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Glycosyl Thiocarbamates As New Building Blocks for Chemical Glycosylation

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Abstract

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Having multiple functions in biological systems e.g. fertilization, blood group determination, cell growth; carbohydrates have remained attractive subjects for the study. They are also involved in various life threatening biological processes, such as viral and bacterial infections, tumor development, etc. Understanding of these involvements/interactions of carbohydrates in such critical processes is essential for the development of carbohydrate based vaccines and therapeutics. Although carbohydrates are present abundantly in nature, their isolation is cumbersome and low yielding, which is why, the synthesis of carbohydrate units has been of interest to many scientists. Efforts have been made to make these synthetic methods more and more efficient with the primary focus on the yield and stereoselectivity of glycosylation reactions.

Over the years, researchers have observed various factors that influence the outcome of the glycosylation reaction, most of which are dependent on the structure of two coupling components of the glycosylation reaction, i. e. the glycosyl donor and glycosyl acceptor. This topic also became the basis for this doctoral dissertation work wherein the study has been focused on the development of a new class of glycosyl donors and comparison of their properties with known compounds. The investigation of various leaving groups was conducted with a goal of obtaining glycosyl donors with tunable reactivity and studying the effect of various modifications on the outcome of glycosylation reactions.

This dissertation is dedicated to my family
with love and respect

Acknowledgments

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Varun, whose love, optimism and guidance has helped me in this challenging final stretch of my dissertation. I also want to mention my parents-in-law, Mrs. Erawati and Mr. Bhalchandra Bhalerao for all the cheerful and encouraging conversations. Special thanks should go to my dear friends Sangeeta, Geeta, Pushkar, Priyanka and Nirav, who made my experience in the US a memorable one. I would like to thank all the incredible people who made a difference in my life one-way or the other.

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LIST OF ABBREVIATIONS

Å.....Angstrom

Ac .....Acetyl

$AgBF_4$ .....Silver tetrafluoroborate

$AgClO_4$ ..... Silver perchlorate

Ag_2CO_3 ..... Silver carbonate

$AgNO_3$.....Silver nitrate

Ag_2O ..... Silver oxide

AgOTf ..... Silver trifluoromethanesulfonate

AP..... 2-Allylphenyl

$AuCl_3$ ..... Gold(III) chloride

BF_3-OEt_2 ..... Boron trifluoride etherate

BINAP..... 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

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

Bn ..... Benzyl

BnBr ..... Benzyl bromide

BSP..... 1-Benzenesulfinyl piperidine

Bu_4NBr.....Tetrabutylammonium bromide

Bz ..... Benzoyl

COD..... 1,5-Cyclooctadiene

Cp ..... Cyclopentyl

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

d..... Doublet

DABCO..... 1,4–Diazabicyclo[2.2.2]octane

DCE.....1,2-Dichloroethane

dd..... Doublet of doublets

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

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

DPSO..... Diphenyl sulfoxide

DTBMP Di-*tert*-butyl-4-methylpyridine

E..... Electrophile

Et ..... Ethyl

EtOAc .....Ethyl acetate

Et_2O.....Diethyl ether

EtOH ..... Ethanol

Et_3SiH ..... Triethylsilane

$FeCl_3$ ..... Iron(III) chloride

Glc..... Glucose

h..... Hour(s)

$HgBr_2$ ..... Mercury(II) bromide

$HgCl_2$ ..... Mercury(II) chloride

$Hg(CN)_2$ ..... Mercury(II) cyanide

$Hg(NO_3)_2$ ..... Mercury(II) nitrate

$HgSO_4$ ..... Mercury(II) sulfate

HPLC ..... High Performance Liquid Chromatography

HR-EI MS .....High Resolution Electron Ionization mass spectrum

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

Hz .....Hertz

IDCP ..... Iodonium (di-γ-collidine) perchlorate

^{i}Pr ..... Isopropyl

IR..... Infra red

KOH.....Potassium hydroxide

LG ..... Leaving group

$LiClO_4$ ..... Lithium perchlorate

m .....Multiplet

Me ..... Methyl

MeCN..... Acetonitrile

MeI.....Methyl iodide

MeOH ..... Methanol

MeOTf..... Methyl trifluoromethanesulfonate

Me_2S_2 ..... Dimethyl disulfide

min ..... Minute(s)

