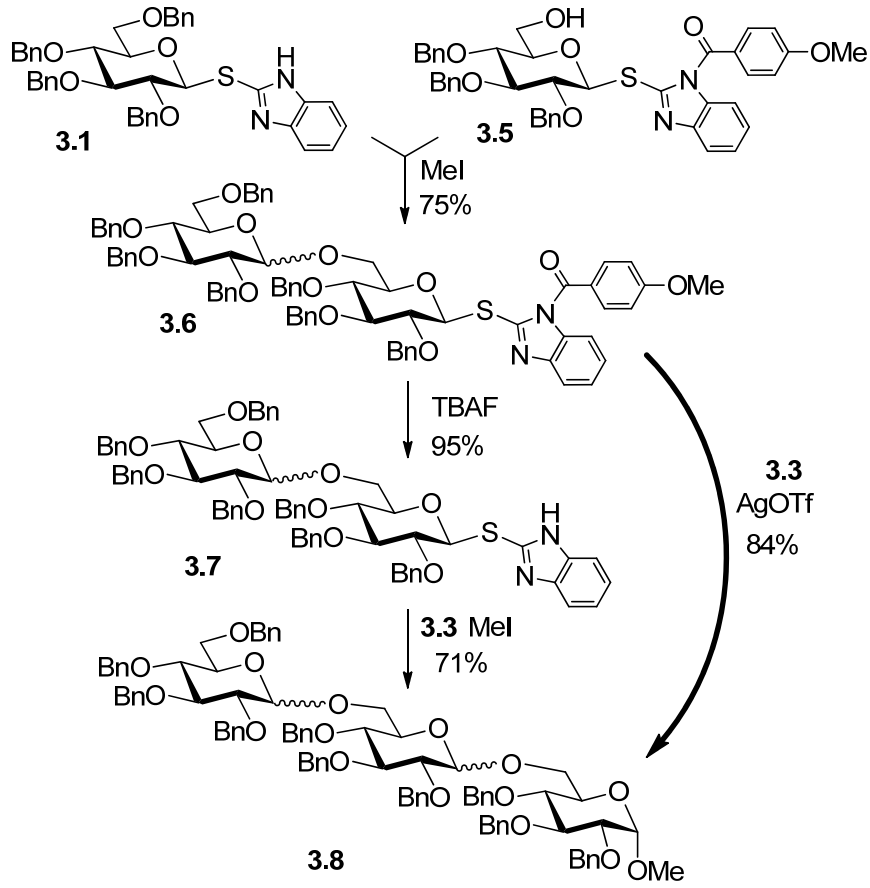
Scheme 3.1. Competition experiment between SBiz donor **3.1** (active) and its *N*-anisoylated counterpart **3.2** (latent) in the presence of MeI.



Direct chemoselective activations clearly demonstrated the viability of the SBiz-based active-latent concept. Thus, MeI-promoted glycosylation between building blocks **3.1** and **3.5** produced disaccharide **3.6** containing the AnSBiz anomeric moiety in 75% yield (Scheme 3.2). After that, the *N*-anisoyl group was removed by treatment with tetrabutylammonium fluoride (TBAF); it should be noted that NaOMe or guanidine are also effective reagents. The resulting disaccharide **3.7** bearing the HSBiz moiety was subsequently activated with MeI to afford trisaccharide **3.8** in 71% yield. This two-step SBiz activation sequence with the intermediate deprotection step (**3.1** → **3.6** → **3.7** → **3.8**) mimics the traditional active-latent pathway for oligosaccharide synthesis.[8] Additionally, we demonstrated that the intermediate disaccharide **3.6** can be directly activated for reaction with acceptor **3.3**. This activation required the stronger promoter

silver(I) triflate (AgOTf), which is able to activate both HSBiz and AnSBiz, and the requisite trisaccharide **3.8** was isolated in 84% yield.[8] The extended mechanistic study made us believe that the deactivation effect of the *N*-anisoyl moiety is electronic, and the latter pathway for the synthesis of trisaccharide **3.8** (**3.1** → **3.6** → **3.8**) resembles an armed-disarmed-like activation. The disarming effect discovered herein from the well-documented disarming effect in glycosylation,[17] in that the disarming is achieved by acylation of the leaving group, not by introducing neighboring acyl substituents in the sugar moiety.

Scheme 3.2. Synthesis of disaccharide **3.8** via the active-latent and an armed-disarmed fashion.



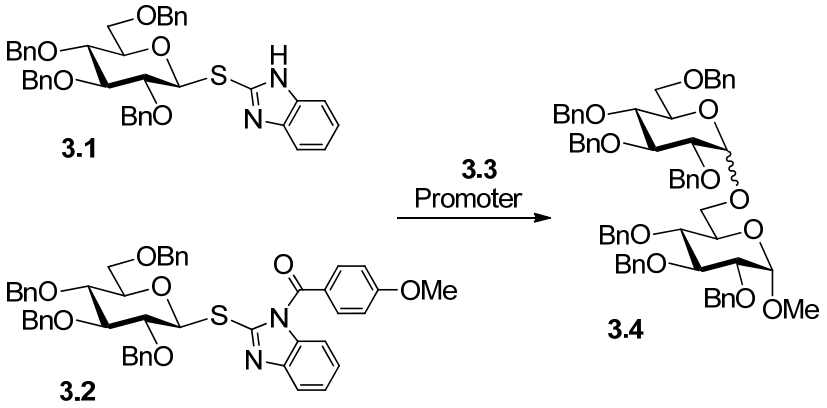
3.2 Results and Discussion

Building upon this earlier discovery that the application of the SBiz moiety allows executing rapid oligosaccharide assembly via active/latent and armed/disarmed concepts we continued screening for new systems and platforms for orthogonal activation. This will be timely and innovative as it will help universalize this promising concept for oligosaccharide synthesis. Therefore, studying SBiz glycosides as a new platform for orthogonal synthesis appealed to us as an important and timely venue. Promoters selected included silver tetrafluoroborate ($AgBF_4$) that was shown to be a potent activator for thioimidates[18] and common promoters for thioglycoside activation: methyl triflate (MeOTf), *N*-iodosuccinimide (NIS) /triflic acid (TfOH), iodonium dicollidine perchlorate (IDCP), and dimethyl(thiomethyl) sulfonium triflate (DMTST).[19] The gylcosides choosen were the perbenzylated HSBiz donor **3.1** and AnSBiz donor **3.2** were coupled with glycosyl acceptor **3.3** under various reaction conditions (Table 3.1). Both glycosyl donors **3.1** and **3.2** were found to be readily activated with MeOTf, NIS/TfOH, IDCP and $AgBF_4$ producing disaccharide **3.4** in 15 min to 12 h in 81-96% yield. It is noteworthy that DMTST failed to activate the HSBiz glycoside **3.1**, even after 120 h (entry 5, Table 3.1). When AnSBiz donor **3.2** was subjected to DMTST-mediated activation disaccharide **3.4** was smoothly produced in 12 h in 86% yield (entry 10). This result is opposite to that obtained for MeI-mediated reactions.[8] Hence, the subsequent study focuses on MeI and DMTST, promoters that showed the greatest difference in the activation profile between donors **3.1** and **3.2**

To our surprize, when a competition experiment between glycosyl donors **3.1** and **3.2**, similar to that described in Scheme 3.1, was set up in the presence of DMTST, only

the AnSBiz donor **3.2** reacted! This is opposite to that of the earlier results: HSBiz donor **3.1** remained intact and could be recovered nearly quantitatively (96%, Scheme 3.3). In our opinion, the set of competition experiments presented in Schemes 3.1 and 3.3 are clearly indicative of the purely orthogonal character of the HSBiz and AnSBiz leaving groups.

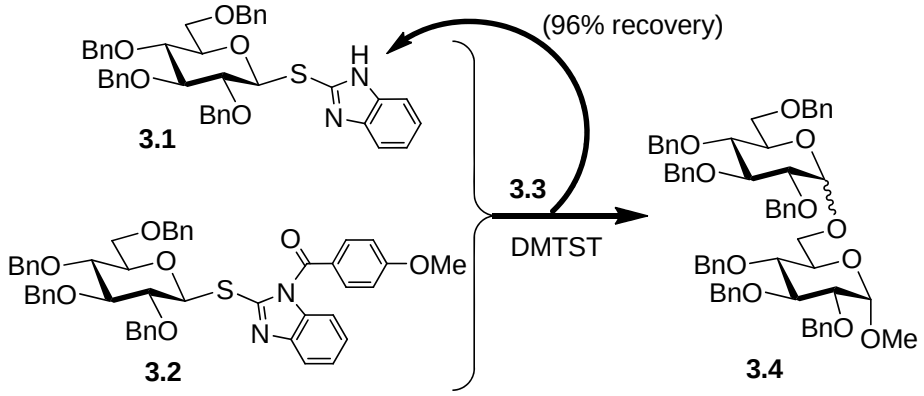
Table 3.1. Glycosidation of glycosyl donors **3.1** and **3.2** with glycosyl acceptor **3.3** in the presence of various promoters.



entry	donor	promoter[a]	time, h	yield of 4 (α/β ratio)
1	**3.1**	MeOTf	0.25	94% (1.7/1)
2	**3.1**	NIS/TfOH	0.25	91% (1.2/1)
3	**3.1**	IDCP	12	89% (1/1.1)
4	**3.1**	$AgBF_4$	0.25	81% (2.3/1)
5	**3.1**	DMTST	120	no reaction
6	**3.2**	MeOTf	1.5	92% (1.5/1)
7	**3.2**	NIS/TfOH	0.25	96% (1.6/1)
8	**3.2**	IDCP	12	87% (1/1.5)
9	**3.2**	$AgBF_4$	0.25	94% (1.3/1)
10	**3.2**	DMTST	12	86% (3.3/1)

[a] Performed in 1,2-dichloroethane the presence of molecular sieves 3 Å at rt.

Scheme 3.3. Opposite reactivity of glycosyl donors **3.1** (latent) and **3.2** (active) observed in the presence of DMTST.



Selective activation wherein one leaving group is activated over another offers a relatively straightforward access to oligosaccharides although aligning multiple leaving groups is not always feasible. In this respect, the orthogonal strategy that relies on two orthogonal leaving groups, and requires a pair of orthogonal activators, is conceptually the most attractive.[20-23] Yet, this strategy remains somewhat underdeveloped with too few known examples to become universally applicable. Only the following examples are known to date: originally reported *S*-phenyl vs. fluoride,[20,21,24] thioimidate-based approaches developed by us,[25-28] Hotha's *O*-pentenyl vs. *O*-propargyl,[29] and *O*-allylphenyl-based approach introduced by our group.[30] We also reported a related, albeit less flexible, semi-orthogonal approach using *S*-ethyl vs. *O*-pentenyl,[31] which was extended to fluoride vs. *O*-pentenyl by Fraser-Reid and Lopez.[32]

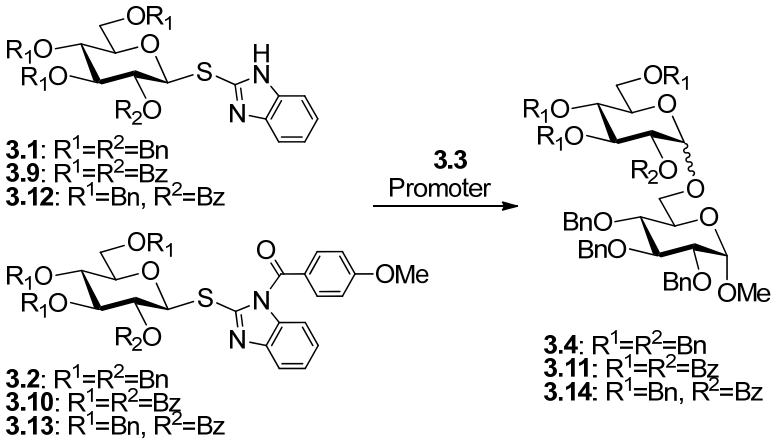
To determine the relative reactivity of differentially protected SBiz glycosides toward glycosidation we investigated the 2,3,4,6-*O*-benzoylated (disarmed) HSBiz donor **3.9** and its *N*-anisoylated counterpart **3.10**.[8] When attempting to glycosidate HSBiz donor **3.9** in the presence of DMTST, no disaccharide **3.11** formation was expected based

on our observation with the armed benzylated donor **3.2**. Strickingly, donor **3.9** "disappeared" within 2 h (entry 5)! An in depth study showed that no disaccharide **3.11** was produced; instead donor **3.9** was entirely converted into its *N*-thiomethylated derivative **3.15** (see Table 3.2 footnote and discussion *vide infra*). When donor **3.9** was subjected to MeI-promoted activation, no reaction took place (entry 6). Since the per-benzylated donor **3.1** was smoothly glycosylated within 12 h (entry 2) we attribute this result to the electron-withdrawing nature of benzoyl substituents (Fraser-Reid's armed-disarmed concept).

Results obtained with AnSBiz donor **3.10** were more predictable. DMTST-promoted activation was completed within 24 h and afforded disaccharide **3.11** in 88% yield. For comparison, the armed donor **3.2** reacted faster (12 h, entry 3), which is also indicative of the armed-disarmed-like activation. No glycosidation of **3.10** took place with MeI even after 120 h (entry 8). We then began investigating glycosidation of glycosyl donors of the superarmed series.[33-35] Glycosidation of the HSBiz donor **3.12** resulted in an interesting outcome: both DMTST and MeI were effective and the corresponding disaccharide **3.14** was obtained in 8 and 15 h respectively (entries 9 and 10). Once again results obtained with AnSBiz donor **3.13** were more predictable: very fast reaction with DMTST that produced disaccharide **3.14** in 45 min (entry 11) and no reaction with MeI (entry 12).

To investigate these seemingly mixed results obtained with HSBiz donors **3.1**, **3.9**, and **3.12** in the presence of DMTST, we first set out to determine how the *O*-protecting groups influence the outcome of the reaction: no reaction for **3.1**, formation of a stable intermediate **3.15** for **3.9**, and smooth glycosylation for **3.12**. Since the disarmed

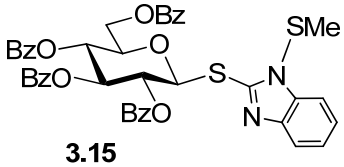
Table 3.2. Glycosidation of differentially protected SBiz and *N*-anisoyl SBiz glycosyl donors.



entry	donor	promoter[a]	time, h	product (yield, α/β ratio)
1	**3.1**	DMTST	120	no reaction
2	**3.1**	MeI	12	**3.4** (89%, 4.8/1)[8]
3	**3.2**	DMTST	12	**3.4** (86%, 3.3/1)
4	**3.2**	MeI	120	no reaction[8]
5	**3.9**	DMTST	2	no disaccharide[b]
6	**3.9**	MeI	120	no reaction
7	**3.10**	DMTST	24	**3.11** (88%, β only)
8	**3.10**	MeI	120	no reaction
9	**3.12**	DMTST	8	**3.14** (94%, β only)
10	**3.12**	MeI	15	**3.14** (88%, β only)
11	**3.13**	DMTST	0.75	**3.14** (92%, β only)
12	**3.13**	MeI	120	no reaction

[a] performed in 1,2-dichloroethane in the presence of molecular sieves 3 Å at 35 °C (MeI) or rt (DMTST)

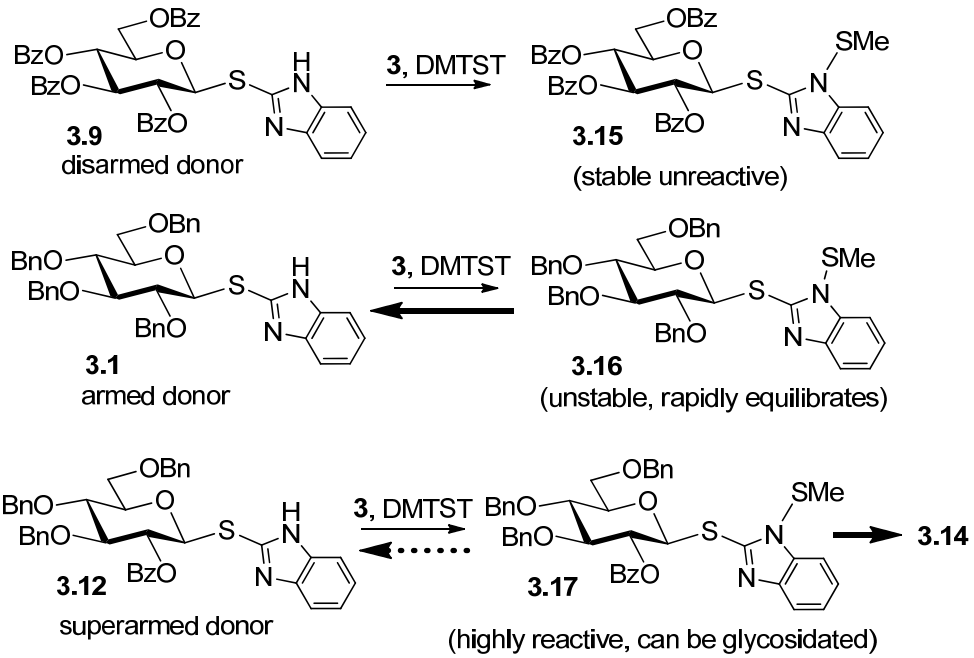
[b] The following compound was produced as the only product



3.15

donor **3.9** produced a stable intermediate **3.15**, we attempted to search a similar intermediate **3.16** in glycosidation with other series of HSBiz donors (Scheme 3.4). Upon a more detailed investigation by NMR, we determined that small amounts of the unstable compound **3.16** were present in the reaction mixture that originated from **3.1**. This unstable reaction intermediate could not be glycosidated (since no disaccharide **3.4** was produced), but instead it is rapidly equillibrated into the starting material **3.1**. Therefore, the reaction outcome is overall indicative of DMTST being deactivated by the interaction with donor **3.1**.

Scheme 3.4. Activation of HBiz donors with DMTST.

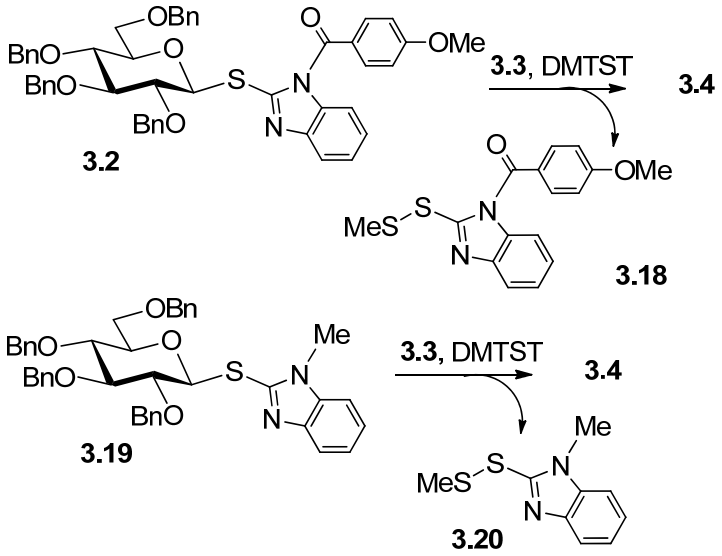


In case of the superarmed glycosyl donor **3.12**, the reaction intermediate **3.17** is highly reactive. It is possible that it equillibrates back to the starting material **3.12**, but it can also be glycosidated to form disaccharide **3.14**. In our opinion, the relatively slow

reaction time of 8 h is indicative of the high rate of the competitive equillibration. For comparison, the anisoylated superarmed donor **3.13** is glycosidated in 45 min.

To build upon this discovery, we began studying the activation pathway of AnSBiz donor **3.2**. The DMTST-mediated activation of donor **3.2** resulted in the formation of disulfide 1-methyl-2-(methyldisulfanyl)-1*H*-benzimidazole 18 as the departing aglycone (Scheme 3.5). To further investigate this finding, *N*-methylated donor **3.19** was obtained and subjected to glycosidation with DMTST. This reaction smoothly produced disaccharide **3.4** (15 h, 79%) along with the departed aglycone 1-anisoyl-2-(methyldisulfanyl)-1*H*-benzimidazole **3.20**.

Scheme 3.5. Activation of HSBiz, AnSBiz, and MeSBiz donors with DMTST.



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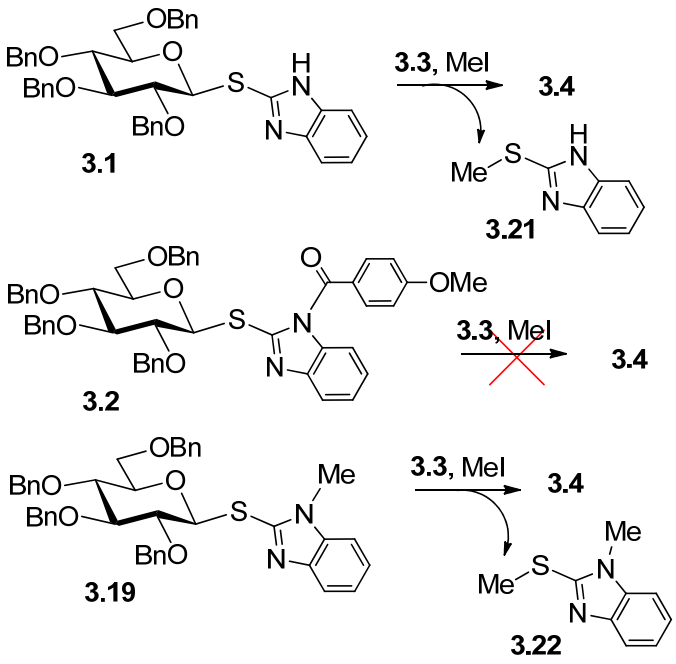
With the set of results presented in Schemes 3.4 and 3.5, it became apparent that nitrogen protection is required for the activation of SBiz glycosides with DMTST (except for those of the superarmed series). The nature of the substituent is somewhat less

importance as both electron-withdrawing *N*-anisoyl and electron-donating *N*-methyl protection produced similar results.

Scheme 3.6. Activation of HSBiz, AnSBiz, and MeSBiz donors with MeI.



We then attempted to compare the activation pathways for the armed donors **3.1**, **3.2**, and **3.19** with MeI. Previously, we reported that benzyl bromide-mediated glycosylation of HSBiz donor **3.1** produced **3.2**-benzylsulfanyl-1*H*-benzimidazole[36,37] indicating the activation via the sulfur atom.[8] Similarly, when donor **3.1** was glycosidated in the presence of MeI, disaccharide **3.4** was obtained along with the departed aglycone 2-methylsulfanyl-1*H*-benzimidazole **3.21** (Scheme 3.6). This result also indicates that the MeI-mediated activation formally follows the direct activation pathway. When a similar experiment was conducted with donor **3.2**, neither disaccharide nor products derived from the departed aglycone were detected in the reaction mixture.

When *N*-methylated donor **3.19** was subjected to glycosidation with MeI, disaccharide **3.4** was smoothly produced (15 h, 79%) along with the departed aglycone that was determined to be 1-methyl-2-methylsulfanyl-1*H*-benzimidazole **3.22** (Scheme 3.6).

Overall, this mechanistic work has ultimately proven the activation pathways of the differentally *N*- and *O*-substituted SBiz glycosides. We also discovered that the *N*-methylated SBiz leaving group can be smoothly activated independently of the type of the activation conditions used. The extended study of the *N*-methylated SBiz donors as well as the *N*-allyl and *N*-benzyl counterparts thereof will be reported in chapter four.

3.3 Conclusions

In conclusion, we have performed further reactivity exploitations of SBiz glycosides in the presence of DMTST. Extended mechanistic study of the DMTST-mediated activation pathway made us believe that the nitrogen protection is essential to achieve glycosylations with SBiz glycosides. Also demonstrated was an orthogonal strategy wherein *N*-protection along with careful promoter selection allow for essentially the same anomeric group to be used for both the donor and the acceptor conterparts.

3.4 Experimental Section

General remarks

Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). 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 ^{o}C. CH_2Cl_2 and

$ClCH_2CH_2Cl$ were distilled from CaH_2 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 CaH_2 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 using a 'Jasco P-1020' polarimeter. ^{1}H-n.m.r. spectra were recorded in $CDCl_3$ at 300 MHz, ^{13}C-n.m.r. spectra were recorded in $CDCl_3$ at 75 MHz (Bruker Avance) unless otherwise noted. HRMS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer.

Synthesis of glycosyl donors

1-Anisoylbenzimidazol-2-yl 2-*O*-benzoyl-3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (3.13). Anisoyl chloride (0.58 mL, 4.29 mmol) was added dropwise to a stirring solution of benzimidazol-2-yl 2-*O*-benzoyl-3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**3.12**, 1.0 g, 1.4 mmol) in pyridine (10 mL). The resulting reaction mixture was stirred under argon for 15 min at rt. After that, the volatiles were removed *in vacuo* and the residue was co-evaporated with toluene (3 x 10 mL). The residue was diluted with CH_2Cl_2 (~200 mL), and washed with water (20 mL), 1 N aq. HCl (20 mL), water (20 mL), sat. aq. $NaHCO_3$ (2 x 20 mL), and water (3 x 10 mL). The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford

the title compound (1.05 g, 91%) as an off-white foam. Analytical data for **3.13**: R_f = 0.52 (ethyl acetate/toluene, 1/9, v/v); $[\alpha]_D^{27}$ +119.5 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.89-4.08 (m, 4H, H-4, 5, 6a, 6b), 4.11 (dd, 1H, $J_{3,4}$ = 8.7 Hz, H-3) 4.68 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.85 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 4.85 (dd, 2H, ^2J = 11.1 Hz, CH_2Ph), 5.63 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 6.27 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 6.93-7.67 (m, 28H, aromatic) ppm; ^{13}C-n.m.r.: δ, 55.7, 68.7, 72.8, 73.5, 75.1, 75.4, 77.8, 80.1, 83.6, 84.3, 113.3, 114.2, 118.9, 123.3, 124.1, 124.4, 127.7, 127.8, 127.9, 128.0 (x6), 128.2 (x2), 128.4 (x3), 128.5 (x2), 129.6 (x2), 130.0 (x3), 132.6 (x2), 132.9, 133.3, 134.6, 137.8, 138.1, 143.6, 151.6, 164.4, 165.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{49}H_{44}N_2O_8SNa$ 843.2716, found 843.2699.

1-Thiomethylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (3.15). Dimethyl(thiomethyl)sulfonium triflate (0.024 g, 0.094 mmol) was added to a solution of benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**3.9**, 0.035 g, 0.047 mmol) in 1,2-dichloroethane (1.0 mL) and the resulting reaction mixture was stirred for 2 h at rt. After that, triethylamine (~0.25 mL) and CH_2Cl_2 (~100 mL) were added and the resulting mixture was washed water (2 x 20 mL). The organic phase was separated, dried with Na_2SO_4 and concentrated *in vacuo*. The crude residue was used to obtain ^{1}H-n.m.r. and ^{13}C-n.m.r. without further purification. Selected analytical data for **3.15**: R_f = 0.66 (ethyl acetate/toluene, 1/5, v/v); ^{1}H-n.m.r.: δ, 2.44 (s,3H, SCH_3), 4.50 (m, 2H, $J_{5,6b}$ = 4.9 Hz, $J_{6a,6b}$ = 14.3 Hz, H-5, 6a), 4.62 (dd, 1H, H-6b), 5.76 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 5.84 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 6.15 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 6.36 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 7.18-7.88 (m, 24H, aromatic) ppm; ^{13}C-n.m.r.: δ, 23.0,

63.3, 69.6, 70.9, 74.3, 83.9, 110.2, 119.0, 123.2, 128.4 (x2), 128.5 (x4), 128.6 (x3), 128.8 (x2), 128.9, 129.7, 129.8 (x3), 129.9 (x2), 130.0 (x2), 130.1 (x2), 133.1, 133.5, 133.6, 133.7, 138.7, 143.9, 155.3, 165.4 (x2), 165.6, 165.8 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{42}H_{35}N_2O_9S^+$ 775.1784, found 775.1773.

1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (3.19). Methyl iodide (0.14 mL, 2.2 mmol) was added to a solution of **3.1** (0.25 g, 0.37 mmol) and KOH (0.10 g, 1.9 mmol) in tetrahydrofuran (5.0 mL) and the resulting mixture was stirred under argon for 30 min at rt. Upon completion (TLC), the reaction mixture was diluted with CH_2Cl_2 (~100 mL) and washed with water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and water (3 x 20 mL). The organic phase was separated, dried over $NaSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane gradient elution) to afford the title compound (0.229 g, 90% yield) as a colorless syrup. Analytical data for **3.19**: R_f = 0.55 (ethyl acetate/hexane 3/7, v/v); $[\alpha]_D^{18}$ +3.7 (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.51-3.79 (m, 6H, H-2, 3, 4, 5, 6a, 6b), 3.74 (s, 3H, NCH_3), 4.44 (dd, 2H, ^2J = 11.9 Hz, C*H*$_2$Ph), 4.66 (dd, 2H, ^2J = 10.9 Hz, C*H*$_2$Ph), 4.87 (dd, 2H, ^2J = 10.9 Hz, C*H*$_2$Ph), 5.02 (dd, 2H, ^2J = 10.7 Hz, C*H*$_2$Ph), 5.68 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1), 7.14-7.78 (m, 24H, aromatic) ppm; ^{13}C-n.m.r.: δ, 31.0, 68.9, 73.5, 75.1, 75.5, 75.9, 79.2, 81.0, 86.2, 86.7, 109.5, 119.6, 122.4, 122.9, 127.8, 127.9 (x2), 128.0 (x3), 128.2 (x2), 128.4, 128.5 (x6), 128.6 (x6), 129.1, 136.8, 138.1, 138.2, 138.3, 138.5, 143.4, 147.2 ppm; HRMS–MS (*m*/*z*): $[M + Na]^+$ calcd for $C_{42}H_{42}N_2O_5SNa$, 709.2712; found, 709.2719

1-Methyl-2-(methylthio)-1*H*-benzimidazole (3.22) was isolated by column chromatography from the reaction mixture resulting from the glycosylation between **3.19** and **3.3** in the presence of MeI. Analytical data for **3.22**: R_f = 0.43 (ethyl acetate/hexane, 1/1, v/v); m. p. 121-124 °C (dichloromethane-toluene); ^{1}H-n.m.r.: δ, 2.80 (s, 3H, SCH_3), 3.67 (s, 3H, NCH_3), 7.15-7.71 (m, 4H, aromatic) ppm; ^{13}C-n.m.r.: δ, 14.8, 30.1, 108.5, 118.2, 121.9 (x2), 137.1, 143.6, 153.4 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_9H_{10}N_2S^+$ 179.0643, found 179.0645.

General procedure for DMTST-promoted glycosylations

A mixture of glycosyl donor (0.045 mmol), glycosyl acceptor (0.038 mmol), and freshly activated molecular sieves (4Å, 100 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. DMTST (0.090 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Tables), Et_3N (0.3 mL) was added and the resulting mixture was stirred for 30 min. The solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with sat. aq. $NaHCO_3$ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried with sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - toluene gradient elution). Anomeric ratios were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

3.5 References

(1) Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Bertozzi, C. R.; Stanley, P.; Hart, G. W.; Etzler, M. E.: *Essentials of Glycobiology*; Second ed.; CSH Laboratory Press: New York, 2009.

(2) Demchenko, A. V.: General aspects of the glycosidic bond formation. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 1-27.

(3) Zhu, X.; Schmidt, R. R.: New principles for glycoside-bond formation. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934.

(4) Boltje, T. J.; Buskas, T.; Boons, G. J.: Opportunities and challenges in synthetic oligosaccharide and glycoconjugate research. *Nature Chemistry* **2009**, *1*, 611-622.

(5) Smoot, J. T.; Demchenko, A. V.: Oligosaccharide synthesis: from conventional methods to modern expeditious strategies. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 161-250.

(6) Szeja, W.; Grynkiewicz, G.: Xanthates, thioimidates and other thio derivatives. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinhein, Germany, 2008; pp 329-361.

(7) Hasty, S. J.; Demchenko, A. V.: Glycosyl thioimidates as versatile building blocks for organic synthesis. *Chem. Heterocycl. Compd.* **2012**, *48*, 220-240.

(8) Hasty, S. J.; Kleine, M. A.; Demchenko, A. V.: S-Benzimidazolyl glycosides as a platform for oligosaccharide synthesis by an active-latent strategy *Angew. Chem. Int. Ed.* **2011**, *50*, 4197-4201.

(9) Roy, R.; Andersson, F. O.; Letellier, M.: "Active" and "latent" thioglycosyl donors in oligosaccharide synthesis. Application to the synthesis of α-sialosides. *Tetrahedron Lett.* **1992**, *33*, 6053-6056.

(10) Fraser-Reid, B.; Udodong, U. E.; Wu, Z. F.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R.: n-Pentenyl glycosides in organic chemistry: a contemporary example of serendipity. *Synlett* **1992**, 927-942 and references therein.

(11) Boons, G. J.; Isles, S.: Vinyl glycosides in oligosaccharide synthesis. Part 1: A new latent-active glycosylation strategy. *Tetrahedron Lett.* **1994**, *35*, 3593-3596.

(12) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J.: 2-(Hydroxycarbonyl)benzyl glycosides: a novel type of glycosyl donors for highly efficient β-mannopyranosylation and oligosaccharide synthesis by latent-active glycosylation. *J. Am. Chem. Soc.* **2001**, *123*, 8477-8481.

(13) Kim, K.-S.; Jeon, H.-B.: Anomeric transglycosylation. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 185-223.

(14) Hinklin, R. J.; Kiessling, L. L.: Glycosyl sulfonylcarbamates: new glycosyl donor with tunable reactivity. *J. Am. Chem. Soc.* **2001**, *123*, 3379-3380.

(15) Huang, L.; Wang, Z.; Huang, X.: One-pot oligosaccharide synthesis: reactivity tuning by post-synthetic modification of aglycone. *Chem. Commun.* **2004**, 1960-1961.

(16) Wang, P.; Haldar, P.; Wang, Y.; Hu, H.: Simple glycosylation reaction of allyl glycosides. *J. Org. Chem.* **2007**, *72*, 5870-5873.

(17) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H.: Armed/disarmed effects in glycosyl donors: rationalization and sidetracking. *J. Org. Chem.* **1990**, *55*, 6068-6070.

(18) Kaeothip, S.; Pornsuriyasak, P.; Demchenko, A. V.: Silver(I) tetrafluoroborate as a potent promoter for chemical glycosylation. *Tetrahedron Lett.* **2008**, *49*, 1542-1545.

(19) Zhong, W.; Boons, G.-J.: Glycoside synthesis from 1-sulfur/selenium-substituted derivatives: thioglycosides in oligosaccharide synthesis. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 261-303.

(20) Kanie, O.; Ito, Y.; Ogawa, T.: Orthogonal glycosylation strategy in oligosaccharide synthesis. *J. Am. Chem. Soc.* **1994**, *116*, 12073-12074.

(21) Ito, Y.; Kanie, O.; Ogawa, T.: Orthogonal glycosylation strategy for rapid assembly of oligosaccharides on a polymer support. *Angew. Chem. Int. Ed.* **1996**, *35*, 2510-2512.

(22) Paulsen, H.: Progress in oligosaccharide synthesis through a new orthogonal glycosylation strategy. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1432-1434.

(23) Kanie, O.: Orthogonal strategy in oligosaccharide synthesis. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, New York, 2000; Vol. 1; pp 407-426.

(24) Kanie, O.; Ohtsuka, I.; Ako, T.; Daikoku, S.; Kanie, Y.; Kato, R.: Orthogonal glycosylation reactions on solid phase and synthesis of a library consisting of a

complete set of fucosyl galactose isomers. *Angew. Chem. Int. Ed.* **2006**, *45*, 3851-3854.

(25) Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N.: Potent, versatile, and stable: thiazolyl thioglycosides as glycosyl donors. *Angew. Chem. Int. Ed.* **2004**, *43*, 3069-3072.

(26) Pornsuriyasak, P.; Demchenko, A. V.: S-Thiazolinyl (STaz) glycosides as versatile building blocks for convergent selective, chemoselective, and orthogonal oligosaccharide synthesis. *Chem. Eur. J.* **2006**, *12*, 6630-6646.

(27) Kaeothip, S.; Pornsuriyasak, P.; Rath, N. P.; Demchenko, A. V.: Unexpected orthogonality of S-benzoxazolyl and S-thiazolinyl derivatives: application to expeditious oligosaccharide assembly. *Org. Lett.* **2009**, *11*, 799-802.

(28) Ranade, S. C.; Kaeothip, S.; Demchenko, A. V.: Glycosyl alkoxythioimidates as complementary building blocks for chemical glycosylation. *Org. Lett.* **2010**, *12*, 5628-5631.

(29) Vidadala, S. R.; Thadke, S. A.; Hotha, S.: Orthogonal activation of propagyl and n-pentenyl glycosides and 1,2-orthoesters. *J. Org. Chem.* **2009**, *74*, 9233-9236.

(30) Premathilake, H. D.; Demchenko, A. V.: 2-Allylphenyl glycosides as complementary building blocks for oligosaccharide and glycoconjugate synthesis. *Beilstein J. Org. Chem.* **2012**, *8*, 597-605.

(31) Demchenko, A. V.; De Meo, C.: semi-Orthogonality of O-pentenyl and S-ethyl glycosides: application for the oligosaccharide synthesis. *Tetrahedron Lett.* **2002**, *43*, 8819-8822.

(32) Lopez, J. C.; Uriel, C.; Guillamon-Martin, A.; Valverde, S.; Gomez, A. M.: IPy_2BF_4-Mediated transformation of *n*-pentenyl glycosides to glycosyl fluorides: a new pair of semiorthogonal glycosyl donors. *Org. Lett.* **2007**, *9*, 2759-2762.

(33) 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.

(34) Mydock, L. K.; Demchenko, A. V.: Application of the superarmed glycosyl donor to chemoselective oligosaccharide synthesis. *Org. Lett.* **2008**, *10*, 2107-2110.

(35) Mydock, L. K.; Demchenko, A. V.: Superarming the S-benzoxazolyl glycosyl donors by simple 2-O-benzoyl-3,4,6-tri-O-benzyl protection. *Org. Lett.* **2008**, *10*, 2103-2106.

(36) Kumar, R. V.; Gopal, K. R.; Seshu Kumar, K. V. S. R.: Facile synthesis and antimicrobial properties of 2-(substituted-benzylsulfanyl)-1H-benzimidazoles. *J. Heterocycl. Chem.* **2005**, *42*, 1405-1408.

(37) Yavo, E. A.; Kakou-Yao, R.; Coulibaly, S.; Abou, A.; Tenon, A. J.: 2-Benzylsulfanyl-1H-benzimidazole *Acta Cryst., Sec. E* **2007**, *E63*, o4551.

Chapter 4

Extending the *S*-benzimidazolyl platform: *N*-alkylated SBiz glycosyl donors with the universal activation profile

4.1 Introduction

The development of efficient and practical building blocks for chemical glycosylation is instrumental in obtaining complex carbohydrates.[1] During the designing of synthetic routes to acquire oligosaccharides, multiple components, conditions, and other features have to be considered. Ideally, glycosides should be generated from easily accessible starting material and would require a minimal number of steps.[2] Furthermore, selection of an appropriate leaving group at the anomeric position is needed to ensure that its activation can be conducted by reliable methods using common promoters.[3] Carefully designed building blocks and refined reaction conditions help to obtain high yields and ensure the reproducibility of syntheses.

In our previous studies dedicated to the development of a new glycosylation methodology based on *S*-benzimidazolyl glycosides, we found that the unfuntionalized HSBiz leaving group can be readily activated with methyl iodide (MeI, Chapter 2).[4] Conversely, a more recent study showed that the *N*-anisoylated SBiz (AnSBiz) leaving group is activated with dimethyl(thiomethyl)sulfonium triflate[5] (DMTST), but not with methyl iodide (Chapter 3). This cooperative finding allowed us to create a new SBiz-based orthogonal approach to expeditious oligosaccharide synthesis.[6] While conducting a mechanistic study to understand the driving forces for this differential reactivity, we obtained *N*-methylated SBiz (MeSBiz) derivatives. These compounds were initially intended to perform a comparative study to understand the effect of the electron-withdrawing anisoyl group in AnSBiz derivatives. The most intriguing outcome of that study was the discovery that both MeI and DMTST could smoothly activate MeSBiz. Since this feature is unavailable with neither HSBiz nor AnSBiz donors, this finding creates a very

promising avenue for further study of SBiz glycosides and derivatives thereof. The main purpose of the study described in this Chapter is to investigate the scope of a new series of the SBiz moiety-based glycosyl donors with a universal activation profile.

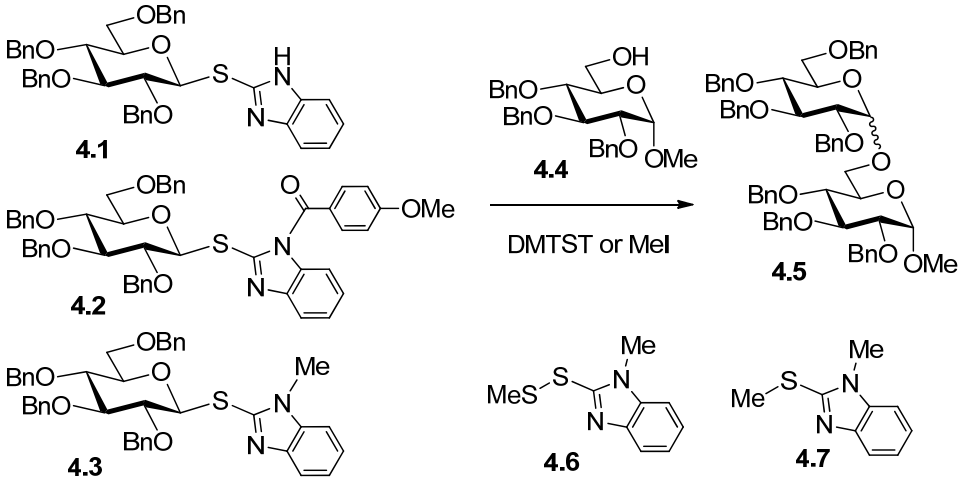
4.2 Results and Discussion

A set of side-by-side comparison experiments was performed to confirm the viability of our previous observation that MeSBiz can be universally activated both with MeI and DMTST. As aforementioned, other glycosyl donors of this series demonstrate affinity towards only one activator of these activators, but not both. For instance, no disaccharide **4.5**[7] was obtained when DMTST was employed to activate HSBiz glycosyl donor **4.1** for reaction with acceptor **4.4**[8] (Table 4.1, entry 1). When donor **4.1** was activated in the presence of MeI, disaccharide **4.5** was obtained in 89% yield (α/β = 4.8/1, entry 2). Conversely, when the *N*-anisoylated counterpart **4.2** was subjected to the same promoters, disaccharide **4.5** was obtained from the DMTST-mediated experiment only, but not from the one involving MeI-mediated activation (entries 3 and 4, respectively). The working hypothesis to explain these findings is that the electron-withdrawing anisoyl group deactivates the SBiz moiety to prevent MeI from initiating the glycosidation process, even after 120 h.

When donor **4.3** was promoted with DMTST, dissacharide **4.5** was isolated in 79% yield (α/β = 2.5/1, entry 5). While we have yet been unable to isolate aglycone **4.6** to confirm the activation pathway, we theorize that the leaving group is activated via the anomeric sulfur. Interestingly, a decrease in reaction time was observed in this experiment in comparison to that involving DMTST-mediated activation of AnSBiz donor **4.2** (8 h versus 15 h, entries 5 and 3, respectively). When donor **4.3** was activated with MeI, disaccharide **4.5** was produced in 79% yield (α/β = 6.1/1, entry 6).

The outcome of the latter reaction was deemed similar to that of MeI-mediated activation of HSBiz donor **4.1**. The activation mode via the anomeric sulfur was ultimately determined by isolation and characterization of departed aglycone **4.7** (entry 2).

Table 4.1. Summary of glycosidation of donors **4.1**-**4.3** in the presence of DMTST or MeI.



Entry	Donor	Promoter[a]	Time, h	Product (yield, α/β ratio)
1	**4.1**	DMTST	120	no reaction
2	**4.1**	MeI	12	**4.5** (89%, 4.8/1)
3	**4.2**	DMTST	15	**4.5** (86%, 3.3/1)
4	**4.2**	MeI	120	no reaction
5	**4.3**	DMTST	8	**4.5** (79%, 2.5/1)
6	**4.3**	MeI	15	**4.5** (79%, 6.1/1)

[a] performed in 1,2-dichloroethane in the presence of molecular sieves 3 Å at 35 °C (MeI) or rt (DMTST)

While the discovery of the universal activation profile of *N*-methylated SBiz donor **4.3** was promising, its synthesis remained cumbersome. Since methylation of the imidazole ring of HSBiz glycoside **4.1** with MeI required a strong base (NaH), this protocol was mainly compatible with compounds of the *O*-benzylated series. All

attempts to access *O*-acylated building blocks resulted in very low yields or even failed entirely due to a low stability of the ester groups in the presence of NaH. Additionally, even with the *O*-benzylated series, these conditions (MeI/NaH) could lead low yield of **4.3** due to the competitive HSBiz leaving group activation taking place via the *S*-methylation pathway[4] instead of the desired *N*-methylation. Therefore, prior to undertaking further steps for investigating glycosyl donors containing *N*-methylated SBiz leaving group in glycosylations, we decided to conduct a systematic study to improve their synthesis. Alongside, we were curious to investigate other *N*-alkylated derivatives to gain better understanding of the reactivity and other properties of these compounds.

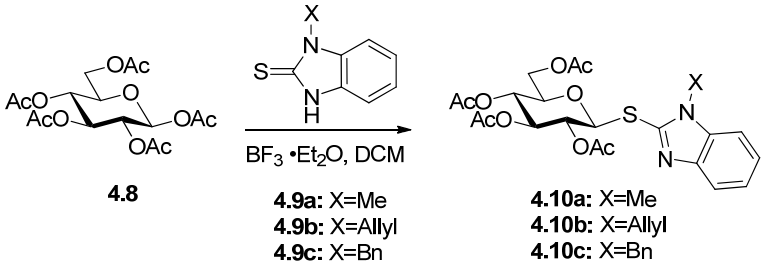
We theorized that advantages of the alkylation of 2-mercaptobenzoxazole prior to introducing it to the anomeric position would be two-fold. First, since one of the nitrogen atoms is protected, the subsequent synthesis of glycosyl thioimidates will be simplified because the main competing reaction leading to the *N*-linked glycoside would become less likely. Second, this protocol should be compatible with acylated derivatives because a base-mediated reaction is conducted prior to conjugation with the sugar moiety. Additionally, we were curious to investigate whether introducing the aglycone via an anomeric acetate would be a viable pathway. Although the synthesis of glycosyl thioimidates via bromides is broadly used in the field, this reaction often leads to the formation the glycal by-product.[4,9-12] Since bromides are also obtained from the acetate precursors,[13] the direct synthesis of thioimidates from glycosyl acetates would be shorter.

With these considerations in mind, we first synthesized aglycones **4.9a-c** according to known protocols.[14] Commercially available 2-mercaptobenzimidazole was first *S*-tritylated with trityl chloride in the presence of triethylamine in

tetrahydrofuran. After filtration of solids, the imidazole nitrogen was alkylated using KOH in acetone. Finally, the trityl group was removed by refluxing in a 10% acetic acid/methanol solution for 30 min to afford aglycones **4.9a-c** in 58-87% yield.

Glucose pentaacetate **4.8** was then reacted with the *N*-methyl aglycone **4.9a** in the presence of boron trifluoride diethyl etherate (BF_3•Et_2O) at reflux to afford glycosyl donor **4.10a** in 97% yield (Table 4.2, entry 1). Similarly, allylated glycosyl donor **4.10b** (AllSBiz) and benzylated donor **4.10c** (BnSBiz) were obtained in 94% and 92% yields respectively (entries 2 and 3). The allylated and benzylated derivatives were obtained for studying their reactivity alongside their methylated counterpart **4.10a**. If the anticipated similarity in reactivity were confirmed, derivatives **4.10b** and **4.10c** would allow for more synthetic versatility than MeSBiz **4.10a**. Furthermore, having temporary *N*-protecting groups, rather than the permanent *N*-methyl, provides straightforward access to building blocks of the HSBiz and, consequently, *N*-anisoyl SBiz series.

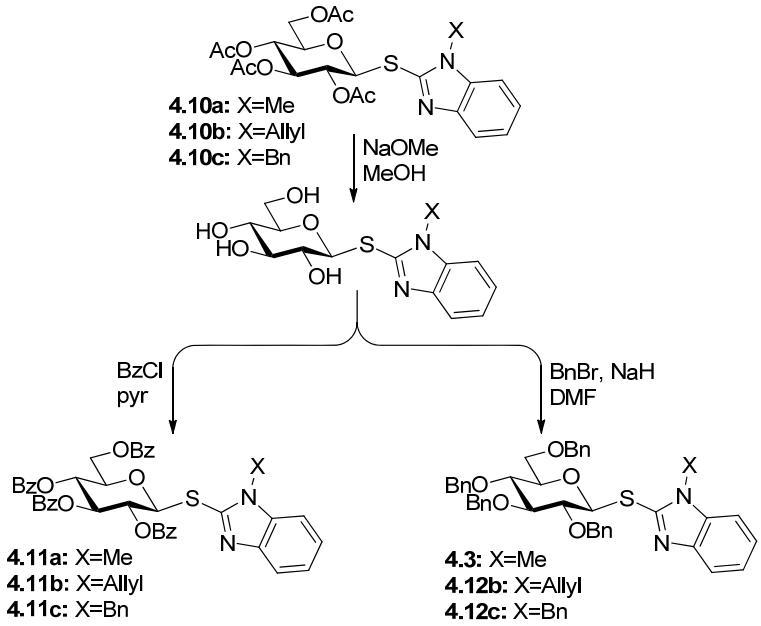
Table 4.2. Synthesis of *N*-alkylated SBiz donors with BF_3•Et_2O.