MPBT..... *S*-(4-methoxyphenyl) benzenethiosulfinate

MS..... Molecular sieves

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

NaOH..... Sodium hydroxide

NaOMe..... Sodium methoxide

NBS ..... *N*-Bromosuccinimide

NIS ..... *N*-Iodosuccinimide

NMR ..... Nuclear magnetic resonance

NPOE..... *n*-Pentenyl othoester

Nu..... Nucleophile

P..... Protecting group

PF_5 ..... Phosphorus(V) fluoride

Ph ..... Phenyl

PhSCl ..... Phenylsulfenyl chloride

PhSeOTf ..... Phenylselenyl trifluoromethanesulfonate

ppm .....Parts per million

PTFAI..... N-phenyl trifluoroacetimidate

R_f .....Retention factor

rt .....Room temperature

s ..... Singlet

SBaz ..... *S*-Benzothiazolyl

SBiz.....*S*-Benzimidazolyl

SBox..... *S*-Benzoxazolyl

$Sn(OTf)_2$ ..... Tin(II) trifluoromethanesulfonate

$Sm(OTf)_2$ ..... Samarium(III) trifluoromethanesulfonate

STaz ..... *S*-Thiazolinyl

t .....Triplet

TBDMS.....*tert*-Butyldimethylsilyl

TBPA..... Tris(4-bromophenyl)ammoniumyl hexachloroantimonate

TBSOTf..... *tert*-Butylsilyl trifluoromethanesulfonate

TCAI..... Trichloroacetimidate

TFA.....Trifluoroacetic acid

Tf..... Trifluoromethanesulfonate

TfOH ..... Trifluoromethanesulfonic (triflic) acid

THF..... Tetrahydrofuran

TLC .....Thin layer chromatography

TMS..... Trimethylsilyl

TMSOTf..... Trimethylsilyl trifluoromethanesulfonate

TMTSB..... Methyl bis-methylthiosulfonium hexachloroantimonate

Tol..... Tolyl

TOPCAT..... 2-Thiopyridyl carbonate

Tr..... Triphenylmethyl

$TrClO_4$ ..... Trityl perchlorate

Ts..... 4-Tolylsulfonyl

TTBP..... Tri-*tert*-butylphosphine

UV..... Ultra violet

$Yb(OTf)_3$ ..... Ytterbium(III) trifluoromethanesulfonate

$ZnCl_2$ ..... Zinc(II) chloride

$Zn(OTf)_2$ ..... Zinc(II) trifluoromethanesulfonate

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CHAPTER 1

Mechanism of Chemical Glycosylation: Focus on the Mode of Activation and Departure of Anomeric Leaving Group

Ranade, S. C.; Demchenko A. V. "Mechanism of chemical glycosylation: focus on the mode of activation and departure of anomeric leaving groups", Journal of Carbohydrate Chemistry, 2013, in press

1.1 Introduction and Outline

Carbohydrates are present on mammalian and bacterial cell walls as glycoproteins, glycopeptides, polysaccharides etc.[1] These "essential molecules of life"[2] act as receptors during various biological processes involving cell-cell interactions and growth, immunoresponse, fertilization, and blood group determination are only few to mention.[3] Carbohydrates are also involved in life-threatening processes such as tumor development, metastasis, bacterial and viral infections, and others.[4-10] It has been of special interest in the field of carbohydrate science to understand how they interact with other cells during the progression of these deadly diseases. In-depth understanding of carbohydrate involvement will help in the development of effective treatments against these diseases.[11-15]

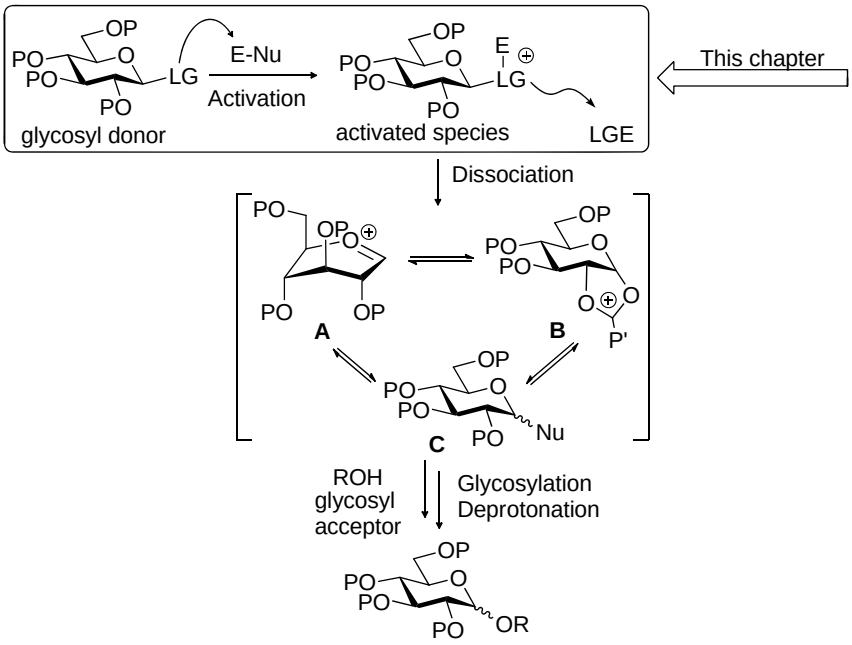
In spite of being the most abundant biomolecules on the Earth, isolation of complex or disease-specific carbohydrates from natural sources in pure form is cumbersome. To address this challenge, complex carbohydrate molecules are often obtained using chemical and/or enzymatic methods. However, synthesis of these complex molecules presents certain challenges. The key reaction in the chemical synthesis of oligomeric carbohydrates is the glycosylation reaction, which involves coupling of monomeric sugar units to each other via glycosidic bonds.[16,17] The development of new effective methods for glycosylation and strategies to enable efficient oligosaccharide assembly to streamline access to complex oligosaccharides has been a very active area of research. Nevertheless, chemical synthesis of oligosaccharides of even moderate complexity still remains a notable challenge for synthetic chemists. Achieving complete stereocontrol during glycosylation reactions is difficult although certain classes