Entry	Product	Yield
1	**4.10a**	97%
2	**4.10b**	94%
3	**4.10c**	92%

With peracetylated *N*-alkyl SBiz glycosides in hand, we turned our attention to determine the stability of the leaving group toward Zemplen conditions. For this purpose, compounds **4.10a**, **4.10b**, and **4.10c** were treated with a 1 N NaOMe/MeOH solution until the reaction mixture reached a pH=9. Removal of *O*-acetyl protecting groups proceeded cleanly and no visible by-products were observed (TLC). With a straightforward access to the unprotected glycosides, we were set to investigate the synthesis of different *O*-substituted derivatives of this class.

Table 4.3. Synthesis of per-benzoylated and per-benzylated *N*-alkyl SBiz donors.



Entry	Product	Yield
1	**4.11a**	87%
2	**4.11b**	90%
3	**4.11c**	87%
4	**4.3**	83%
5	**4.12b**	87%
6	**4.12c**	89%

We first attempted *O*-benzoylation using benzoyl chloride in the presence of pyridine: all three unprotected SBiz glycosides derived from **4.10a-c** produced their respective *O*-benzoylated counterparts **4.11a-c** in 87-90% yield for two steps (Table 4.3, entries 1-3).

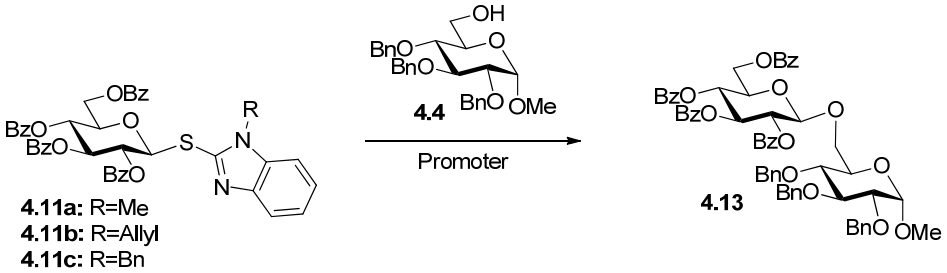
Having synthesized per-*O*-benzoylated glycosides **4.11a-c**, we set out to acquire their per-*O*-benzylated counterparts **4.3**, **4.12b**, and **4.12c** by *O*-alkylation of the deprotected precursors using benzyl bromide in the presence of NaH. The three donors (**4.3**, **4.12b**, and **4.12c**) were isolated in respectable yields of 83-89% (entries 4-6). These successful syntheses imply that all *N*-alkylated SBiz moieties are stable toward strongly basic reaction conditions, NaOMe required for deprotection and NaH used for benzylation. Pleased with these routes and overall yields, we turned our attention to investigating the reactivity of these glycosyl donors employing common promoters that have been utilized in previous studies of SBiz glycosides: DMTST, MeI, copper(II) triflate ($Cu(OTf)_2$), and silver(I) triflate (AgOTf).

First, per-benzoylated (disarmed)[15] glycosyl donors **4.11a-c** were subjected to glycosidation with glycosyl acceptor **4.4** in the presence of various activators and the results of this study are summarized in Table 4.4. Thus, with DMTST promotion all three donors activated quite readily and afforded the corresponding disaccharide **4.13**[16] in 83-88% yield (entries 1-3). MeI failed to activate donor **4.11a** (entry 4). Perhaps, *O*-acyl substituents rendered the MeSBiz moiety unreactive in the presence of this very weak promoter. A similar outcome (no reaction) was obtained with other *O*-benzylated glycosyl donors **4.11b** and **4.11c** (entries 5 and 6).

We then turned our efforts toward investigating the activation of the *N*-alkylated SBiz moieties with metal-based promoters, which were expected to be more powerful reagents for the activation of thioimidates.[12] Indeed, when we conducted

glycosylations using AgOTf all alkylated donors **4.11a-c** reacted readily (2.5-3 h) and afforded disaccharide **4.13** in high yields of 92-94% (entries 7-9). Lastly, when employing $Cu(OTf)_2$, a mild metal-based promoter, glycosylation reactions with donors **4.11a-c** required longer reaction time (60 h), but still afforded disaccharide **4.13** in good yields (82-89%, entries 10-12).

Table 4.4. Glycosidations of per-benzoylated *N*-alkyl SBiz glycosides.

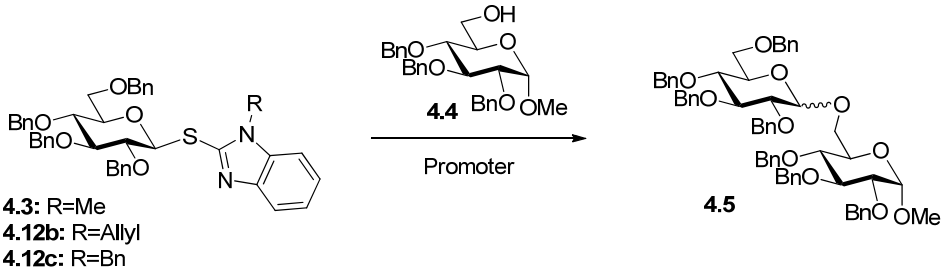


Entry	Donor	Promoter	Time	Yield	α/β ratio
1	**4.11a**	DMTST	9 h	87%	β only
2	**4.11b**	DMTST	12 h	83%	β only
3	**4.11c**	DMTST	15 h	88%	β only
4	**4.11a**	MeI	120 h	NR	-
5	**4.11b**	MeI	120 h	NR	-
6	**4.11c**	MeI	120 h	NR	-
7	**4.11a**	AgOTf	3 h	92%	β only
8	**4.11b**	AgOTf	2.5 h	94%	β only
9	**4.11c**	AgOTf	2.5 h	92%	β only
10	**4.11a**	$Cu(OTf)_2$	60 h	89%	β only
11	**4.11b**	$Cu(OTf)_2$	60 h	84%	β only
12	**4.11c**	$Cu(OTf)_2$	60 h	82%	β only

We next turned our efforts toward studying per-*O*-benzylated (armed)[15] glycosyl donors **4.3**, **4.12b**, and **4.12c**. This study employed the same set of promoters as that used for studying per-benzoylated (disarmed) counterparts and the

key results are summarized in Table 4.5. When DMTST was utilized, the trio of the armed donors glycosidated with acceptor **4.4** to afford disaccharide **4.5** in 8-9 h and 79-91% yield (α/β = 1.6-2.3/1, entries 1-3). Since no glycosylation took place with the disarmed donors **4.11a-c** in the presence of MeI (see Table 4.4), we were particularly curious about studying this promoter with the armed glycosyl donors. In this case, MeI-promoted activations of donors **4.3**, **4.12b**, and **4.12c** were smoothly completed in 15 h and produced disaccharide **4.14** in 79-90% yield (entries 4-6, Table 4.5).

Table 4.5. Glycosidations of per-benzylated *N*-alkyl SBiz glycosides.



Entry	Donor	Promoter	Time	Yield	α/β ratio
1	**4.3**	DMTST	8 h	79%	2.5/1
2	**4.12b**	DMTST	9 h	91%	1.6/1
3	**4.12c**	DMTST	9 h	87%	2.3/1
4	**4.3**	MeI	15 h	79%	6.1/1
5	**4.12b**	MeI	15 h	90%	1.0/1
6	**4.12c**	MeI	15 h	84%	2.2/1
7	**4.3**	AgOTf	15 min	92%	1.0/1
8	**4.12b**	AgOTf	15 min	92%	1.3/1
9	**4.12c**	AgOTf	15 min	94%	1.2/1
10	**4.3**	$Cu(OTf)_2$	15h	80%	2.3/1
11	**4.12b**	$Cu(OTf)_2$	18 h	83%	1.8/1
12	**4.12c**	$Cu(OTf)_2$	18 h	86%	1.7/1

Expectedly, all AgOTf-promoted glycosylations with the armed glycosyl donors were very fast and disaccharide **4.5** was obtained in 15 min in 92-94% yield (α/β = 1-1.3/1, entries 10-12). In the presence of $Cu(OTf)_2$, the per-*O*-benzylated donors afforded disaccharide **4.5** in 15 h (vs. 60 h for the disarmed counterparts) and in good yields (80-86% yield, α/β = 1.7-2.3/1, entries 7-9).

As a means to provide an efficient route to access HSBiz glycosides, we investigated if deprotection of the imidizole nitrogen was probable. Adapting procedures developed for carbohydrates[17] and heterocycles,[18] deprotection of the *N*-benzyl protecting group was conducted in DMSO with 1 M potassium *tert*-butoxide in the presence of O_2 to afford glycoside **4.1** in 92% yield.

4.3 Conclusion

In conclusion, we have demonstrated that *N*-alkylated SBiz glycosides can be synthesized in an efficient and concise manner. All glycosyl donors were synthesized from *N*-protected SBiz aglycones by Lewis acid-mediated coupling with commercially available penta-*O*-acetyl glucopyranose precursor. The *N*-alkylated SBiz moiety was found to be stable under strong basic conditions and can survive common protecting group manipulations. This, in turn, allowed us to obtain both armed and disarmed *N*-alkylated SBiz donors. Glycosylations with these donors gave good yields and displayed properties that bridge our previous studies.

4.4 Experimental Section

General remarks

Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). 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 ^{o}C. CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled from CaH_2 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 CaH_2 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. DOWEX MONOSPHERE 650C (H) was washed three times with MeOH and stored under MeOH. Optical rotations were measured using a 'Jasco P-1020' polarimeter. ^{1}H-NMR. spectra were recorded in $CDCl_3$ at 300 MHz, ^{13}C-NMR spectra were recorded in $CDCl_3$ at 75 MHz (Bruker Avance) unless otherwise noted. HRMS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer.

1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (4.10a). 2-Mercapto-1-methylbenzimidazole[14] (1.26 g, 7.7 mmol) and BF_3-OEt_2 (2.6 mL, 20.5 mmol) were added to a solution of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (2.00 g, 5.12 mmol) in CH_2Cl_2 (20 mL) and the resulting reaction mixture was heated at reflux for 2 h. After that, the reaction mixture 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 (2.26 g, 89%

yield) as white crystals. Analytical data for **4.10a**: R_f = 0.37 (ethyl acetate/hexane, 3/5, v/v); m.p. 148–149 °C (diethyl ether-hexanes); $[\alpha]_D^{24}$ +33.2 (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 1.90 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 3.76 (s, 3H, NCH_3), 3.80-3.87 (m, 1H, H-5), 4.06 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6a}$ = 2.1 Hz, H-6a), 4.22 (dd, 1H, $J_{5,6b}$ = 4.9 Hz, H-6b), 5.12 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 5.22 (dd, 1H, $J_{2,3}$ = 10.1 Hz, H-2), 5.33 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 5.68 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 7.24-7.77 (m, 5H, aromatic) ppm; ^{13}C-n.m.r.: δ, 20.7 (x2), 20.8 (x2), 30.1, 61.8, 68.2, 70.1, 73.8, 76.2, 84.8, 109.4, 119.2, 122.5, 123.0, 136.7, 143.2, 147.0, 169.6, 169.9, 170.1, 170.6 ppm; HRMS–MS (*m*/*z*): $[M + Na]^+$ calcd for $C_{22}H_{26}N_2O_9S$, 494.1359; found, 495.1437.

1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (4.10b) was obtained from 1-allyl-2-mercapto-benzimidazole[14] and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose as described for the synthesis of **4.10a** in 94% yield as white crystals. Analytical data for **4.10b**: R_f = 0.46 (ethyl acetate/hexane, 3/5, v/v); m.p. 108 °C (diethyl ether-hexanes); $[\alpha]_D^{24}$ -16.2 (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 1.88 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.82 (m, 1H, $J_{5,6a}$ = 2.2 Hz, $J_{5,6b}$ = 5.0 Hz , H-5), 4.06 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.21 (dd, 1H, , H-6b), 4.73-4.89 (m, 2H, CH=CH_2), 5.12 (dd, 1H, $J_{4,5}$ = 10.1 Hz, H-4), 5.13 (dd, 2H, ^2J = 17.1 Hz, -CH=CH_2), 5.21 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2), 5.33 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 5.67 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 5.90 (m, 1H, -C*H*=CH_2), 7.23-7.78 (m, 4H, aromatic) ppm; ^{13}C-n.m.r.: δ, 20.7 (x2), 20.8 (x2), 46.8, 61.8, 68.2, 70.2, 73.9, 76.2, 85.0, 110.0, 118.2, 119.3, 122.7, 123.2, 131.6, 136.0, 143.2, 146.9, 169.6, 169.9, 170.1, 170.7 ppm; HRMS–MS (*m*/*z*): $[M + H]^+$ calcd for $C_{24}H_{28}N_2O_9S^+$, 521.1594; found, 521.1591.

1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (4.10c) was obtained from 1-benzyl-2-mercapto-benzimidazole[14] and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose as described for the synthesis of **4.10a** in 90% yield as white crystals. Analytical data for **4.10c**: R_f = 0.37 (ethyl acetate/ hexane, 3/5, v/v); m.p. 139-144 °C (diethyl ether-hexanes); $[\alpha]_D^{24}$ -17.2 (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 1.89 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 3.80-3.87 (m, 1H, $J_{5,6a}$ = 2.1 Hz, $J_{5,6b}$ = 4.9 Hz , H-5), 4.06 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.22 (dd, 1H, H-6b), 5.14 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 5.23 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 5.35 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 5.42 (s, 2H, NC*H*$_2$Ph) 5.76 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 7.14-7.79 (m, 9H, aromatic) ppm; ^{13}C-n.m.r.: δ, 20.7 (x2), 20.8 (x2), 48.1, 61.8, 68.2, 70.2, 73.9, 76.3, 85.3, 110.2, 119.4, 122.7, 123.2, 126.9 (x2), 128.2, 129.0 (x2), 135.7, 136.2, 143.6, 147.2, 169.6, 169.8, 170.1, 170.7 ppm; HRMS–MS (*m*/*z*): $[M + H]^+$ calcd for $C_{28}H_{31}N_2O_9S$, 571.1750; found, 571.1744.

1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (4.11a). Compound **4.10a** (1.00 g, 2.02 mmol) was dissolved in methanol (10 mL), and the pH was adjusted (pH 9) by addition of a 1 M solution of $NaOCH_3$ in MeOH (~0.25 mL). The reaction mixture was stirred for 1.5 h at rt, then Dowex (H^+) was added until neutral pH was achieved. The resin was filtered off and rinsed with methanol (3 × 5 mL). The combined filtrate (~25 mL) was concentrated *in vacuo* and dried. The residue was dissolved in pyridine (10 mL) and benzoyl chloride (1.1 mL, 10.1 mmol) was added. The resulting reaction mixture was stirred under argon for 3.5 h at rt. After that, methanol was added (~1 mL) and the volatiles were removed *in vacuo.* The residue was co-evaporated with toluene (3 x 5 mL), then diluted with CH_2Cl_2 (~150 mL), and washed with water (15 mL), 1 M aq. HCl (15 mL), water (15

mL), sat. aq. $NaHCO_3$ (2 x 20 mL), and water (3 x 10 mL). The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford the title compound (1.30 g, 87% yield) as a white amorphous solid. Analytical data for **4.11a**: R_f = 0.55 (ethyl acetate/hexane, 3/7, v/v); $[\alpha]_D^{21}$ +68.0 (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.66 (s, 3H, OCH_3), 4.34 (m, 1H, $J_{5,6a}$ = 5.9, $J_{5,6b}$ = 2.1 Hz, H-5), 4.45 (dd, 1H, $J_{6a,6b}$ = 11.9 Hz, H-6a), 4.60 (dd, 1H, H-6b), 5.77 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 5.80 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 6.11 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 6.21 (dd, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 7.13-7.97 (m, 24H, aromatic) ppm; ^{13}C-n.m.r.: δ, 30.6, 63.2, 69.4, 71.1, 74.1, 85.1, 109.4, 119.0, 122.6, 122.9, 128.5 (x7), 128.6 (x2), 128.7 (x2), 128.9, 129.5, 129.8 (x2), 129.9 (x2), 130.0 (x2), 130.1 (x2), 130.3, 133.2, 133.5, 133.7, 136.7, 143.2, 147.4, 165.3, 165.6, 165.8, 166.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{42}H_{34}N_2O_9S^+$ 743.2063, found 743.2062.

1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (4.11b) was obtained from **4.10b** as described for the synthesis of **4.11a** in 90% yield as a white amorphous solid. Analytical data for **4.11b**: R_f = 0.56 (ethyl acetate/toluene, 1/9, v/v); $[\alpha]_D^{22}$ +45.5 (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 4.33 (m, 1H, $J_{5,6a}$ = 5.8, $J_{5,6b}$ = 2.4 Hz, H-5), 4.40 (dd, 1H, $J_{6a,6b}$ = 12.1 Hz, H-6a), 4.54 (dd, 1H, H-6b), 4.62-4.69 (m, 2H, CH=CH_2), 4.98 (dd, 2H, ^2J = 17.1 Hz, CH_2-CH), 5.66-5.81 (m, 3H, H-2, 4, C*H*=CH_2), 6.06 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 6.14 (dd, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 7.13-7.95 (m, 29H, aromatic) ppm; ^{13}C-n.m.r.: δ, 46.6, 63.2, 69.4, 71.1, 74.1, 79.2, 85.1, 109.9, 118.1, 119.1, 122.6, 122.9, 128.4 (x2), 128.5 (x4), 128.6 (x2), 128.7 (x2), 128.8, 129.1, 129.5, 129.8 (x2), 129.9 (x2), 130.0 (x2), 130.1 (x2), 131.3, 133.1,

133.4, 133.7, 135.9, 143.4, 147.3, 165.3, 165.6, 165.8, 166.2 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{44}H_{37}N_2O_9S^+$ 769.2220, found 769.2230.

1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (4.11c) was obtained from **4.10c** as described for the synthesis of **4.11a** in 87% yield as a white amorphous solid. Analytical data for **4.11c**: R_f = 0.57 (ethyl acetate/toluene, 3/5, v/v); $[\alpha]_D^{22}$ +32.8 (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 4.35 (m, 1H, $J_{5,6a}$ = 5.9 Hz, $J_{5,6b}$ = 2.1 Hz, H-5), 4.40 (dd, 1H, $J_{6a,6b}$ = 11.9 Hz, H-6a), 4.55 (dd, 1H, H-6b), 5.25 (s, 2H, NC*H*$_2$Ph), 5.72 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 5.75 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 6.07 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 6.19 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 6.99-7.97 (m, 29H, aromatic) ppm; ^{13}C-n.m.r.: δ, 47.9, 63.2, 71.0, 74.0, 85.3, 110.1, 119.1, 122.7, 123.0, 126.8 (x2), 128.0, 128.4 (x5), 128.5 (x2), 128.6 (x3), 128.7, 128.8, 128.9, 129.0 (x3), 129.5, 129.7 (x2), 129.8 (x2), 130.0 (x2), 130.1 (x2), 133.1, 133.4, 133.6, 135.4, 136.0, 143.5, 147.7, 165.3, 165.5, 165.8, 166.2 ppm; HRMS–MS (*m*/*z*): $[M + H]^+$ calcd for $C_{48}H_{39}N_2O_9S^+$, 819.2376; found, 819.2369.

1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (4.12a). Compound **4.10a** (1.00 g, 2.02 mmol) was dissolved in methanol (10 mL), and the pH was adjusted (pH 9) by addition of a 1 M solution of $NaOCH_3$ in MeOH (~0.25 mL). The reaction mixture was stirred for 1.5 h at rt, then Dowex (H^+) was added until neutral pH was achieved. The resin was filtered off and rinsed with methanol (3 × 5 mL). The combined filtrate (~25 mL) was concentrated *in vacuo* and dried. The residue was dissolved in dimethylformamide (15 mL) and benzyl bromide (1.2 mL, 10.1 mmol) added. The mixture was cooled to 0° C, sodium hydride (*ca.* 60% dispersion in mineral oil; 0.606 g, 15.2 mmol) was added portionwise, and the

resulting mixture was stirred for 3 h at rt. After that, the reaction mixture was quenched with ice-water (150 mL) and extracted with cold ether/ethyl acetate (3 x 80 mL, 1/1, v/v). The combined extract (~250 mL) was washed successively with ice-cold water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and water (2 x 20 mL). The organic layer was separated, dried with $NaSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the title compound (1.25 g, 83% yield) as a white amorphous solid. Analytical data for **4.12a**: R_f = 0.55 (ethyl acetate/hexane, 3/7, v/v); $[\alpha]_D^{18}$ +3.7 (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.51-3.79 (m, 6H, H-2, 3, 4, 5, 6a, 6b), 3.74 (s, 3H, NCH_3), 4.44 (dd, 2H, ^2J = 11.9 Hz, C*H*$_2$Ph), 4.66 (dd, 2H, ^2J = 10.9 Hz, C*H*$_2$Ph), 4.87 (dd, 2H, ^2J = 10.9 Hz, C*H*$_2$Ph), 5.02 (dd, 2H, ^2J = 10.7 Hz, C*H*$_2$Ph), 5.68 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1), 7.14-7.78 (m, 24H, aromatic) ppm; ^{13}C-n.m.r.: δ, 31.0, 68.9, 73.5, 75.1, 75.5, 75.9, 79.2, 81.0, 86.2, 86.7, 109.5, 119.6, 122.4, 122.9, 127.8, 127.9 (x2), 128.0 (x3), 128.2 (x2), 128.4, 128.5 (x6), 128.6 (x6), 129.1, 136.8, 138.1, 138.2, 138.3, 138.5, 143.4, 147.2 ppm; HRMS–MS (*m*/*z*): $[M + Na]^+$ calcd for $C_{42}H_{42}N_2O_5SNa$, 709.2712; found, 709.2719

1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (4.12b) was obtained from **4.10b** as described for the synthesis of **4.12a** in 89% yield as a white amorphous solid. Analytical data for **4.12b**: R_f = 0.65 (ethyl acetate/hexane, 3/7, v/v); $[\alpha]_D^{22}$ -10.9 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.60-3.87 (m, 6H, H-2, 3, 4, 5, 6a, 6b), 4.51 (dd, 2H, ^2J = 11.9 Hz, C*H*$_2$Ph), 4.74 (dd, 2H, ^2J = 10.9 Hz, C*H*$_2$Ph), 4.87 (dd, 1H, ^2J = 10.2 Hz, CH=C*H*$_2^a$), 4.93 (dd, 2H, ^2J = 10.9 Hz, C*H*$_2$Ph), 5.03 (dd, 2H, C*H*$_2$-CH), 5.07 (dd, 2H, ^2J = 10.6 Hz, C*H*$_2$Ph), 5.23 (dd, 1H, ^2J = 10.2 Hz, CH=C*H*$_2^b$), 5.35 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1), 5.94 (m, 1H, -C*H*=CH$_2$), 7.15-7.89 (m, 24H,

aromatic) ppm; ^{13}C-n.m.r.: δ, 46.9, 68.5, 73.5, 75.1, 75.4, 75.9, 77.6, 79.4, 81.0, 86.3, 86.7, 110.0, 117.7, 119.6, 122.4, 127.7, 127.8 (x 2), 127.9 (x 4), 128.0 (x 4), 128.2 (x 2), 128.4 (x 3), 128.5 (x 2), 128.6 (x 3), 132.1, 136.0, 138.2 (x 2), 138.2, 138.5, 143.6, 147.2 ppm.; HR-FAB MS $[M+H]^+$ calcd for $C_{44}H_{45}N_2O_5S^+$ 713.3049, found 713.3054.

1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (4.12c) was obtained from **4.10c** as described for the synthesis of **4.12a** in 89% yield as a white amorphous solid. Analytical data for **4.12c**: R_f = 0.65 (ethyl acetate/hexane, 3/7, v/v); $[\alpha]_D^{22}$ -14.7 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.58-3.87 (m, 6H, H-2, 3, 4, 5, 6a, 6b), 4.48 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.74 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 4.94 (dd, 2H, ^2J = 11.0 Hz, CH_2Ph), 5.02 (dd, 2H, ^2J = 10.6 Hz, CH_2Ph), 5.39 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1), 5.46 (dd, 2H, ^2J = 16.5 Hz, CH_2Ph), 7.12-7.89 (m, 29H, aromatic) ppm; ^{13}C-n.m.r.: δ, 48.1, 68.9, 73.6, 75.2, 75.5, 75.9, 79.4, 81.0, 86.4, 86.7, 110.1, 119.7, 122.5, 123.0, 127.0 (x3), 127.8, 127.9 (x6), 128.0 (x3), 128.1 (x3), 128.3 (x2), 128.5 (x3), 128.6 (x6), 129.0 (x2), 136.1, 136.2, 138.1, 138.2 (x2), 138.5, 143.7, 147.8 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{48}H_{47}N_2O_5S^+$ 763.31206, found 763.3195.

General procedures for glycosylations

Typical DMTST-promoted glycosylation procedure. A mixture of glycosyl donor (0.036 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (4Å, 100 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. DMTST (0.090 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Tables), Et_3N (0.3 mL) was added and the resulting mixture was stirred for 30 min. The solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with sat. aq. $NaHCO_3$ (10 mL) and water

(3 x 10 mL). The organic phase was separated, dried with sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - toluene gradient elution). Anomeric ratios were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Typical methyl iodide-promoted glycosylation procedure. A mixture of glycosyl donor (0.036 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (4Å, 125 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. Methyl iodide (0.216 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Tables), the solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with sat. aq. $NaHCO_3$ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried with sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - toluene gradient elution). Anomeric ratios were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Typical AgOTf-promoted glycosylation procedure. A mixture of glycosyl donor (0.036 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (3Å, 125 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. AgOTf (0.072 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Tables), the solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with sat. aq. $NaHCO_3$ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried with sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica

gel (ethyl acetate - toluene gradient elution). Anomeric ratios were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Typical $Cu(OTf)_2$-promoted glycosylation procedure. A mixture of glycosyl donor (0.036 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (4Å, 125 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. $Cu(OTf)_2$ (0.036 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Tables), the solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with sat. aq. $NaHCO_3$ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried with sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - toluene gradient elution). Anomeric ratios were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Preparation of 4.1 via N-debenzylation of 4.12c

Potassium *tert*-butoxide (0.39 mmol, 1 M soln. in THF) was added to a stirring solution of **4.12c** (0.043 g, 0.056 mmol) in DMSO (0.25 mL). Oxygen was then bubbled through the reaction mixture for 15 min. Upon completion (TLC), the reaction was diluted with CH_2Cl_2 (~30 mL) and washed with water (10 mL), sat. aq. $NaHCO_3$ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried with sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - toluene gradient elution) to afford glycoside **4.1** in 92% yield.

4.5 References

(1) Smoot, J. T.; Demchenko, A. V.: Oligosaccharide synthesis: from conventional methods to modern expeditious strategies. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 161-250.

(2) *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

(3) Ranade, S. C.; Demchenko, A. V.: Mechanism of chemical glycosylation: focus on the mode of activation and departure of anomeric leaving groups. *J. Carbohydr. Chem.* **2013**, *32*, 1-43.

(4) Hasty, S. J.; Kleine, M. A.; Demchenko, A. V.: S-Benzimidazolyl glycosides as a platform for oligosaccharide synthesis by an active-latent strategy *Angew. Chem. Int. Ed.* **2011**, *50*, 4197-4201.

(5) Ravenscroft, M.; Roberts, R. M. G.; Tillett, J. G.: The reaction of some cyclic and open-chain disulphides with methyl trifluoromethanesulphonate. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1569-1972.

(6) Hasty, S. J.; Rath, N. P.; Demchenko, A. V.: Expanding upon the S-benzimidazolyl (SBiz) platform for expeditious oligosaccharide synthesis: active-latent, armed-disarmed, selective and orthogonal activations. **2013**, in preparation.

(7) Garcia, B. A.; Gin, D. Y.: Dehydrative glycosylation with activated diphenyl sulfonium reagents. Scope, mode of C(1)-hemiacetal activation, and detection of reactive glycosyl intermediates. *J. Am. Chem. Soc.* **2000**, *122*, 4269-4279.

(8) Kuester, J. M.; Dyong, I.: Partially benzylated carbohydrates, 2. Synthesis of all methyl mono-, di-, and tri-O-benzyl-α-D-glucopyranosides. *Justus Liebigs Ann. Chem.* **1975**, 2179-2189.

(9) Demchenko, A. V.; Kamat, M. N.; De Meo, C.: S-Benzoxazolyl (SBox) glycosides in oligosaccharide synthesis: novel glycosylation approach to the synthesis of β-D-glucosides, β-D-galactosides, and α-D-mannosides. *Synlett* **2003**, 1287-1290.

(10) Demchenko, A. V.; Malysheva, N. N.; De Meo, C.: S-Benzoxazolyl (SBox) glycosides as novel, versatile glycosyl donors for stereoselective 1,2-cis glycosylation. *Org. Lett.* **2003**, *5*, 455-458.

(11) Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N.: Potent, versatile, and stable: thiazolyl thioglycosides as glycosyl donors. *Angew. Chem. Int. Ed.* **2004**, *43*, 3069-3072.

(12) Hasty, S. J.; Demchenko, A. V.: Glycosyl thioimidates as versatile building blocks for organic synthesis. *Chem. Heterocycl. Compd.* **2012**, *48*, 220-240.

(13) Lemieux, R. U.: Acylglycosyl halides. Tetra-O-acetyl-α-D-glucopyranosyl bromide. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolform, M. L., Eds.; Academic Press Inc.: New York and London, 1963; Vol. 2; pp 221-222.

(14) Doerge, D. R.; Cooray, N. M.: Synthesis of N-substituted benzimidazole-2-thiones. *Synth. Commun.* **1991**, *21*, 1789-1795.

(15) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H.: Armed/disarmed effects in glycosyl donors: rationalization and sidetracking. *J. Org. Chem.* **1990**, *55*, 6068-6070.

(16) Huang, K. T.; Winssinger, N.: IPy2BF4-Mediated glycosylation and glycosyl fluoride formation. *Eur. J. Org. Chem.* **2007**, 1887-1890.

(17) Gigg, R.; Conant, R.: Conversion of the N-benzylacetamido group into the acetamido group by autoxidation in potassium t-butoxide–dimethyl sulphoxide. *J. Chem. Soc., Chem. Commun.* **1983**, 465-466.

(18) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V.: An efficient method for the N-debenzylation of aromatic heterocycles. *Tetrahedron Lett.* **2002**, *43*, 399-402.

Chapter 5

A study of silver(I) perchlorate as an effective promoter for chemical glycosylation with thioimidates and thioglycosides

5.1 Introduction

An aspiration to understand the involvement of carbohydrates in practically all life-sustaining and many life-threatening biological processes has been the major driving force in the field of glycoscience.[1] A key to the understanding the biological roles that carbohydrates play, is to have a straightforward access to synthetic oligosaccharides and conjugates thereof. Acquiring complex oligosaccharides, particularly those containing 1,2-*cis* glycosidic linkages, in high purity and significant quantity has long been considered a major challenge.[2]

Monosaccharide units in complex carbohydrates are connected via *O*-glycosidic linkages that can be formed by the glycosylation reaction. It is already appreciated that various factors, such as protecting and leaving groups, promoter/activator, solvent, temperature, etc. may have a significant effect on the course and the outcome of the glycosylation reaction.[3] Nevertheless, there are still significant gaps in our knowledge of the glycosylation reactions and its mechanism. For instance, the effect of the counter-anion remains quite elusive. A vast majority of promoters rely on the use of triflates and the role of triflate as the counter-anion, or as the covalently-bound reaction intermediate, has been acknowledged and studied quite extensively. The effect of other counter-ions, in particular that of perchlorate derived from tritylium,[4-6] iodonium(di-γ-collidine),[7,8] and lithium,[9-13] salts on the stereoselectivity of glycosylation has also been documented.[14] However, the exact nature of this effect that often favors the formation of 1,2-*cis* glycosides remains unclear. To the best of our knowledge, no systematic studies of perchlorate salts as promoters of glycosylation have yet been reported. Expanding upon previous use of silver(I) perchlorate ($AgClO_4$) as a promoter[15] or as an additive in glycosylations,[12,16]

herein we report the systematic study of this promoter for the activation of various thioimidoyl and thioglycosyl donors.

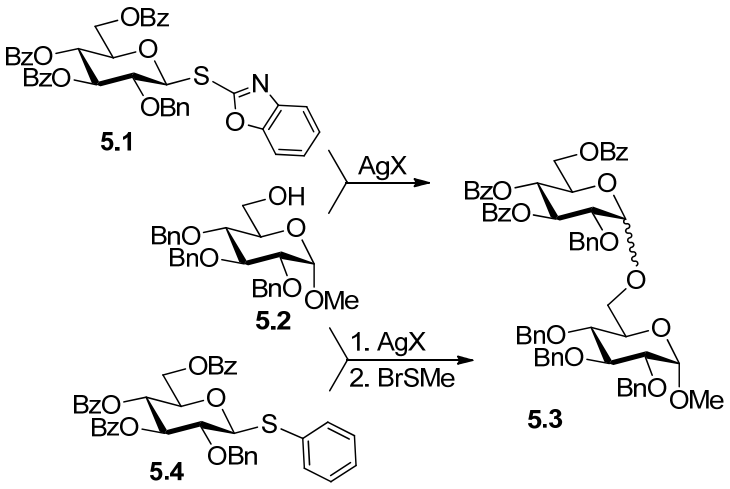
5.2 Results and Discussion

Over the last decade, we have been interested in the syntheses and applications of various glycosyl thioimidates as new versatile donors for chemical glycosylation and expeditious oligosaccharide synthesis.[17] *S*-Benzoxazolyl (SBox),[18] *S*-thiazolinyl (STaz),[19] *O*-methyl phenylcarbamothioate (SNea),[20] and *S*-benzimidazolyl (SBiz)[21] are all commonly activated with silver(I) triflate (AgOTf), and this activation pathway often gives superior yields and stereoselectivity to that of other activators based on metal salts, thiophilic or alkylating reagents. AgOTf, however, is very sensitive to moisture, and typically requires thorough conditioning prior to use. To address this, we introduced the use of silver(I) tetrafluoroborate ($AgBF_4$) as a powerful activator for thioimidates.[22] Nevertheless, the synthesis of 1,2-*cis* glycosides in a majority of applications provided only marginal stereoselectivity.

In our preliminary evaluation of a series of other silver(I) salts, $AgClO_4$ provided consistently superior 1,2-*cis* selectivity, which stimulated our interest in a systematic study of this compound as promoter in glycosylations with thioimidate and thioglycosides donors. To pursue this aim, we obtained SBox donor **5.1**[23] that was subjected to a series of parallel glycosylations using various silver(I) salts (Table 5.1). Thus, the reaction of glycosyl donor **5.1** with primary glycosyl acceptor **5.2**[20] in the presence of $AgClO_4$ afforded disaccharide **5.3** in 95% yield and a very commendable stereoselectivity of $\alpha/\beta = 11.9/1$ (entry 1, Table 5.1). Very similar outcomes in terms of yields and reactivity were detected in cases when AgOTf, $AgPF_6$, and $AgBF_4$ were used as promoters of glycosylation of acceptor **5.2** with SBox donor **5.1** (entries 2-4).

In all cases, disaccharide **5.3** was isolated in good yields (87-94%), but with significantly reduced selectivity ranging from good (α/β = 7.8/1, entry 2) for AgOTf to poor (α/β = 2.1/1, entry 3 and α/β = 1.6/1, entry 4) for $AgPF_6$, and $AgBF_4$, respectively. Since all other reaction conditions remained essentially the same and no significant changes in the reaction rate were observed (all reactions completed within 1 h), this differential stereoselectivity is indicative of the effect of the counter anion.

Table 5.1. Comparative study of $AgClO_4$ vs. other silver(I) salts.

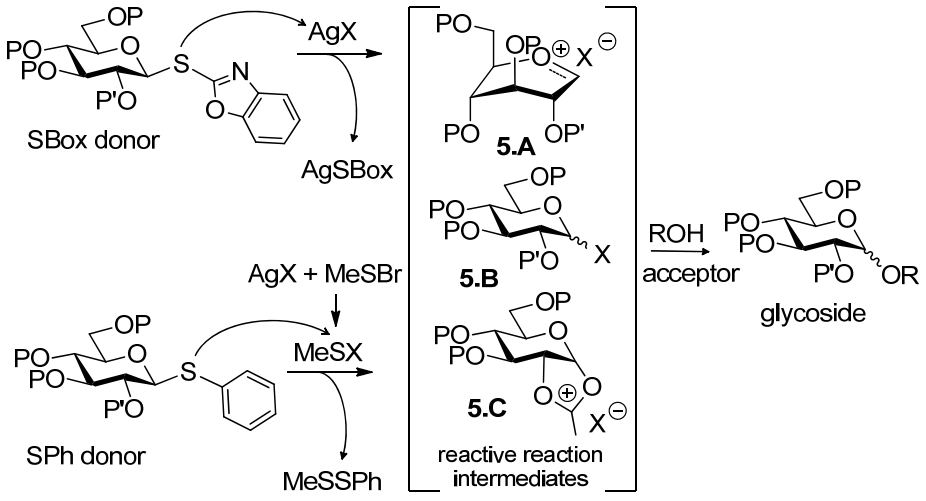


Entry	Donor	AgX	Time	Yield of 5.3	α/β ratio
1	**5.1**	$AgClO_4$	1 h	95%	11.9/1
2	**5.1**	AgOTf	1 h	94%	7.8/1
3	**5.1**	$AgPF_6$	1 h	87%	2.1/1
4	**5.1**	$AgBF_4$	1 h	91%	1.6/1
5[a]	**5.4**	$AgClO_4$	1.25 h	89%	10.1/1
6[a]	**5.4**	AgOTf	1.3 h	91%	7.3/1
7[a]	**5.4**	$AgPF_6$	1.75 h	82%	2.6/1
8[a]	**5.4**	$AgBF_4$	2 h	87%	2.4/1

[a] – performed in the presence of MeSBr

The results surveyed clearly indicate that perchlorate creates the most favorable environment for the formation of α-glucoside **5.3**. In general, the counter anion may have an effect on glycosylation in a variety of modes, although this key effect is often overlooked apart from triflate that has been thoroughly studied by Crich and co-workers.[24,25] As it was previously demonstrated for AgOTf, the activation of the SBox leaving group takes place via the anomeric sulfur.[26] The resultant glycosyl cation is often stabilized via the oxacarbenium ion and anion (X) interaction (**5.A**, Scheme 5.1) or even via formal covalent attachment of X (**5.B**). If the neighboring substituent at C-2 is an acyl group, glycosylations may also proceed via acyloxonium intermediate (**5.C**). The glycosyl acceptor attack in principle can be then influenced by the steric and electronic properties of X, particularly if the reaction proceeds via intermediates **5.A** and **5.B**. It should be noted that all reaction intermediates are quite unstable, therefore, the exact mechanism of chemical glycosylation remains elusive.[27,28]

Scheme 5.1. Schematic representation of the reaction mechanism.



Practically the same trend was observed in the glycosidation of thioglycoside donor **5.4**. Since a silver(I) salt alone fails to activate thioglycosides, therefore its inclusion into the promoter system has been explored. Herein, we chose to investigate a combination of MeSBr, introduced by Garegg as a co-promoter of glycosylation,[29] and AgX (Table 5.1). Another possibility would be to use NIS/AgX combination because NIS/AgOTf is a rather common promoter system for thioglycoside activation.[30] To carry out this reaction, the glycosyl donor and acceptor were initially stirred in the presence of AgX. Subsequently, MeSBr is added and the formation of insoluble yellow AgBr precipitate can be detected momentarily. Apparently, MeSX is also formed at this time (Scheme 5.1), which then undergoes a nucleophilic attack by the anomeric sulfur forming the glycosyl sulfonium intermediate. According to the generally accepted protocol of the activation mechanism,[31] the leaving group then departs as a disulfide PhSSMe leading to the activated intermediates (**5.A**-**5.C**) or a combination thereof depending on the original structure and other factors (*vide supra*).

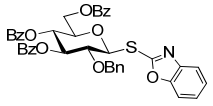
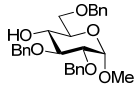
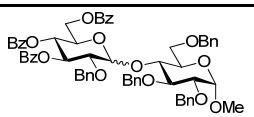
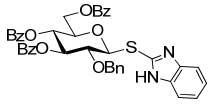
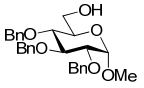
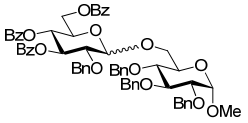
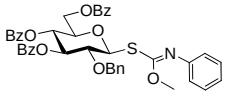
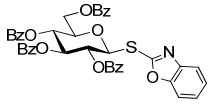
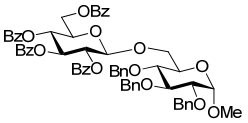
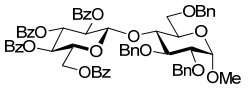
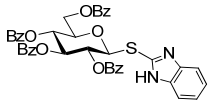
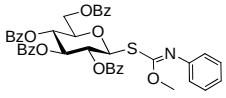
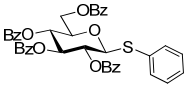
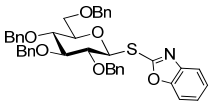
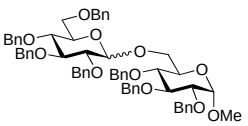
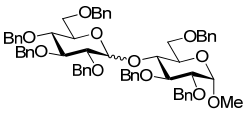
Following this pathway, activation of SPh donor **5.4** with MeSBr/$AgClO_4$ for reaction with primary acceptor **5.2** afforded disaccharide **5.3** in 89% yield and a very commendable stereoselectivity of α/β =10.1/1 (entry 5, Table 5.1). Very similar outcomes in terms of yields and reactivity were detected in cases when AgOTf, $AgPF_6$, and $AgBF_4$ were used as promoters of glycosylation of acceptor **5.2** with SPh donor **4** (entries 6-8). Thus, disaccharide **5.3** was isolated in good yields (82-91%), but with significantly reduced selectivity (α/β =2.4-7.3/1). Since the difference in the reaction rates between different promoters was insignificant, it is very likely that it is the effect of the counter anion that influences the stereoselectivity of glycosylations. Once again, the results indicate that perchlorate is the most favorable counter ion for

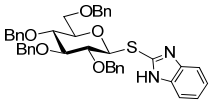
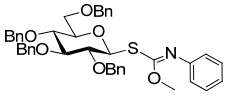
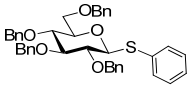
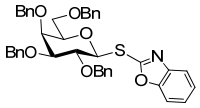
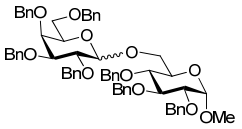
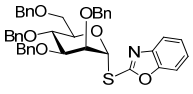
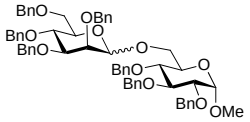
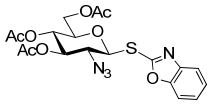
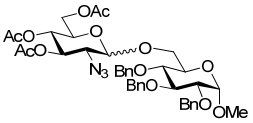
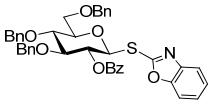
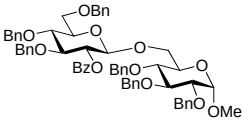
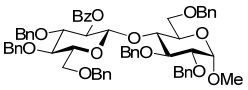
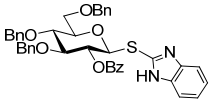
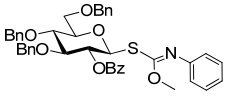
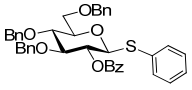
the formation of α-glucoside **5.3**. We deemed these results both practical and intriguing and decided to undergo subsequent comprehensive investigation of this promising promoter.

To determine the efficacy of $AgClO_4$ in the context of other classes of glycosidic linkages we examined a wider range of glycosyl donors. The key findings of this study are summarized in Table 5.2. As a direct continuation of our preliminary work, we set up a series of experiments with superdisarmed 2-*O*-benzyl-3,4,6-*O*-benzoyl thioimidoyl donors.[32] First, we performed glycosylation of the secondary glycosyl acceptor **5.5**[20] with SBox donor **5.1**. This coupling produced disaccharide **5.6** in 92% yield and an impressive stereoselectivity of α/β = >20/1 (entry 1, Table 5.2). Likewise, the glycosyl donor bearing the SBiz moiety **5.7** readily underwent coupling with acceptor **5.2** producing disaccharide **5.3** in 93% yield in 2 h (α/β = 11.2/1, entry 2). It was observed that glycosidation involving the acyclic SNea donor **5.8** took substantially longer (7 h), but nevertheless disaccharide **5.3** was isolated in 92% yield (α/β = 6.6/1, entry 3).

Pleased with the activation of the unreactive superdisarmed series, we turned our attention to glycosidations involving the per-benzoylated (disarmed) glycosyl donors. Here we found that thioimidate donors **5.9**,[23] **5.12**,[21] and **5.13**[20] underwent coupling smoothly producing the expected 1,2-*trans*-linked disaccharides **5.10**[20] and **5.11**[20] in excellent yields (88-94%, entries 4-7). All reactions were relatively swift and completed in 30-45 min. Disarmed thioglycoside **5.14**[33] reacted even quicker (20 min) in the presence of MeSBr and $AgClO_4$ (86%, entry 8). We then began studying a series of per-benzylated (armed) glycosyl donors. Although all yield recorded were very commendable, the stereoselectivity observed was rather poor, most likely due to our inability to slow this reaction.

Table 5.2. Investigation of $AgClO_4$ as a promoter of glycosylation.

Entry	Donor	Acceptor	Time	Product	Yield	α/β ratio
1	 **5.1**	 **5.5**	1 h	 **5.6**	92%	>20/1
2	 **5.7**	 **5.2**	2 h	 **5.3**	93%	11.2/1
3	 **5.8**	**5.2**	7 h	**5.3**	92%	6.6/1
4	 **5.9**	**5.2**	30 min	 **5.10**	91%	β only
5	**5.9**	**5.5**	30 min	 **5.11**	88%	β only
6	 **5.12**	**5.2**	45 min	**5.10**	94%	β only
7	 **5.13**	**5.2**	45 min	**5.10**	92%	β only
8[a]	 **5.14**	**5.2**	20 min	**5.10**	86%	β only
9	 **5.15**	**5.2**	15 min	 **5.16**	96%	1.3/1
10	**5.15**	**5.5**	15 min	 **5.17**	89%	1.6/1

11	 **5.18**	**5.2**	15 min	**5.16**	89%	1.4/1
12	 **5.19**	**5.2**	15 min	**5.16**	91%	1.3/1
13[a]	 **5.20**	**5.2**	20 min	**5.16**	86%	1.5/1
14	 **5.21**	**5.2**	15 min	 **5.22**	83%	1/1.2
15	 **5.23**	**5.2**	15 min	 **5.24**	87%	1/1.1
16	 **5.25**	**5.2**	2 h	 **5.26**	89%	3.4/1
17	 **5.27**	**5.2**	5 min	 **5.28**	97%	β only
18	**5.27**	**5.5**	5 min	 **5.29**	95%	β only
19	 **5.30**	**5.2**	5 min	**5.28**	88%	β only
20	 **5.31**	**5.2**	5 min	**5.28**	82%	β only
21[a]	 **5.32**	**5.2**	5 min	**5.28**	82%	β only

[a] – performed in the presence of MeSBr

Lowering the reaction temperature did not help here because it was favoring the formation of kinetic (β-linked) product. Thus, coupling of SBox donor **5.15**[23] with acceptor **5.2** produced disaccharide **5.16**[34] in 96% yield within 15 min (α/β = 1.3/1, entry 9). Similarly, donor **5.15** glycosidated with secondary glycosyl acceptor **5.5** to afford disaccharide **5.17**[34] in 89% yield in 15 min (α/β = 1.6/1, entry 10). Evaluation of per-benzylated thioimidoyl donors bearing the SBiz **5.18** and SNea **5.19** moieties was conducted and their reactivity was found to be similar to that of the previously mentioned donors (89% and 91% yield, α/β = 1.4/1 and 1.3/1, entries 18 and 19, respectively). Thiophenyl donor **5.20**[35] also rapidly underwent coupling with $AgClO_4$/MeSBr producing disaccharide **5.16** in 86% yield in 20 min (α/β = 1.5/1, entry 13).

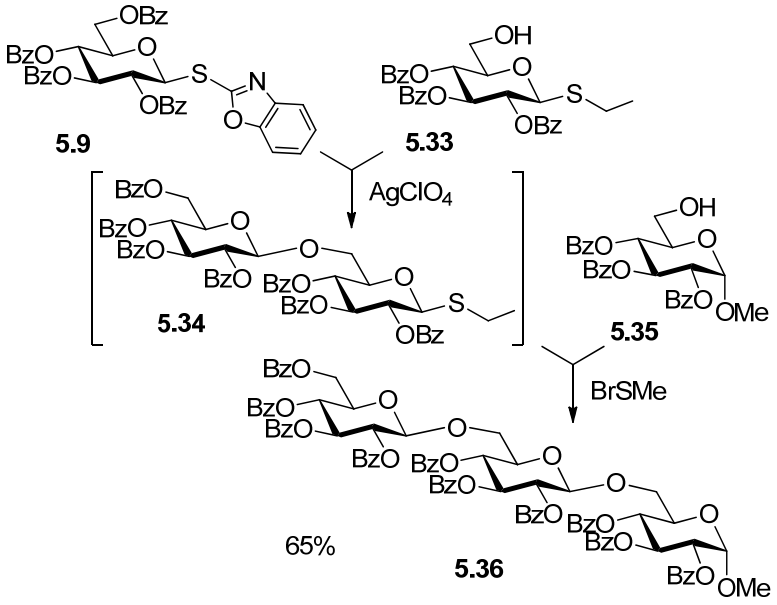
Glycosylations with SBox galactosyl **5.21**, mannosyl **5.23**, and 2-azido-2-deoxy **5.25** donors were also conducted. It was observed that galactosyl and mannosyl glycosyl donors **5.21** and **5.23** underwent coupling with glycosyl acceptor **5.2** in the presence of $AgClO_4$ in 15 min with the corresponding disaccharides **5.22** and **5.24** isolated in 83% and 87% yield, respectively. Unfortunately, no stereoselectivity was observed in these couplings (α/β = 1/1.2 and 1/1.1, entries 14 and 15, respectively). When we glycosidated 2-azido-2-deoxy donor **5.25** with acceptor **5.2**, disaccharide **5.26** was produced in 89% yield (α/β = 3.4/1).