of glycosidic linkages can be accessed routinely. A notable effort has been placed on the refinement of the reaction conditions;[18] along with these studies, a general idea of the key mechanistic steps has also began to emerge.[19,20] However, the general complexity of the reaction components and a plethora of synthetic steps by which the reactants are converted into final products of glycosylation, significantly hinder the progress in this field.

1.2 General Mechanism of Glycosylation

Glycosylation reaction is a coupling reaction between two building blocks to form a new linkage termed a glycosidic bond, most commonly an *O*-linkage, but examples leading to *S*- and *N*-glycosides are also plentiful. In a typical *O*-glycosylation reaction one building block, glycosyl donor, is equipped with the anomeric leaving group (LG, Scheme 1.1). Another building block, glycosyl acceptor, is equipped with a hydroxyl group that acts as a nucleophile and displaces the leaving group of the glycosyl donor. Typically, all other functional groups on both glycosyl donor and acceptor counterparts are masked with temporary protecting groups (P), although examples wherein unprotected or partially protected building blocks are used are not uncommon.[21,22] Generally, it is considered that the glycosylation reaction follows an S_N1-like mechanism, but examples of the S_N2-like displacements are also seen throughout the literature.[23-26] Regardless of the molecularity of the rate-determining step, practically any glycosylation reaction begins by the interaction taking place between the activator/promoter (E-Nu) and the glycosyl donor. This results in the formation of an activated species followed by the dissociation of a leaving group. A common prototype of a monomolecular mechanism of

the leaving group displacement with the glycosyl acceptor is shown in Scheme 1.1. The reaction may proceed via the formation of a flattened glycosyl cation that can be stabilized via oxacarbenium ion intermediate (A). If the neighboring group is an acyl, an acyloxonium intermediate (B) can be formed as a result of the participation from the carbonyl group at C-2. These intermediates can be glycosidated with the glycosyl acceptor (ROH) either directly, or can first interact with other nucleophilic (Nu) species that might be present in the reaction medium: promoter counterion, solvent, additives, moisture, etc. It is this interaction that can lead to other reactive intermediates in the reaction (C), but can also lead to unreactive side products: hydrolysis, elimination, cyclization, rearrangement, etc. The hydroxyl moiety of a glycosyl acceptor then attacks the intermediate A, B, or C. Depending on the structure of the key reaction intermediate, the acceptor attack may result in the formation of either a β-glycoside or an α-glycoside or, very commonly, a mixture of both.



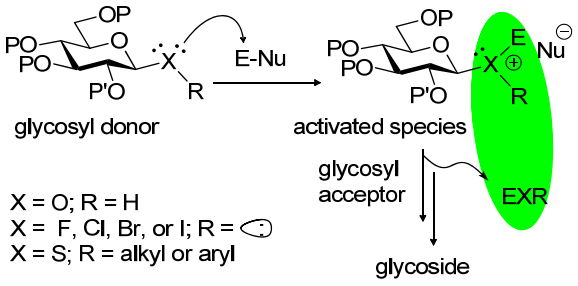
Scheme 1.1. General Mechanism of the Glycosylation Reaction

Many factors influence the outcome of chemical glycosylation, and a significant effort has been made to develop efficient methods for stereocontrolled glycosylation. Particularly, mechanistic studies by Bols,[27-32] Crich,[20,23,24,33-38] Gin,[39-45] Whitfield,[46-50] and Woerpel,[51-56] have been particularly influential in the past decade.[19] A plethora of new leaving groups have also been developed.[16] Some reactive reaction intermediates have been proposed and elucidated, although the first activation step of practically every glycosylation is frequently overlooked and the modes by which leaving groups interact with promoters is often simply assumed. More recent studies resulted in the investigation of polyfunctional leaving groups that, in principle, can be activated via different pathways and using different classes of activators. Resultantly, the question emerged about the mode by which leaving groups interact with the promoter to form an activated species and eventually leading to its departure. This chapter will focus on studies dedicated to the investigation of the activation mechanism of various leaving groups that have subjectively classified as follows.