Finally, we investigated highly reactive, superarmed glycosyl donors equipped with the 2-*O*-benzoyl-3,4,6-*O*-benzyl protecting group pattern. All glycosidations of SBox **5.27**, SBiz **5.30**, and SNea **5.31** donors with glycosyl acceptors **5.2** and **5.5** in the presence of $AgClO_4$ were exceptionally swift (less than 5 min). The respective disaccharides **5.28** or **5.29** were isolated in 82-97% yield (entries 17-20). A similar reaction rate was observed when SPh glycosyl donor **5.32** was subjected to the

$AgClO_4$/MeSBr activation conditions affording disaccharide **5.28** in 82% yield (entry 21). As anticipated, all glycosylations with glycosyl donors of the superarmed series proceeded with complete β-selectivity.

Based on these results, we also determined that a two-step, one-pot sequential activation using building blocks with thioimidoyl and thioglycosyl leaving groups was attainable by proper choice of promoter. The sequence we envisioned was to first selectively activate thioimidoyl donor with thioglycoside acceptor in the presence of $AgClO_4$. The expectation was that the resulting disaccharide could be activated directly followed by the addition of BrSMe and a new acceptor. To explore this possibility, we coupled SBox thioimidate donor **5.9** with SEt thioglycosyl acceptor **5.33** employing $AgClO_4$ as the promoter. Upon disappearance of acceptor **5.33**,[36] as judged by TLC, the newly formed disaccharide **5.34** (not isolated) was then activated by the addition of BrSMe and glycosyl acceptor **5.35**. Resultantly, trisaccharide **5.36** was obtained in 65% yield.

Scheme 5.2. One-pot synthesis of trisaccharide **5.36** via selective two-step activation in one pot.



5.3 Conclusion

In conclusion, we demonstrated the effectiveness of silver(I) perchlorate as a powerful promoter towards glycosyl thioimidate activation. It has been utilized with a variety of donors of the gluco, galato, manno and amino series. Also investigated was the use of $AgClO_4$ as an additive when paired with methyl sulfenyl bromide to activate glycosyl thioglycosides. With superdisarmed glycosyl donors equipped with the 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl protecting group pattern $AgClO_4$ was found to display superior 1,2-*cis* selectivity to compared that of other silver(I) salts including the very commonly used AgOTf. The cooperative use of these activation protocols was applied to a one-pot two-step sequential activation of thioimidates and thioglycosides.

5.4 Experimental Section

General Remarks.

Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh); reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). 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 ^{o}C. CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled from CaH_2 directly prior to application. Acetonitrile was dried by refluxing with CaH_2, distilled and stored over molecular sieves (3 Å). THF was refluxed for 2 h and distilled over sodium using benzophenone as an indicator under argon directly before use. Acetone was dried by refluxing with K_2CO_3, distilled and stored over molecular sieves (3 Å). Molecular sieves (3 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. $AgClO_4$ (Aldrich), $AgPF_6$ (Acros), and $AgBF_4$ (Acros) were used as is. AgOTf (Acros) was co-

evaporated with toluene (3 x 10 mL) and dried *in vacuo* for 2-3 h directly prior to application. Optical rotations were measured using a 'Jasco P-1020' polarimeter. ^{1}H-n.m.r. spectra were recorded in $CDCl_3$ at 300 MHz, ^{13}C-n.m.r. spectra were recorded in $CDCl_3$ at 75 MHz (Bruker Avance) unless otherwise noted. HRMS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer.

Synthesis of glycosyl donors

Phenyl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside (5.4). A solution of NaSPh in THF (5.0 mL, freshly prepared from 60% NaH, 2.36 mmol and HSPh, 2.36 mmol) and 15-crown-5 (0.16 mL, 0.8 mmol) were added to a solution of 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-α-D-glucopyranosyl bromide[20] (0.85 g, 1.6 mmol) in dry THF (5.0 mL) and the resulting mixture was stirred under argon for 2.5 h at rt. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (~100 mL) and washed with water (10 mL), sat. aq. $NaHCO_3$ (10 mL), and water (3 x 10 mL). The organic phase was separated, dried over Na_2SO_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 in 73% yield (0.65 g) as a white foam. Analytical data for **5.4**: R_f = 0.48 (ethyl acetate/hexanes, 3/7, v/v); $[\alpha]_D^{22}$ 10.4 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r: δ, 3.78 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 4.07 (m, 1H, $J_{5,6a}$ = 6.1, $J_{5,6b}$ = 2.8 Hz, H-5), 4.45 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.61 (dd, 1H, H-6b), 4.72 (dd, 2H, ^{2}J = 10.7 Hz, CH_2Ph), 4.91 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 5.50 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.78 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 7.02-8.12 (m, 25H, aromatic) ppm; ^{13}C-n.m.r: δ, 63.5, 69.6, 75.3, 75.9, 76.1, 78.5, 87.8, 127.9, 128.0, 128.1, 128.4 (x 3), 128.5 (x 7), 128.9, 129.1 (x 2), 129.4, 129.8 (x 2), 129.9 (x 3), 130.0 (x 2), 130.3, 132.5, 133.0,

133.3, 133.6, 137.2, 165.6, 165.7, 166.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{40}H_{34}O_8SNa^+$ 697.1872, found 697.1868.

2-Benzimidazolyl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside (5.7). Potassium 2-benzimidazolethione[21] (KSBiz, 0.66 g, 3.5 mmol) and 18-crown-6 (0.12 mg, 0.46 mmol) were added to a solution of 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-α-D-glucopyranosyl bromide (1.25 g, 2.3 mmol) in dry acetone (10 mL) and the resulting mixture was stirred under argon for 4 h at rt. Upon completion, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~250 mL) was washed with water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and water (3 x 20 mL). The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 62% yield (0.82 g) as a white foam. Analytical data for **5.7**: R_f = 0.51 (ethyl acetate/hexanes, 1/1, v/v); $[\alpha]_D^{22}$ -130.9 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r: δ, 3.75 (d, 1H, $J_{2,3}$ = 9.3 Hz, H-2), 4.18 (m, 1H, $J_{5,6a}$ = 6.6 Hz, $J_{5,6b}$ = 2.2 Hz, H-5), 4.62 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.77 (dd, 1H, H-6b), 4.85 (dd, 2H, ^2J = 10.8 Hz, CH_2Ph), 5.05 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 5.53 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.83 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 7.06-8.18 (m, 24H, aromatic), 10.64 (br. s, 1H, NH) ppm; ^{13}C-n.m.r: δ, 62.9, 68.9, 75.3, 75.5, 78.5, 84.5, 123.1, 128.1, 128.4 (x 4), 128.5 (x 3), 128.7 (x 2), 128.8 (x 4), 128.9 (x 2), 129.2, 129.6, 129.9 (x 3), 130.0 (x 3), 130.2 (x 3), 133.4, 133.8, 140.0, 143.8, 165.4, 165.7, 167.4 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{41}H_{34}N_2O_8SNa^+$ 737.1934, found 737.1930.

3,4,6-tri-*O*-Benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (5.8). *O*-Methyl phenylcarbamothioate (HSNea, 0.22 g, 1.29

mmol) and KOH (0.048 g, 0.85 mmol) were added to a stirring solution of 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-α-D-glucopyranosyl bromide (0.46 g, 0.85 mmol) in dry acetone (6.0 mL) and the reaction mixture was stirred under argon for 2.5 h at rt. Upon completion, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with water (10 mL), sat. aq. $NaHCO_3$ (10 mL), and water (3 x 10 mL). The organic phase was separated, dried over Na_2SO_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 in 42% yield (0.22 g) as a white foam. Analytical data for **5.8**: R_f = 0.42 (ethyl acetate/hexanes, 3/7, v/v); $[\alpha]_D^{22}$ -14.3 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r: δ, 3.69 (dd, 1H, $J_{2,3}$ = 9.1 Hz, H-2), 3.90 (s, 3H, OCH_3), 4.13 (m, 1H, $J_{5,6a}$ = 5.9, $J_{5,6b}$ = 2.9 Hz, H-5), 4.44 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.54 (dd, 2H, ^2J = 10.6 Hz, CH_2Ph), 4.58 (dd, 1H, H-6b), 5.41 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 5.47 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.77 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 6.79-8.07 (m, 25H, aromatic) ppm; ^{13}C-n.m.r: δ, 56.6, 63.5, 69.7, 75.4, 76.0, 76.3, 83.1, 121.7 (x 2), 124.12, 128.1, 128.4 (x 8), 128.5 (x 3), 128.9, 129.2 (x 2), 129.3, 129.8 (x 4), 129.9 (x 2), 133.3, 133.4, 133.5, 136.8, 146.8, 155.2, 165.5, 165.7, 166.2 ppm; HR-FAB MS$[M+Na]^+$ calcd for $C_{42}H_{37}NO_9SNa^+$ 754.2081, found 754.2089.

2-Benzoxazolyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-β-D-glucopyranoside (5.25). Potassium 2-mercaptobenzoxazole[37] (KSBox, 0.600 g, 3.17 mmol) and 18-crown-6 (0.67 g, 0.25 mmol) were added to a stirring solution of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide[38] (0.50 g, 1.27 mmol) in dry acetone (10 mL) and the reaction mixture was stirred under argon for 2.5 h at rt. Upon completion, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate

(~250 mL) was washed with water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and water (3 x 20 mL). The organic phase was separated, dried over Na_2SO_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 in 37% yield (0.218 g) as an off-white foam. Analytical data for **5.25**: R_f = 0.49 (ethyl acetate/hexanes, 1/1, v/v); $[\alpha]_D^{22}$ 9.1 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r: δ, 1.99, 2.05, 2.13 (3 s, 9H, 3 x CH_3), 3.91 (m, 1H, $J_{5,6a}$ = 2.2, $J_{5,6b}$ = 4.7 Hz, H-5) 3.94 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 4.12 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.27 (dd, 1H, H-6b), 5.12 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 5.25 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.42 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1), 7.27-7.68 (m, 4H, aromatic) ppm; ^{13}C-n.m.r: 20.7, 20.8 (x 2), 61.8, 63.1, 70.0, 74.7, 76.6, 84.1, 110.4, 119.3, 124.8, 124.9, 141.7, 152.1, 160.1, 169.8, 170.0, 170.7 ppm; HR-FAB MS$[M+H]^+$ calcd for $C_{19}H_{21}N_4O_8S^+$ 465.1080, found 465.1072.

Typical procedure for glycosidation of thioimidates.

A mixture of glycosyl donor (0.045 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (3Å, 125 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. Silver(I)-salt (0.068 mmol) was added and the reaction was monitored by TLC. Upon completion (see Tables), the solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~15 mL) was washed with 1% NaOH (5 mL) and water (3 x 5 mL). The organic layer was separated, dried with Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the corresponding oligosaccharide.

Typical procedure for glycosidation of thioglycosides.

A mixture of glycosyl donor (0.045 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (3Å, 125 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1 h. Silver(I)-salt (0.068 mmol) and freshly prepared MeSBr[29] (amount) and the reaction mixture was monitored by TLC. Upon completion (see Tables), the solid was filtered off and rinsed sucessively with CH_2Cl_2. The combined filtrate (~15 mL) was washed with 1% NaOH (5 mL) and water (3 x 5 mL). The organic layer was separated, dried with Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the corresponding oligosaccharide.

5.6 References

(1) Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Bertozzi, C. R.; Stanley, P.; Hart, G. W.; Etzler, M. E.: *Essentials of Glycobiology*; Second ed.; CSH Laboratory Press: New York, 2009.

(2) Demchenko, A. V.: 1,2-cis O-Glycosylation: methods, strategies, principles. *Curr. Org. Chem.* **2003**, *7*, 35-79.

(3) Demchenko, A. V.: General aspects of the glycosidic bond formation. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 1-27.

(4) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V.: A novel highly stereospecific method of 1,2-cis-glycosylation - synthesis of α-D-glucosyl-D-hexoses and α-D-galactosyl-D-hexoses. *Bioorg. Khim.* **1990**, *16*, 701-710.

(5) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.: Novel highly stereospecific method of 1,2-cis-glycosylation. Synthesis of α-D-glucosyl-D-glucoses. *Tetrahedron Lett.* **1989**, *30*, 5459-5462.

(6) Kaeothip, S.; Akins, S. J.; Demchenko, A. V.: On the stereoselectivity of glycosidation of thiocyanates, thioglycosides, and thioimidates. *Carbohydr. Res.* **2010**, *345*, 2146-2150.

(7) Veeneman, G. H.; van Boom, J. H.: An efficient thioglycoside-mediated formation of a-glycosidic linkages promoted by iodonium dicollidine perchlorate. *Tetrahedron Lett.* **1990**, *31*, 275-278.

(8) Demchenko, A.; Stauch, T.; Boons, G. J.: Solvent and other effects on the stereoselectivity of thioglycoside glycosidations. *Synlett* **1997**, 818-820.

(9) Mukaiyama, T.; Matsubara, K.: Stereoselective glycosylation reaction starting from 1-O-trimethylsilyl sugars by using diphenyltin sulfide and a catalytic amount of active acidic species. *Chem. Lett.* **1992**, 1041-1044.

(10) Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A.: Efficient activation of armed glycosyl trichloroacetimidates with $Sm(OTf)_3$ in the stereoselective glycosidation of saccharidic acceptors. *Tetrahedron Lett.* **2000**, *41*, 9005-9008.

(11) Schene, H.; Waldmann, H.: Activation of glycosyl phosphites under neutral conditions in solutions of metal perchlorates in organic solvents. *Eur. J. Org. Chem.* **1998**, 1227-1230.

(12) Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S.: A stereoselective glycosidation using thioglycosides, activation by combination of N-bromosuccinimide and strong acid salts. *Tetrahedron* **1995**, *51*, 4923-4932.

(13) Worm-Leonhard, K.; Larsen, K.; Jensen, K. J.: 4,6-O-Benzylidene Directed b-Mannosylation Without Intermediate Triflate Formation? Comparison of Trichloroacetimidate and DISAL Donors in Microwave-Promoted Glycosylations under Neutral Conditions. *J. Carbohydr. Chem.* **2007**, *26*, 349–368.

(14) Dalpozzo, R.; Bartoli, G.; Sambri, L.; Melchiorre, P.: Perchloric Acid and Its Salts: Very Powerful Catalysts in Organic Chemistry. *Chem. Rev.* **2010**, *110*, 3501-3551.

(15) Igarashi, K.; Honma, T.; Irisawa, J.: Reaction of glycosyl chlorides with silver perchlorate. *Carbohydr. Res.* **1970**, *15*, 329-337.

(16) Mukaiyama, T.; Murai, Y.; Shoda, S.-i.: An efficient method for glucosylation of hydroxy compounds using glucopyranosyl fluoride. *Chem. Lett.* **1981**, 431-432.

(17) Hasty, S. J.; Demchenko, A. V.: Glycosyl thioimidates as versatile building blocks for organic synthesis. *Chem. Heterocycl. Compd.* **2012**, *48*, 220-240.

(18) Demchenko, A. V.; Malysheva, N. N.; De Meo, C.: S-Benzoxazolyl (SBox) glycosides as novel, versatile glycosyl donors for stereoselective 1,2-cis glycosylation. *Org. Lett.* **2003**, *5*, 455-458.

(19) Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N.: Potent, versatile, and stable: thiazolyl thioglycosides as glycosyl donors. *Angew. Chem. Int. Ed.* **2004**, *43*, 3069-3072.

(20) Ranade, S. C.; Kaeothip, S.; Demchenko, A. V.: Glycosyl alkoxythioimidates as complementary building blocks for chemical glycosylation. *Org. Lett.* **2010**, *12*, 5628-5631.

(21) Hasty, S. J.; Kleine, M. A.; Demchenko, A. V.: S-Benzimidazolyl glycosides as a platform for oligosaccharide synthesis by an active-latent strategy *Angew. Chem. Int. Ed.* **2011**, *50*, 4197-4201.

(22) Kaeothip, S.; Pornsuriyasak, P.; Demchenko, A. V.: Silver(I) tetrafluoroborate as a potent promoter for chemical glycosylation. *Tetrahedron Lett.* **2008**, *49*, 1542-1545.

(23) Kamat, M. N.; Demchenko, A. V.: Revisiting the armed-disarmed concept rationale: chemoselective activation of the S-benzoxazolyl glycosides in oligosaccharide synthesis. *Org. Lett.* **2005**, *7*, 3215-3218.

(24) Crich, D.: Chemistry of glycosyl triflates: Synthesis of β-mannopyranosides (Reprinted from Glycochemistry: Principles, Synthesis, and Applications, pg 53-75, 2001). *J. Carbohydr. Chem.* **2002**, *21*, 667-690.

(25) Crich, D.: Methodology Development and Physical Organic Chemistry: A Powerful Combination for the Advancement of Glycochemistry. *J. Org. Chem.* **2011**, *76*, 9193-9209.

(26) Kamat, M. N.; Rath, N. P.; Demchenko, A. V.: Versatile synthesis and mechanism of activation of S-benzoxazolyl glycosides. *J. Org. Chem.* **2007**, *72*, 6938-6946.

(27) Mydock, L. K.; Demchenko, A. V.: Mechanism of chemical O-glycosylation: from early studies to recent discoveries. *Org. Biomol. Chem.* **2010**, *8*, 497-510.

(28) Crich, D.: Mechanism of a chemical glycosylation reaction. *Acc. Chem. Res.* **2010**, *43*, 1144-1153.

(29) Dasgupta, F.; Garegg, P. J.: Use of sulfenyl halides in carbohydrate reactions. Part I. Alkyl sulfenyl triflate as activator in the thioglycoside-mediated

formation of -glycosidic linkages during oligosaccharide synthesis. Carbohydrate. *Carbohydr. Res.* **1988**, *177*, C13-C17.

(30) Zhong, W.; Boons, G.-J.: Glycoside synthesis from 1-sulfur/selenium-substituted derivatives: thioglycosides in oligosaccharide synthesis. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 261-303.

(31) Ranade, S. C.; Demchenko, A. V.: Mechanism of chemical glycosylation: focus on the mode of activation and departure of anomeric leaving groups. *J. Carbohydr. Chem.* **2013**, *32*, 1-43.

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

(33) Ferrier, R. J.; Furneaux, R. H.: Synthesis of 1,2-trans-related 1-thioglycoside esters. *Carbohydr. Res.* **1976**, *52*, 63-68.

(34) Garcia, B. A.; Gin, D. Y.: Dehydrative glycosylation with activated diphenyl sulfonium reagents. Scope, mode of C(1)-hemiacetal activation, and detection of reactive glycosyl intermediates. *J. Am. Chem. Soc.* **2000**, *122*, 4269-4279.

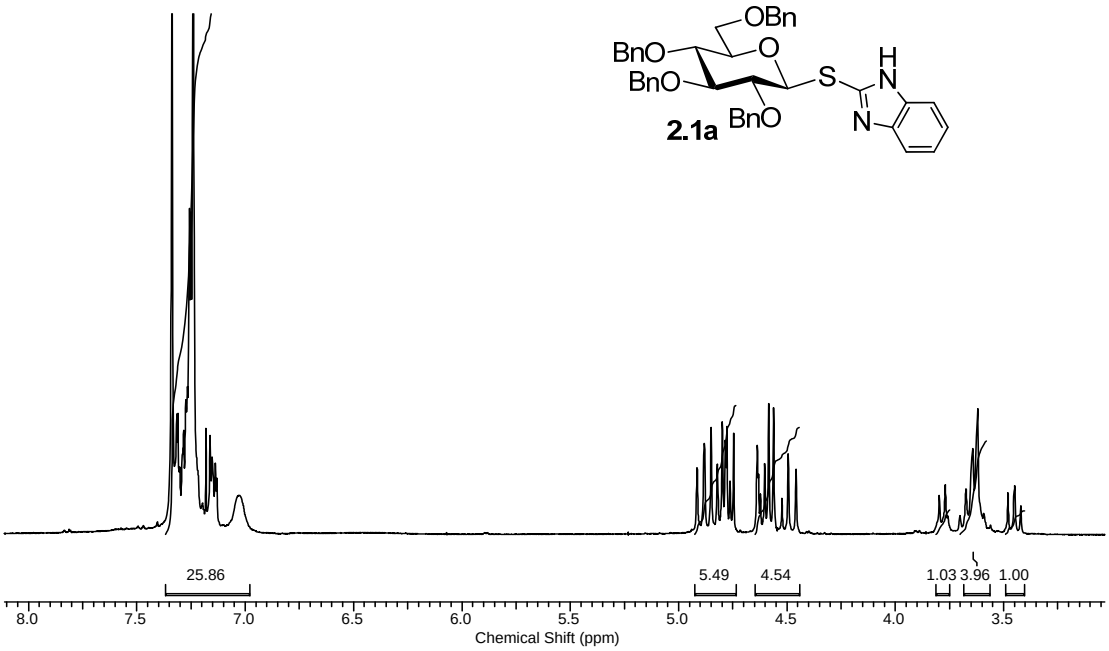
(35) Pfaeffli, P. J.; Hixson, S. H.; Anderson, L.: Thioglycosides having O-benzyl blocking groups as intermediates for the systematic, sequential synthesis of oligosaccharides. Synthesis of isomaltose. *Carbohydr. Res.* **1972**, *23*, 195-206.

(36) Agoston, K.; Kroeger, L.; Dekany, G.; Thiem, J.: On Resin Modification of Monosaccharides. *J. Carbohydr. Chem.* **2007**, *26*, 513-525.

(37) Demchenko, A. V.; Kamat, M. N.; De Meo, C.: S-Benzoxazolyl (SBox) glycosides in oligosaccharide synthesis: novel glycosylation approach to the synthesis of β-D-glucosides, β-D-galactosides, and α-D-mannosides. *Synlett* **2003**, 1287-1290.

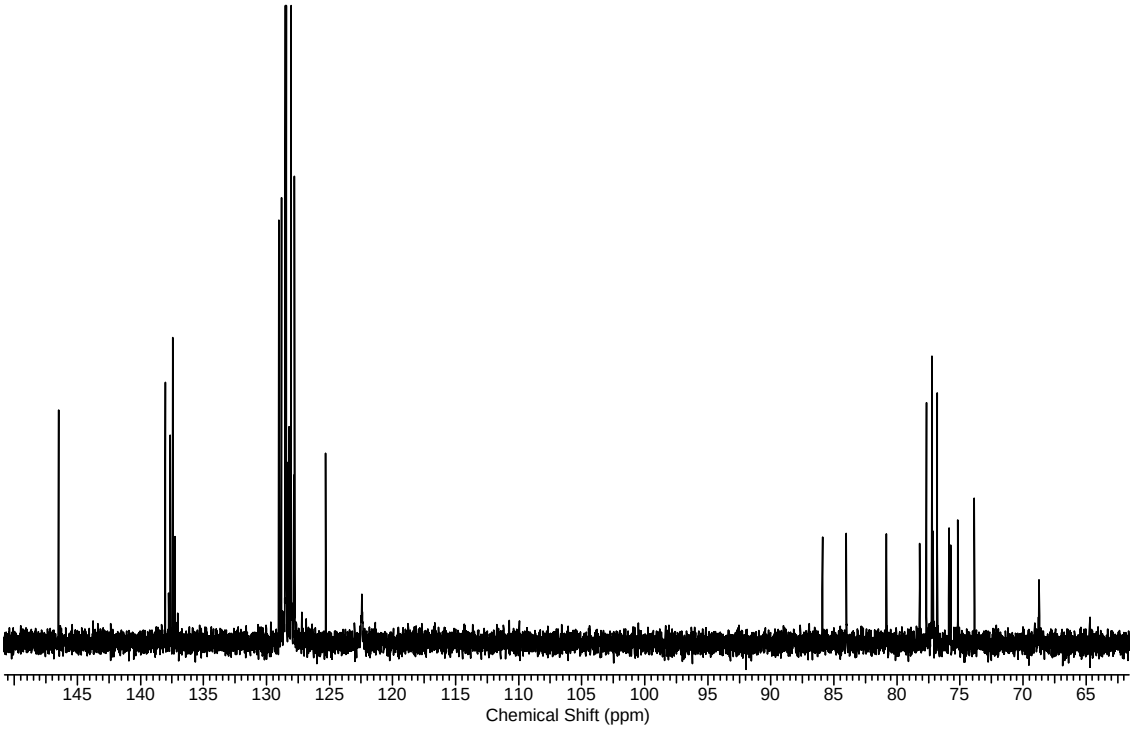
(38) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V.: Stereospecific synthesis of 1,2-cis-glycosides of 2-amino sugars. *Carbohydr. Res.* **1993**, *242*, C7-C10.

Appendix



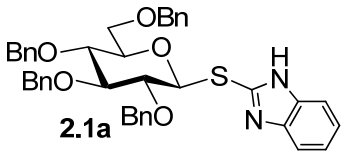
$CDCl_3$ at 300 MHz

Figure A-1: ^{1}H NMR spectrum of Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.1a**).



$CDCl_3$ at 75 MHz

Figure A-2: ^{13}C NMR spectrum of Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.1a**).



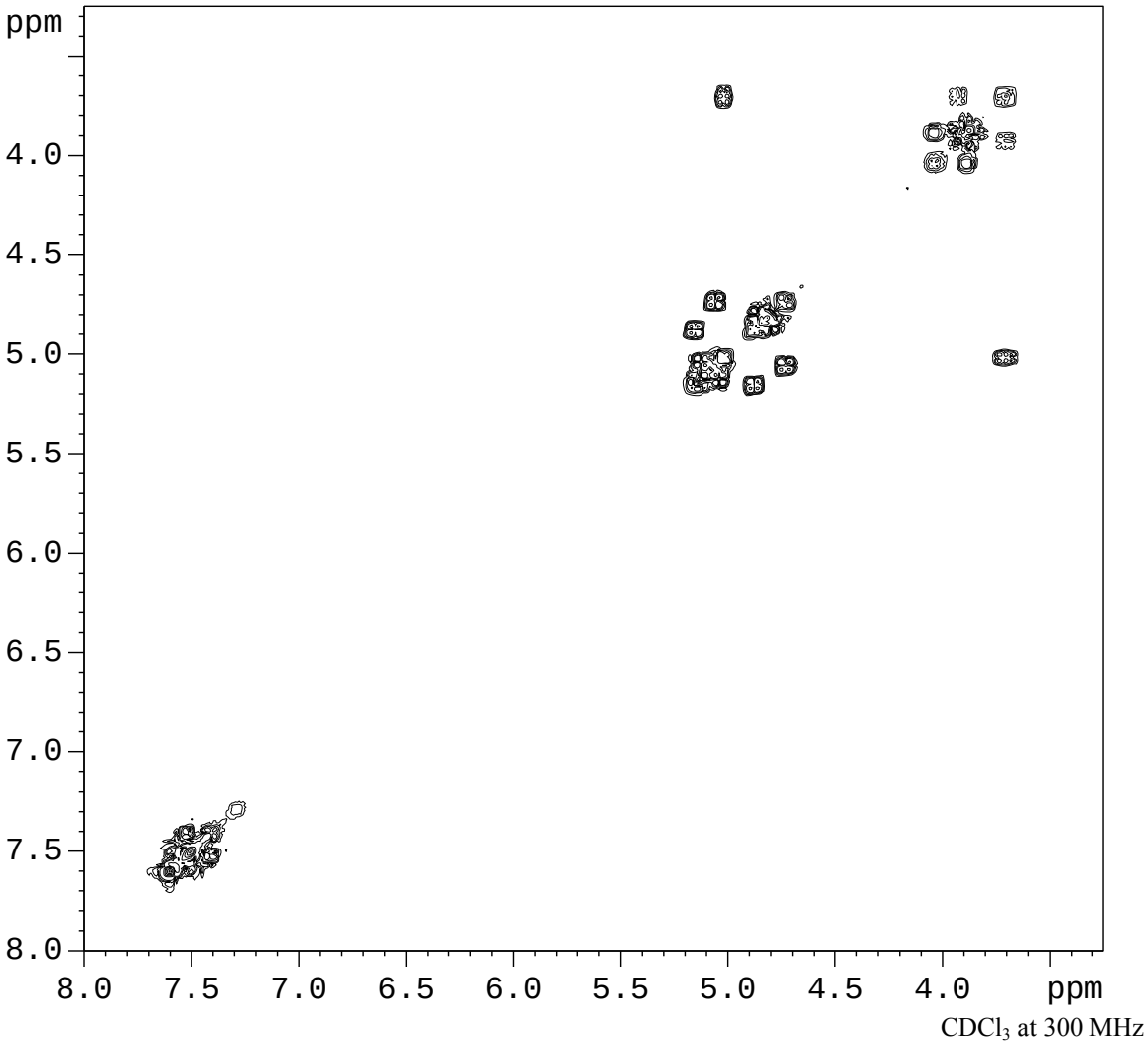
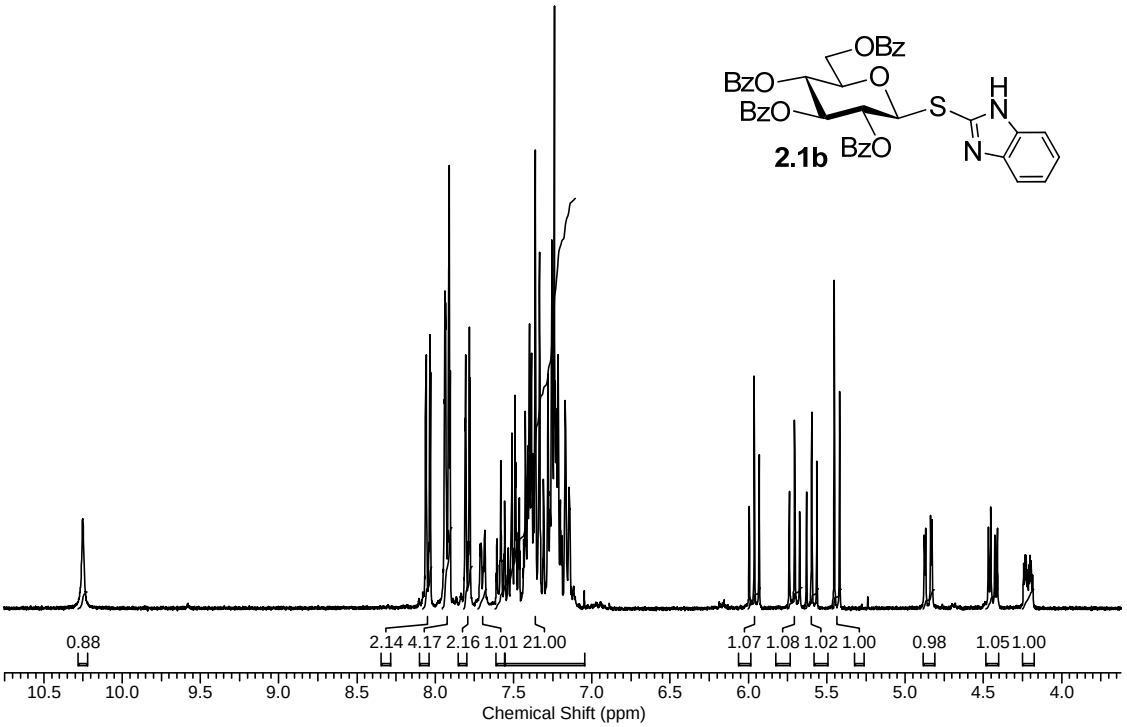
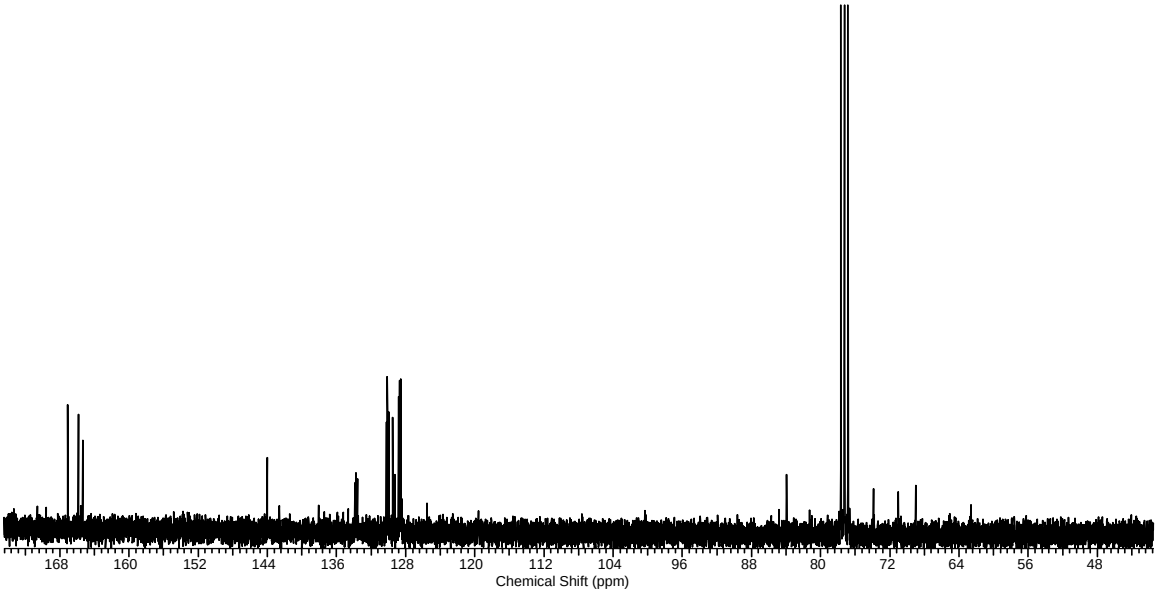


Figure A-3: 2-D NMR COSY spectrum of Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.1a**).



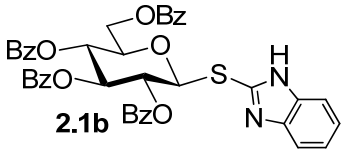
$CDCl_3$ at 300 MHz

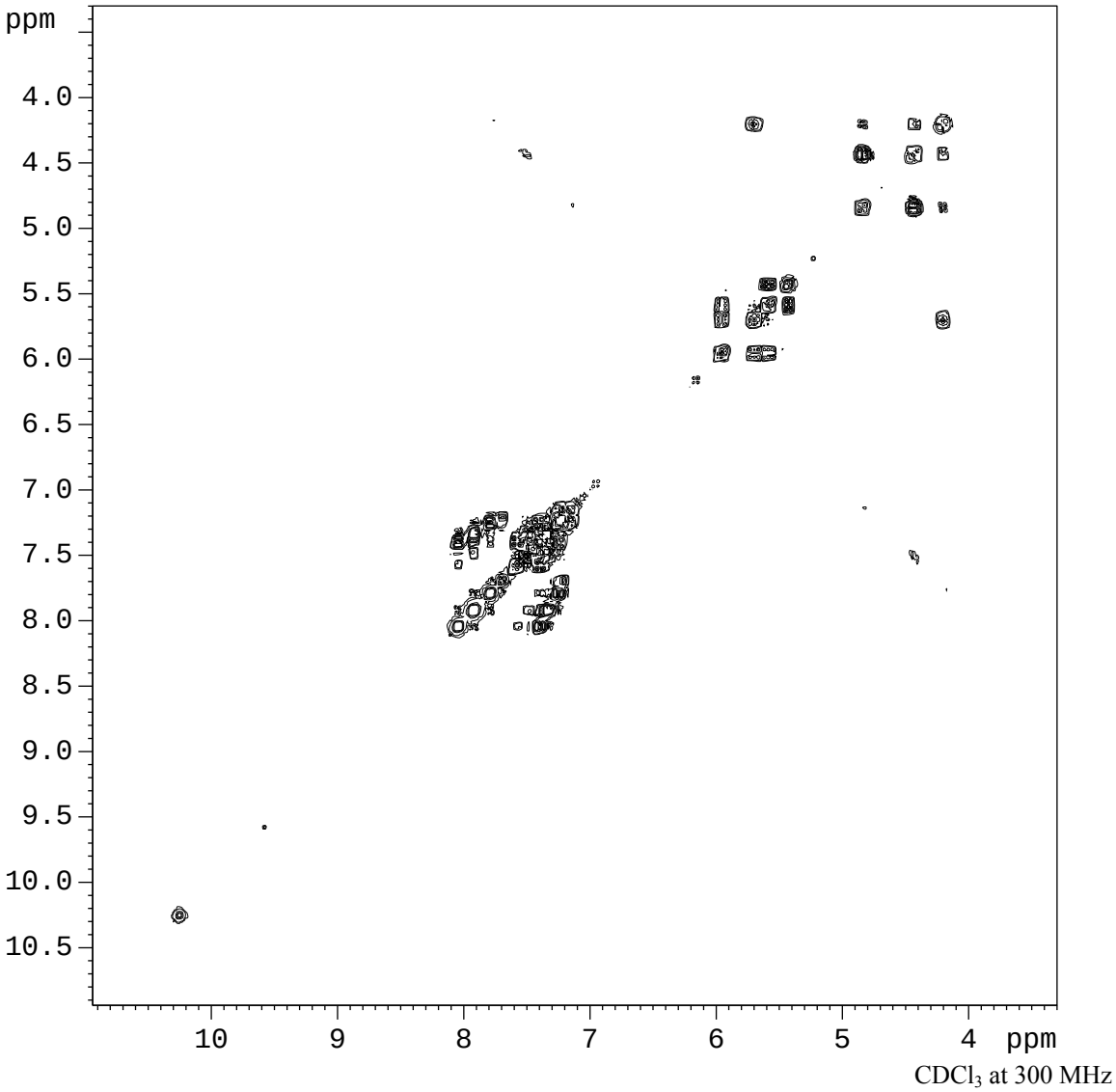
Figure A-4: ^{1}H NMR spectrum of Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.1b**).



$CDCl_3$ at 75 MHz

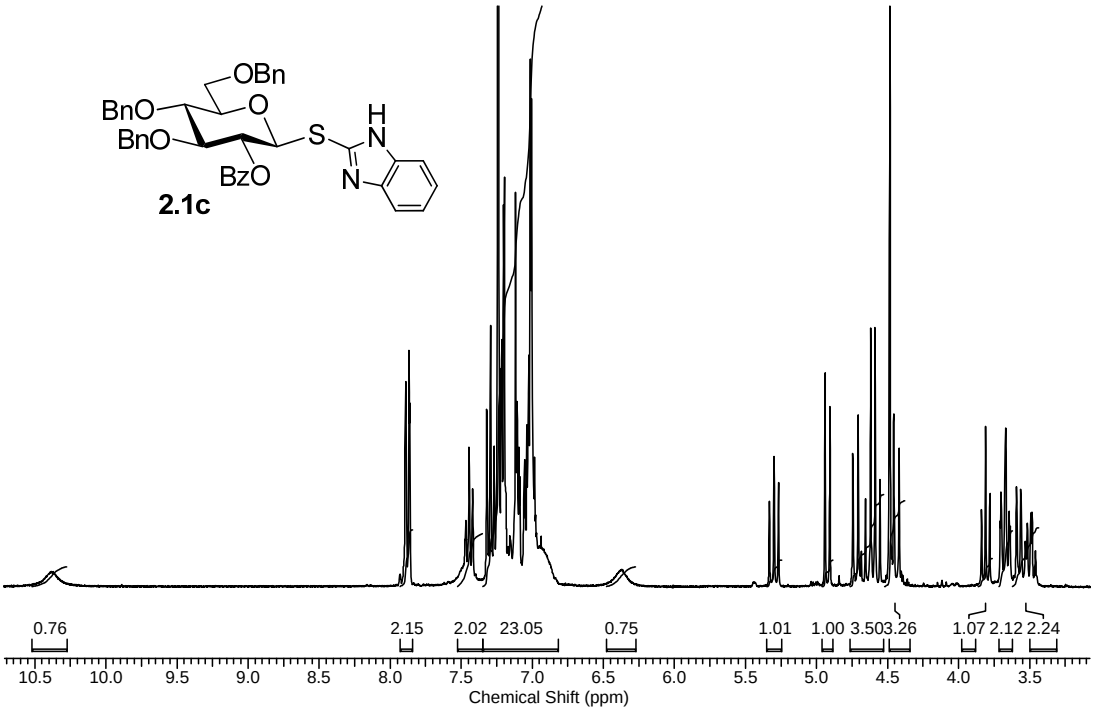
Figure A-5: ^{13}C NMR spectrum of Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.1b**).





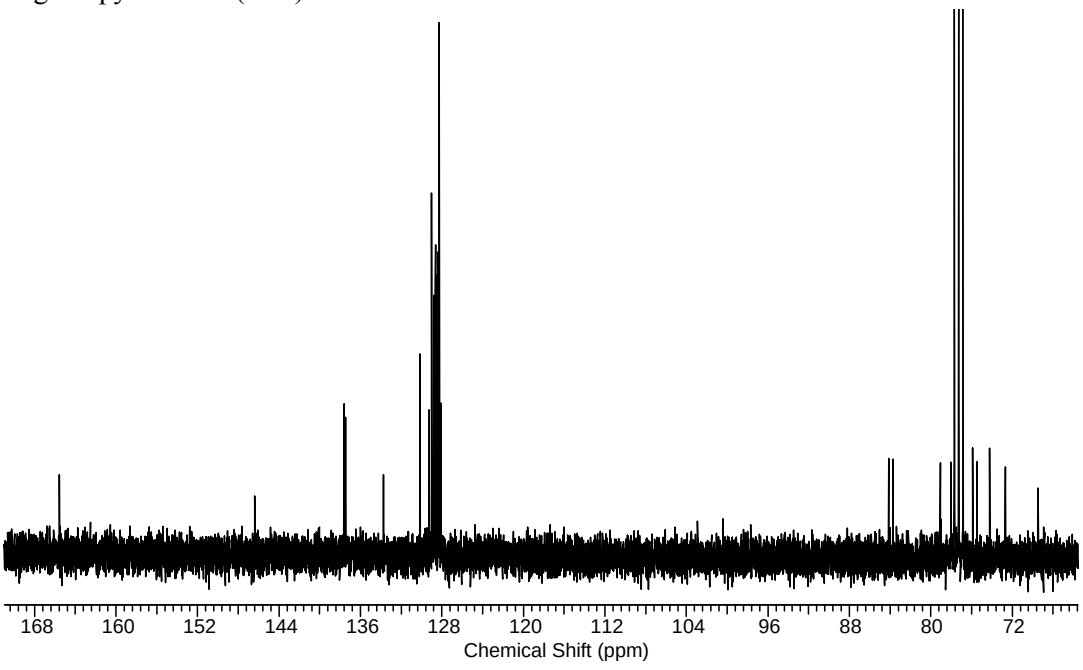
$CDCl_3$ at 300 MHz

Figure A-6: 2-D NMR COSY spectrum of Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.1b**).



$CDCl_3$ at 300 MHz

Figure A-7: ^{1}H NMR spectrum of Benzimidazol-2-yl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.1c**).



$CDCl_3$ at 75 MHz

Figure A-8: ^{13}C NMR spectrum of Benzimidazol-2-yl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.1c**).

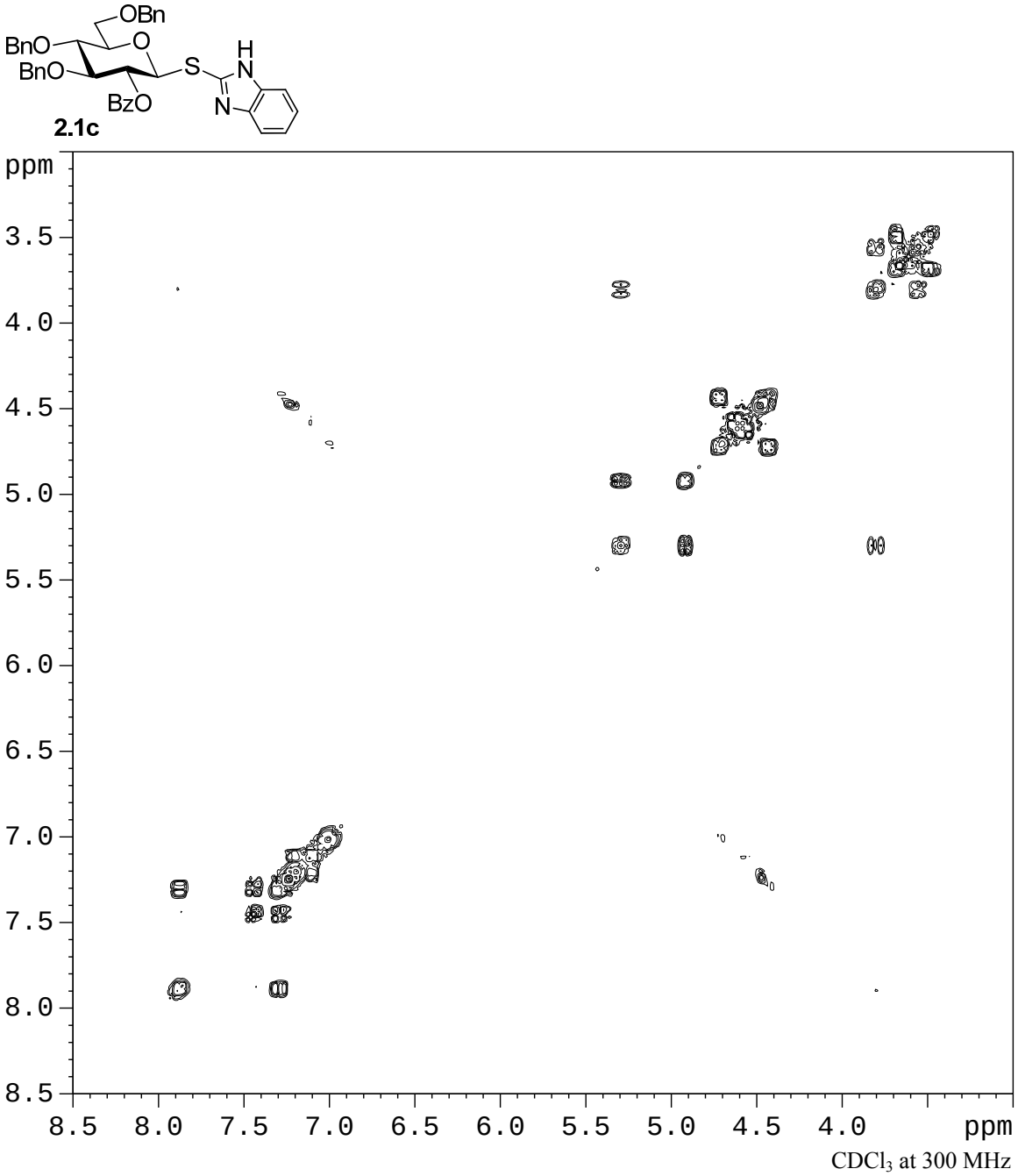


Figure A-9: 2-D NMR COSY spectrum of Benzimidazol-2-yl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.1c**).

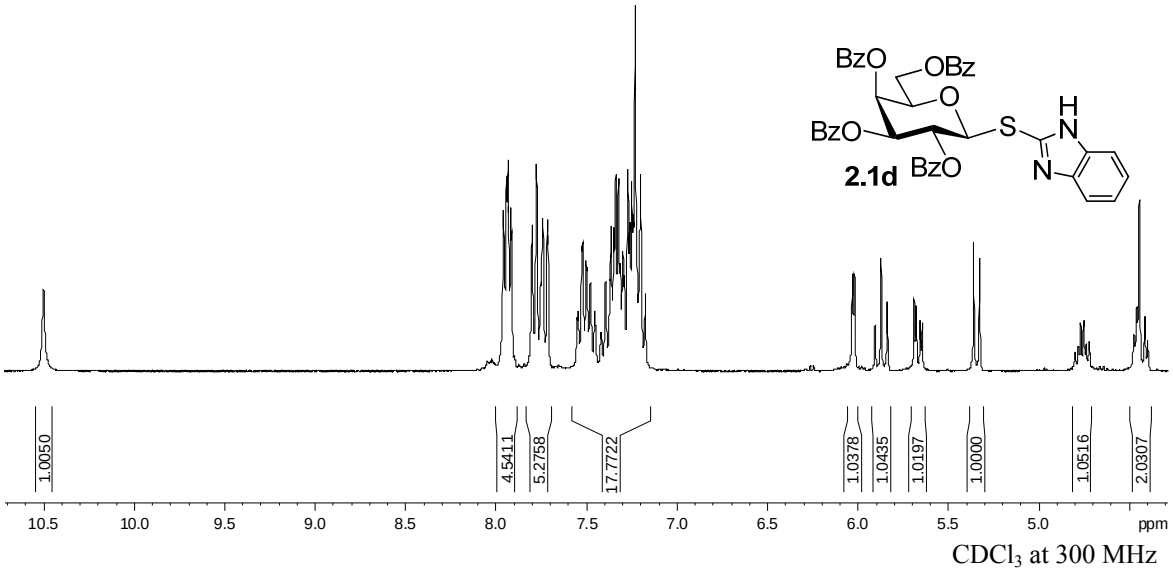


Figure A-10: ^{1}H NMR spectrum of Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (**2.1d**).

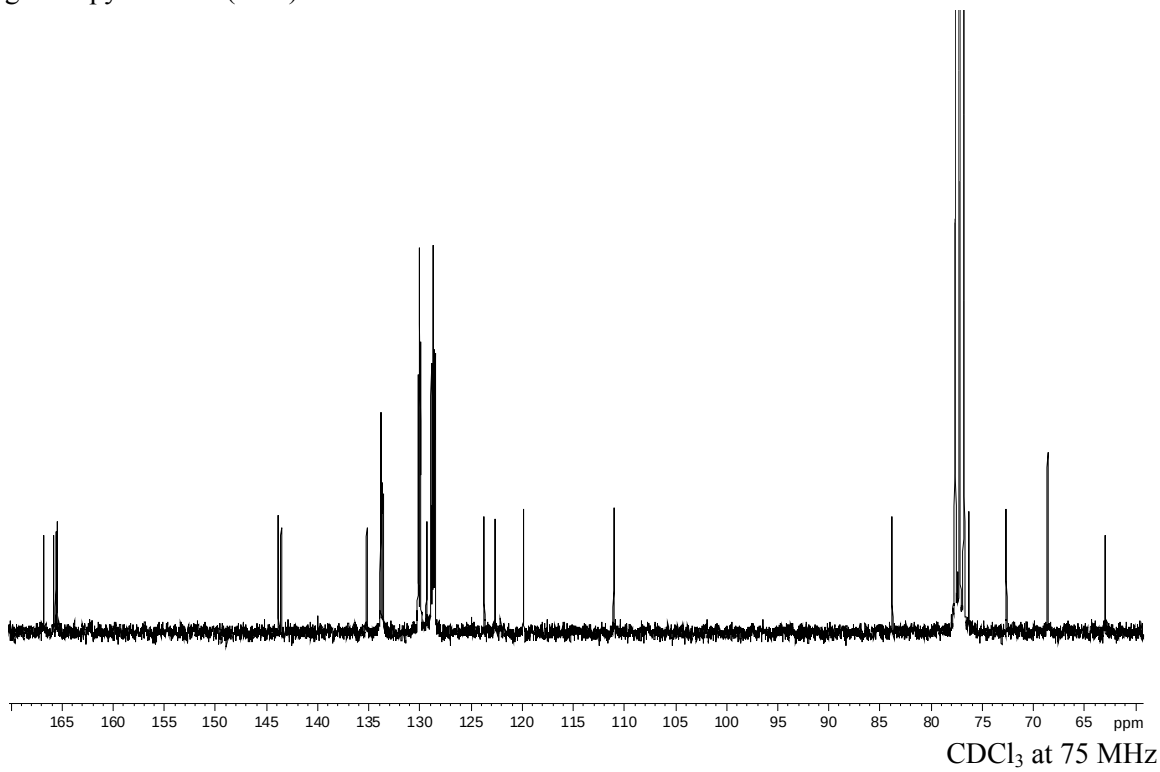
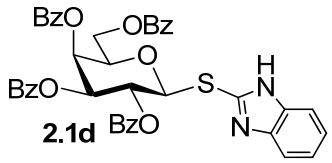


Figure A-11: ^{13}C NMR spectrum of Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (**2.1d**).



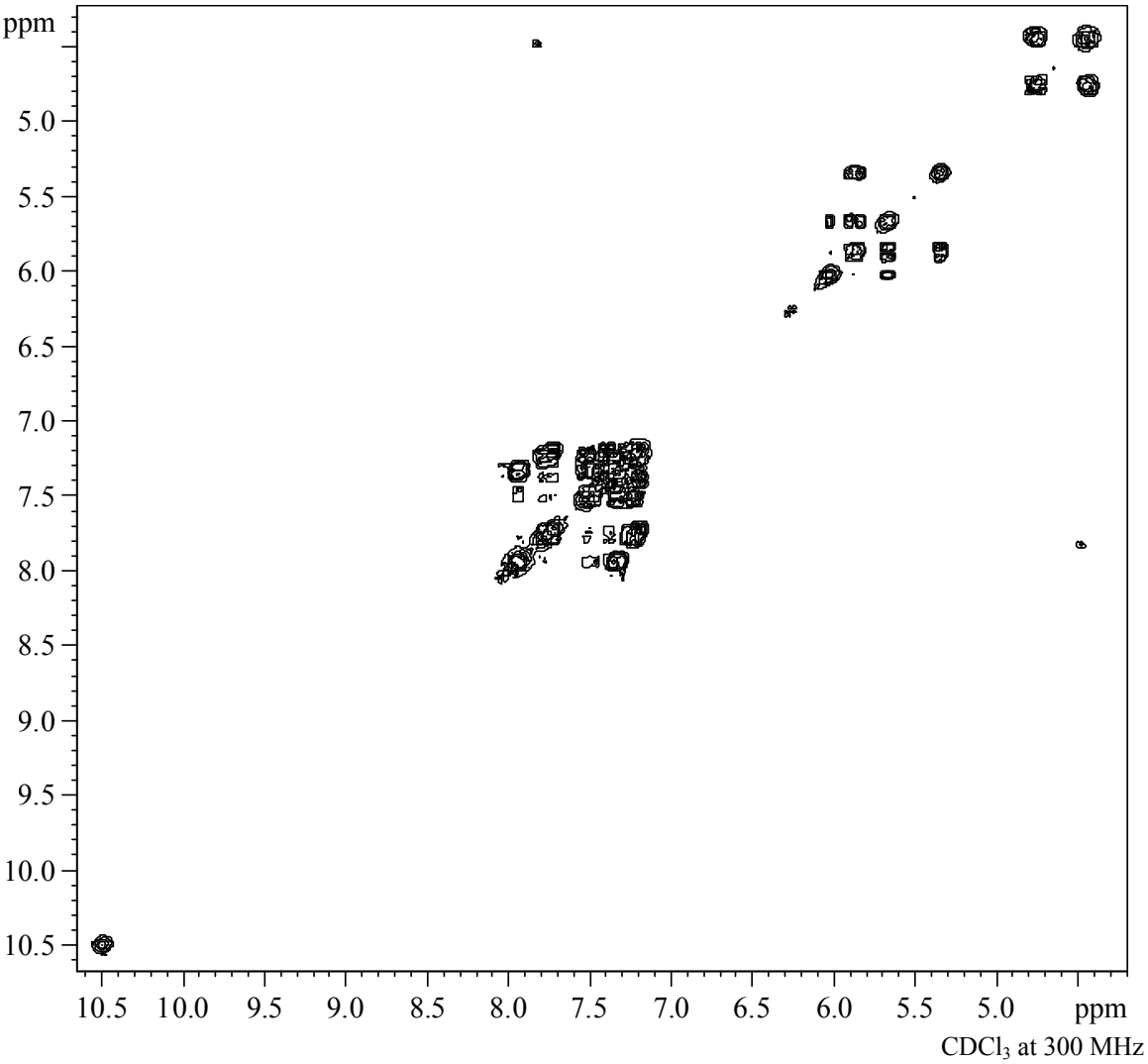
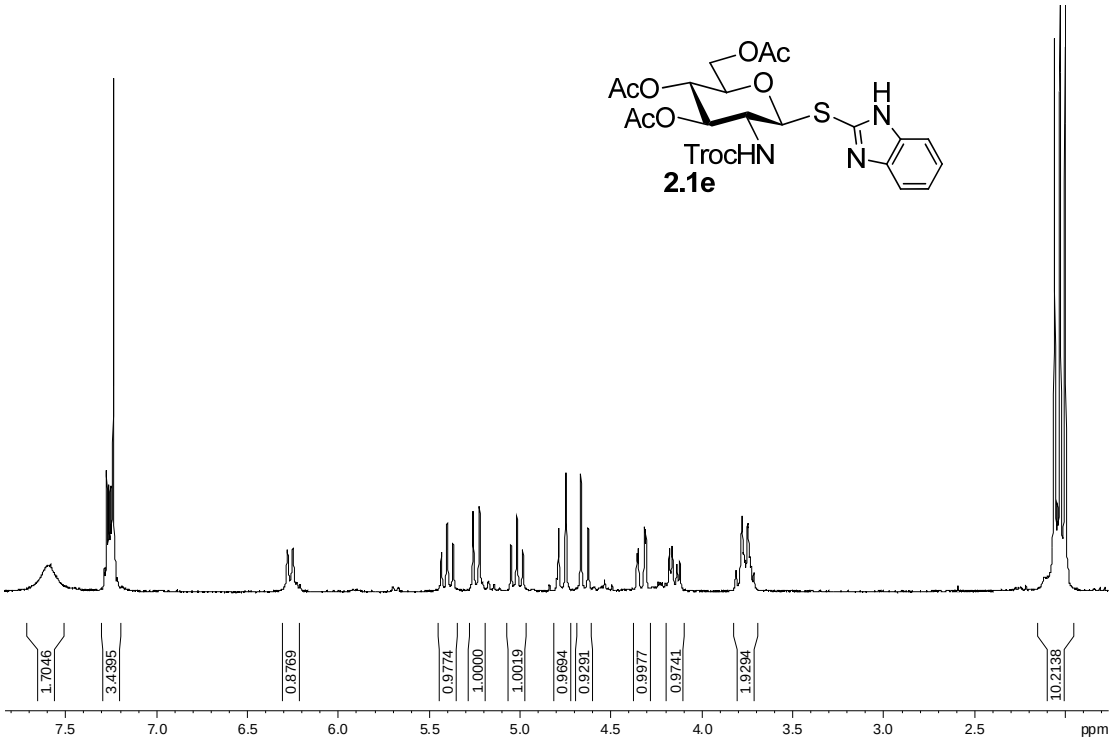
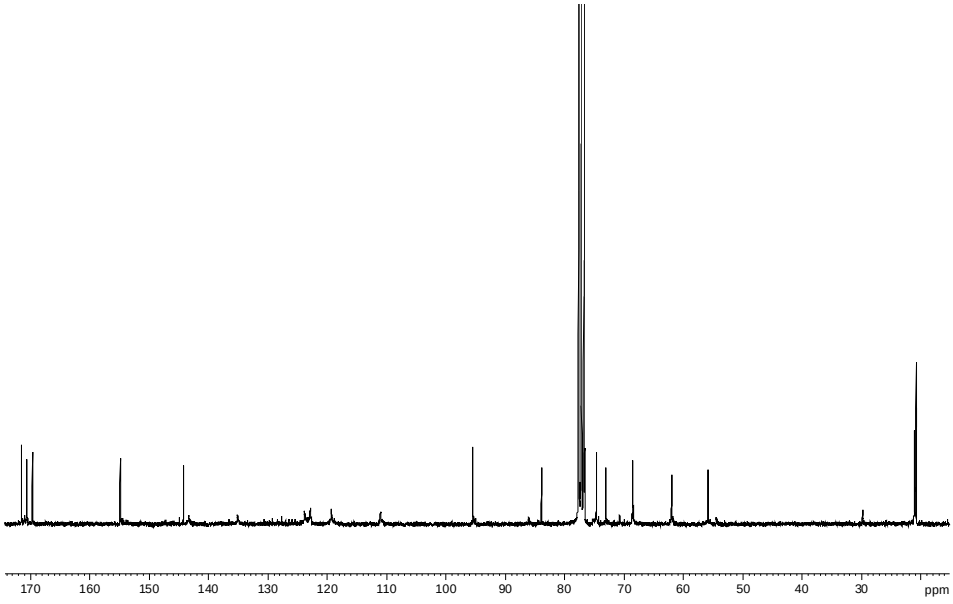


Figure A-12: 2-D NMR COSY spectrum of Benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (**2.1d**).



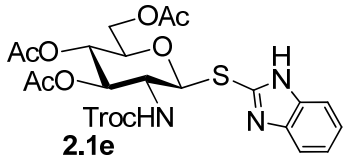
$CDCl_3$ at 300 MHz

Figure A-13: ^{1}H NMR spectrum of Benzimidazol-2-yl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxy)carbamoyl-1-thio-β-D-glucopyranoside (**2.1e**).



$CDCl_3$ at 75 MHz

Figure A-14: ^{13}C NMR spectrum of Benzimidazol-2-yl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxy)carbamoyl-1-thio-β-D-glucopyranoside (**2.1e**).



2.1e

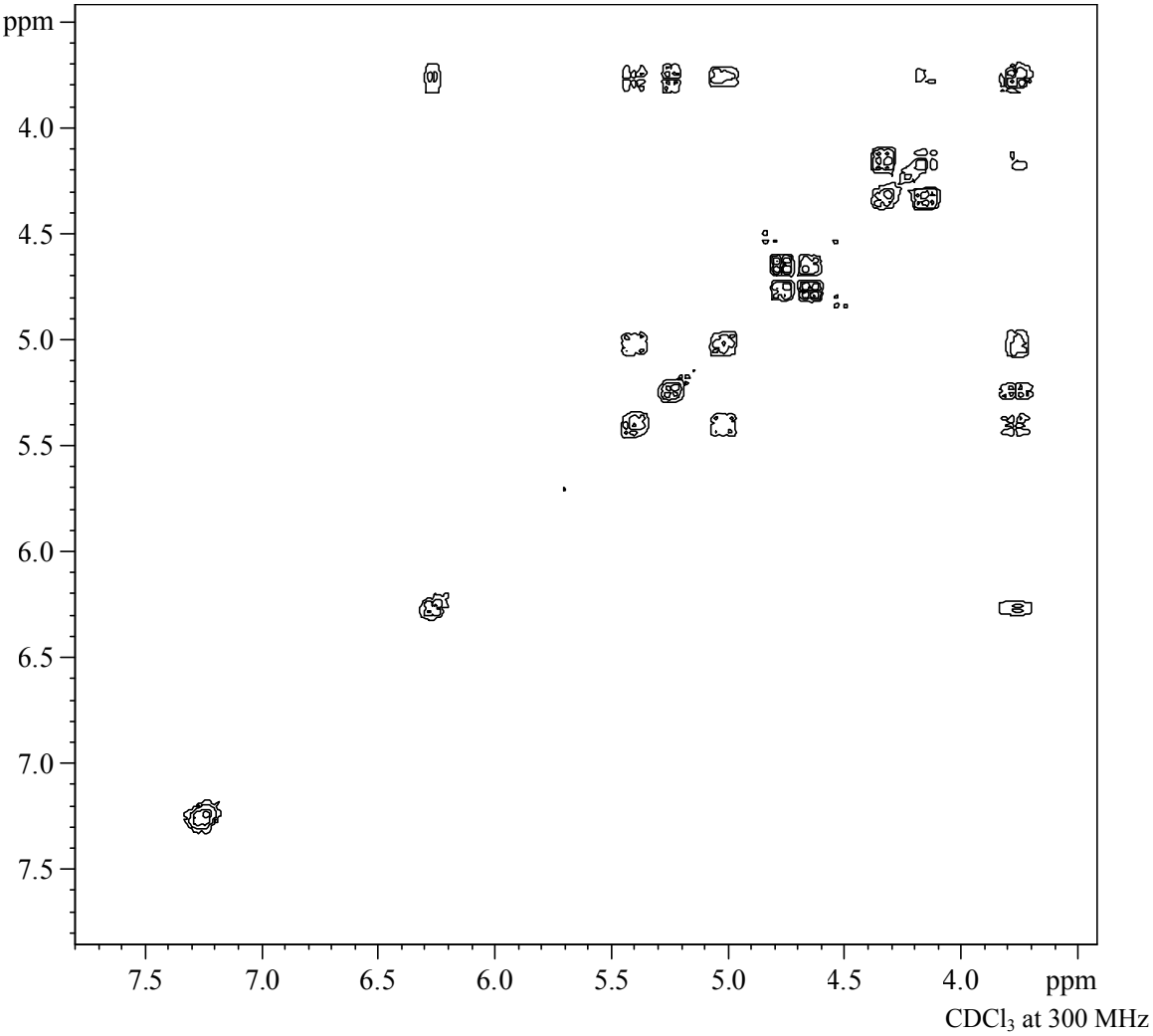
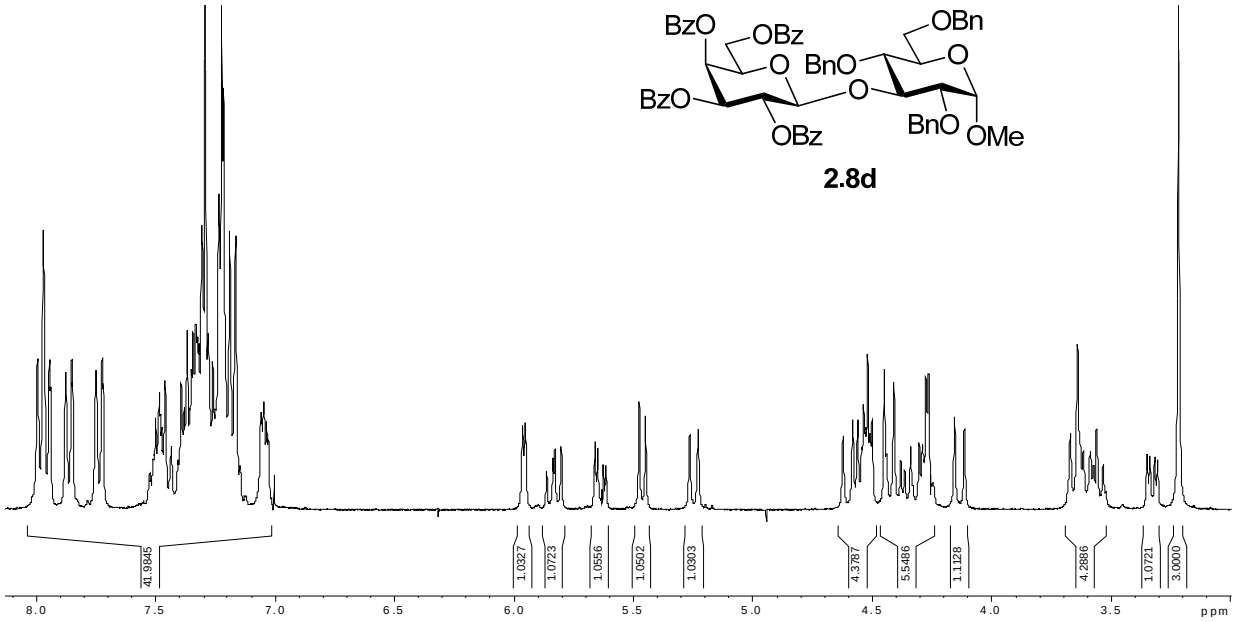
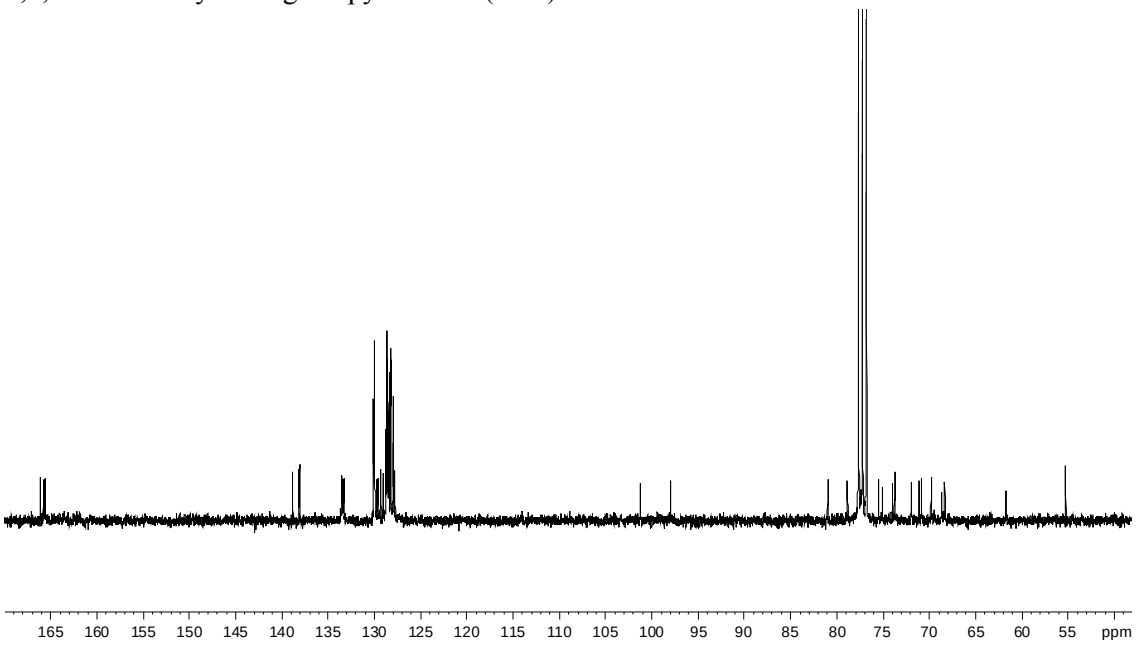


Figure A-15: 2-D NMR COSY spectrum of Benzimidazol-2-yl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxy)carbamoyl-1-thio-β-D-glucopyranoside (**2.1e**).



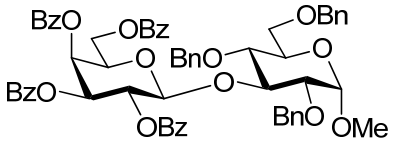
$CDCl_3$ at 300 MHz

Figure A-16: ^{1}H NMR spectrum of Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**2.8d**).



$CDCl_3$ at 75 MHz

Figure A-17: ^{13}C NMR spectrum of Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**2.8d**).



2.8d

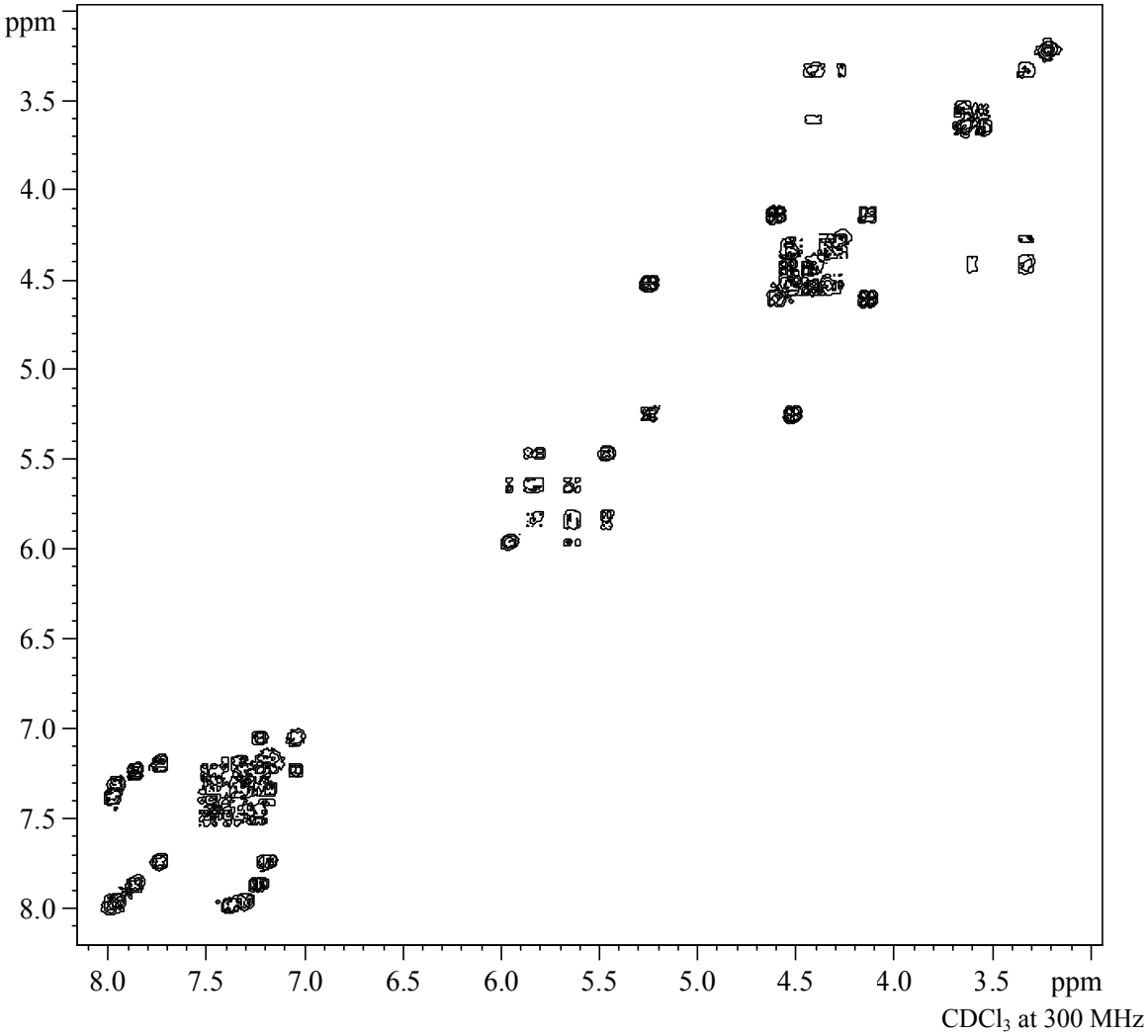
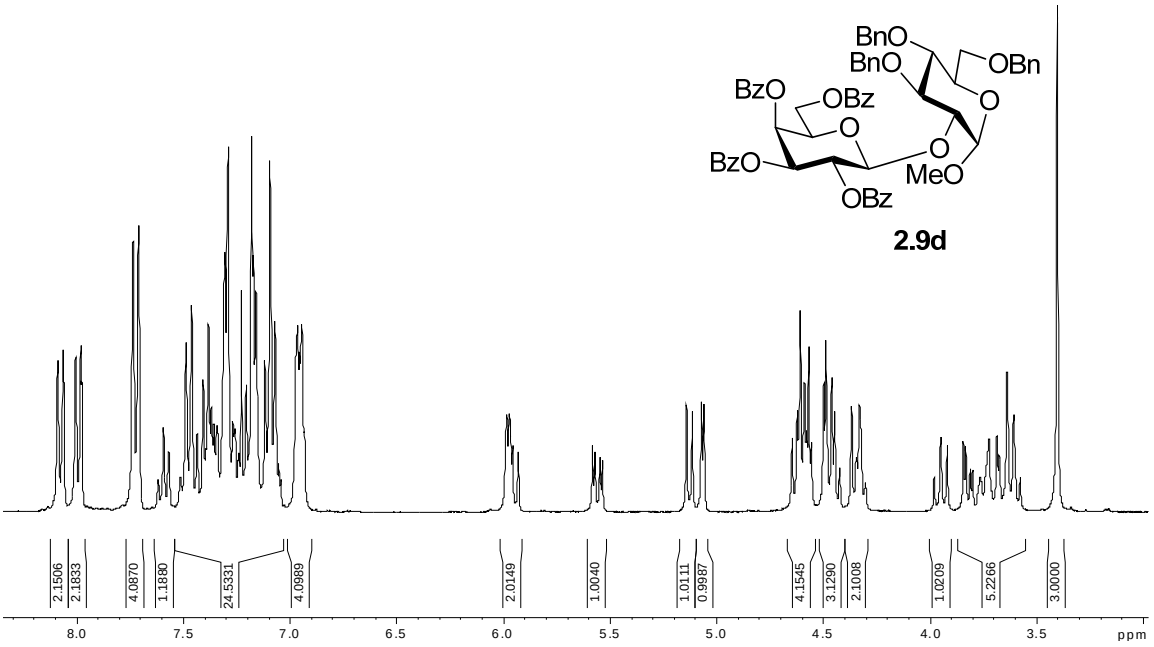
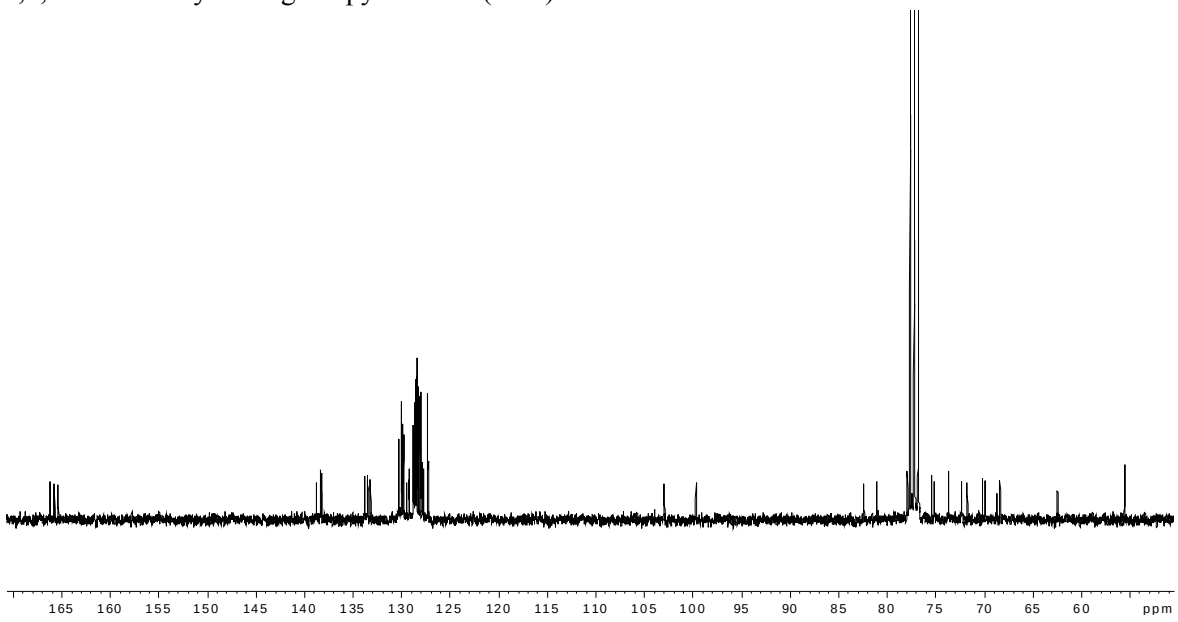


Figure A-18: 2-D NMR COSY spectrum of Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**2.8d**).



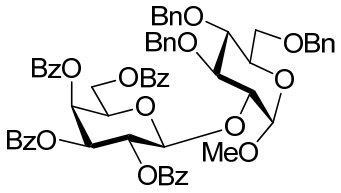
$CDCl_3$ at 300 MHz

Figure A-19: ^{1}H NMR spectrum of Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**2.9d**).



$CDCl_3$ at 75 MHz

Figure A-20: ^{13}C NMR spectrum of Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**2.9d**).



2.9d

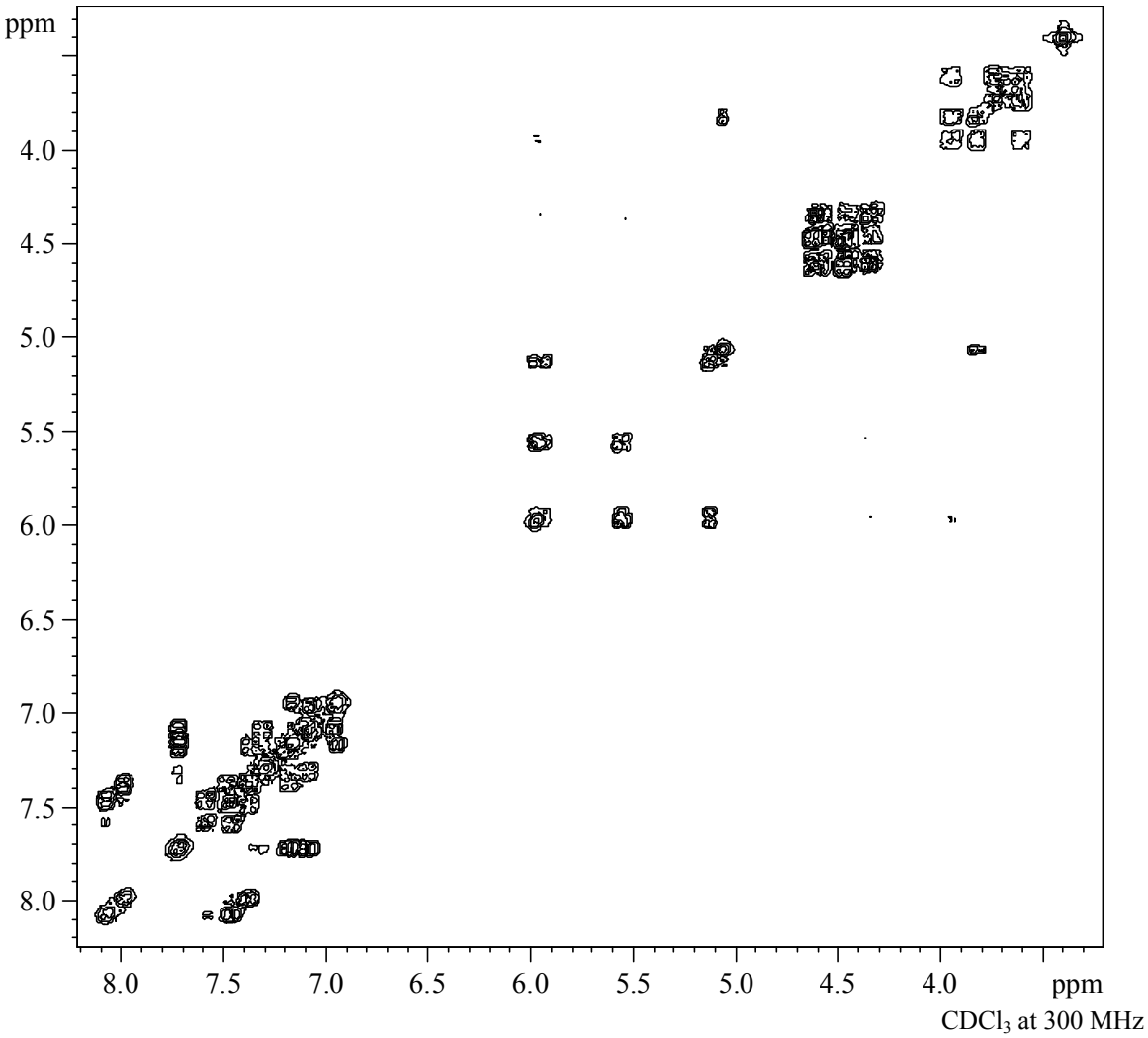
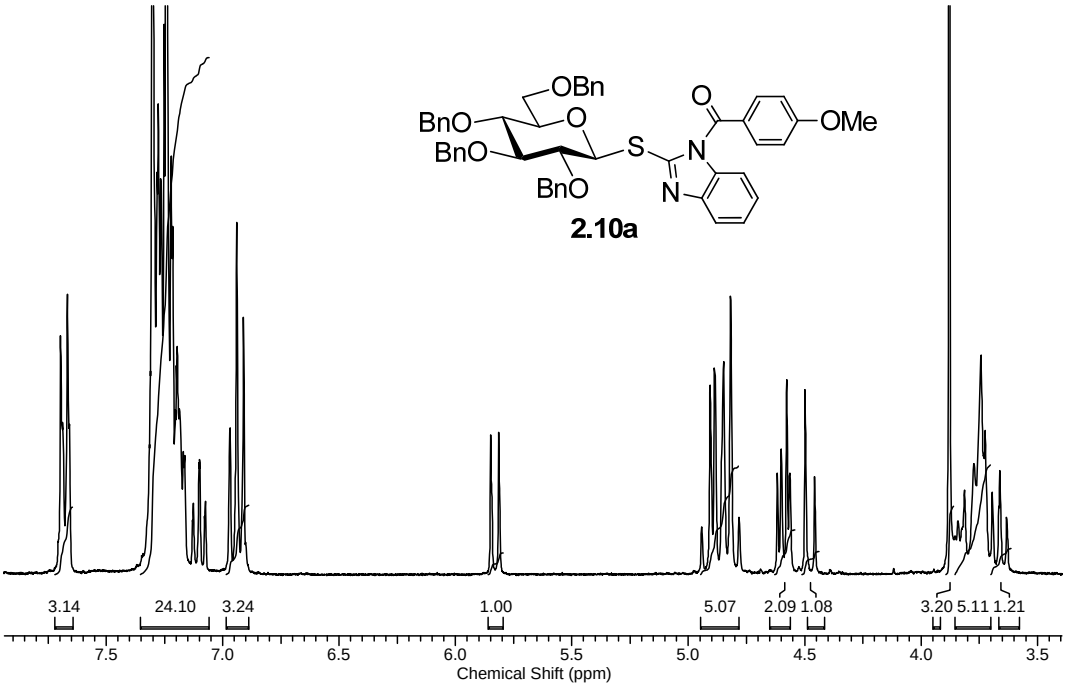
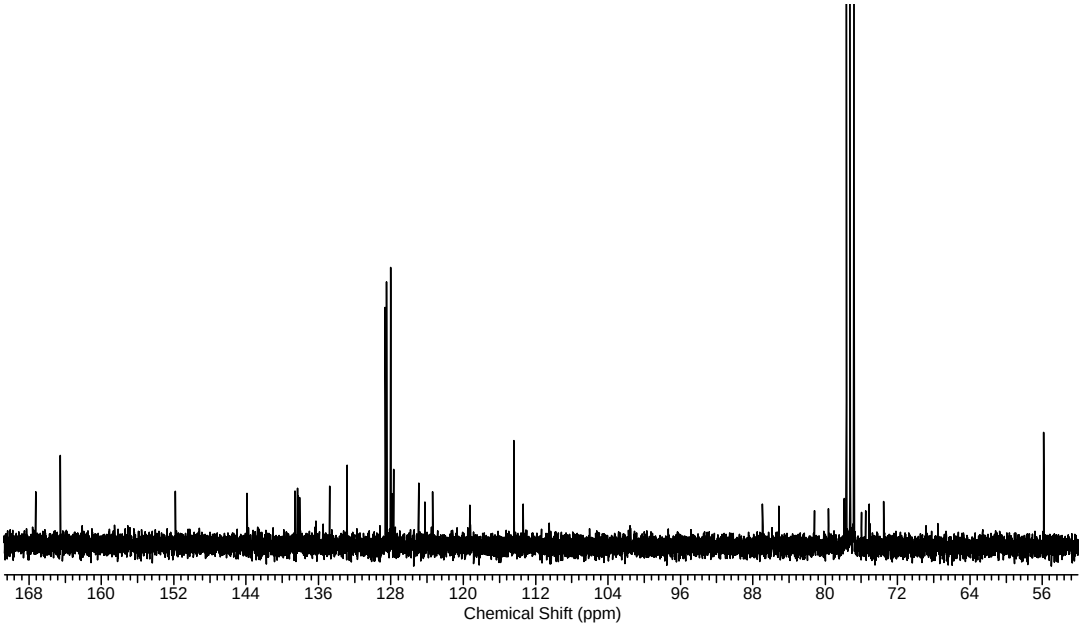


Figure A-21: 2-D NMR COSY spectrum of Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**2.9d**).



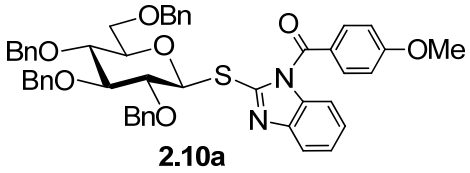
$CDCl_3$ at 300 MHz

Figure A-22: ^{1}H NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.10a**).

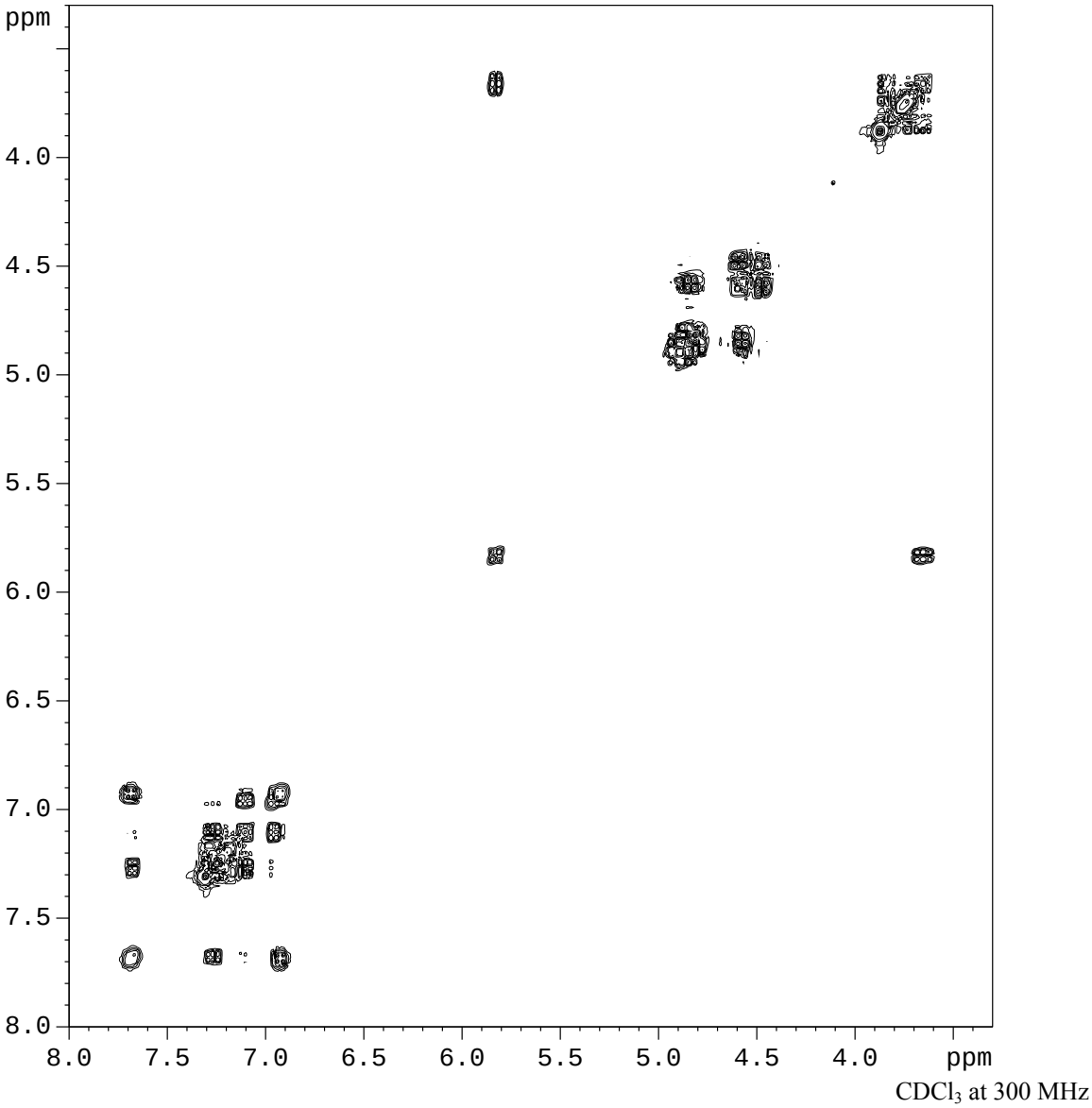


$CDCl_3$ at 75 MHz

Figure A-23: ^{13}C NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.10a**).

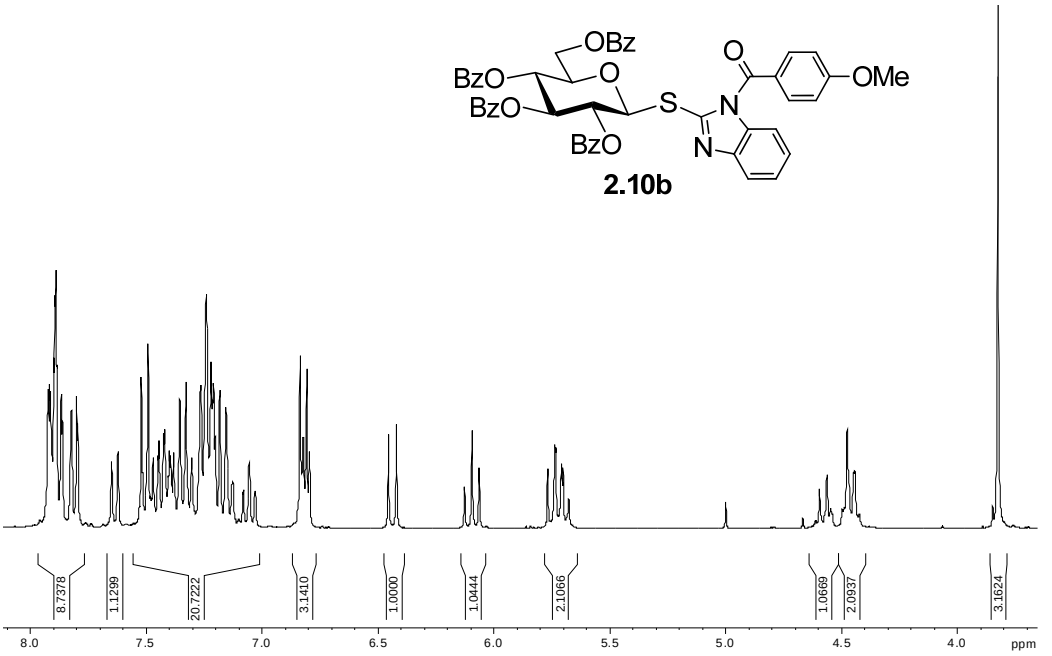


2.10a



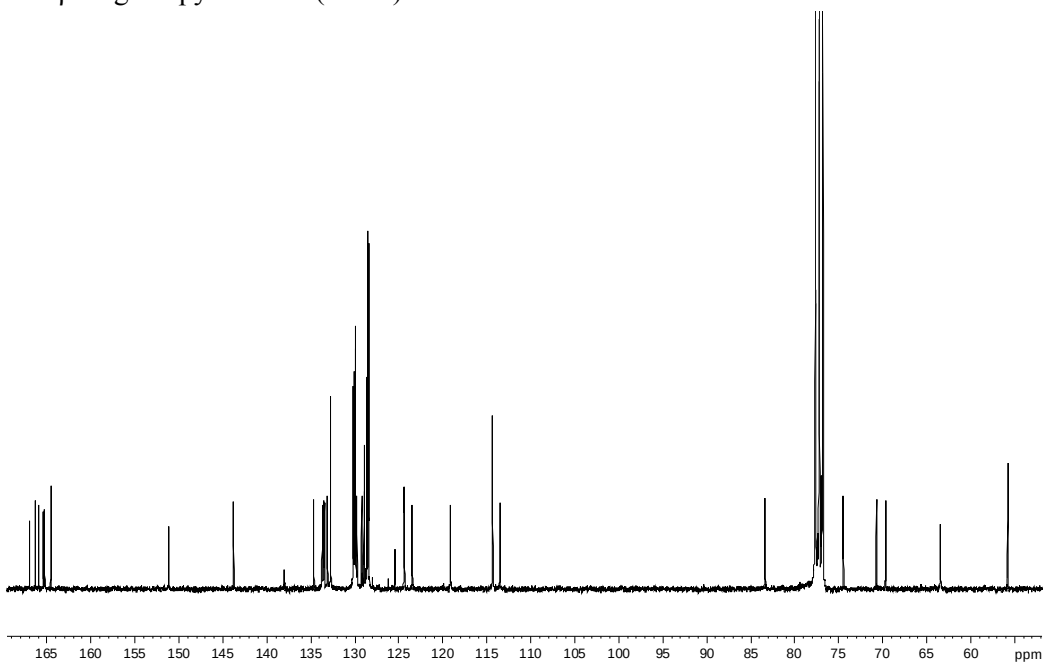
$CDCl_3$ at 300 MHz

Figure A-24: 2-D NMR COSY spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.10a**).



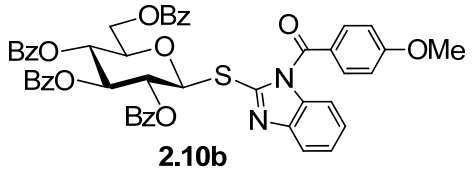
$CDCl_3$ at 300 MHz

Figure A-25: ^{1}H NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.10b**).



$CDCl_3$ at 75 MHz

Figure A-26: ^{13}C NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.10b**).