- Direct Activation wherein the activation of a leaving group takes place at the anomeric heteroatom
- Remote Activation wherein the activation of a leaving group takes place at other remote heteroatoms or remote functional groups
- Bidentate Activation wherein either direct or remote activation, depending on the nature of reagents used, can take place

1.3. Direct Activation (activation via the heteroatom directly adjacent to the anomeric carbon)

A number of leaving groups have only one heteroatom at the anomeric center and no other nucleophilic functionalities, which could be involved in the activation pathway. Most traditional leaving groups, hemiacetals, halides, and simple thioglycosides fall into this category, with the only possible activation pathway envisaged as being the direct anomeric activation. Due to this relative straightforwardness, this activation pathway has been generally assumed and mechanistic studies to actually elucidate its viability are still scarce. As shown in Scheme 1.2, the anomeric heteroatom reacts with an electrophile, upon which the anomeric atom acquires a formal positive charge (or a partial positive charge when the electrophile is a metal forming a coordination complex). This interaction improves the leaving group ability for departure, and the leaving group usually departs as the neutral species or as ligand complexed to the metal-based promoter. These two events, interaction of the anomeric heteroatom of the leaving group (XR) with the electrophile (E) and the structure of the departed aglycone (EXR), are of the central focus of this section (Scheme 1.2).

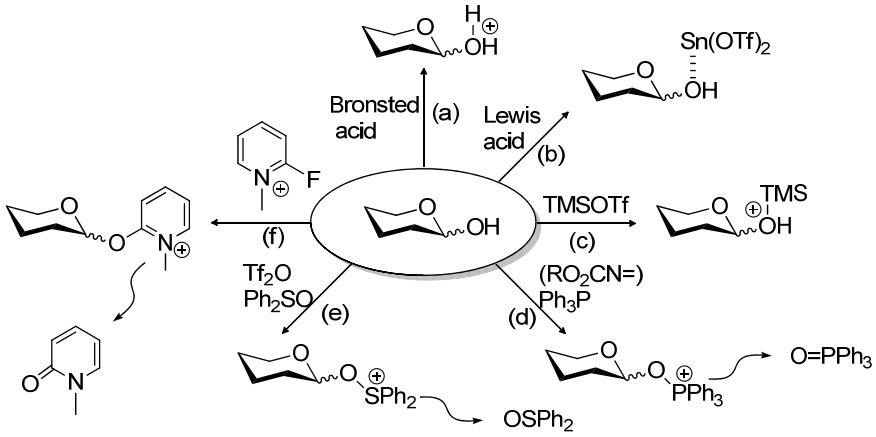


Scheme 1.2. Direct Activation of Leaving Groups for Glycosylation: Focus on the Activated Leaving Group and the Departed Aglycone

1.3.a. Hemiacetal (1-hydroxyl) Derivatives

Although hemiacetals introduced and tested by Emil Fischer were among the first glycosyl donors discovered,[57,58] much improvement in understanding of their activation pathways and, resultantly, appreciating their utility in synthesis has emerged only recently. The traditional Fischer glycosylation approach involves Bronsted acid-catalyzed leaving group departure that assumedly proceeds via the formal protonation of the anomeric hydroxyl group (Scheme 1.3a). The protonation enhances the leaving group ability dramatically and helps to perform the glycosylation at an acceptable rate. Typically a high excess of glycosyl acceptor and at times higher reaction temperature were needed to facilitate the Fischer glycosylations. These drawbacks were also accompanied by the formation of various by-products, and called for further study and over the years many improvements have emerged. Initial studies to broaden the Fischer approach were dedicated to simple screening of other Bronsted and Lewis acid promoters and resulted in the development of a variety of promising reaction conditions that were mediated by methanesulfonic acid/cobalt(II) bromide,[59,60] methoxyacetic acid and $Yb(OTf)_3$,[61] heteropoly acids $H_4SiW_{12}O_{40}$[62] and Montmorillonite K-10 (MK-10),[63] $ZnCl_2$, $FeCl_3$, $Sn(OTf)_2$,[64] $Cu(OTf)_2$, and BF_3-OEt_2 amongst many others.[45] Lewis-acid-catalyzed conversions are assumingly facilitated by the complexation of the anomeric hydroxyl with the metal (Scheme 1.3b). Amongst these, a particular niche is occupied by silicon-mediated reactions including trimethylsilylchloride in combination with zinc(II) triflate,[59] TMSOTf is generated in situ and it is thought to promote the glycosylation via the intermediacy of a TMS glycoside or its protonated form (Scheme 1.3c). The existence of an alternative pathway, however, wherein TMS-protection of glycosyl acceptor takes

place instead could not be ruled out entirely.[65] Other silicon-based promoter systems have been developed along these lines.[66,67]



Scheme 1.3. Activation of Hemiacetals

Another common method to activate hemiacetals is to convert them into a more powerful leaving group with the use of sulfur, phosphorus, and carbon-based electrophilic promoters. All these pathways involve the formal conversion of the -OH group into an unstable leaving group, and since the anomeric oxygen remains intact, these pathways will be discussed within this subsection. Conversely, pathways wherein -OH is formally converted into relatively stable leaving groups including halides, acyls,[68] and sulfonates[69,70] go beyond the scope of this discussion and the reader should be referred to sections detailing those particular types of leaving groups.