2.10b

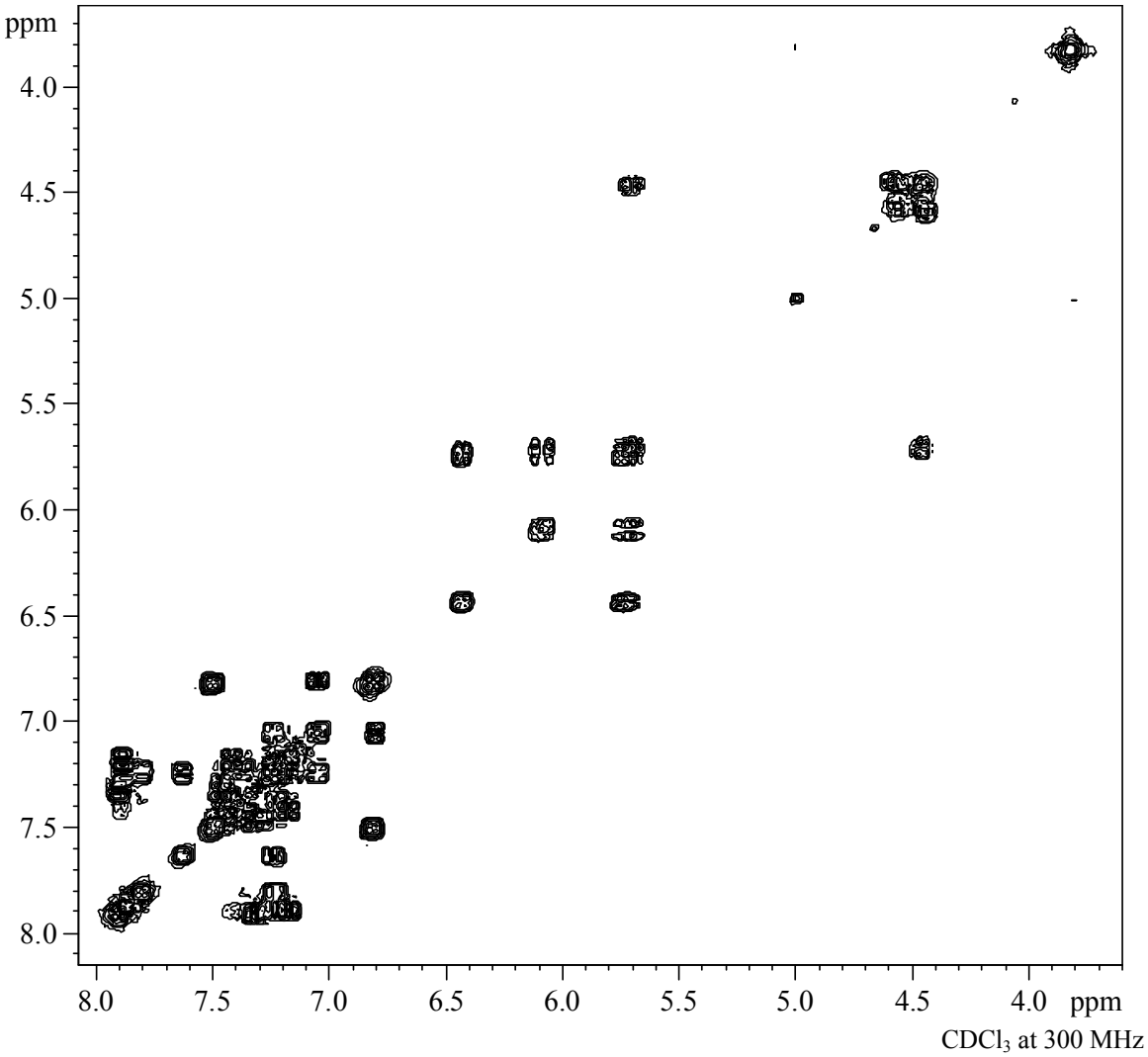
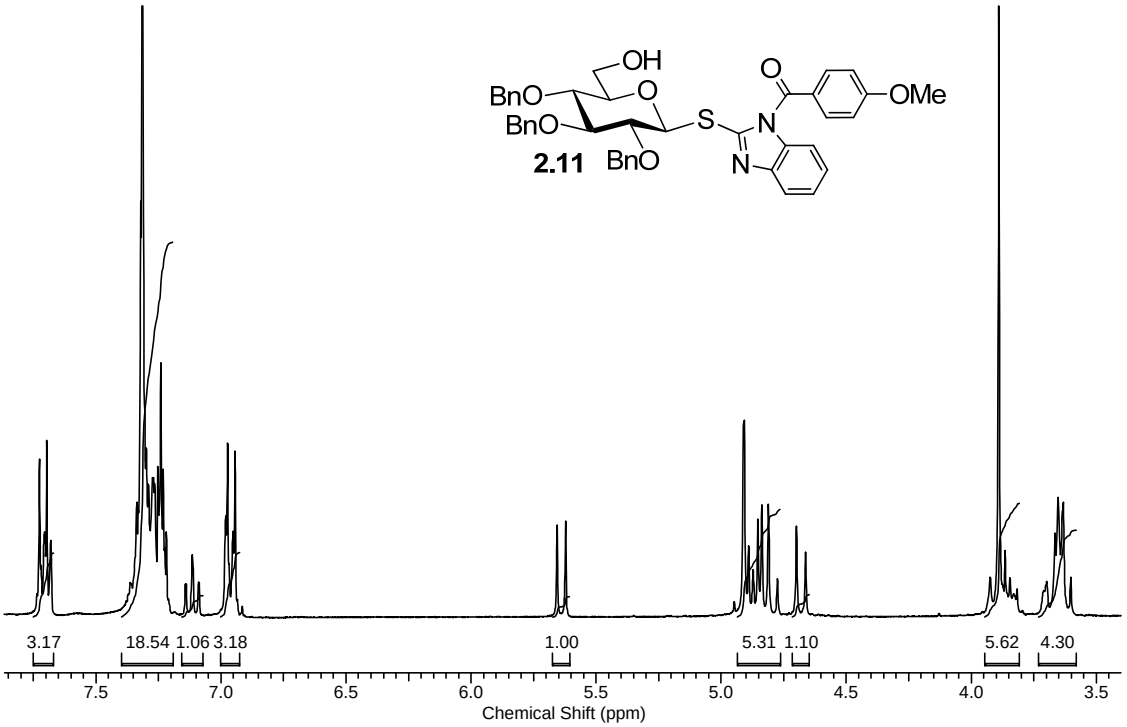
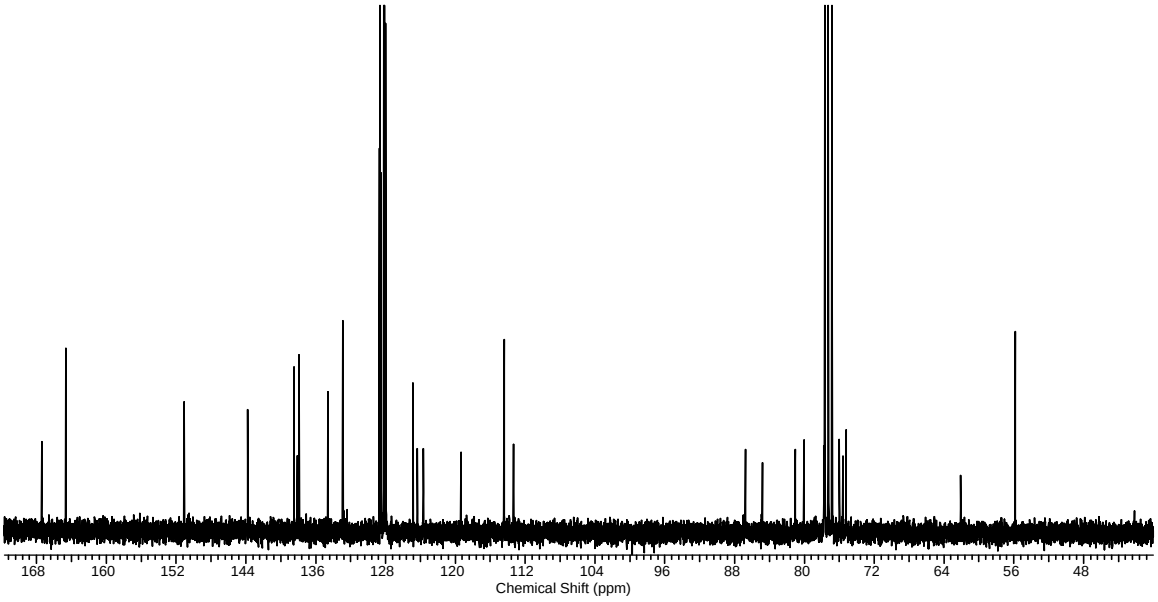


Figure A-27: 2-D NMR COSY spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.10b**).



$CDCl_3$ at 300 MHz

Figure A-28: ^{1}H NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.11**).



$CDCl_3$ at 75 MHz

Figure A-29: ^{13}C NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.11**).

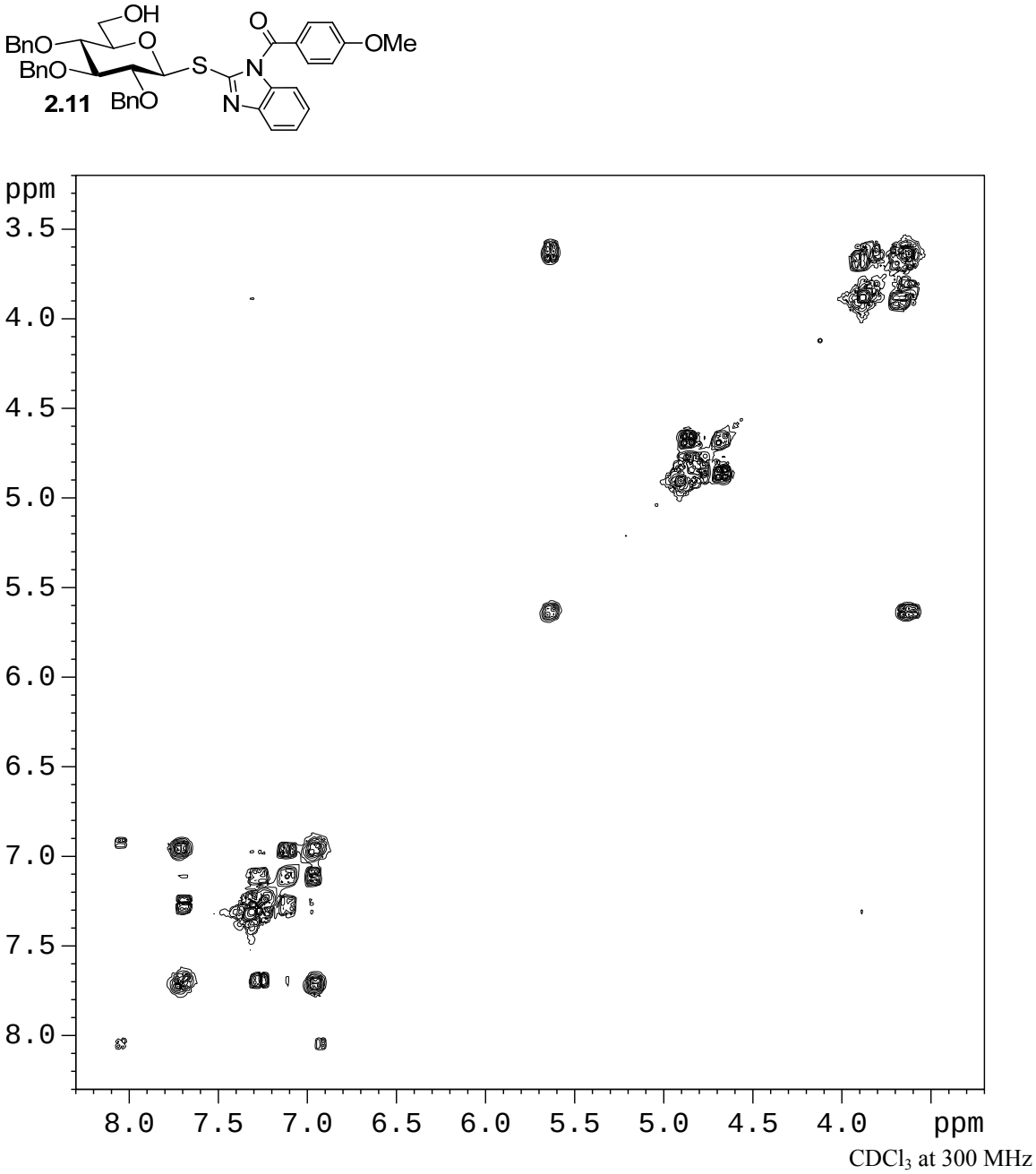
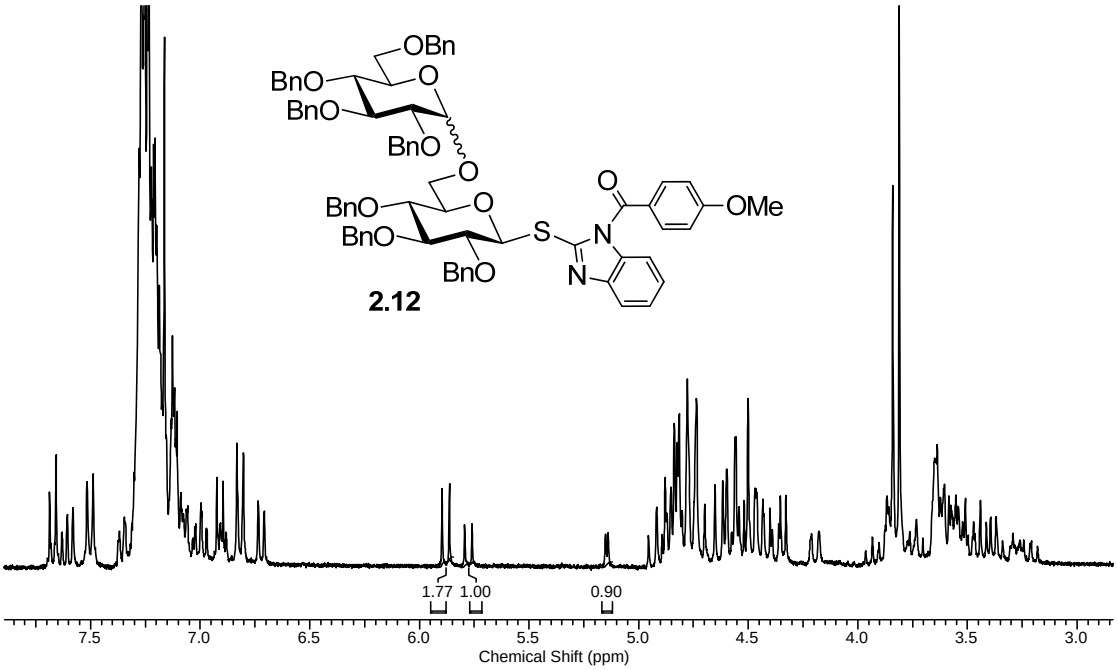
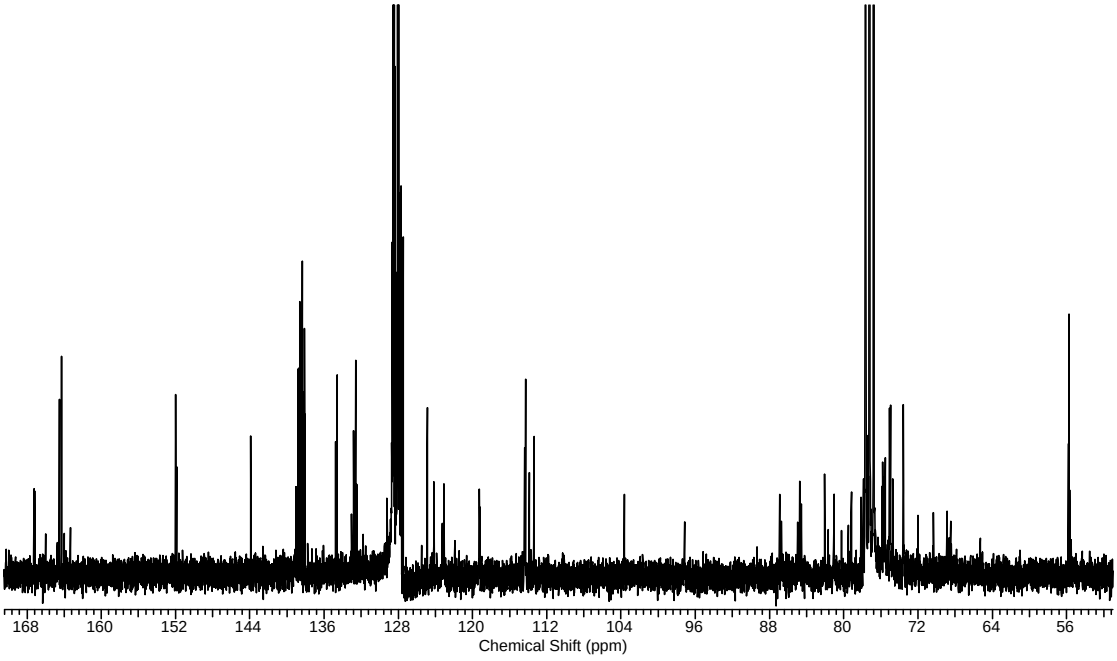


Figure A-30: 2-D NMR COSY spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**2.11**).



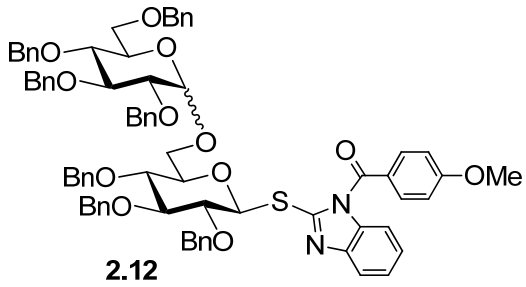
$CDCl_3$ at 300 MHz

Figure A-31: ^{1}H NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 6-*O*-(2,3,4,6-tri-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**2.12**).

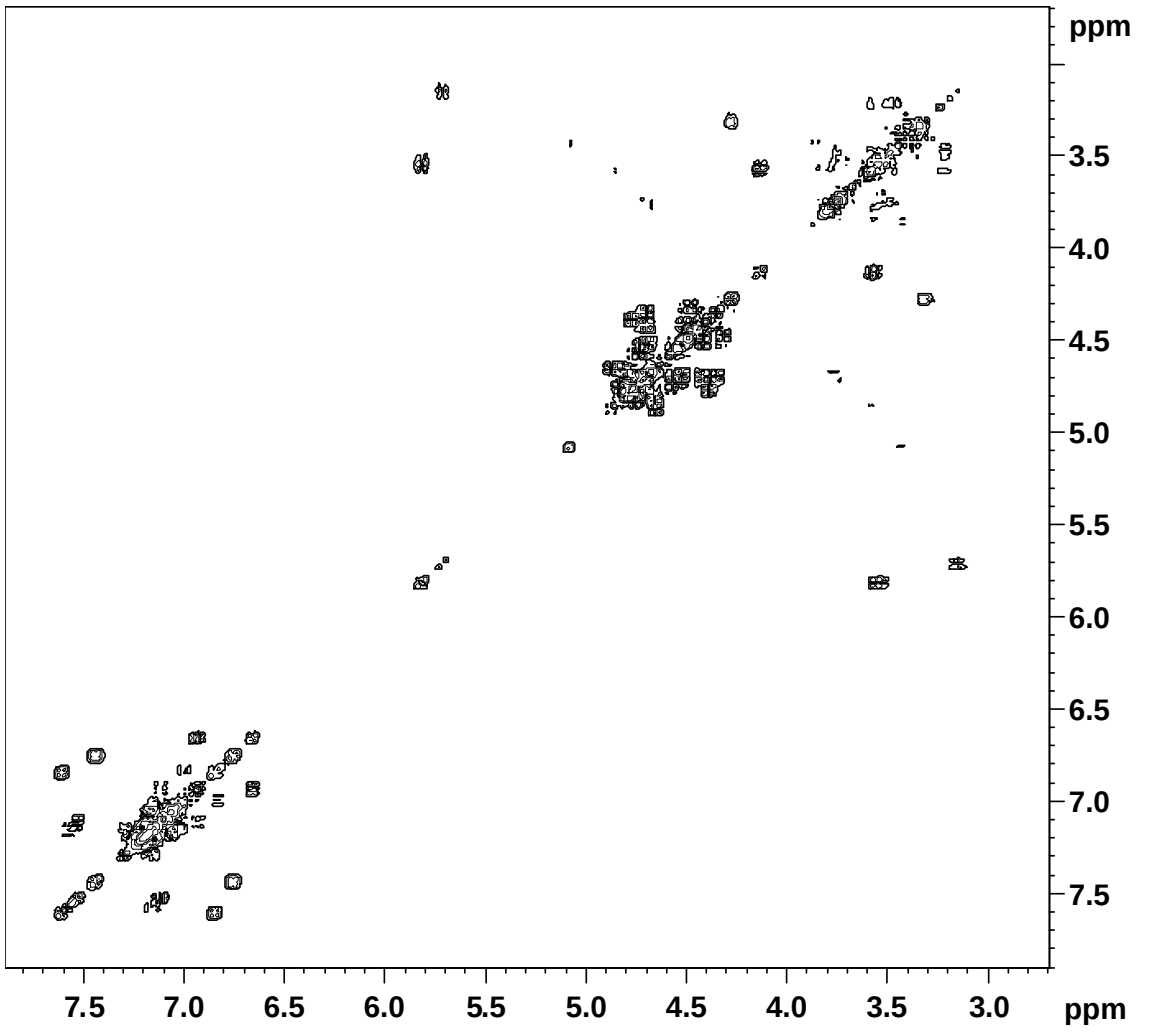


$CDCl_3$ at 75 MHz

Figure A-32: ^{13}C NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 6-*O*-(2,3,4,6-tri-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**2.12**).

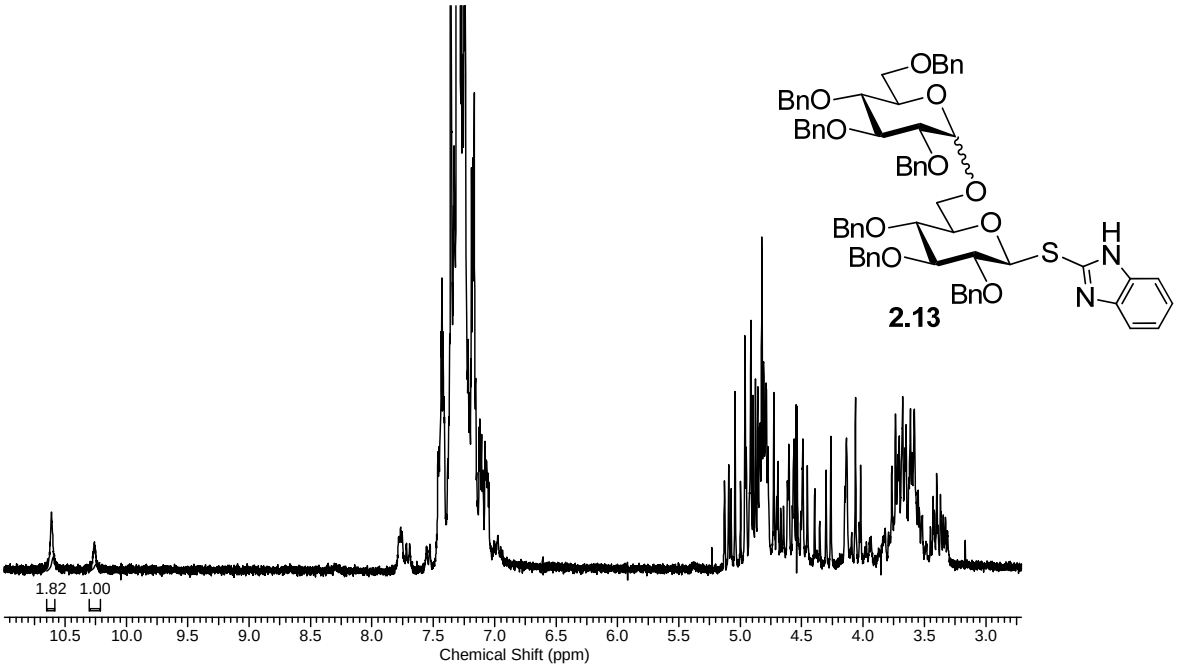


2.12



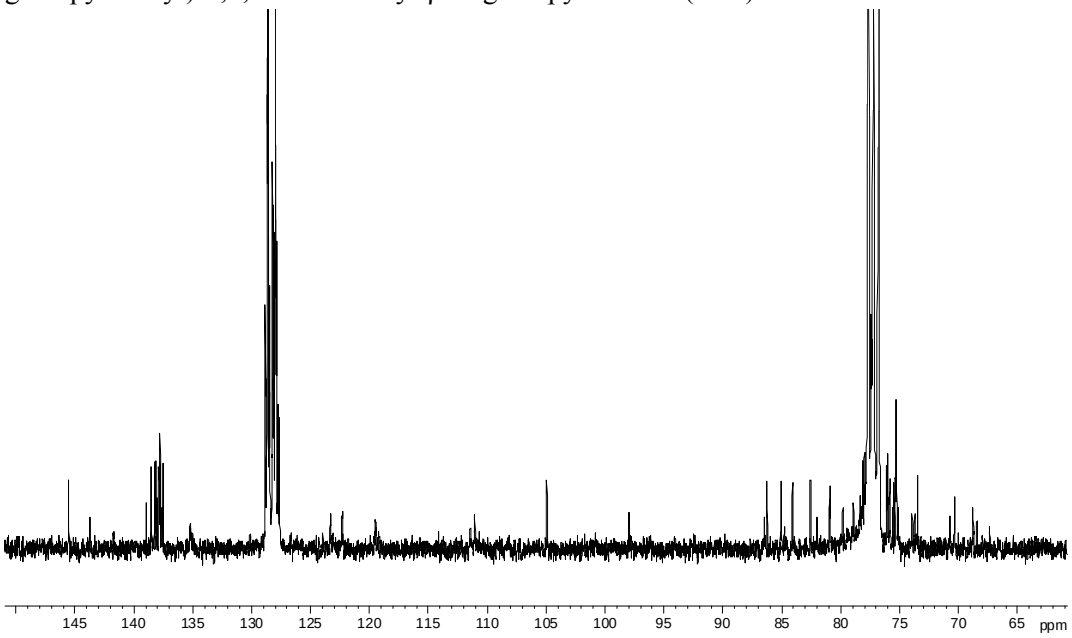
$CDCl_3$ at 300 MHz

Figure A-33: 2-D NMR COSY spectrum of (*N*-Anisoyl)benzimidazol-2-yl 6-*O*-(2,3,4,6-tri-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**2.12**).



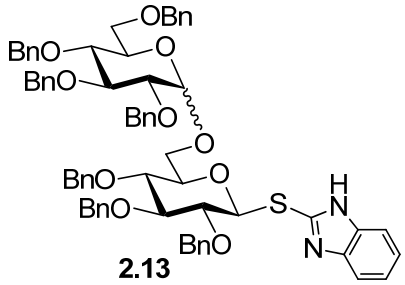
$CDCl_3$ at 300 MHz

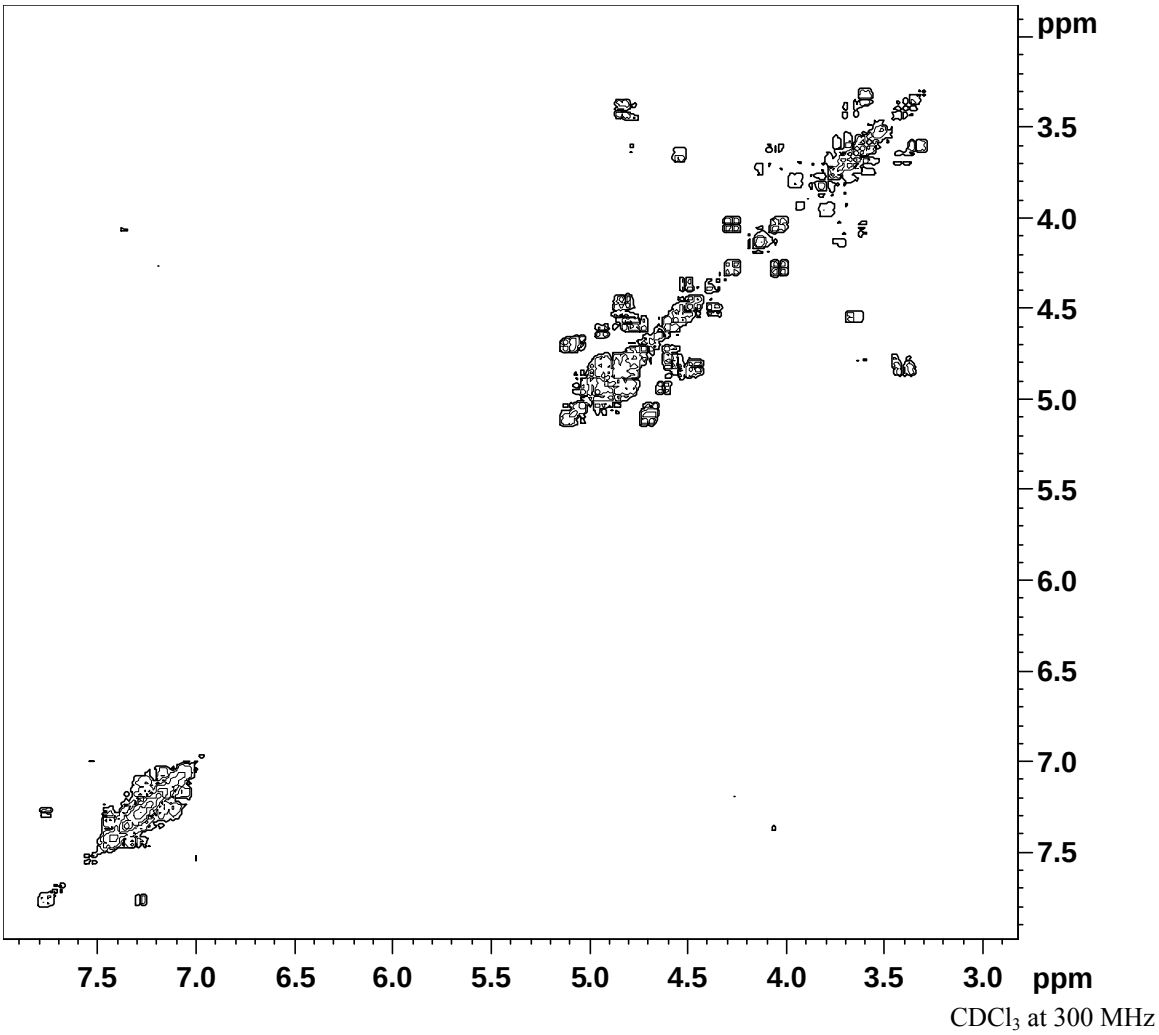
Figure A-34: ^{1}H NMR spectrum of Benzimidazol-2-yl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**2.13**).



$CDCl_3$ at 75 MHz

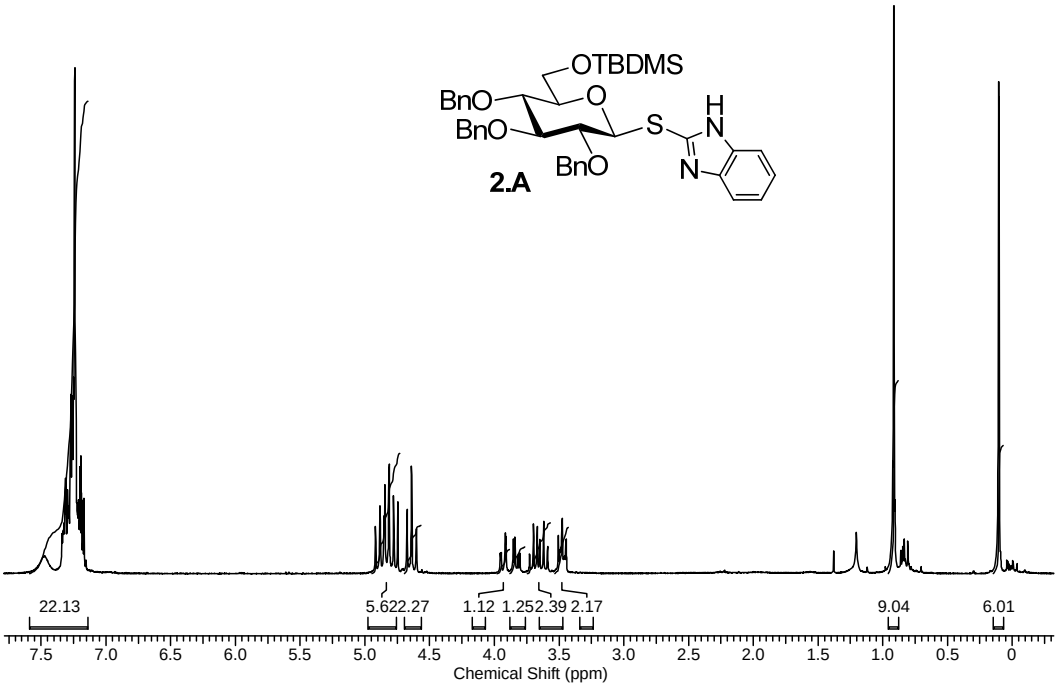
Figure A-35: ^{13}C NMR spectrum of Benzimidazol-2-yl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**2.13**).





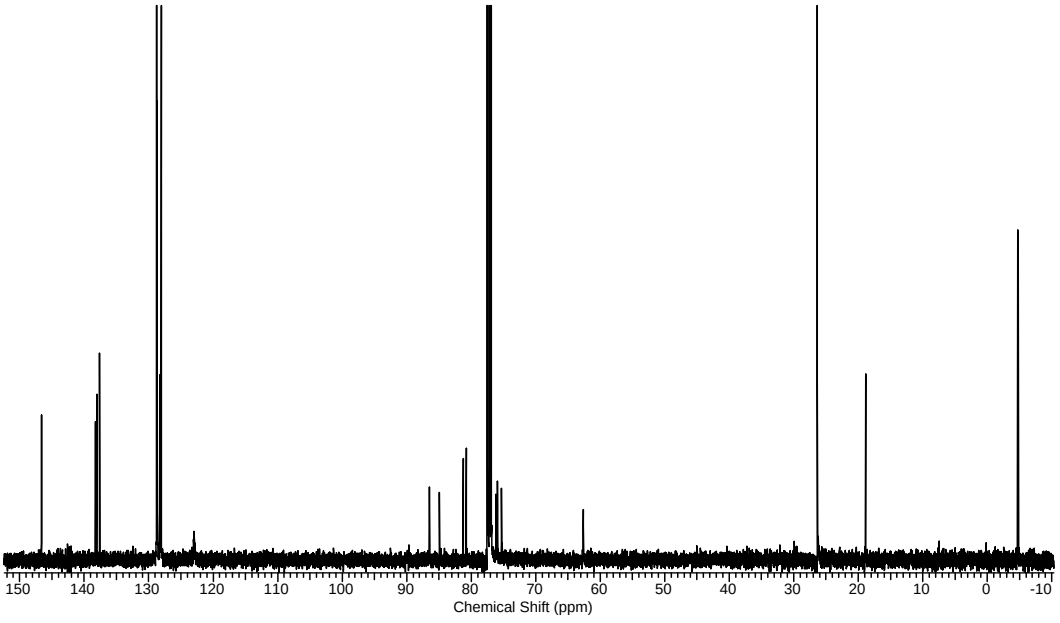
$CDCl_3$ at 300 MHz

Figure A-36: 2-D NMR COSY spectrum of Benzimidazol-2-yl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**2.13**).



$CDCl_3$ at 300 MHz

Figure A-37: ^{1}H NMR spectrum of Benzimidazol-2-yl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**2.A**).



$CDCl_3$ at 75 MHz

Figure A-38: ^{13}C NMR spectrum of Benzimidazol-2-yl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**2.A**).

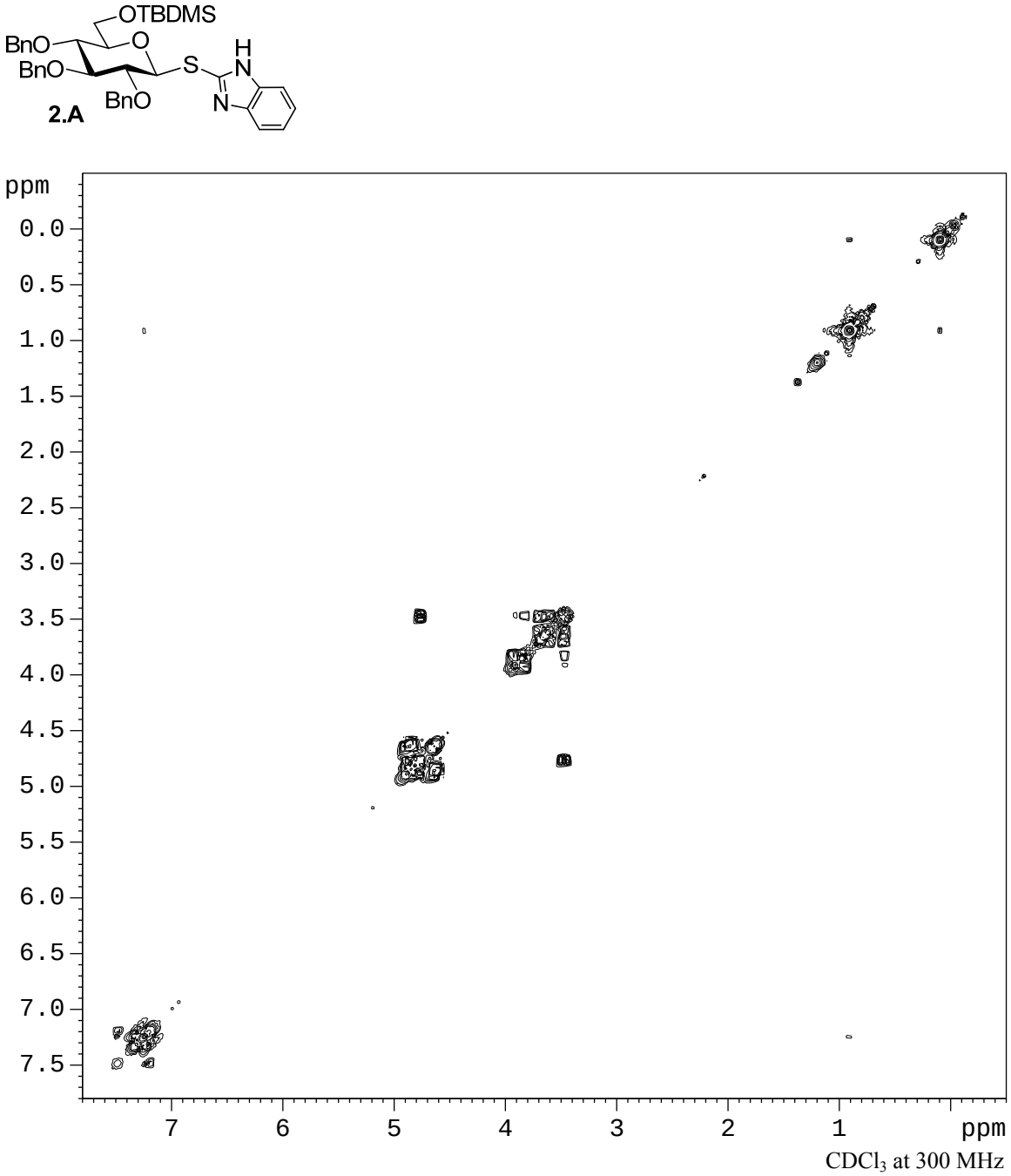
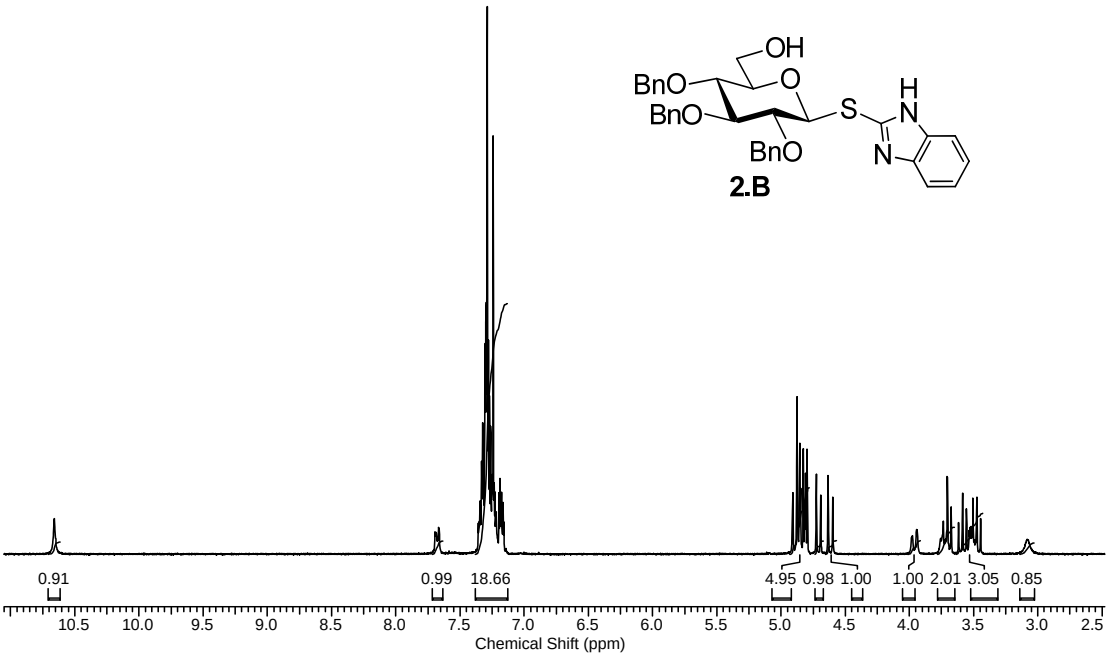
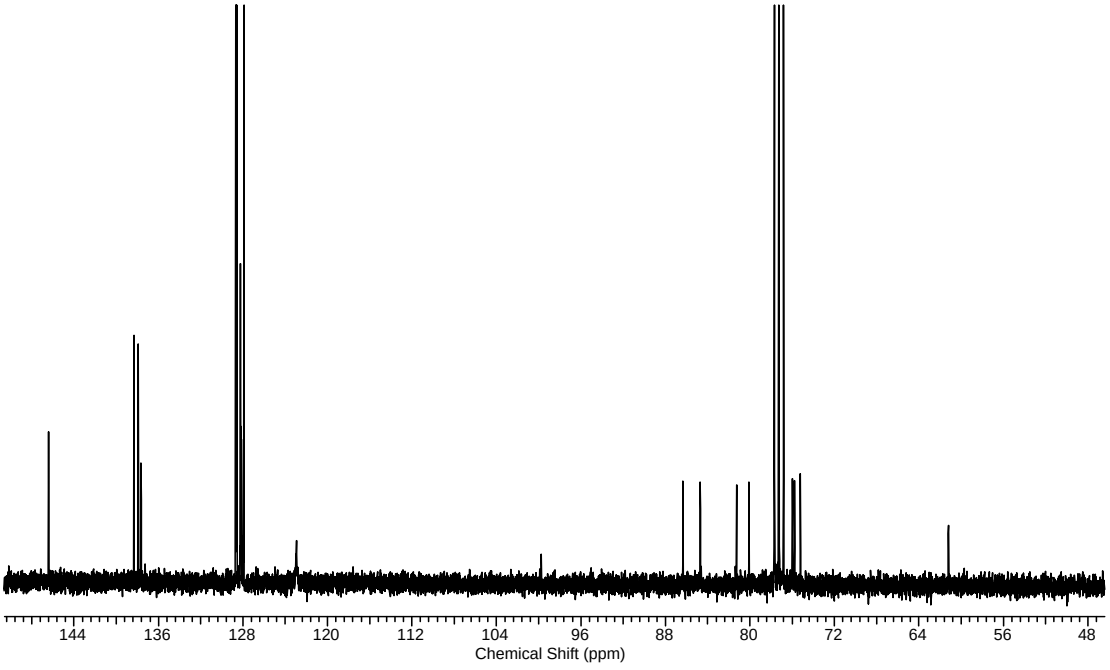


Figure A-39: 2-D NMR COSY spectrum of Benzimidazol-2-yl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**2.A**).



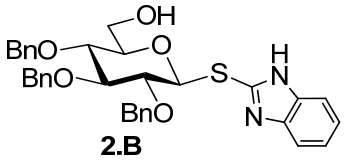
$CDCl_3$ at 300 MHz

Figure A-40: ^{1}H NMR spectrum of Benzimidazol-2-yl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.B**).

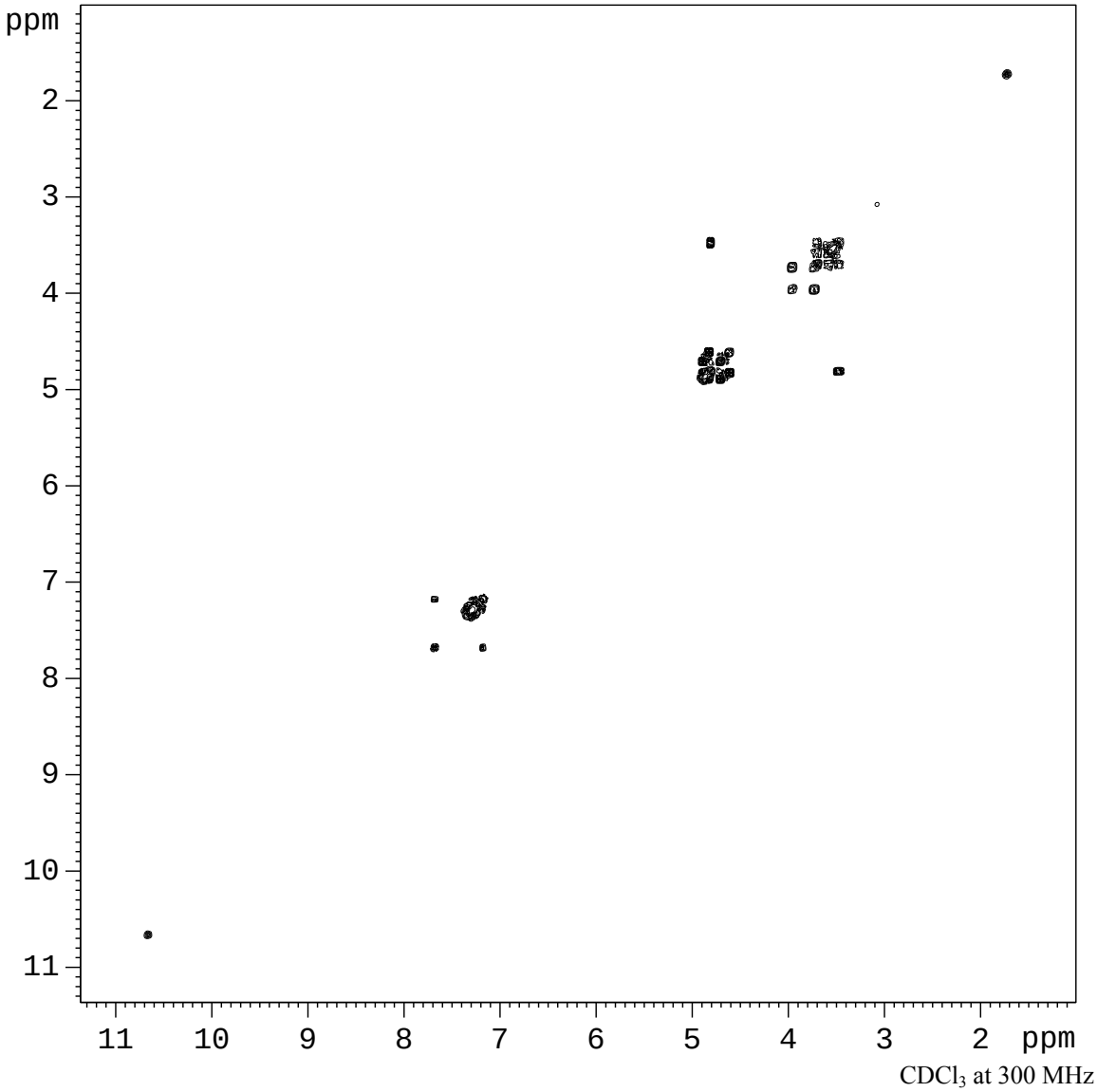


$CDCl_3$ at 75 MHz

Figure A-41: ^{13}C NMR spectrum of Benzimidazol-2-yl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.B**).

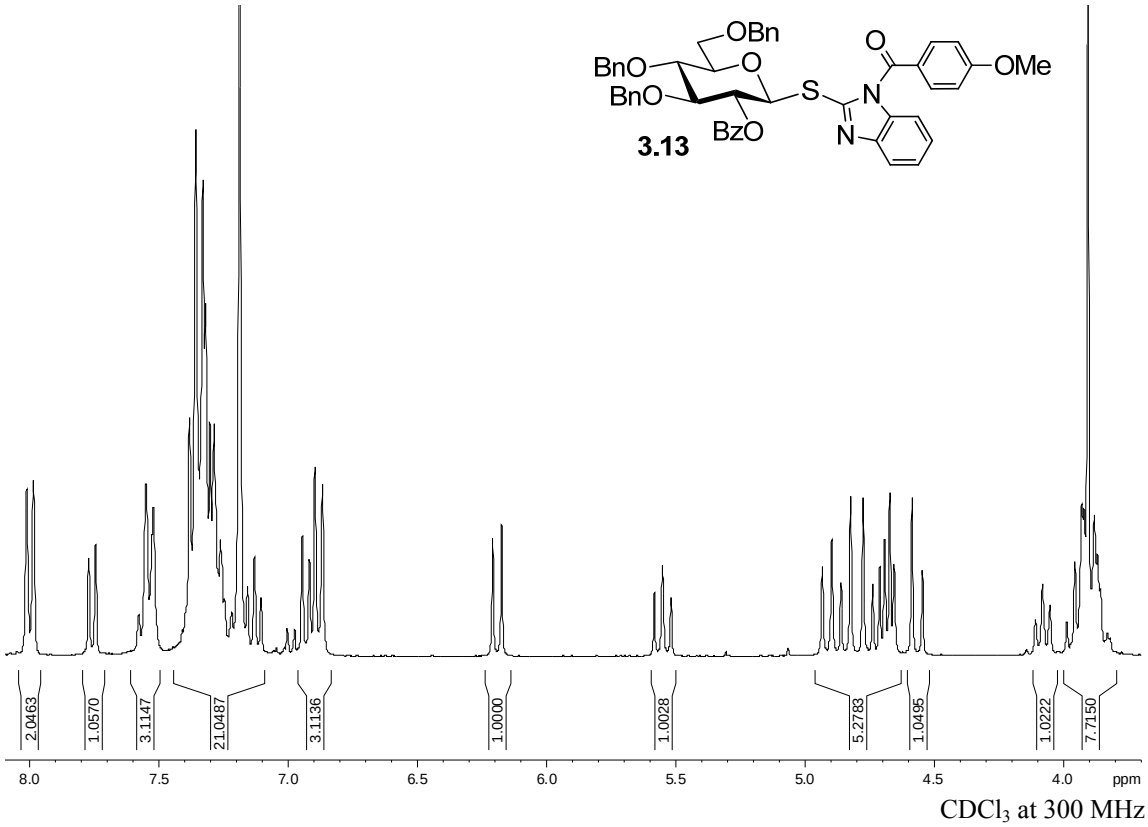


2.B



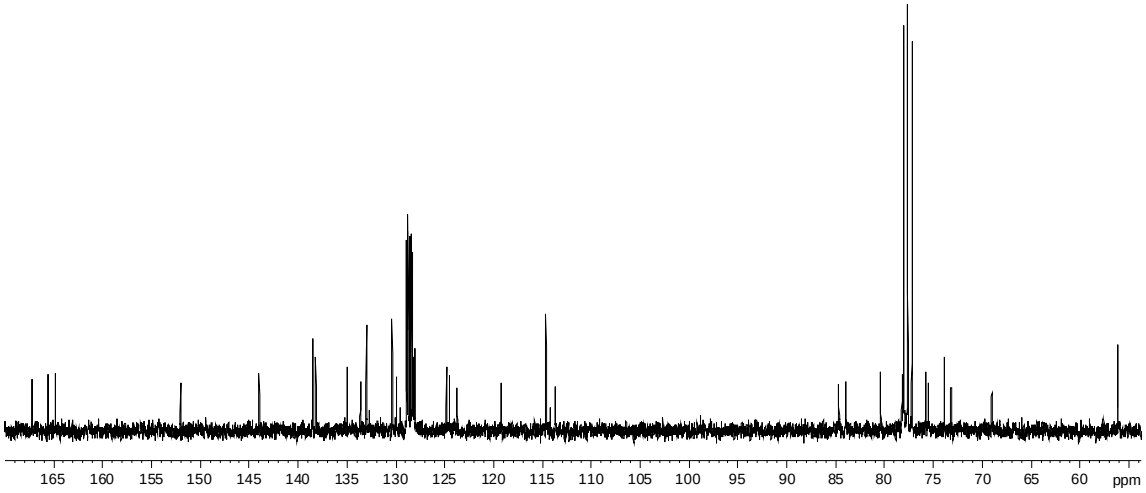
$CDCl_3$ at 300 MHz

Figure A-42: 2-D NMR COSY spectrum of Benzimidazol-2-yl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2.B**).