The use of phosphorus-based electrophiles via the Mitsunobu-type activation[71] or related modes were also found quite advantageous for hemiacetal activation. Szarek *et al.* reported that hemiacetal activation was possible in the presence of a phosphine (most commonly Ph_3P), diethyl azodicarboxylate and a mercuric halide.[72] Presumably, this reaction proceeds via the intermediacy of a glycosyl oxophosphonium intermediate

(Scheme 1.3d). The nucleophilic attack by the glycosyl acceptor on this intermediate releases corresponding phosphine oxide. Alternatively, an oxophosphonium intermediate may convert into a glycosyl halide *en route* to glycosylation. A similar activation pathway was proposed for a triphenyl/alkyl phosphine oxide / triflic anhydride system[73] that forms a diphosphonium salt capable of efficient dehydrative glycosylations.[74]

Sulfonium-based activation of hemiacetals were effectively elaborated upon by Gin *et al.* (Scheme 1.3e).[42] The treatment of diphenyl sulfoxide with triflic anhydride resulted in the formation of a reactive sulfonium bistriflate, which in turn activated the hemiacetal resulting in the formation of an anomeric oxosulfonium intermediate. The structure of the latter was verified by ^{1}H NMR.[39] Gin and co-workers further demonstrated the use of di-(*n*-butyl)sulfoxide in combination with benzenesulfonic anhydride for activation.[43] In attempts to understand the mechanism of sulfoxide-catalyzed activation of the hemiacetal, dynamic monitoring of ^{13}C-$^{16/18}$O isotopic chemical shift perturbations was employed. It was shown that the activation of hemiacetals proceed through initial nucleophilic addition of the hemiacetal hydroxyl to the sulfur(IV)-center of putative sulfonium sulfonate.[43]

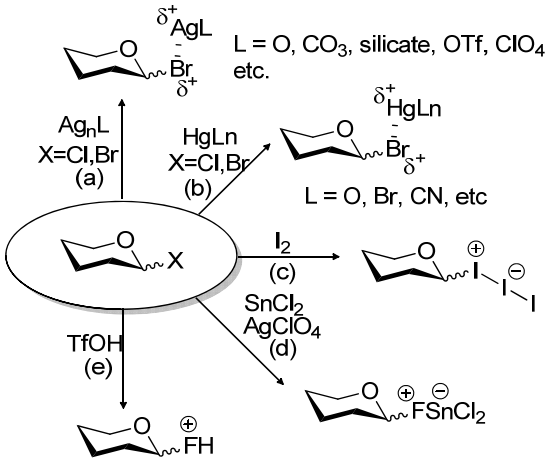
Mukaiyama *et al.* demonstrated activation of hemiacetals using carbon-based electrophiles in the form of *N*-alkyl hetaryl onium salt. These salts can be generated *in situ* and possess good leaving group ability.[75] For example, 2-fluoro-1-methylpyridinium tosylate was used to promote dehydrative glycosylation of hemiacetals as shown in Scheme 1.3f.[76] An interesting approach devised by Mukaiyama and co-workers involves oxotitanium and tin sulfide-based reagents used in combination of triflic anhydride.[77,78]

1.3.b. Glycosyl Halides

In 1901 Koenigs and Knorr[79] (and independently Fischer and Armstrong)[80] discovered that glycosyl chlorides and bromides can react with alcohols. These reactions were performed in the presence of Ag_2CO_3 or Ag_2O as acid (hydrogen halide) scavengers. Some 30 years later it was noticed that silver salts are actively involved in the leaving group departure by complexation with the anomeric halogen (Scheme 1.4a).[81] Efforts to improve understanding of the reaction mechanism led to investigations by Helferich[82-84] and Zemplen[85] dedicated to the search of more effective heavy metal-based catalysts. Amongst them, mercury(II) cyanide-assisted leaving group departure, commonly referred to as the Helferich modification, is the most noteworthy (Scheme 1.4b). Even nowadays, glycosylations of simple alcohols with glycosyl bromides, and more rarely chlorides, are very commonly performed in the presence of AgOTf, Ag_2CO_3, $AgClO_4$, $Hg(CN)_2$, $HgBr_2$, $HgCl_2$, and a desiccant.[86-89] Glycosidations of reactive glycosyl halides were also achieved by metal-free promoters: Lemieux's halide-assisted procedure in the presence of Bu_4NBr has been one of the most stereoselective methods developed to date.[26,90] Since very reactive bromides are required, this method does not involve formal activation of the leaving group that gets displaced via the close ion pair exchange mechanism. Similarly, glycosyl iodides can be activated via Bu_4NI-mediated anion-exchange pathway.[91] Field and co-workers discovered that glycosyl iodides can be also activated in the presence of molecular iodine (Scheme 1.4c).[92]