$CDCl_3$ at 300 MHz

Figure A-43: ^{1}H NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2-*O*-benzoyl-3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**3.13**).



$CDCl_3$ at 75 MHz

Figure A-44: ^{13}C NMR spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2-*O*-benzoyl-3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**3.13**).

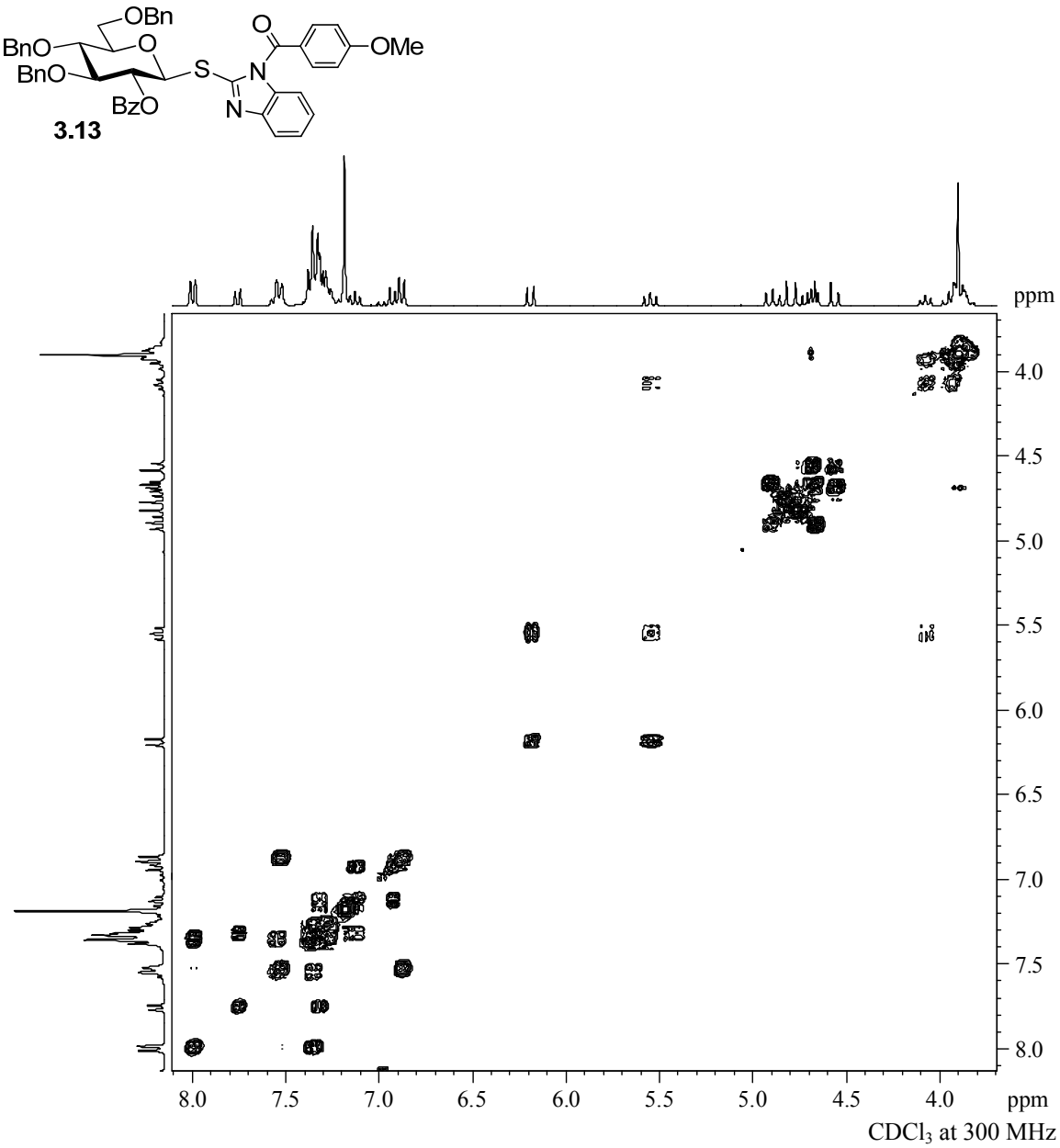


Figure A-45: 2-D NMR COSY spectrum of (*N*-Anisoyl)benzimidazol-2-yl 2-*O*-benzoyl-3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**3.13**).

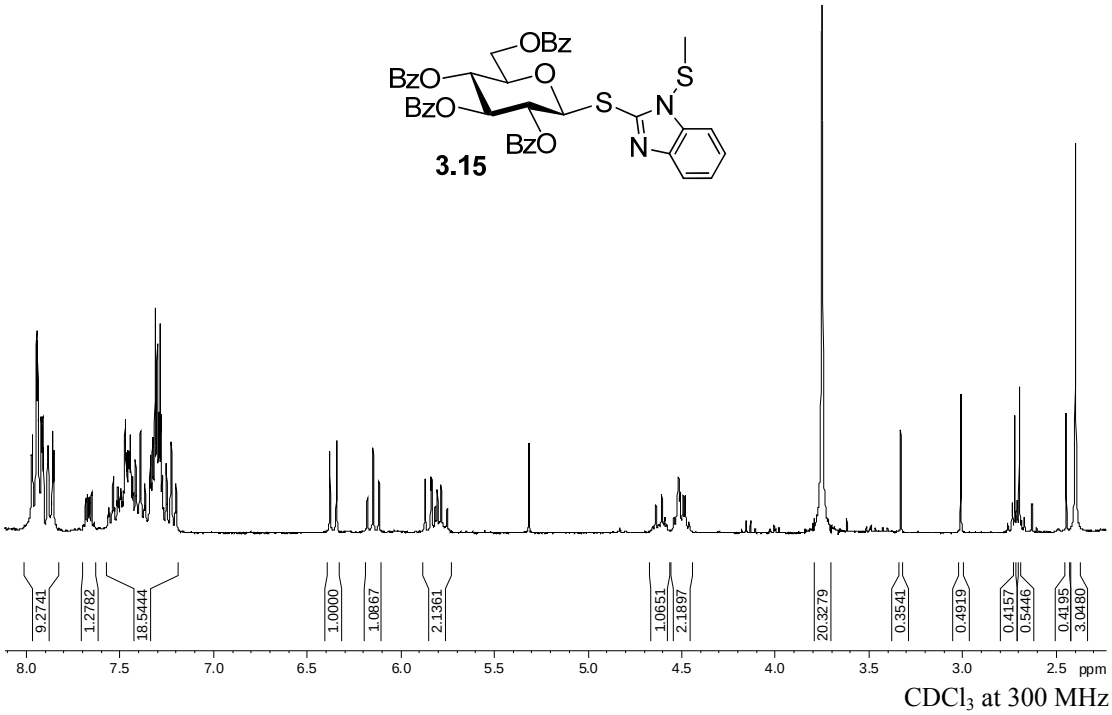


Figure A-46: ^{1}H NMR spectrum of 1-Thiomethylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**3.15**).

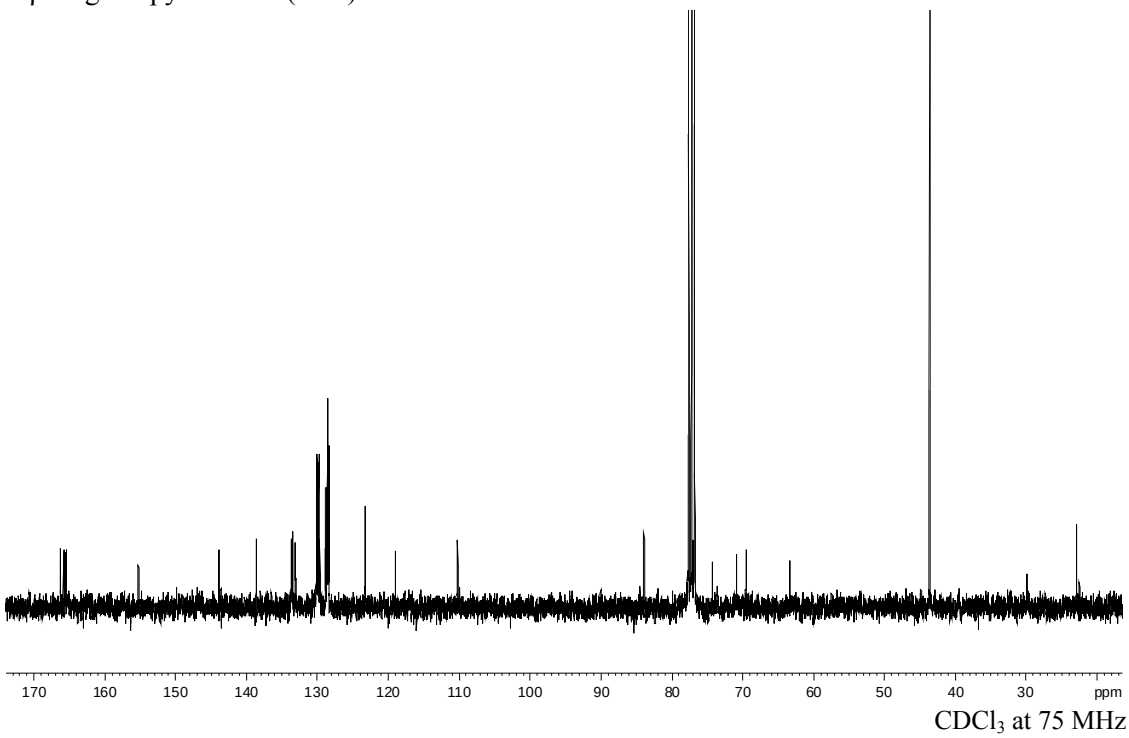


Figure A-47: ^{13}C NMR spectrum of 1-Thiomethylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**3.15**).

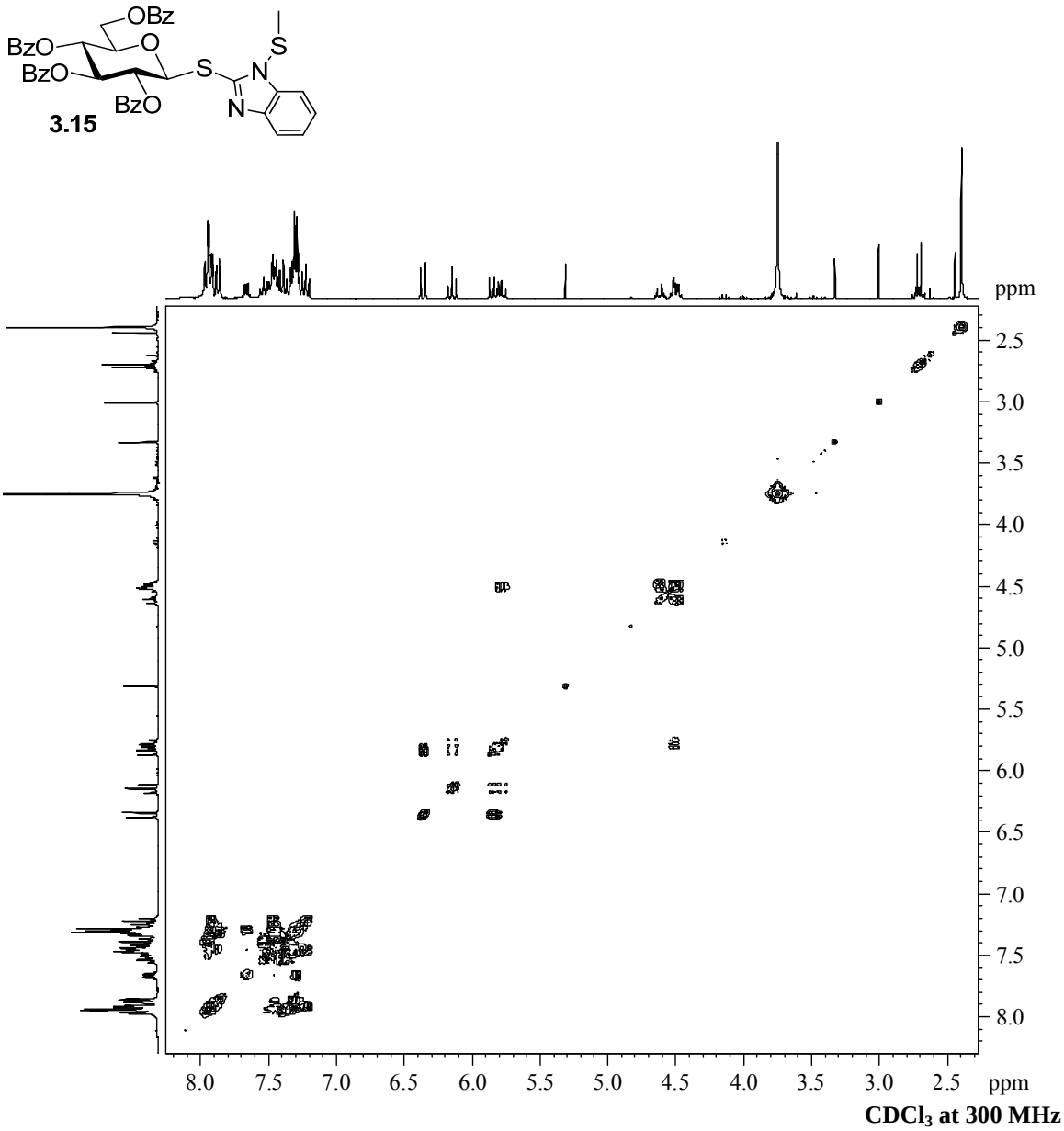


Figure A-48: 2-D NMR COSY spectrum of 1-Thiomethylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**3.15**).

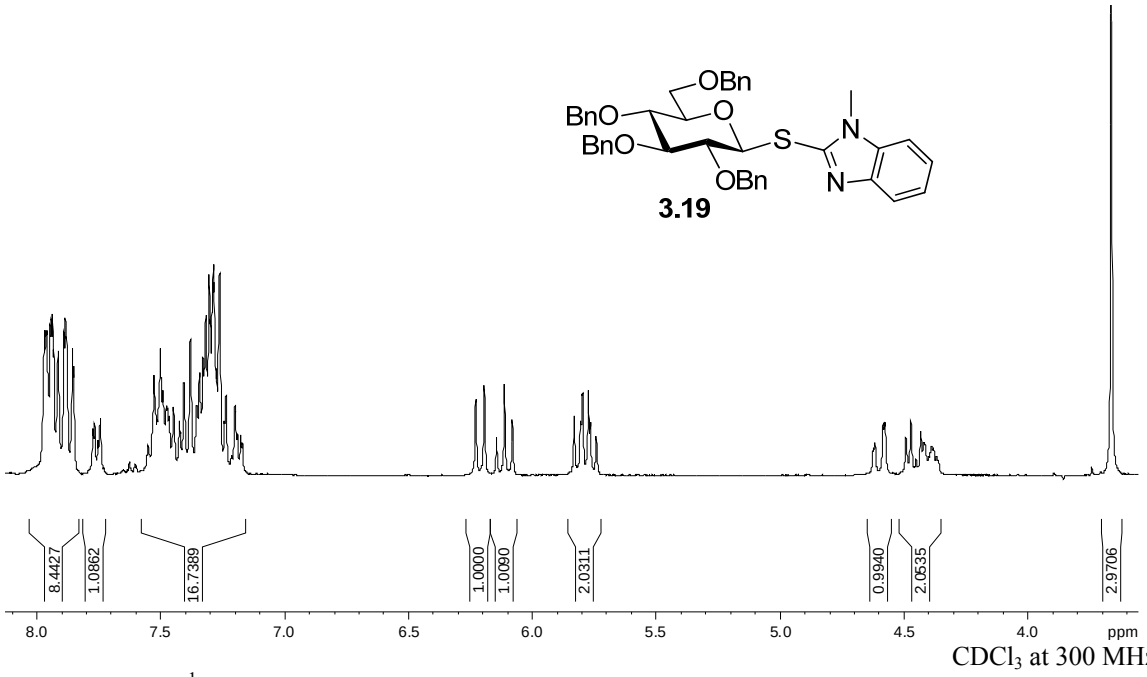


Figure A-49: ^{1}H NMR spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**3.19**).

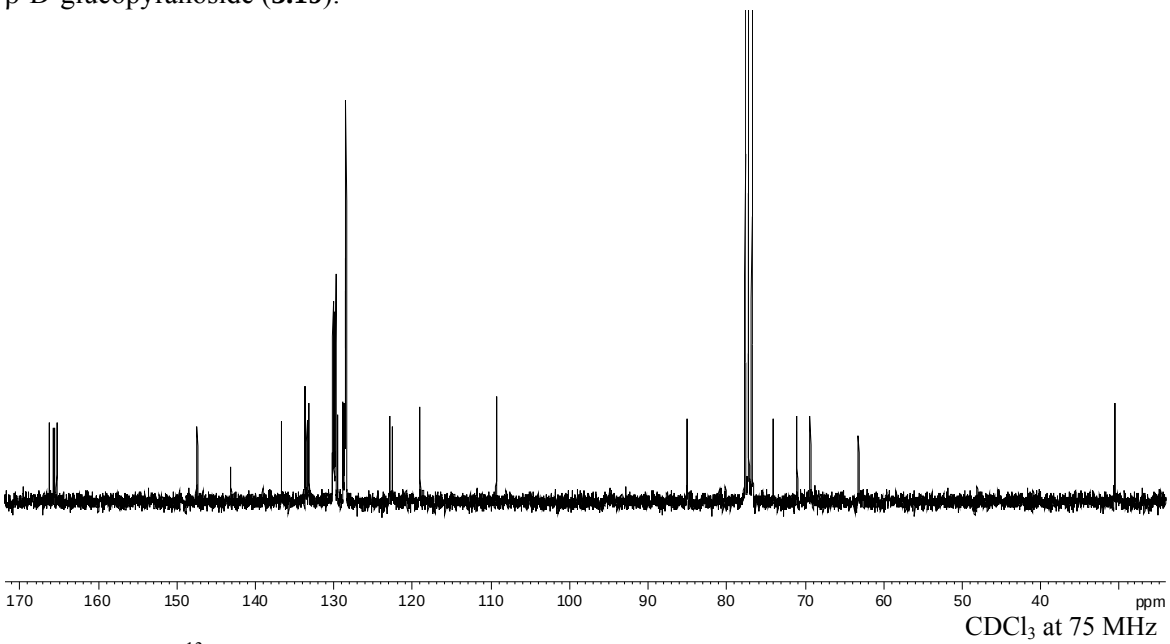


Figure A-50: ^{13}C NMR spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**3.19**).

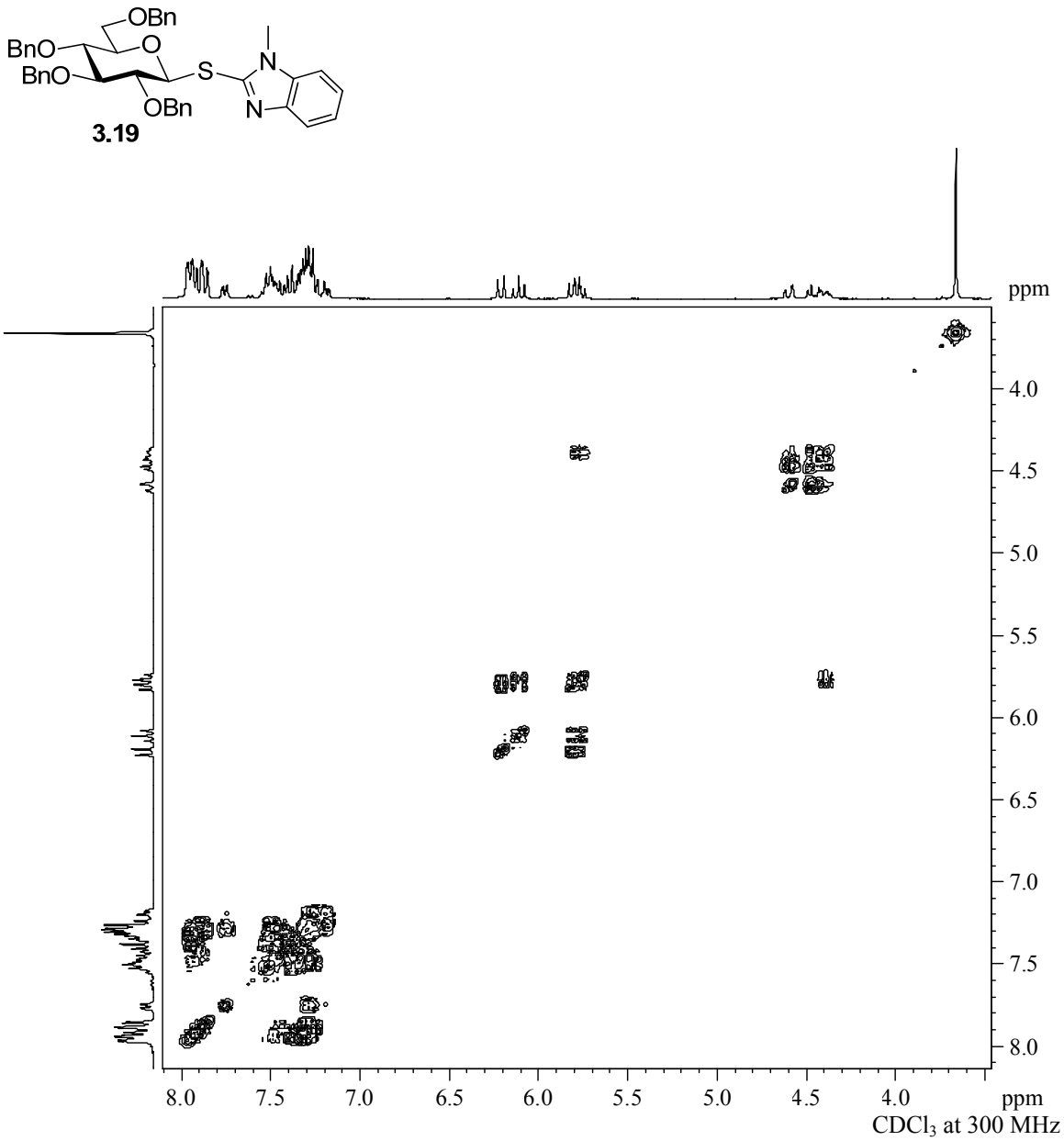


Figure A-51: 2-D NMR COSY spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**3.19**).

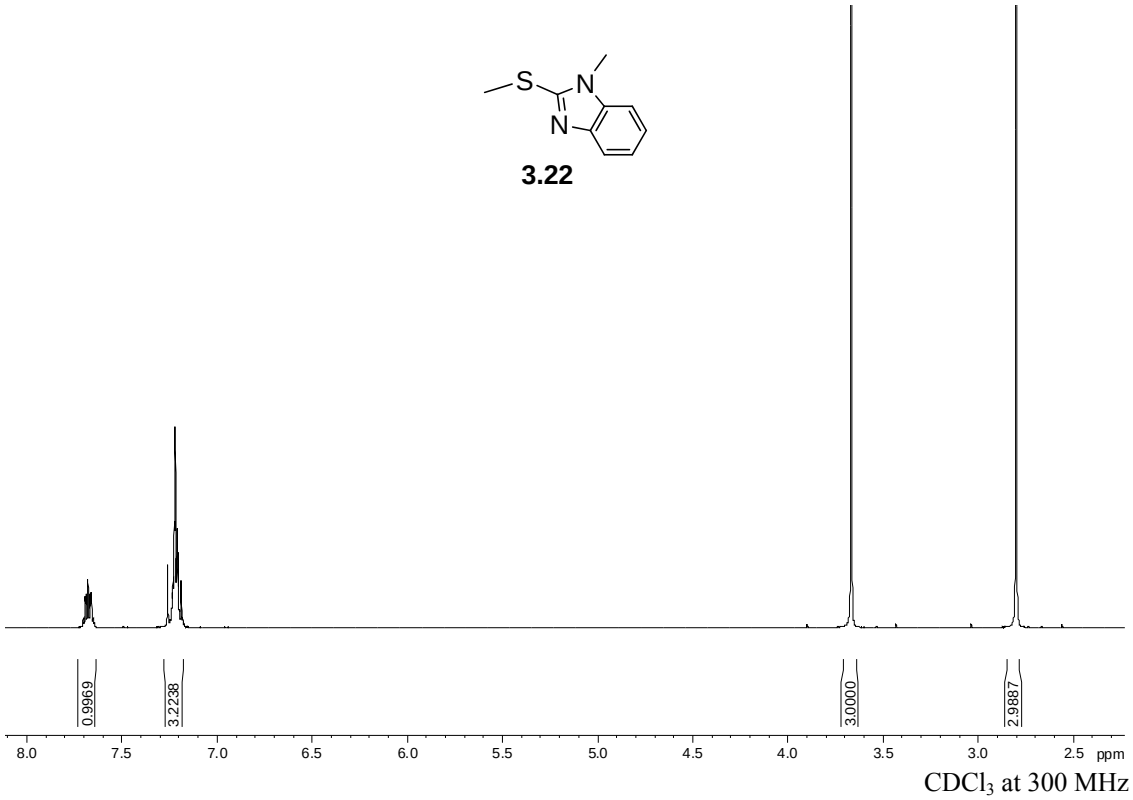


Figure A-52: ^{1}H NMR spectrum of 1-methyl-2-(methylthio)-1*H*-benzimidazole (**3.22**).

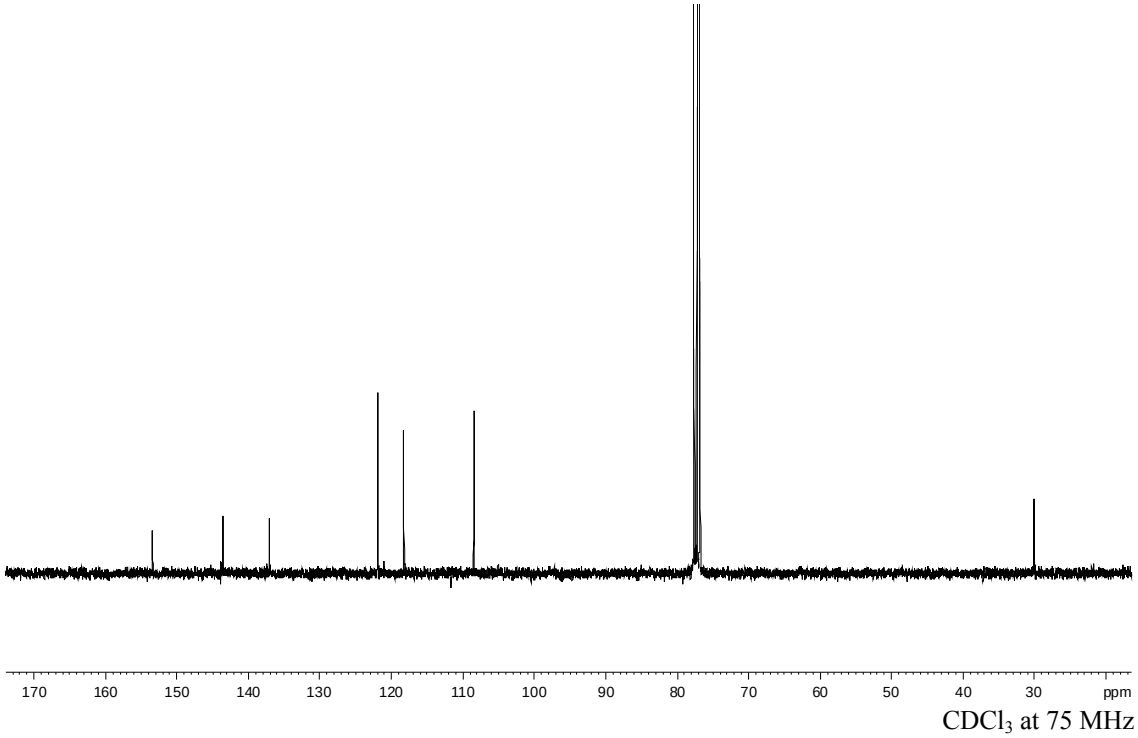


Figure A-53: ^{13}CNMR spectrum of 1-methyl-2-(methylthio)-1*H*-benzimidazole (**3.22**).

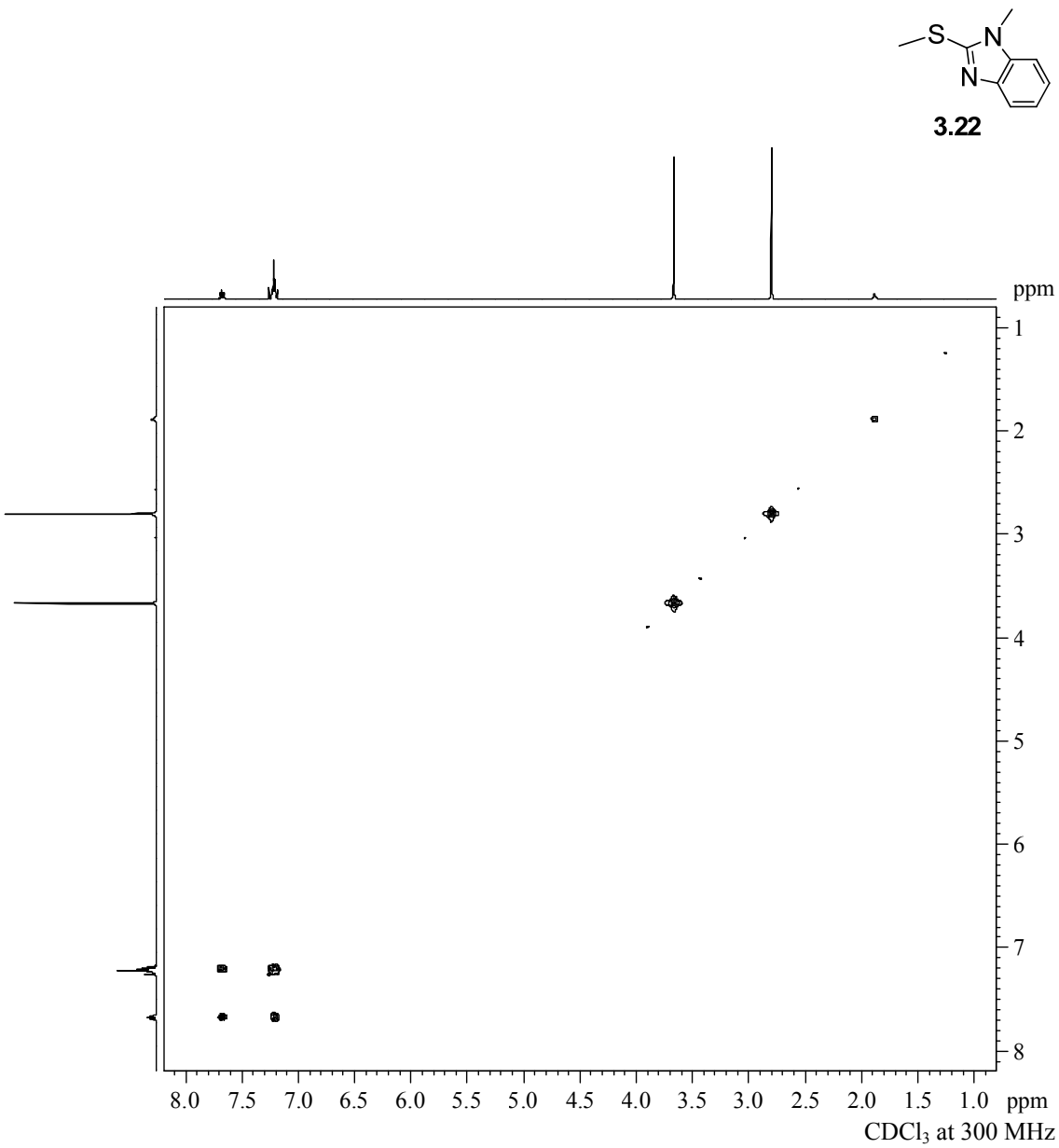
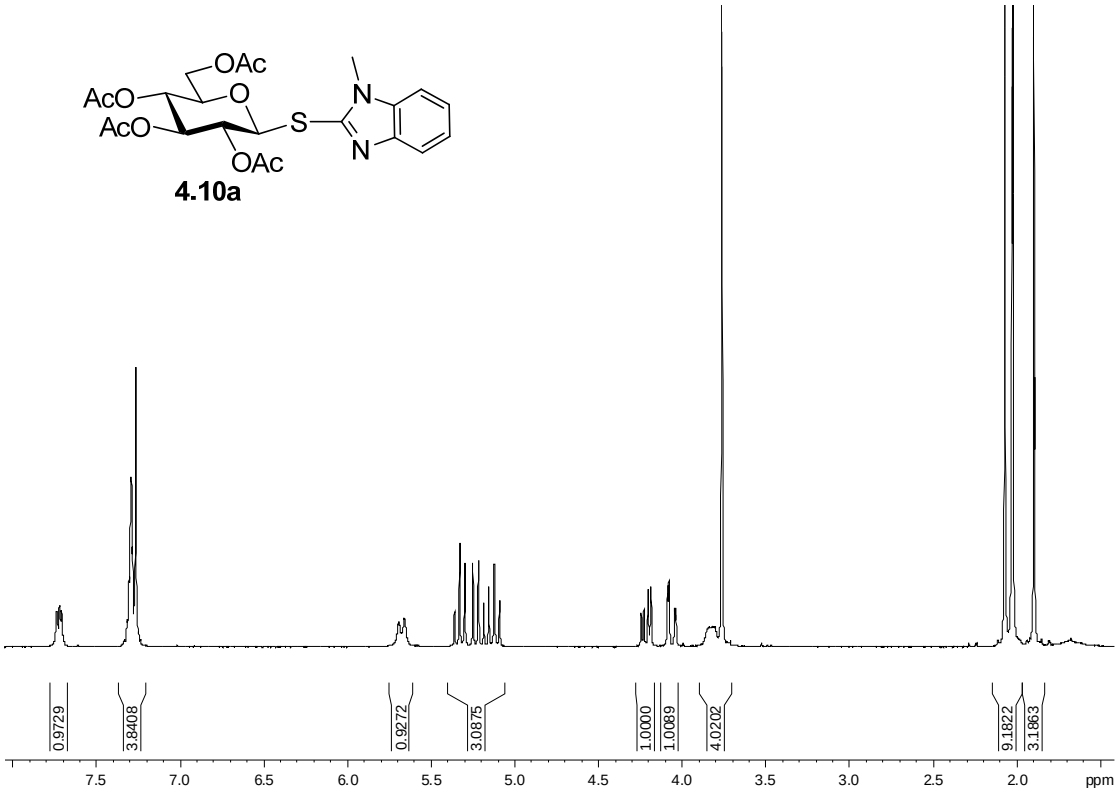
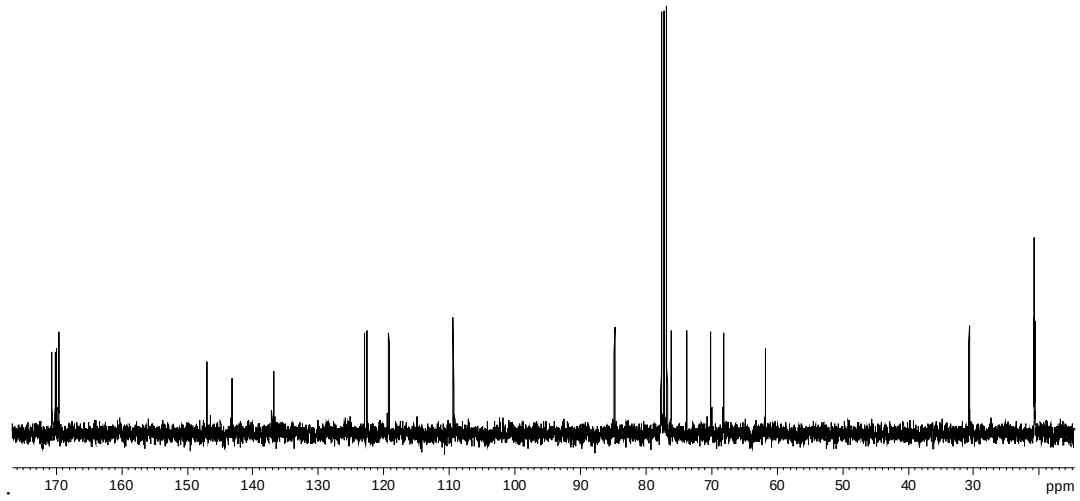


Figure A-54: 2-D NMR COSY spectrum of 1-methyl-2-(methylthio)-1*H*-benzimidazole (**3.22**).



$CDCl_3$ at 300 MHz

Figure A-55: ^{1}H NMR spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4.10a**).



$CDCl_3$ at 75 MHz

Figure A-56: ^{13}C NMR spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4.10a**).

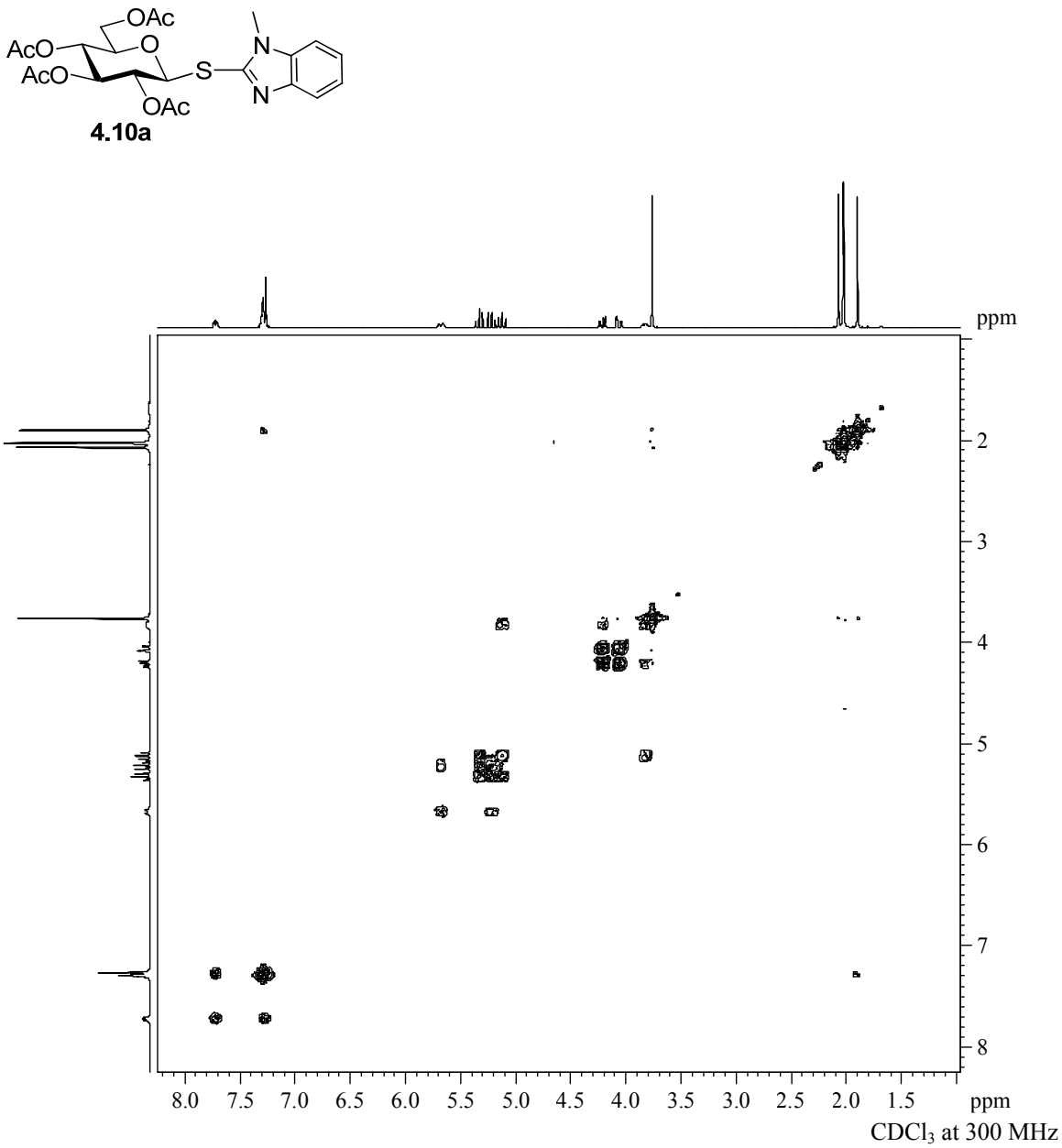
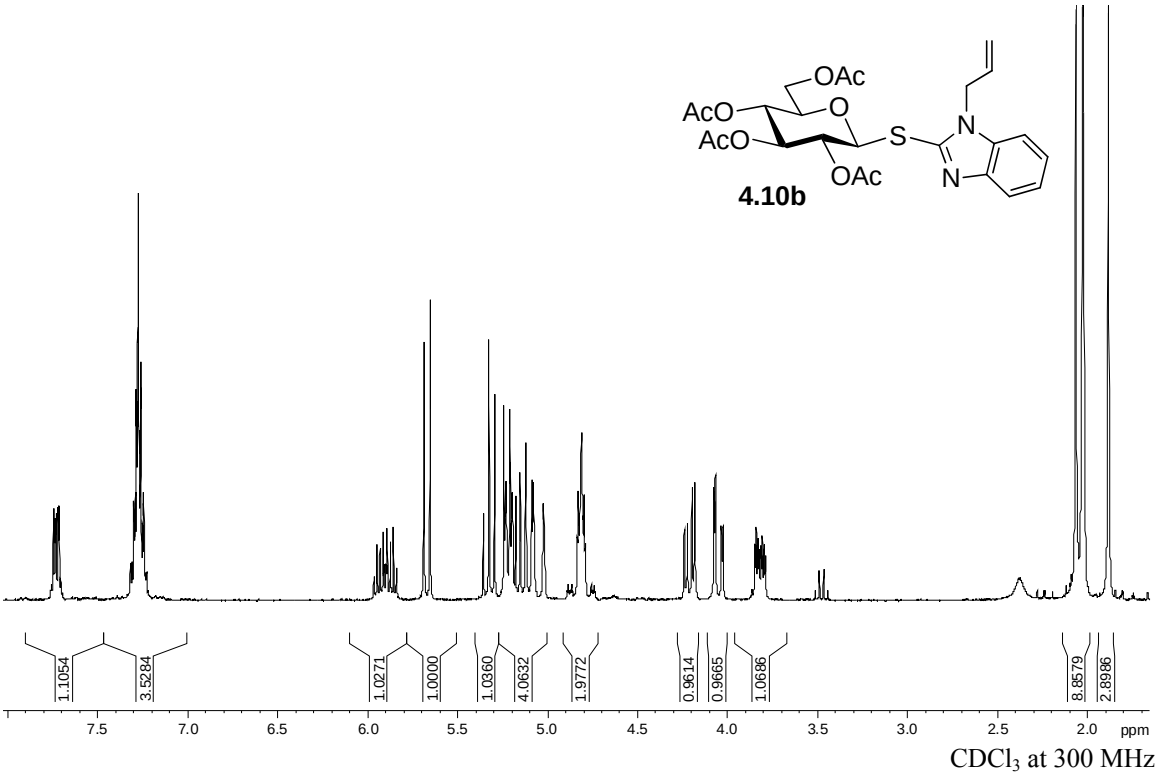
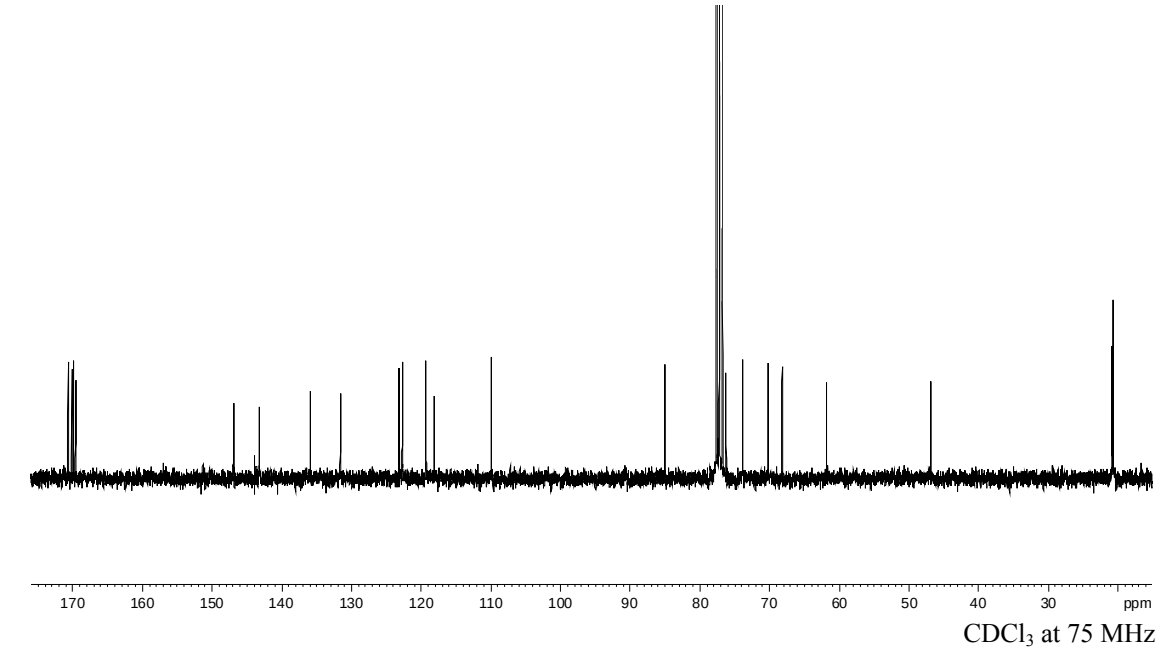


Figure A-57: 2-D NMR COSY spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4.10a**).



$CDCl_3$ at 300 MHz

Figure A-58: ^{1}H NMR spectrum of 1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4.10b**).



$CDCl_3$ at 75 MHz

Figure A-59: ^{13}C NMR spectrum of 1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4.10b**).