Glycosyl fluorides had been considered less useful in comparison to their bromide or chloride counterparts until studies by Mukaiyama, Nicolaou, and many others that clearly showed that fluorides can actually be very efficient glycosyl donors.[93] Early

studies by Mukaiyama and co-workers established the use of $SnCl_2/AgClO_4$ for the activation of glycosyl fluorides (Scheme 1.4d).[93,94]



Scheme 1.4. Activation of Glycosyl Halides

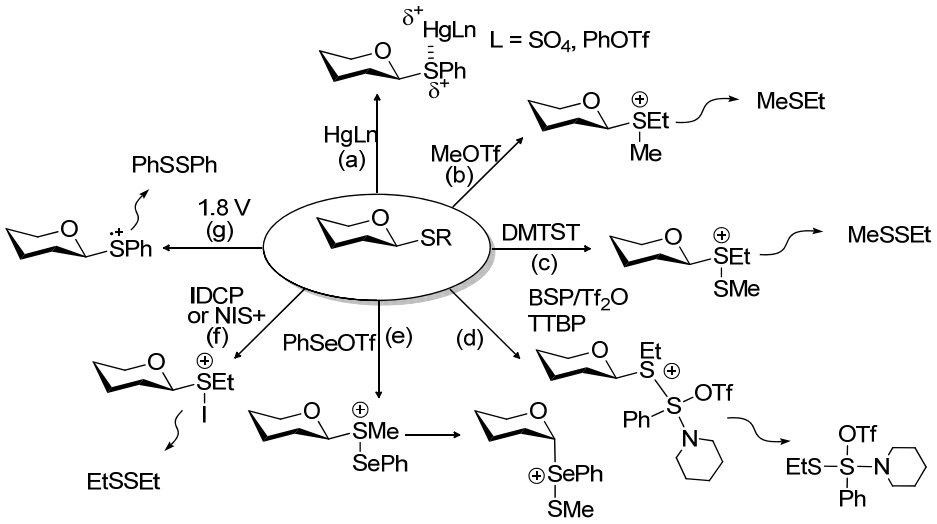
Over time, a number of promoter systems were developed including $SnCl_2/TrClO_4$,[95] TMSOTf,[96] BF_3-Et_2O,[97] Tf_2O.[98] In the latter case, it was proposed that the activation of fluorides takes place due to high affinity of $CF_3SO_2^{\delta+}$ towards F,[98] although this method was found more suitable for unreactive alcohols due to competing trifluoromethanefulfonation observed with highly reactive acceptors.[99] This principle reflects a general trend in the development of new activations that have been emphasizing the fluorophilicity rather than Lewis acidity of the activating reagents.[93] For instance, protic acids, such as TfOH,[100-102] have emerged as efficient activators for glycosyl fluorides due to high fluorophilicity of the proton[93] along with high dissociation energy of the H-F bond in comparison to that of other H-heteroatomic bonds (Scheme 1.4e).[102] Nicolaou *et al*. have applied glycosyl fluorides in the synthesis of a large variety of natural products.[103-108]

1.3.c. Alkyl and Aryl Thioglycosides

Thioglycosides were introduced as glycosyl donors by Ferrier *et al*.[109] Promoters used for the activation of thioglycosides for glycosylation in the early days were limited to mercury(II) based reagents and included $HgSO_4$[109] and PhHgOTf.[110] These promoters were assumed to enhance the leaving group ability by complexing to the anomeric sulfur (Scheme 1.5a). Starting from studies by Lönn who showed that thioglycoside glycosidation can be mediated by methyl triflate,[111] the search for non-metal based promoters has expanded and led to a discovery of a variety of excellent thiophilic promoters. Lönn proposed that methyl triflate act as *S*-methylating reagent to generate glycosyl sulfonium salt (Scheme 1.5b).[111] But it was not until recent studies by Mydock *et al.* that actually confirmed the existence of the proposed sulfonium intermediate and the departed aglycone EtSMe.[112]

Many other promoters have been developed since, and some representative examples will be discussed below. Activation with dimethyl(methylthio)sulfonium triflate (DMTST) was proposed to proceed via the disulfide formation (Scheme 1.5c).[113,114] This pathway was recently confirmed by the *in-situ* detection of the reactive sulfonium intermediate by NMR.[112] Fugedi introduced a new promoter system Me_2S_2/Tf_2O that arguably follows a similar activation pathway.[115] Sulfenyl halide-based activation has become very popular in recent years, particularly with the application of commercially available activators. This activation approach follows similar activation pathway as proposed for methylsulfenyl bromide or triflate promoted activation of thioglycosides.[116] Also, phenylsulfenyl triflate (from PhSCl/AgOTf),[117] and *p*-toluenesulfenyl triflate (from *p*-TolSCl/AgOTf)[118] have been shown to activate

thioglycosides with the release of aglycones as disulfides. Crich demonstrated essentially the same activation principle taking place with the use of *p*-nitrobenzenesulfenyl chloride/AgOTf resulting in the formation of a disulfide derivative.[119] Recently, Ghosh and co-workers demonstrated use of *N*-(*p*-methylphenylthio)-ε-caprolactam/TMSOTf as another alternative for the activation of thioglycosides via the intermediacy of disulfides.[120] In this case the *S*-tolyl leaving group was assumed to depart as TolSSTol. Crich *et al.* demonstrated the application of 1-benzenesulfinyl piperidine (BSP)/Tf_2O in the presence of TTBP as a promoter for the activation of thioglycosides (Scheme 1.5d).[121] Other related activation systems including *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT)/Tf_2O,[122] diphenyl sulfoxide (DPSO)/Tf_2O,[123] [124] benzenesulfinyl morpholine/Tf_2O[125] have been also shown as a new promising alternative to established protocols for thioglycoside activation.



Scheme 1.5. Activation of Thioglycosides

A related mechanism of initial activation was proposed for phenylselenyl triflate (PhSeOTf). It was assumed that it also involves the formation of a sulfonium

intermediate (Scheme 1.5e).[126,127] To explain the high β-stereoselectivity observed in these reactions it was assumed that the sulfonium intermediate rearranges into the corresponding, albeit more stable, selenonium salt.[81] A similar mechanistic rationale was provided for PhSeNPhth/TMSOTf promoter system.[128]

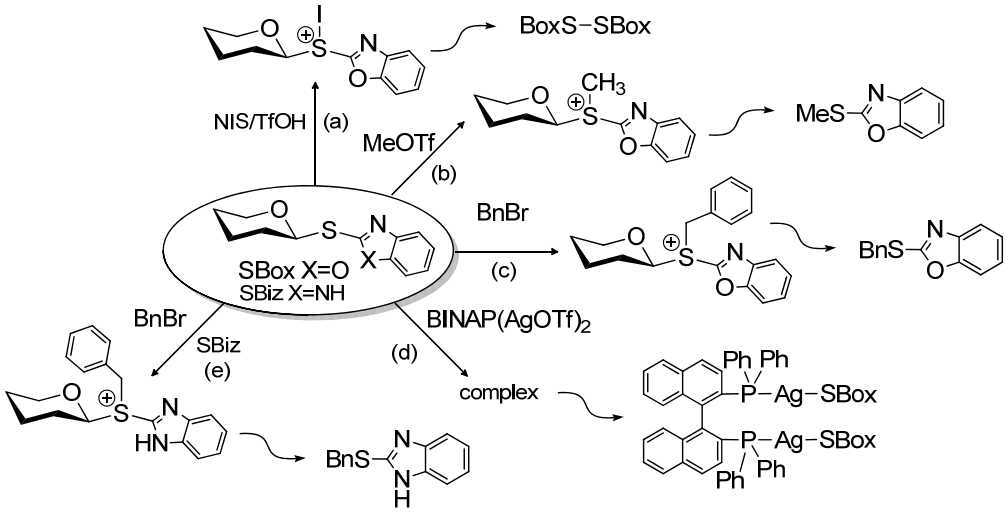
Iodonium (di-γ-collidine) perchlorate (IDCP),[129] *N*-iodosuccinimide/triflic acid (NIS/TfOH), or NIS/TMSOTf[130,131] combinations are all known sources of I^+. Hence, it is assumed that this pathway involves iodination of the anomeric sulfur leading to the departure of ISR. The latter then disproportionates into the corresponding disulfide RSSR and releases molecular iodine (Scheme 1.5f).[130,132] The disulfide can be detected by spectral methods, whereas the characteristic maroon color that this reaction usually turns into soon after the addition of the promoter indicates the formation of the molecular iodine. Activation of thioglycosides with bromine was thought to follow a similar activation pathway[133] and leads to the intermediacy of glycosyl bromides.[134,135] Electrochemical activation using a current of 1.8 V, was introduced by Sinay and co-workers. This pathway was assumed to proceed via a single electron transfer, and the existence of diphenyl disulfide was proven by TLC, HPLC, and mass spectrometry (Scheme 1.5g).[136] Sinay also developed a single electron transfer activation process that made use of tris(4-bromophenyl)ammoniumyl hexachloroantimonate.[137]

1.3.d. *S*-Benzoxazolyl and *S*-benzimidazolyl Thioimidates

Glycosyl thioimidates, compounds with generic leaving group of $SCR_1{=}NR_2$, were introduced as glycosyl donors for remote activation.[138] It was also generally assumed that these leaving groups may proceed through either direct or remote activation

depending on the reaction conditions used. More recent studies showed relatively strict structure dependence on whether the direct or remote pathway would take place. Herein, only SBox and SBiz thioimidates are discussed which were proven to follow the direct activation pathway only, regardless of the activation conditions used. The remaining thioimidates that undergo the remote activation pathway will be discussed in Section 1.4.c.