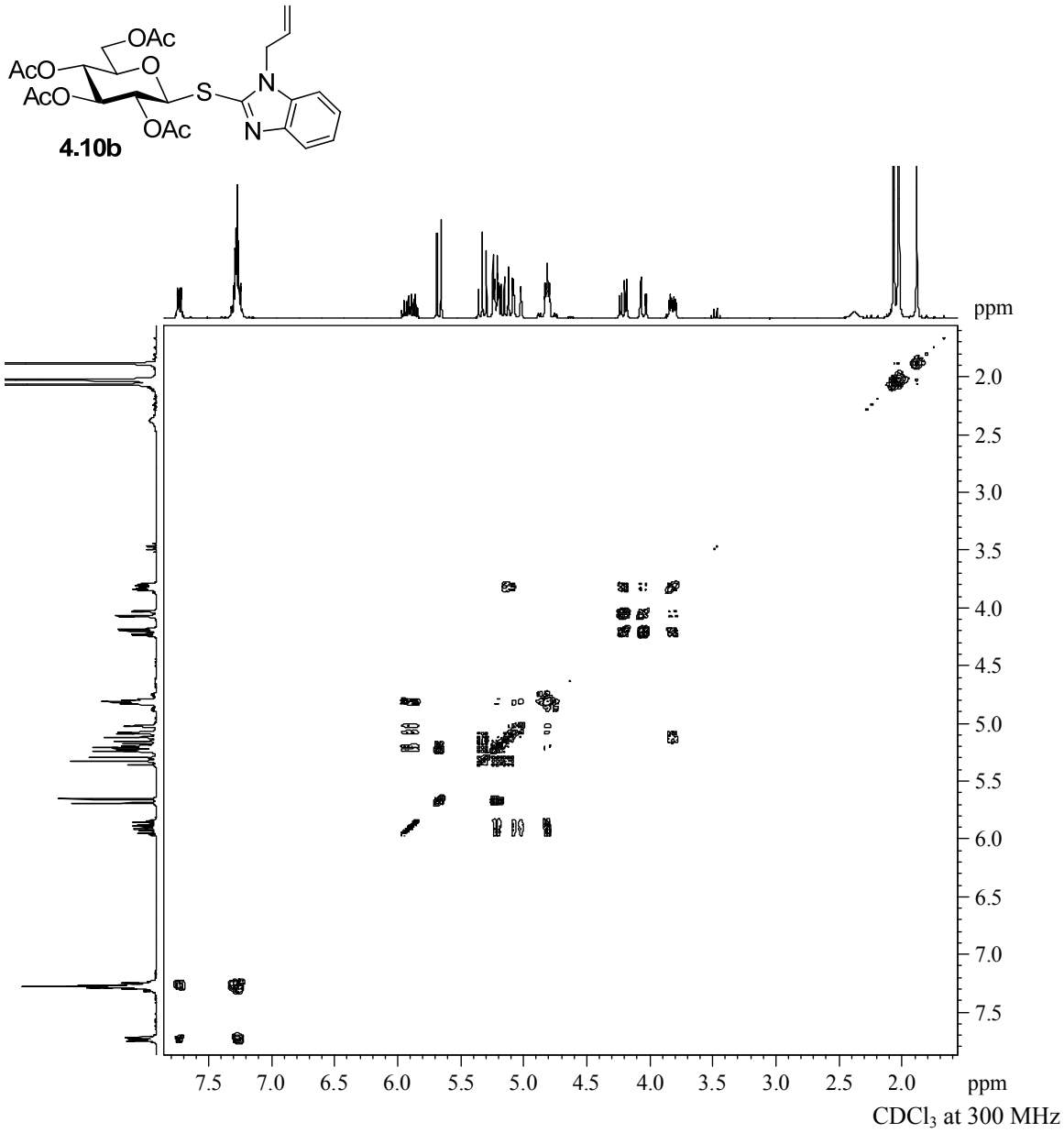
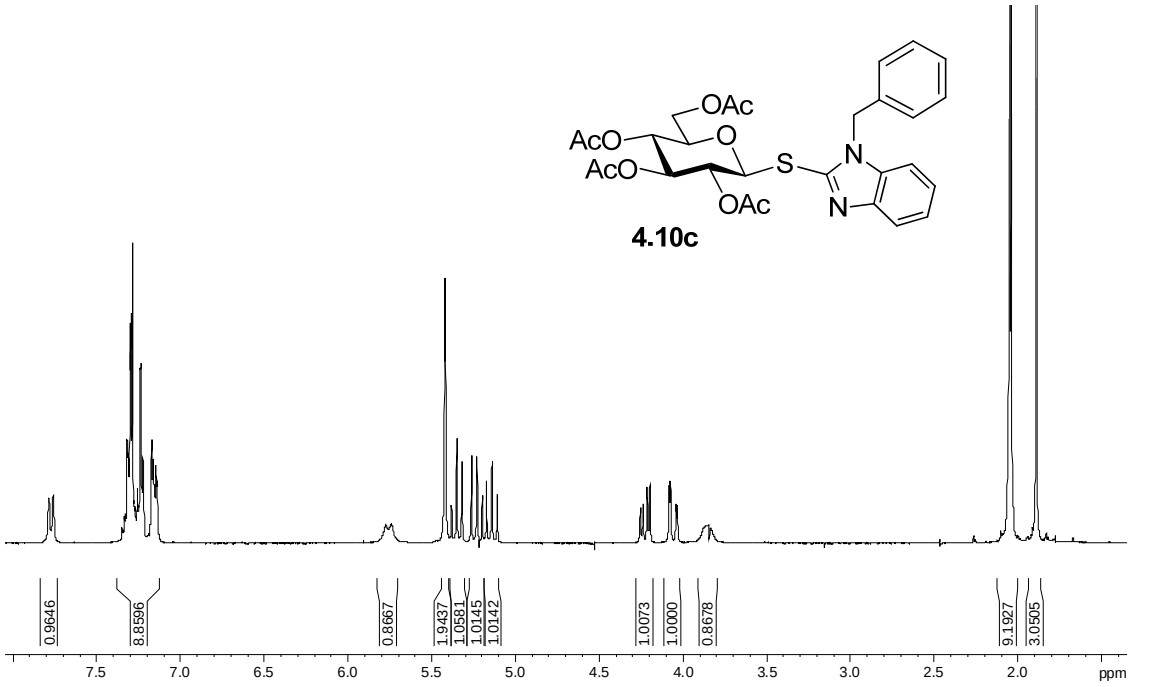
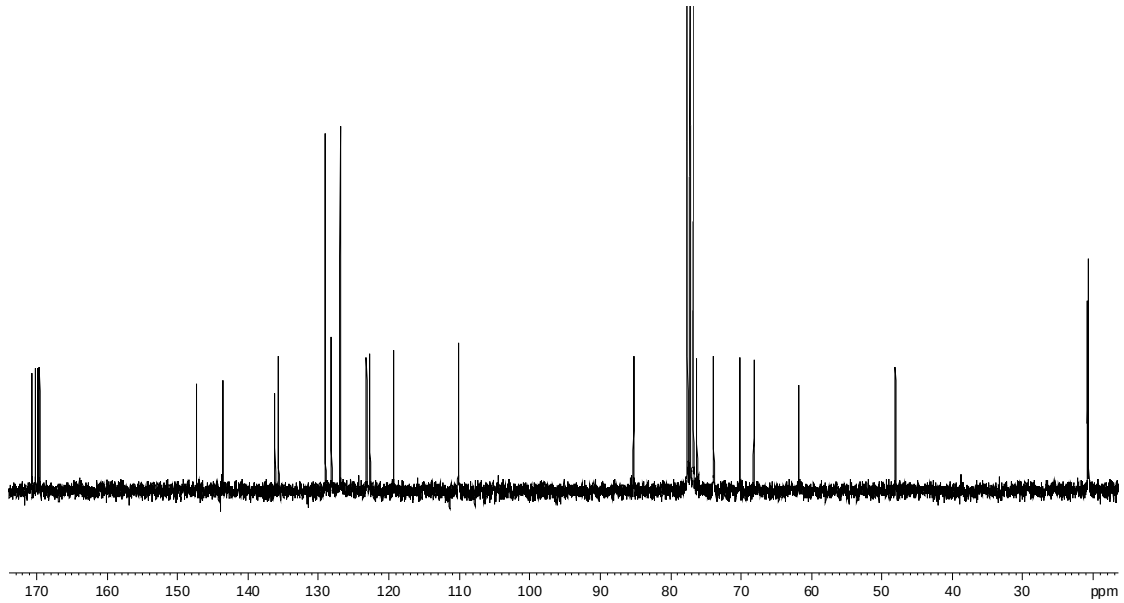


Figure A-60: 2-D NMR COSY spectrum of 1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4.10b**).



$CDCl_3$ at 300 MHz

Figure A-61: ^{1}H NMR spectrum of 1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4.10c**).



$CDCl_3$ at 75 MHz

Figure A-62: ^{13}C NMR spectrum of 1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4.10c**).

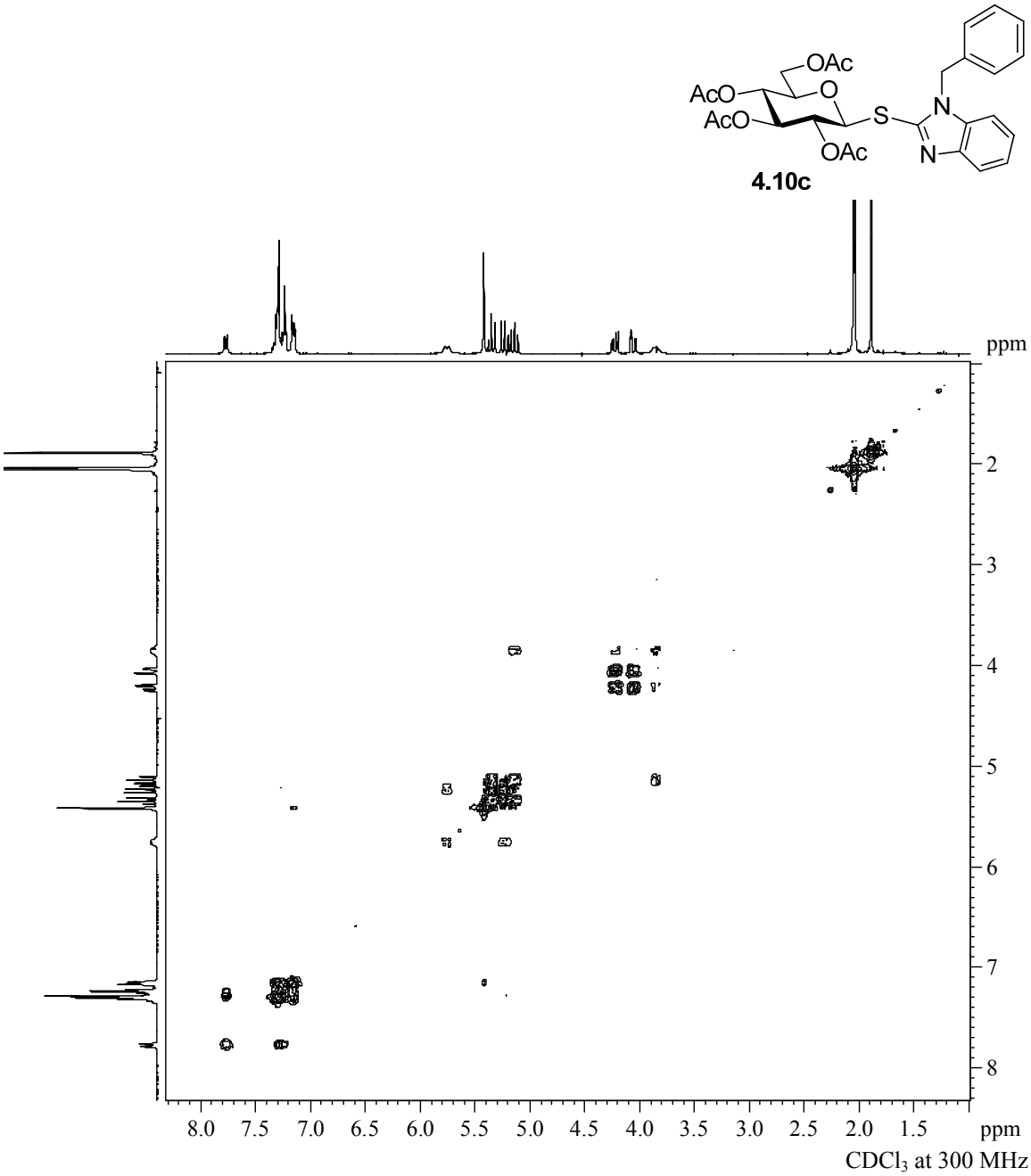


Figure A-63: 2-D NMR COSY spectrum of 1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4.10c**).

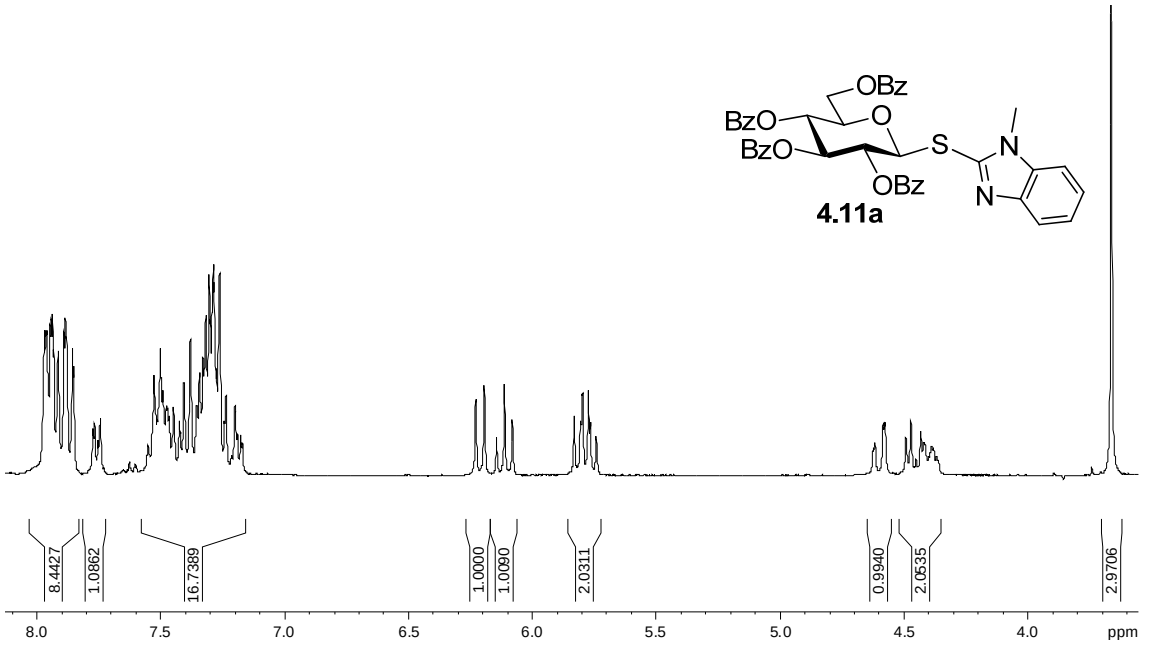


Figure A-64: ^{1}H NMR spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.11a**).

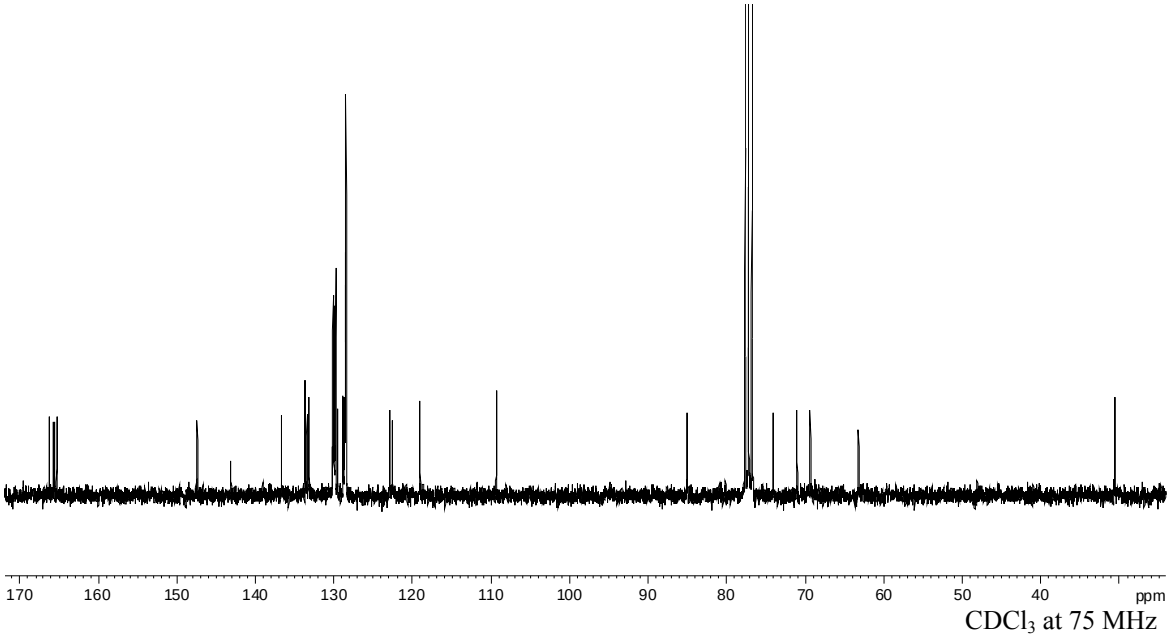


Figure A-65: ^{13}C NMR spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.11a**).

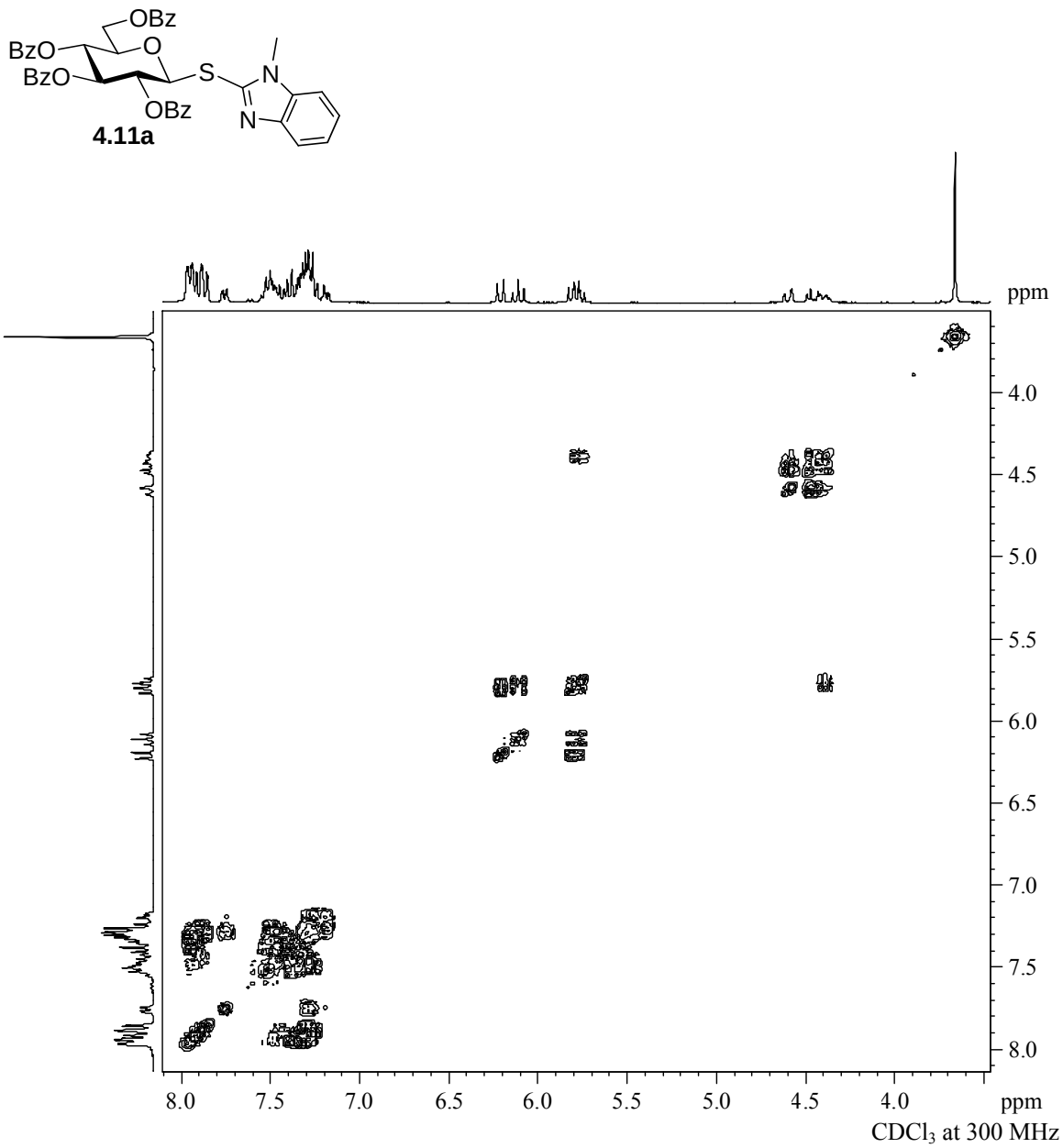
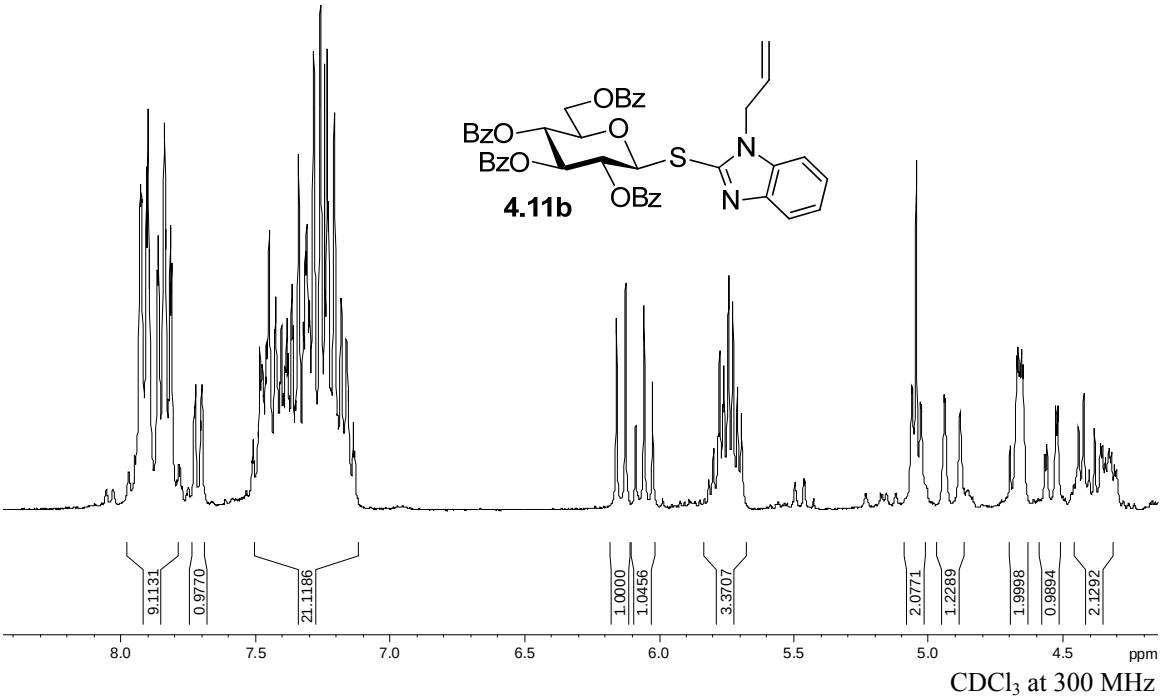
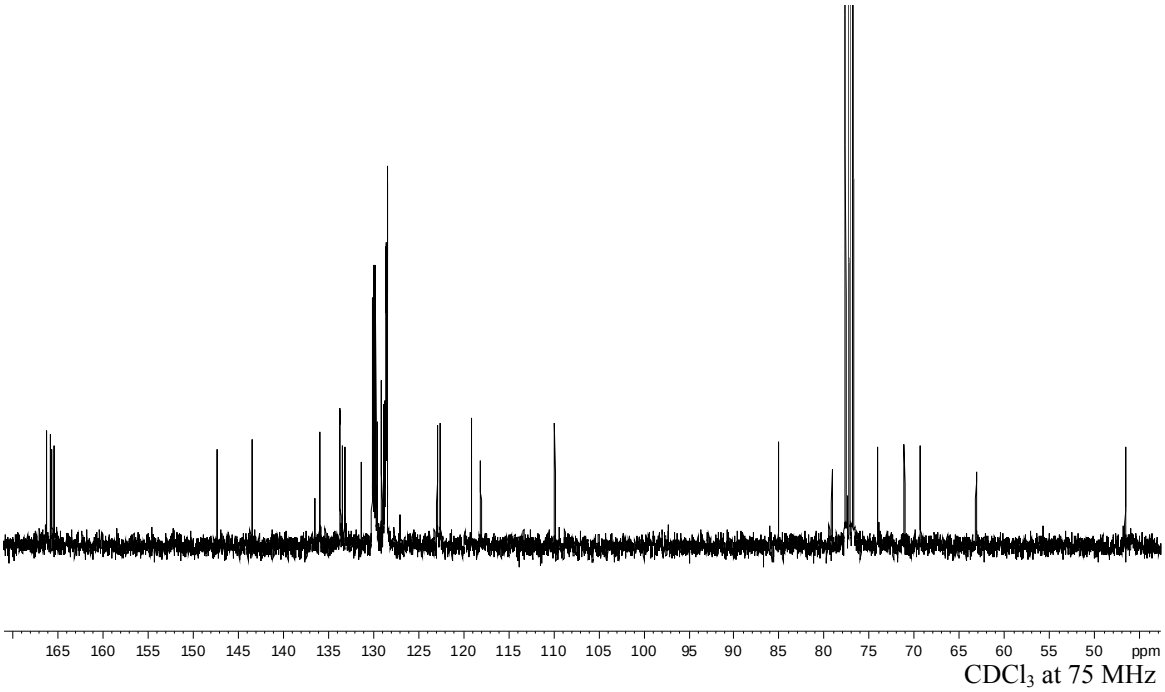


Figure A-66: 2-D NMR COSY spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.11a**).



$CDCl_3$ at 300 MHz

Figure A-67: ^{1}H NMR spectrum of 1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.11b**).



$CDCl_3$ at 75 MHz

Figure A-68: ^{13}C NMR spectrum of 1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.11b**).

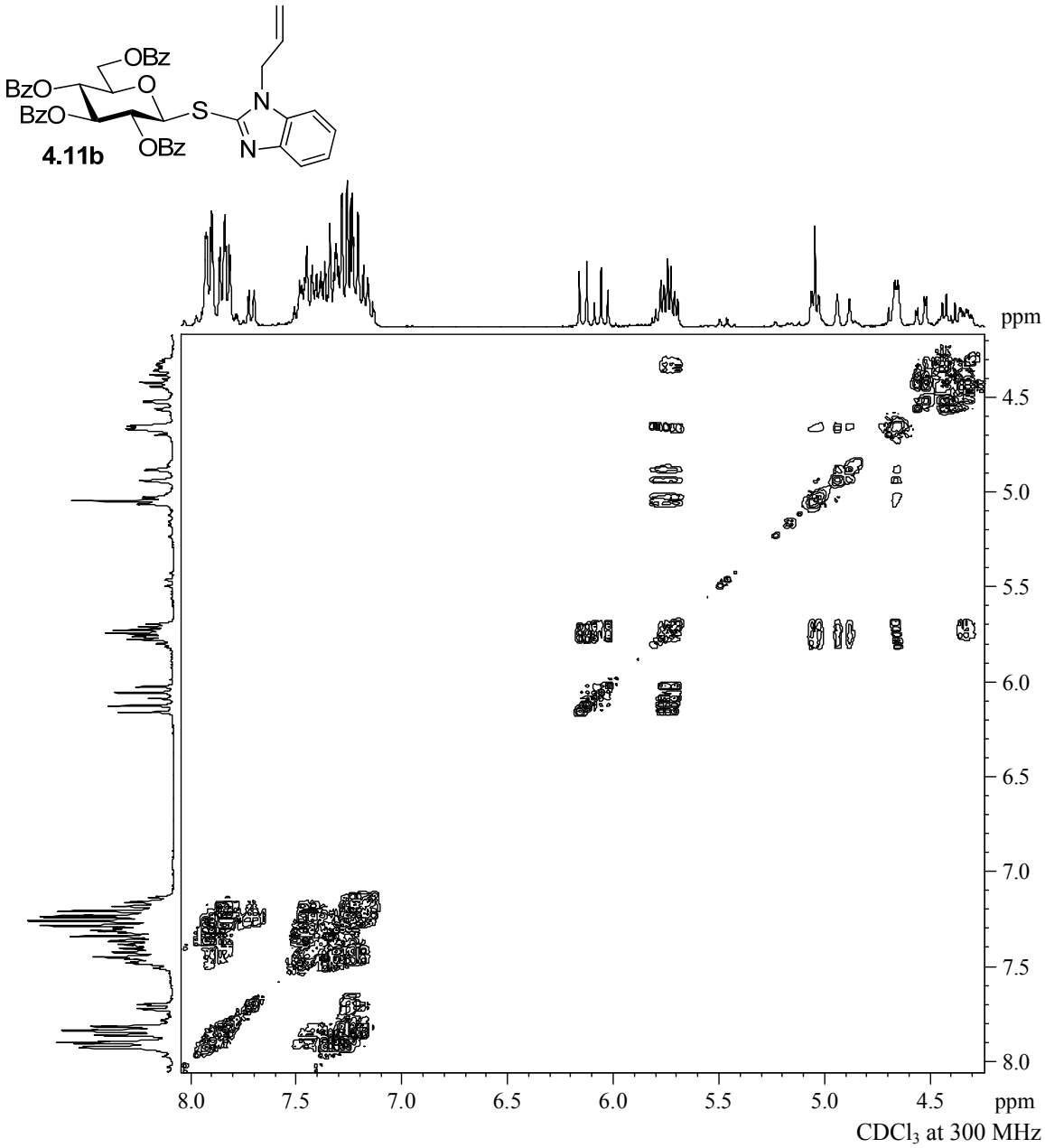
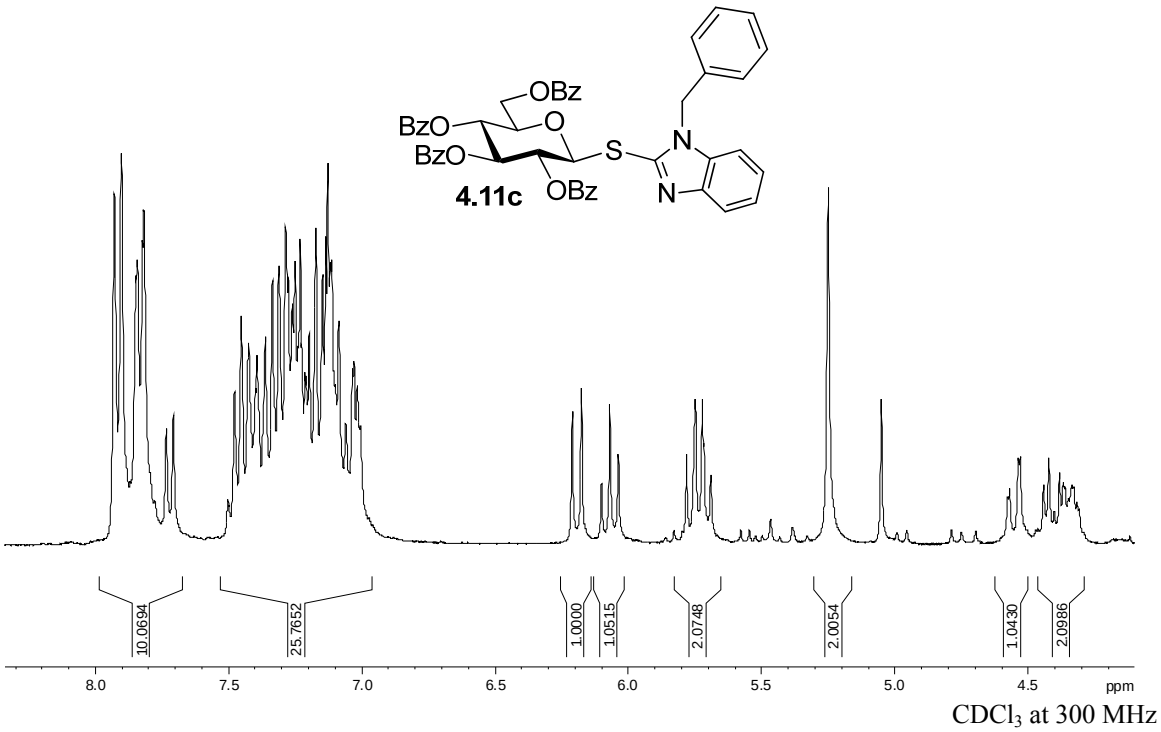
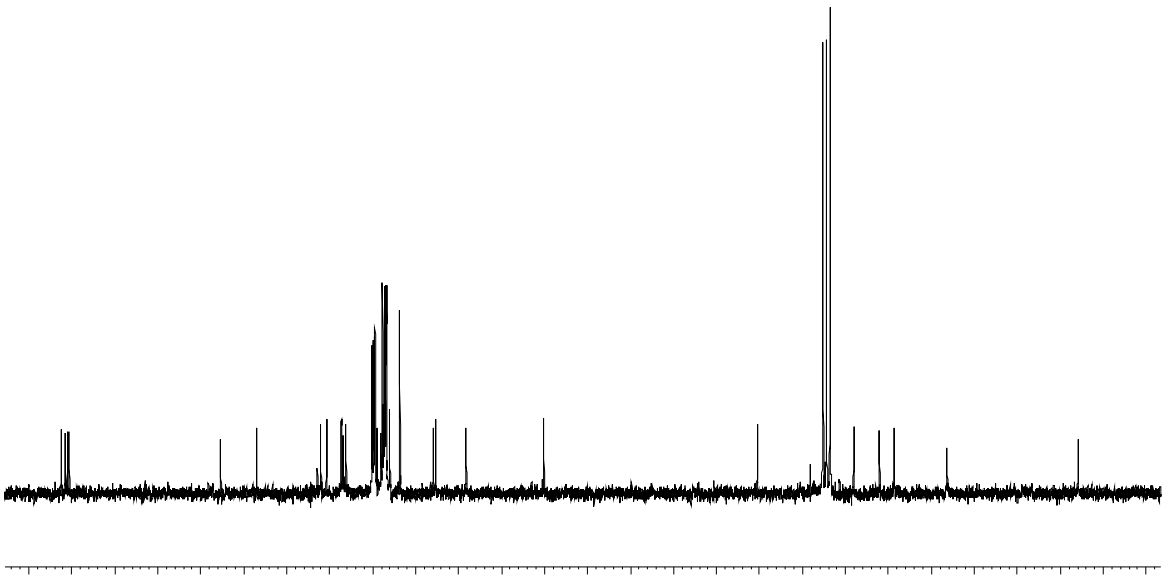


Figure A-69: 2-D NMR COSY spectrum of 1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.11b**).



$CDCl_3$ at 300 MHz

Figure A-70: ^{1}H NMR spectrum of 1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.11c**).



$CDCl_3$ at 75 MHz

Figure A-71: ^{13}C NMR spectrum of 1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.11c**).

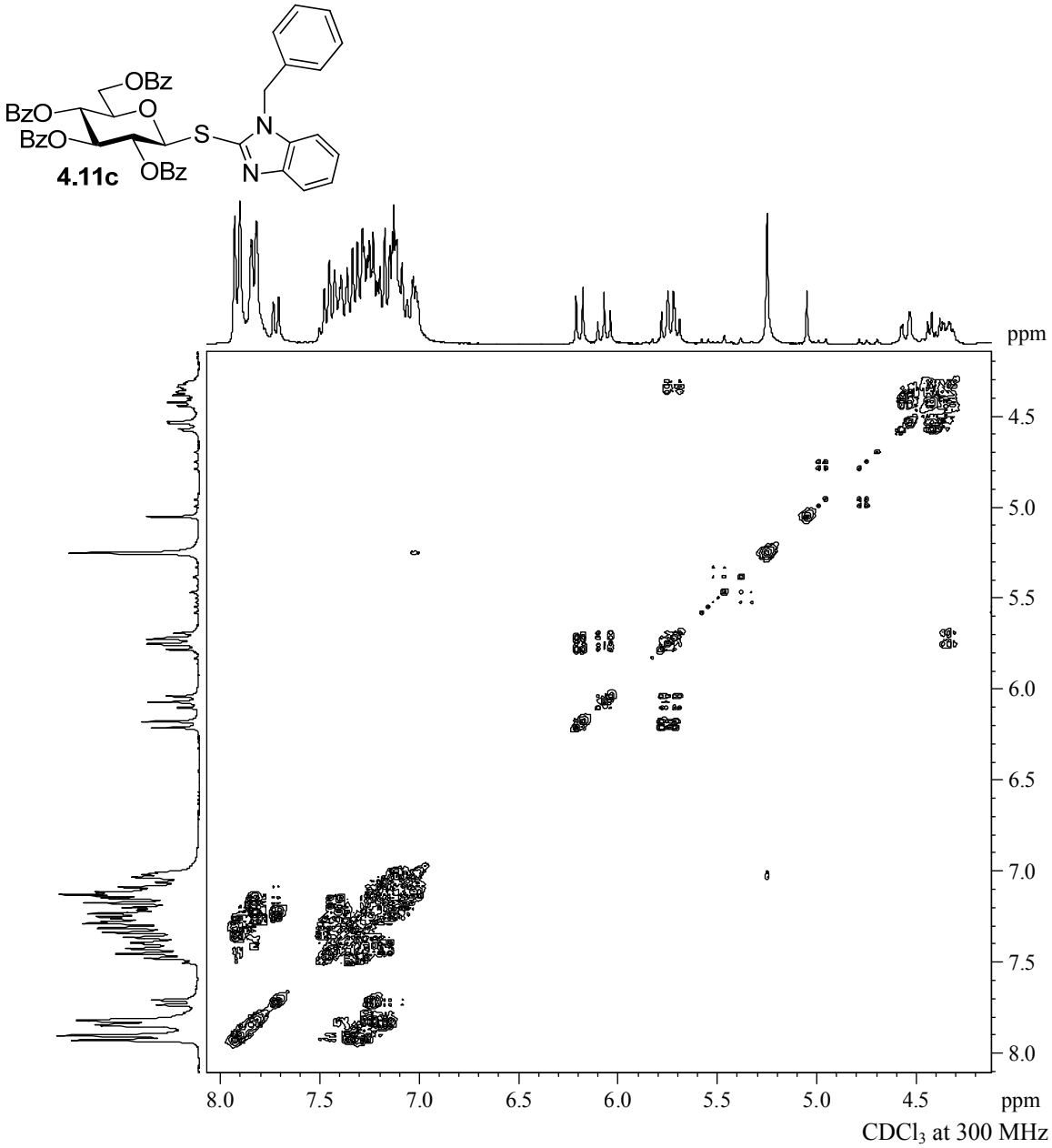
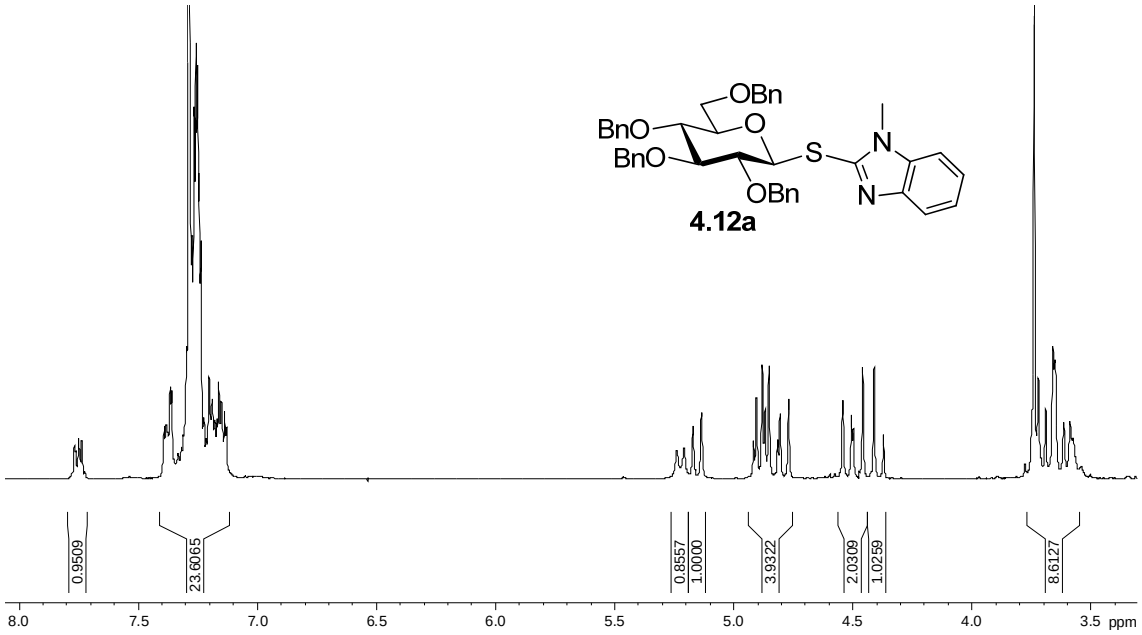
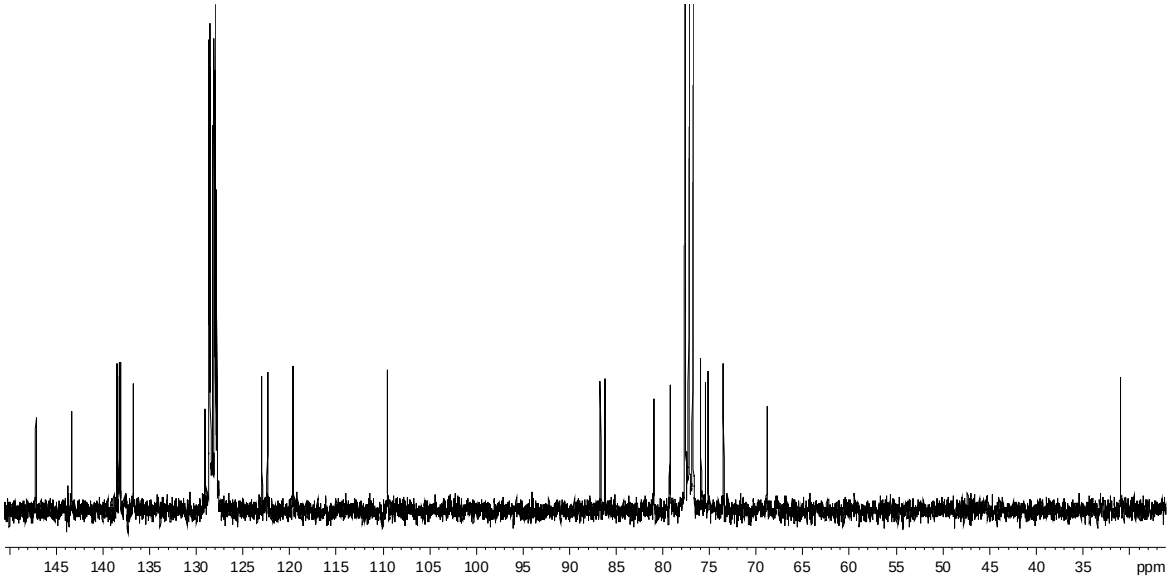


Figure A-72: 2-D NMR COSY spectrum of 1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.11c**).



$CDCl_3$ at 300 MHz

Figure A-73: ^{1}H NMR spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**4.12a**).



$CDCl_3$ at 75 MHz

Figure A-74: ^{13}C NMR spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**4.12a**).

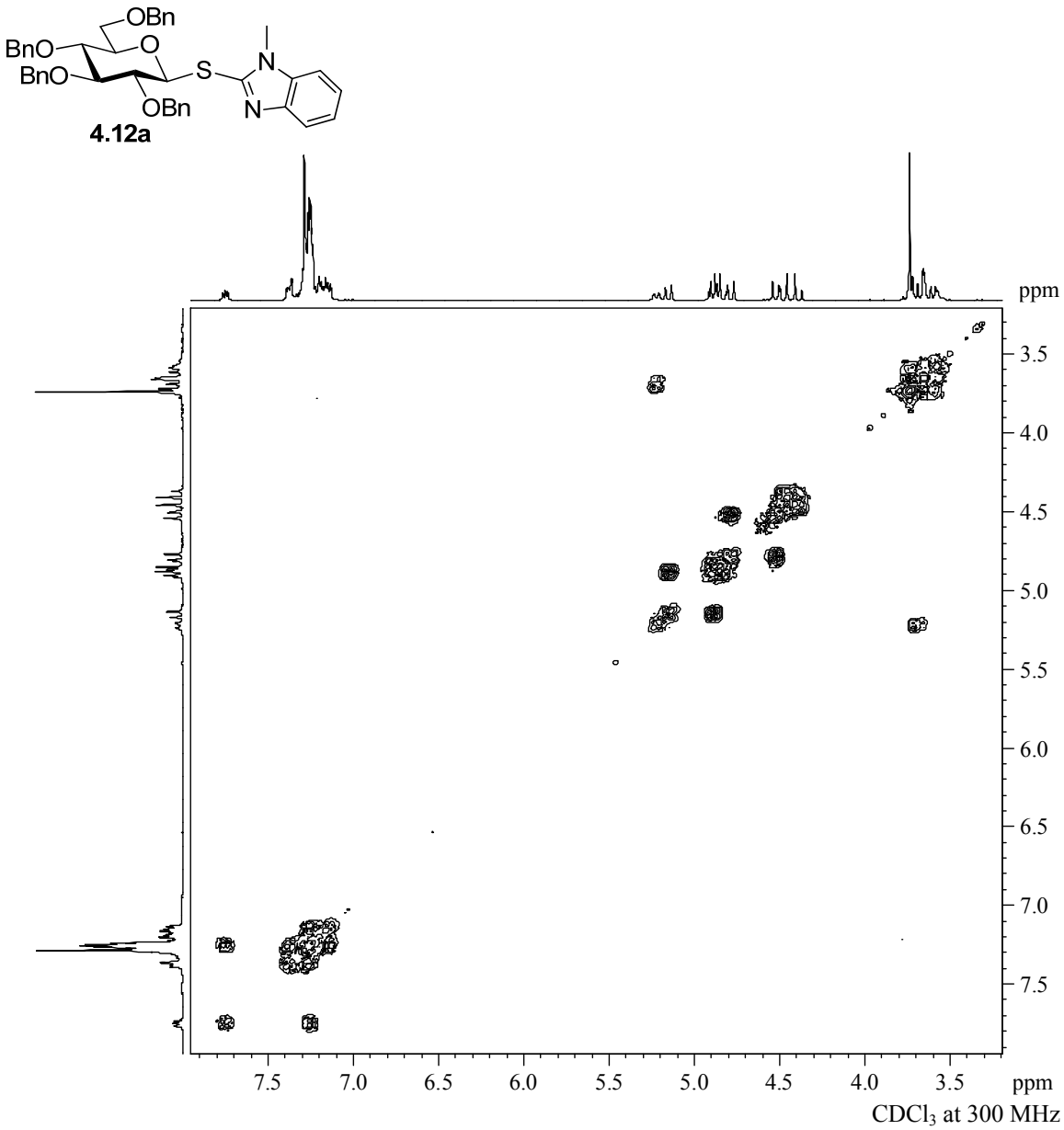


Figure A-75: 2-D NMR COSY spectrum of 1-Methylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**4.12a**).

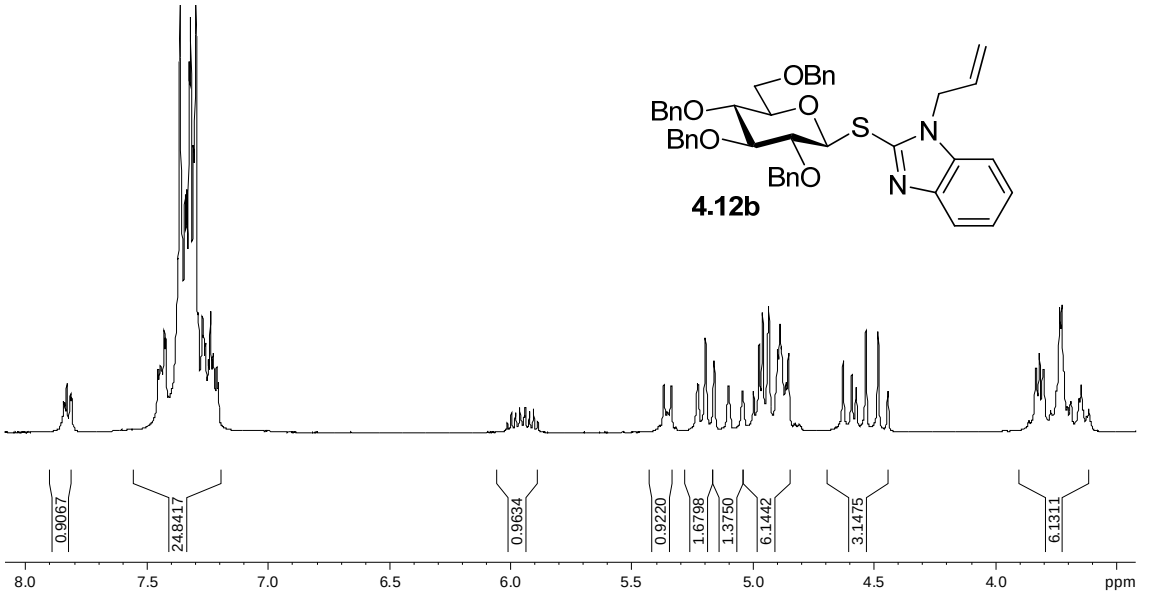


Figure A-77: ^{1}H NMR spectrum of 1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**4.12b**).

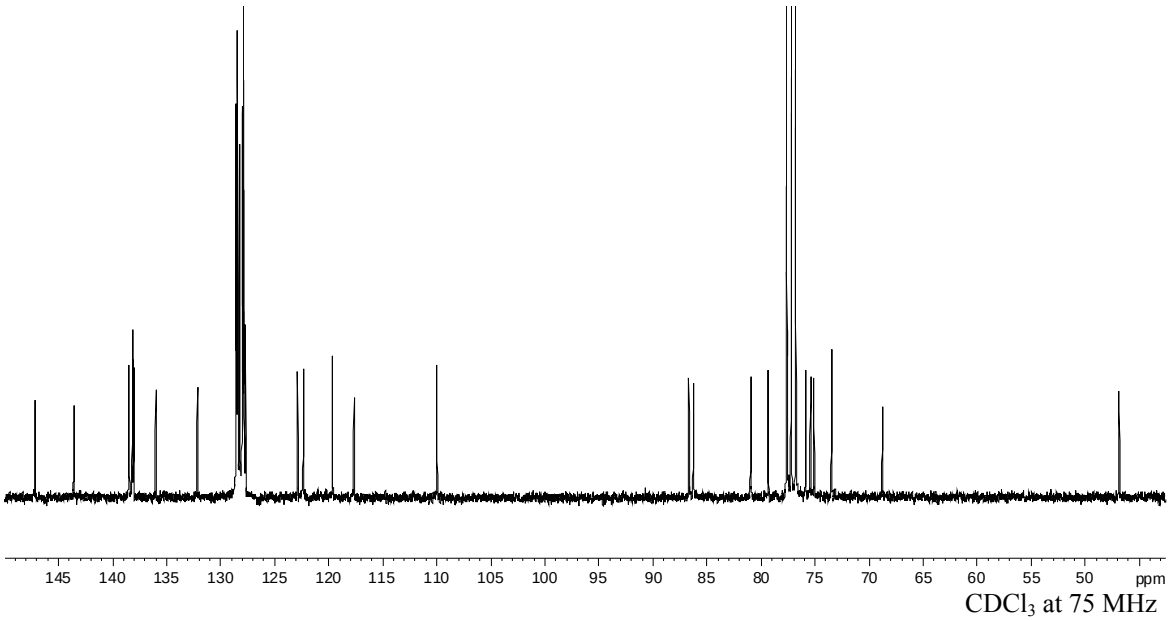


Figure A-78: ^{13}C NMR spectrum of 1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**4.12b**).

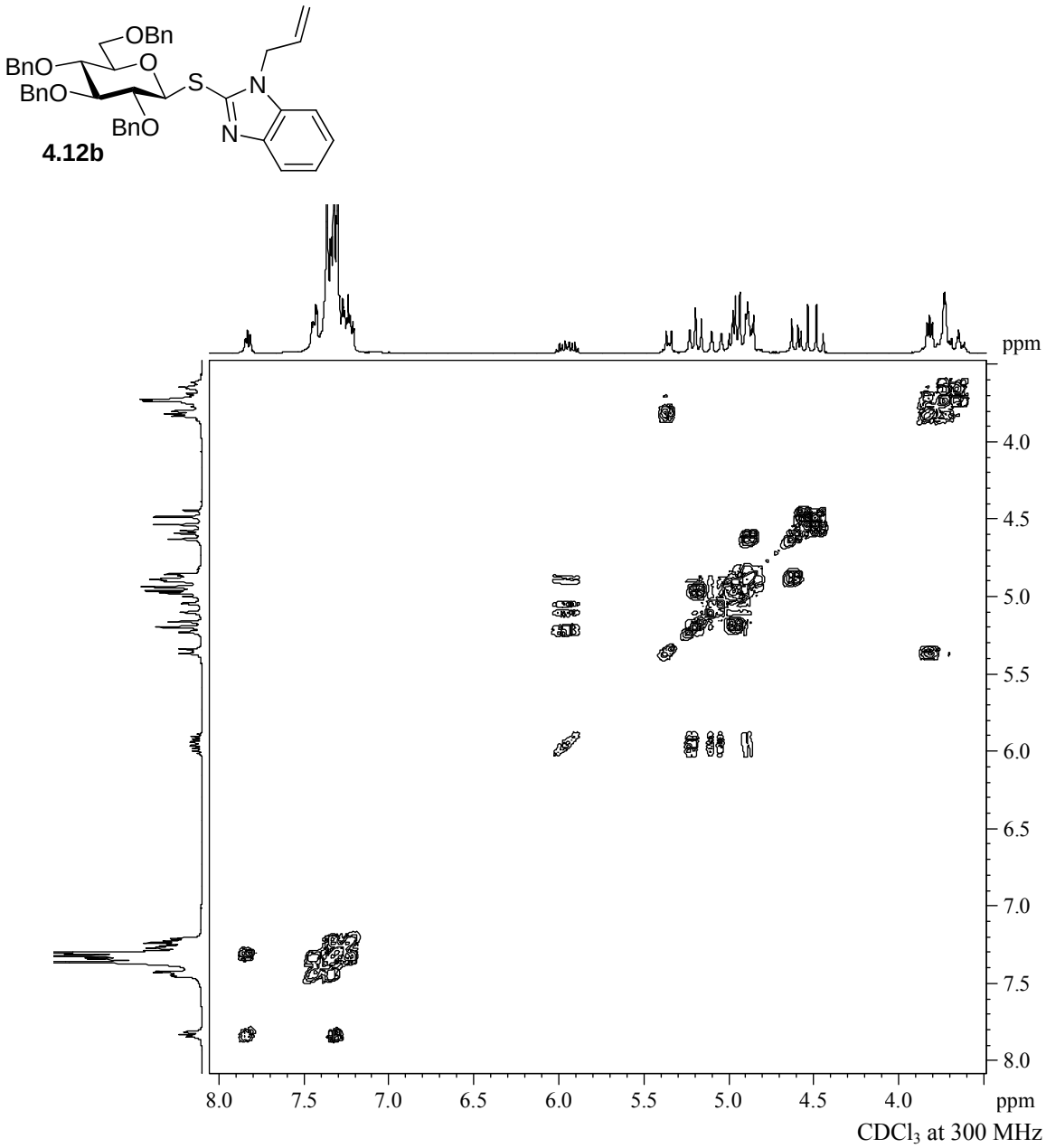
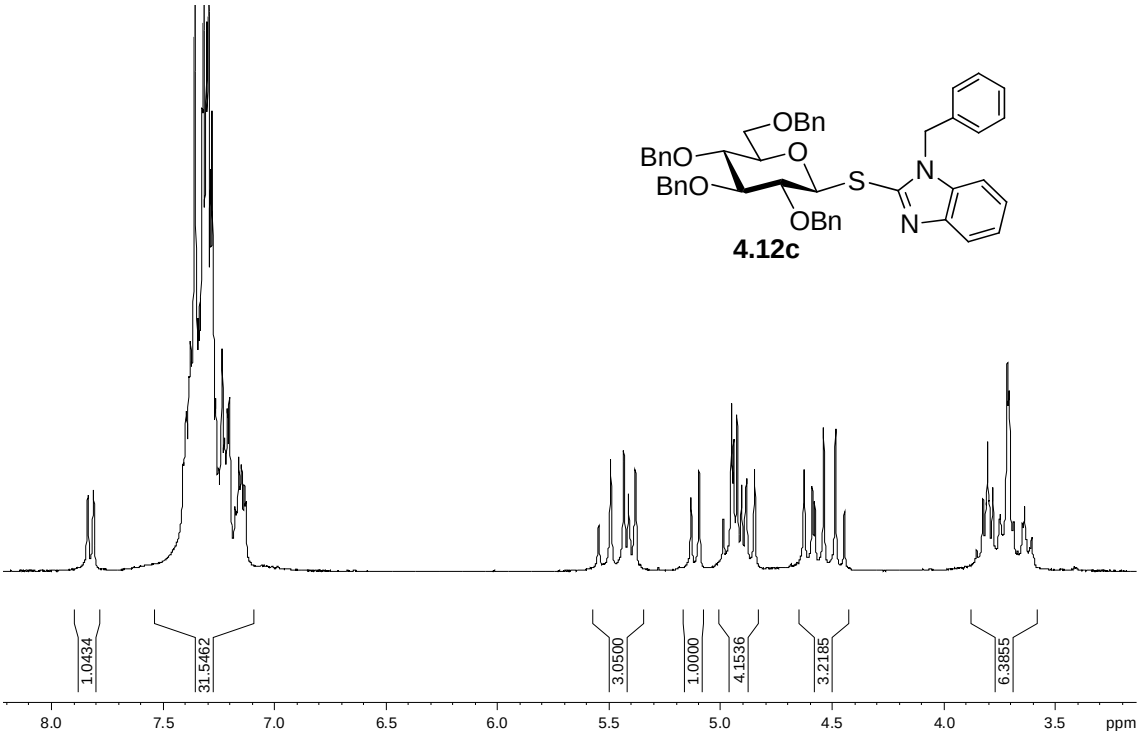
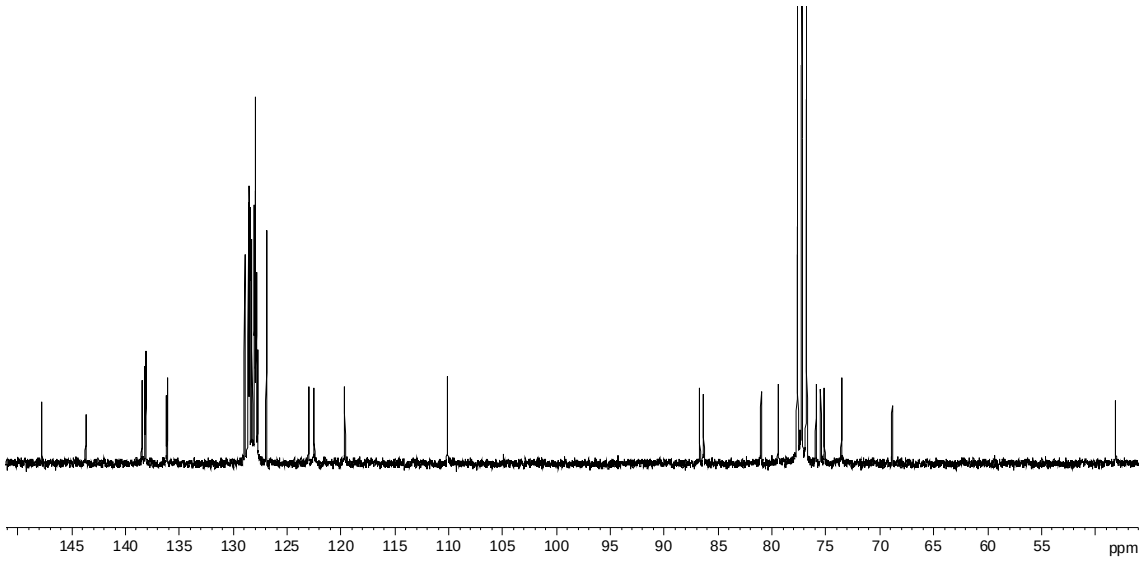


Figure A-78: 2-D NMR COSY spectrum of 1-Allylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**4.12b**).



$CDCl_3$ at 300 MHz

Figure A-79: ^{1}H NMR spectrum of 1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**4.12c**).



$CDCl_3$ at 75 MHz

Figure A-80: ^{13}C NMR spectrum of 1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**4.12c**).

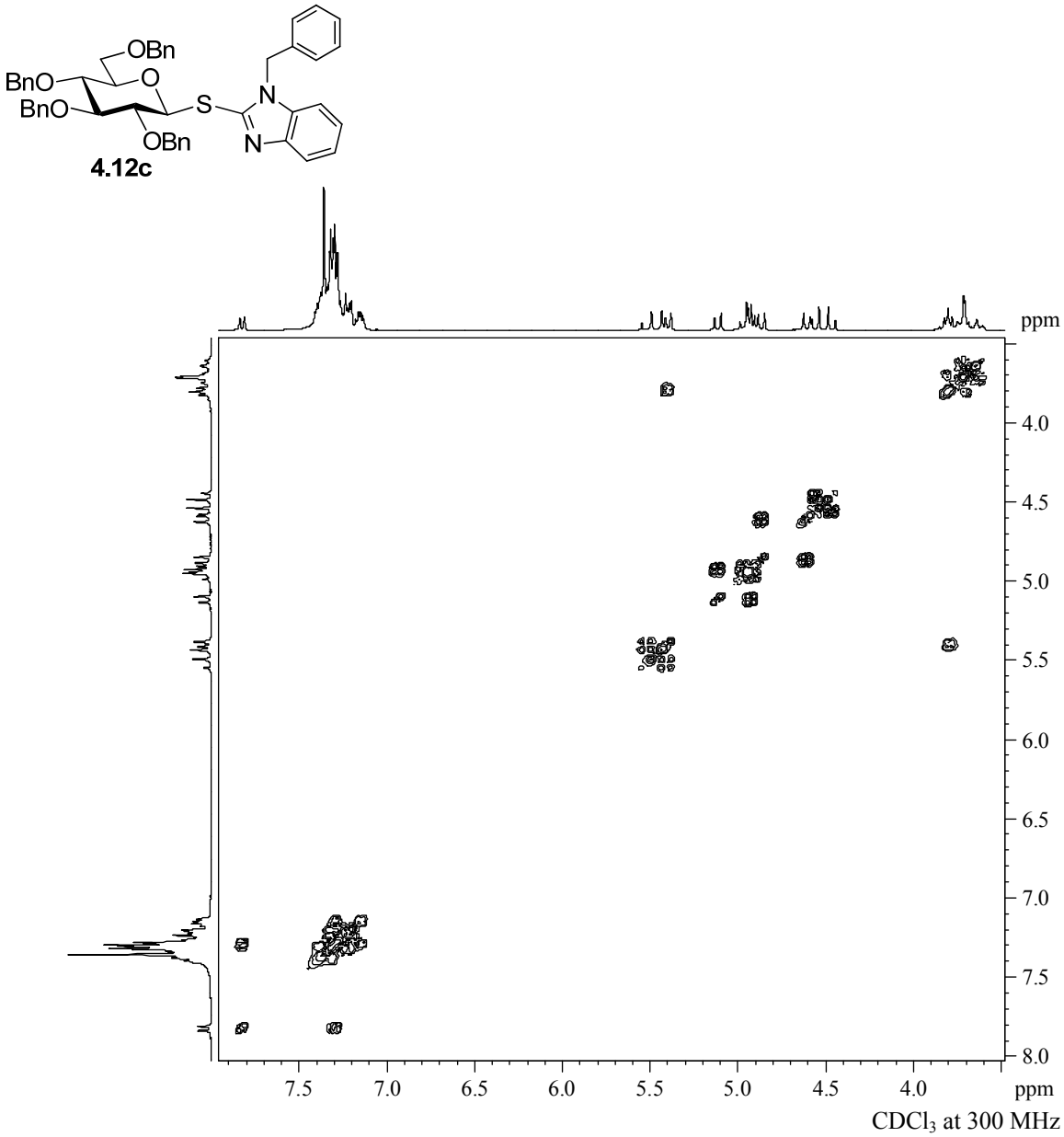
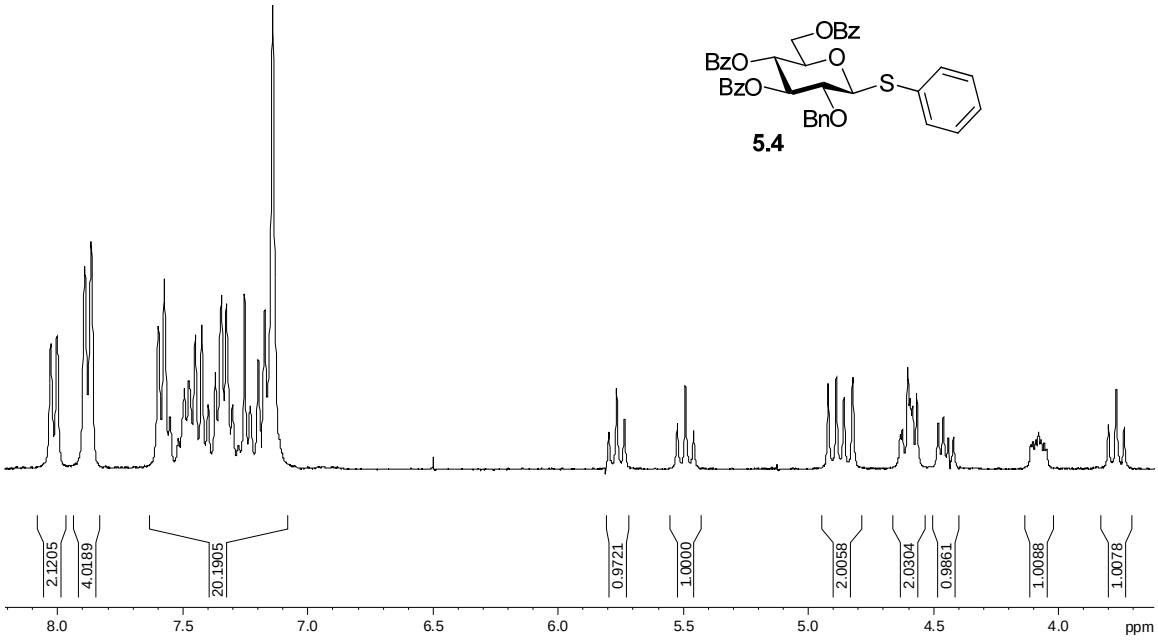
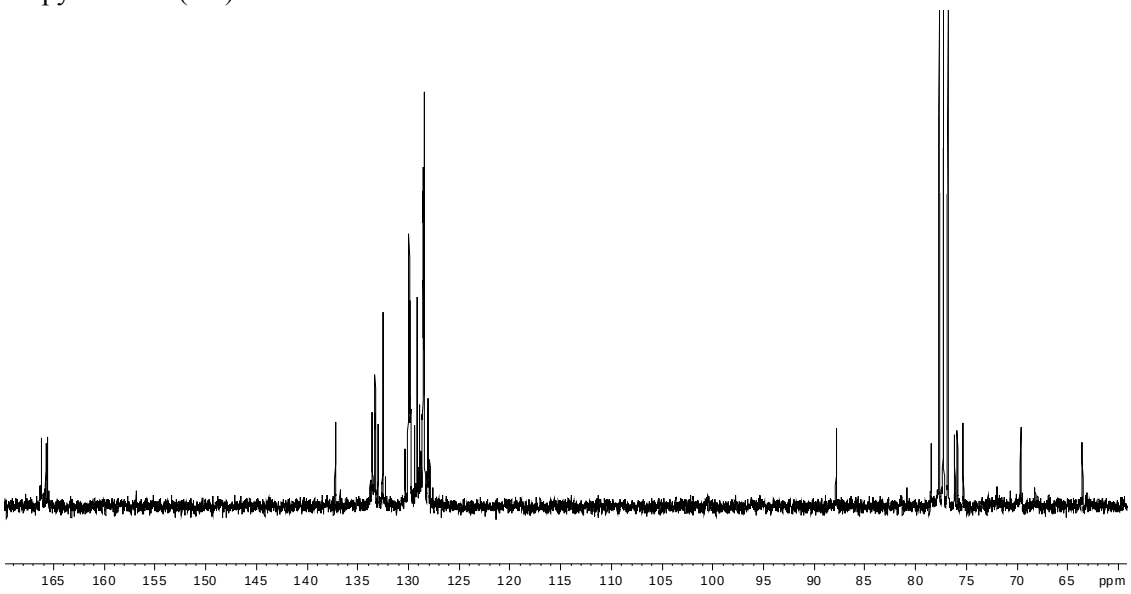


Figure A-81: 2-D NMR COSY spectrum of 1-Benzylbenzimidazol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**4.12c**).



$CDCl_3$ at 300 MHz

Figure A-82: ^{1}H NMR spectrum of Phenyl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside (**5.4**).



$CDCl_3$ at 75 MHz

Figure A-83: ^{13}C NMR spectrum of Phenyl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside (**5.4**).

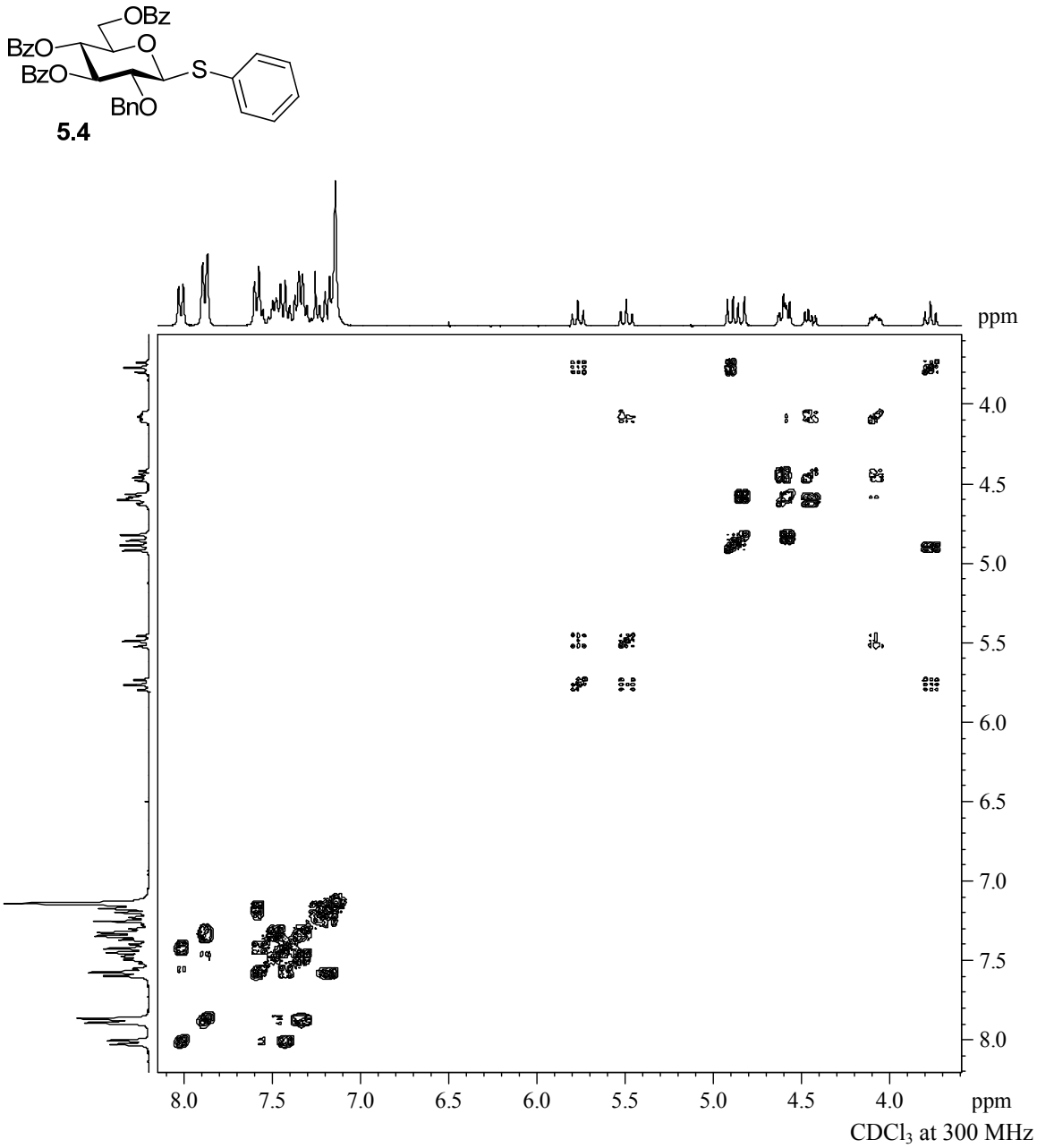
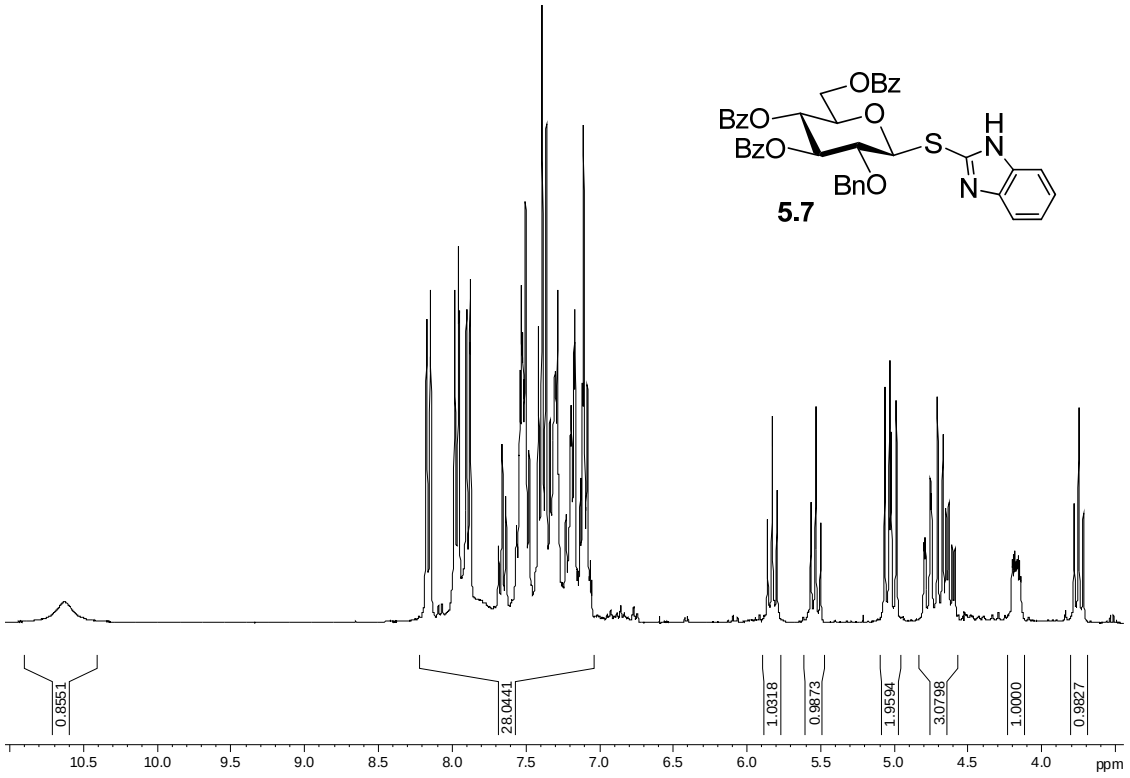


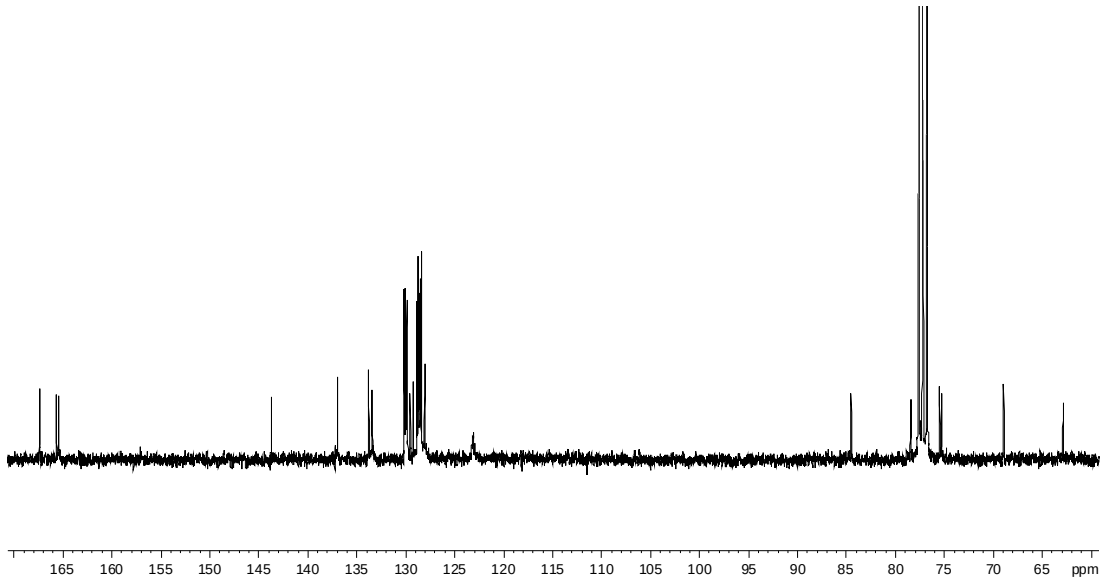
Figure A-84: 2-D NMR COSY spectrum of Phenyl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside (**5.4**).

.



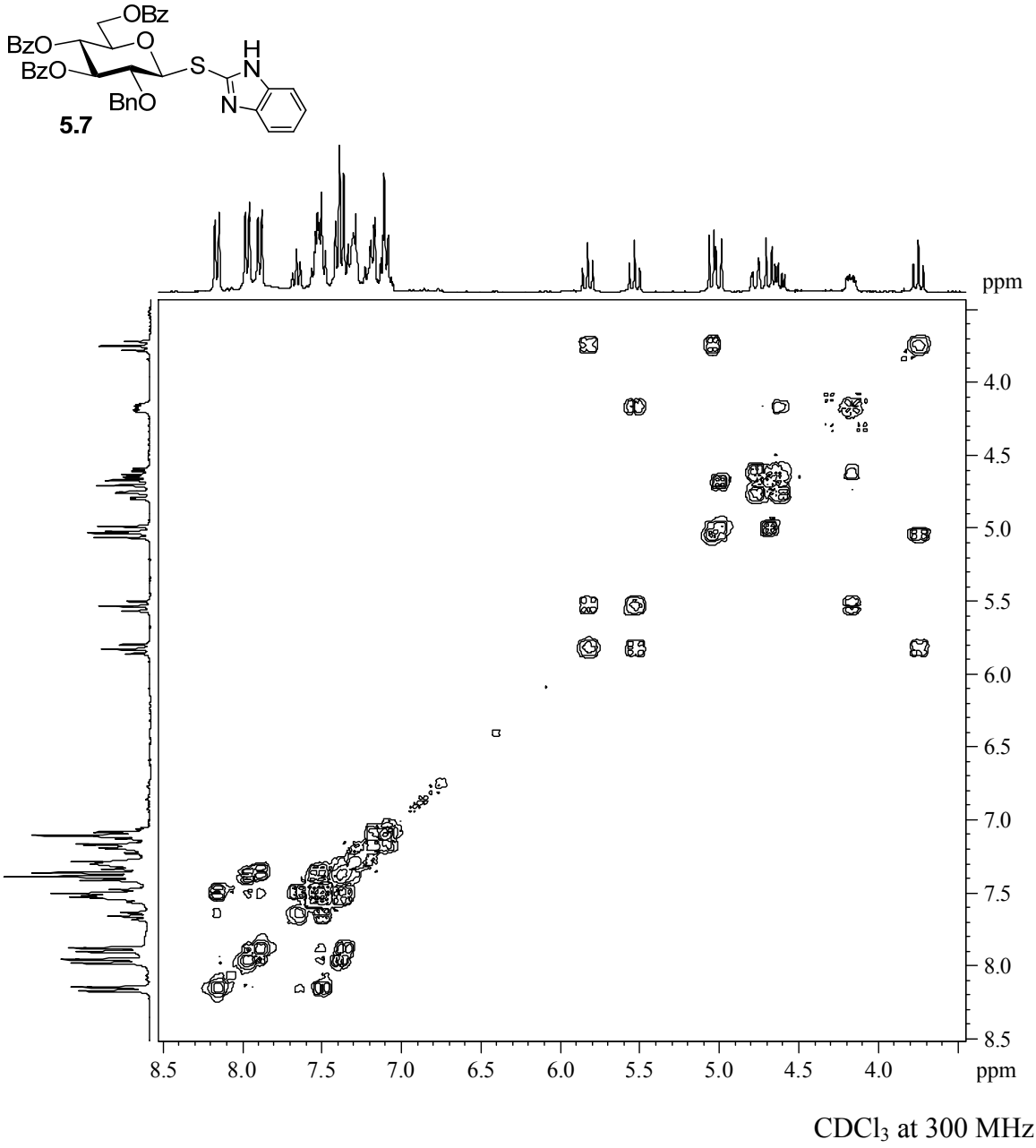
$CDCl_3$ at 300 MHz

Figure A-85: ^{1}H NMR spectrum of Benzimidazol-2-yl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside (**5.7**).



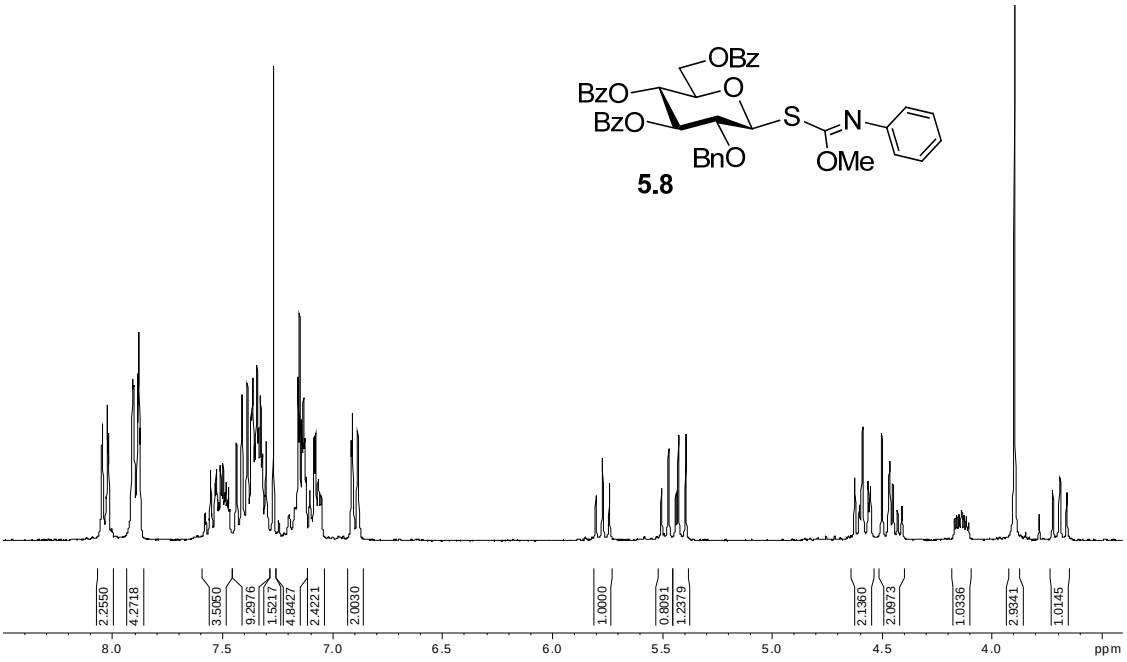
$CDCl_3$ at 75 MHz

Figure A-86: ^{13}C NMR spectrum of Benzimidazol-2-yl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside (**5.7**).



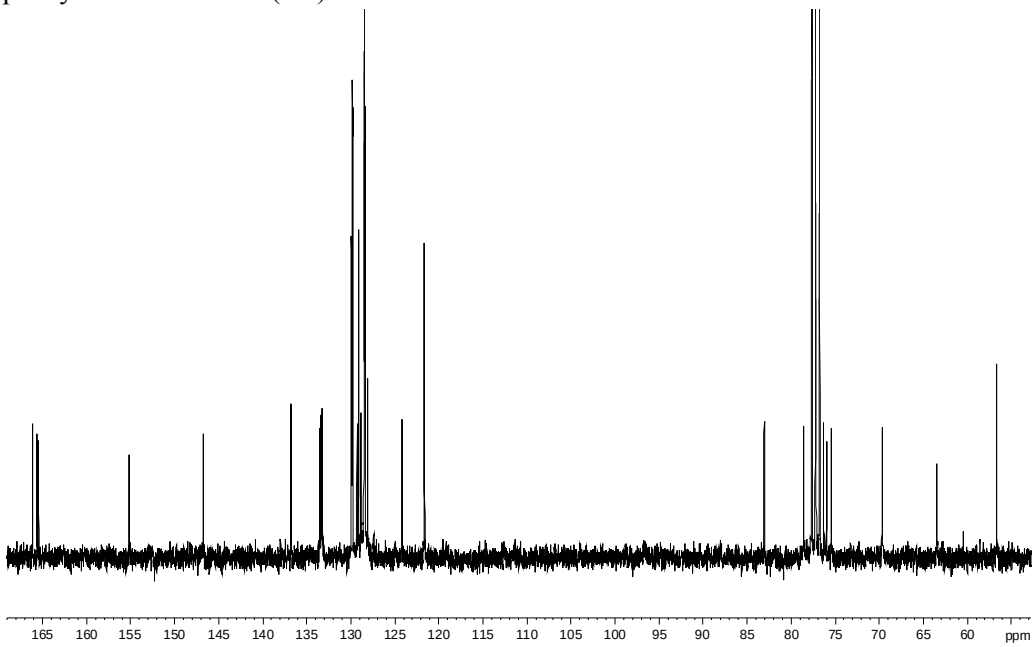
$CDCl_3$ at 300 MHz

Figure A-87: 2-D NMR COSY spectrum of Benzimidazol-2-yl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside (**5.7**).



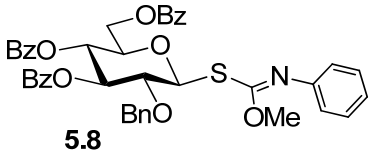
$CDCl_3$ at 300 MHz

Figure A-88: ^{1}H NMR spectrum of 3,4,6-Tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (**5.8**).



$CDCl_3$ at 75 MHz

Figure A-89: ^{1}C NMR spectrum of 3,4,6-Tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (**5.8**)**.**



5.8

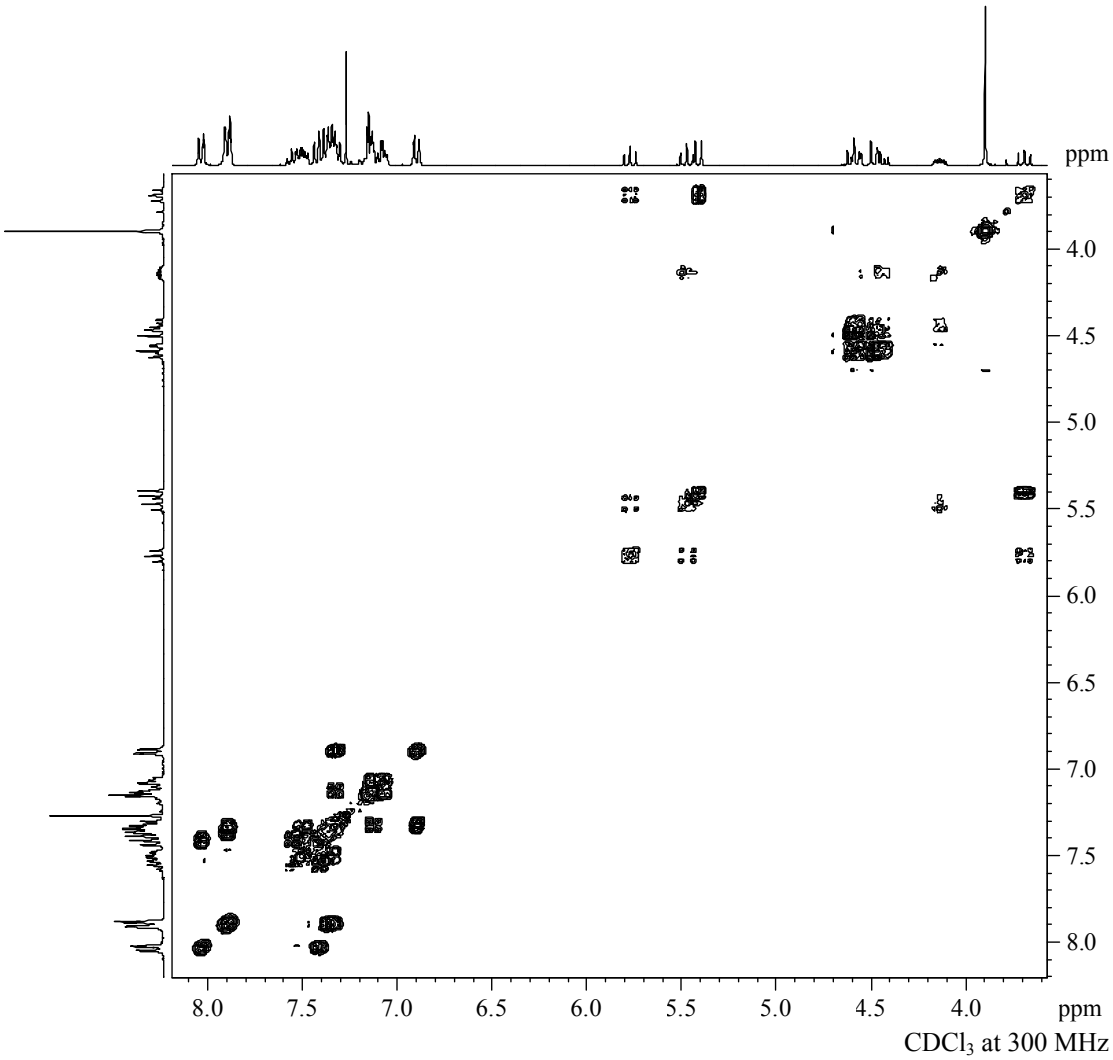
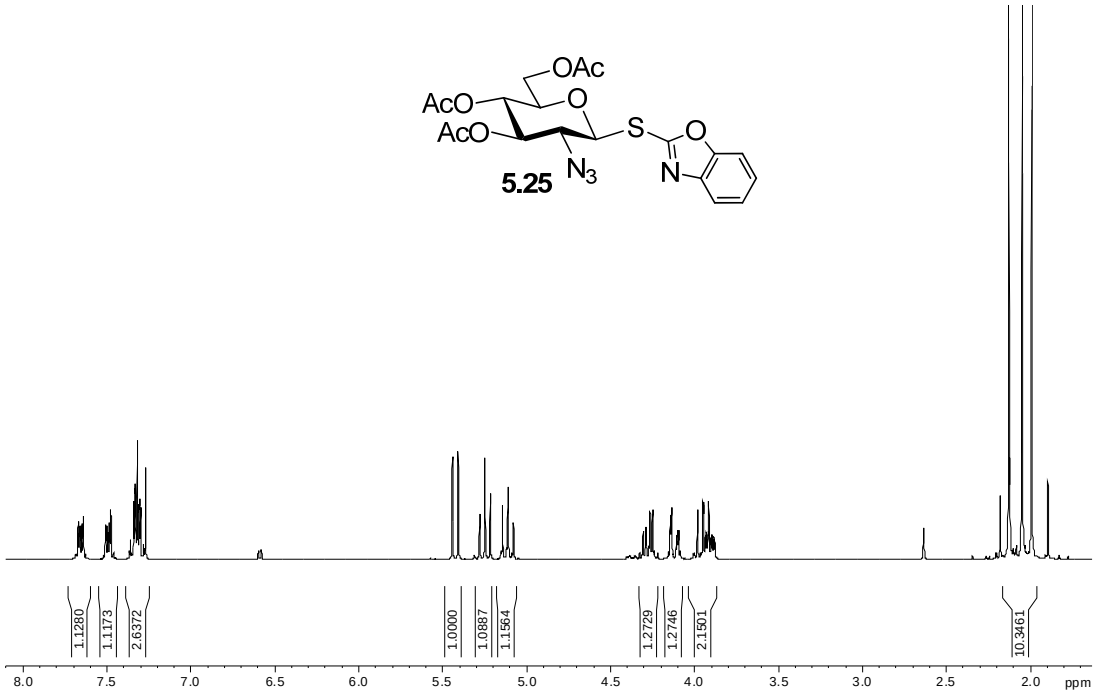
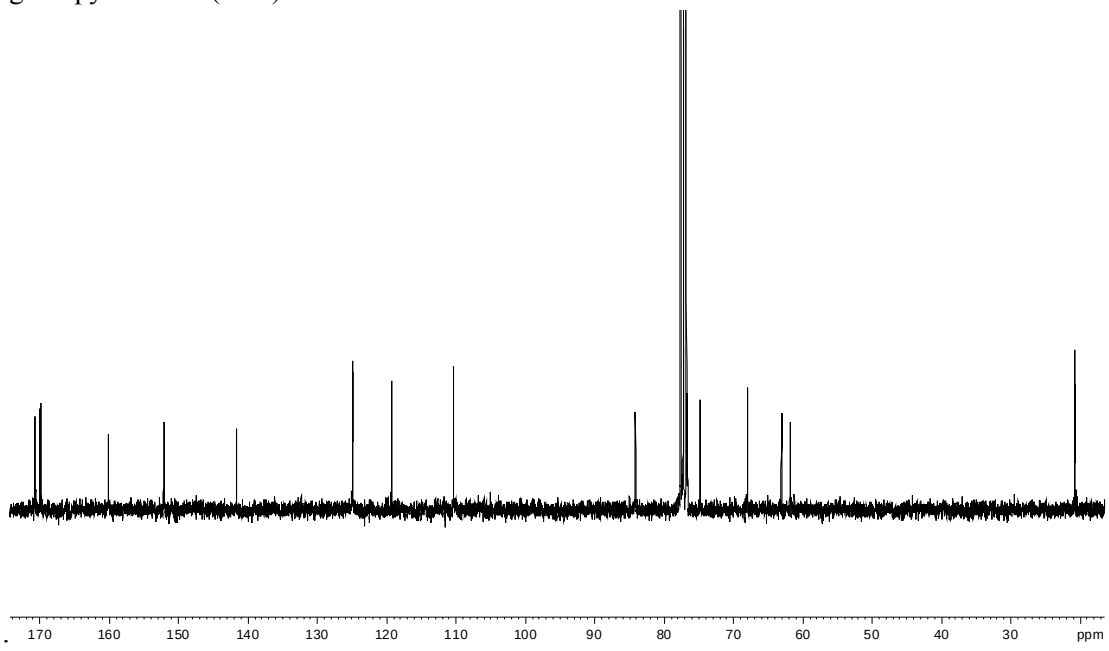


Figure A-90: 2-D NMR COSY spectrum of 3,4,6-Tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (**5.8**).



$CDCl_3$ at 300 MHz

Figure A-91: ^{1}H NMR spectrum of Benzoxazol-2-yl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-β-D-glucopyranoside (**5.25**).



$CDCl_3$ at 75 MHz

Figure A-92: ^{1}C NMR spectrum of Benzoxazol-2-yl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-β-D-glucopyranoside (**5.25**).

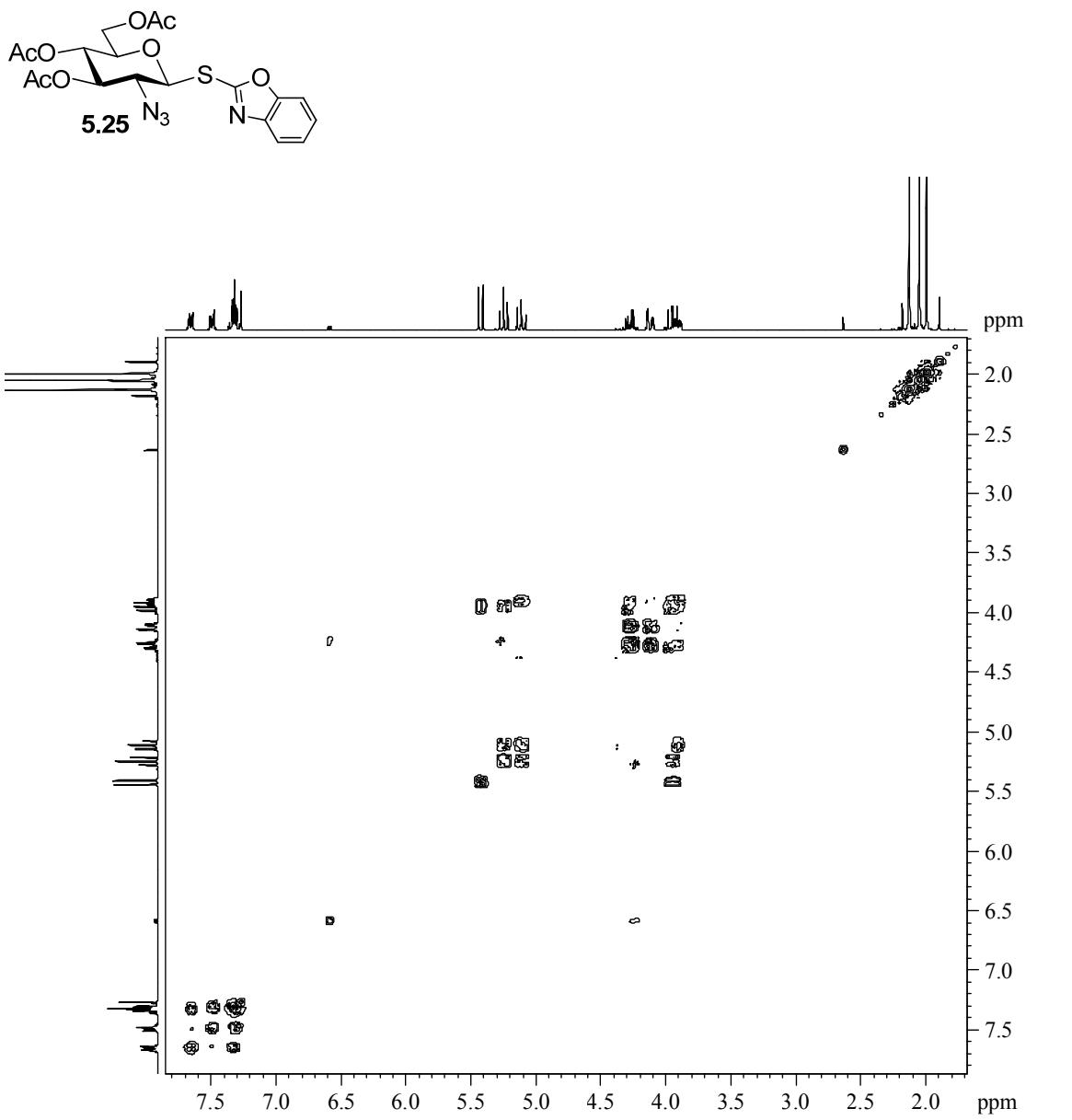


Figure A-93: 2-D NMR COSY spectrum of Benzoxazol-2-yl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-β-D-glucopyranoside (**5.25**).