S-Benzoxazolyl (SBox) glycosides were subjected to extended mechanistic study and the following conditions all showed that SBox glycosides follow the direct activation pathway: NIS/TfOH,[139] MeOTf,[139] BnBr,[140] AgOTf-BINAP complex[139] (Scheme 1.6a-d). The activation pathway was concluded based on the structure of the departed aglycone using NMR, IR, UV spectroscopy as well as X-ray crystallography. It should be noted that some activators did not provide conclusive information. For instance, TfOH-activation could result in the tautomerization of the departed aglycone, whereas AgOTf and $Cu(OTf)_2$ promoted activations led to the formation of metal-inclusion polymer, the structure of which could not be elucidated.



Scheme 1.6. Activation of SBox and SBiz Glycosides

S-Benzimidazolyl glycosides, introduced by Demchenko *et al*. were also shown to undergo direct activation when reacted with alkylating reagents.[141] Experiments were performed to isolate the departed aglycone on completion of glycosylation reactions with BnBr (Scheme 1.6e). The departed aglycone was analyzed using spectral and X-ray methods to find the alkyl group on sulfur of the *S*-benzimidazolyl species. The formation of copper – mercaptobenzothiazole complex forming upon activation of *S*-benzothiazolyl (SBaz) donors was mentioned by Mukaiyama *et al*.[142]

1.3.e. Other Leaving Groups for Direct Activation

Selenoglycosides can be activated via cation-based activation pathway as well as radical cation based activation pathway. Mehta and Pinto demonstrated use of AgOTf in combination with K_2CO_3 for the activation of selenoglycosides.[143,144] Selenoglycosides were also shown to be activated by other promoters such as PhSeOTf,[145] IDCP,[146,147] etc.[148] Yamago *et al.* demonstrated that selenoglycosides can be activated with bromine.[149] These glycosylations proceed via the intermediacy of the corresponding glycosyl bromide. Field *et al*. demonstrated that selenoglycosides were activated with iodine produce the corresponding diselenide, via a route similar to that of the iodonium ion-promoted reactions of thioglycosides.[150]

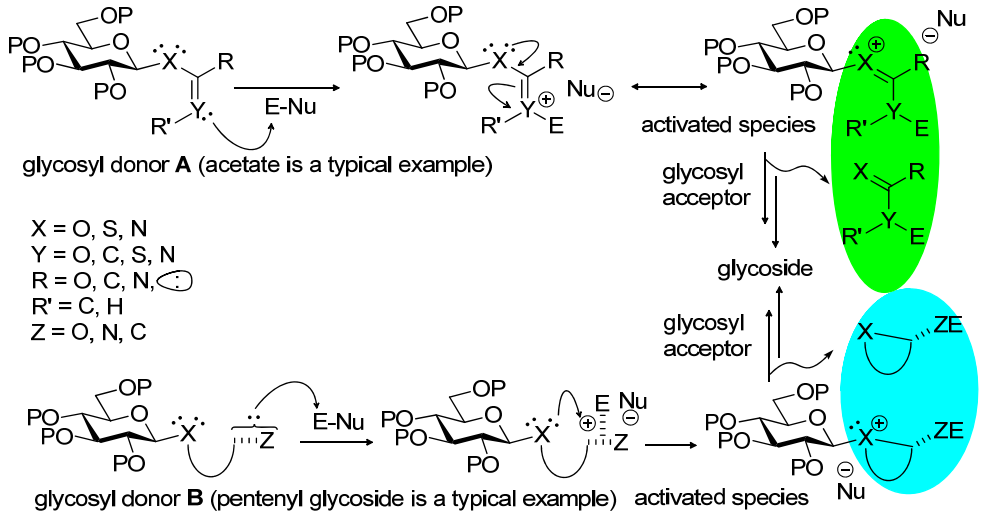
Activation of telluroglycosides was demonstrated independently by Stick and Yamago.[151-155] The activation was achieved in the presence of NIS/TfOH (Stick)[152] and NIS or NBS in the presence of various additives (Yamago).[155] Later on, Yamago *et al*. performed electrochemical analyses and theoretical calculations of arylchalcogenols/ various para-substituted phenylthio, phenylseleno and phenyltelluro glucopyranosides.[156]

The glycosylations performed using aryltelluroglucosyl donors resulted in formation of *O*-glycosides along with ditellurides. Activation of both seleno- and telluroglycosides (as well as thioglycosides, *vide supra*) can be achieved via a single electron transfer activation mechanism. These donors can be activated via photochemical oxidation as well as electrochemical activation.[136,137,154,156,157] Very recently, Cumpstey and Crich developed a *N*-methylquinolinium hexafluorophosphate photosensitizer-mediated glycosidation of selenoglycosides at 350 nm.[158]

Anhydro sugars found broad application in oligosaccharide synthesis, this class of glycosyl donor is activated by a Lewis acid. For instance, 1,6-anhydro derivatives are easily activated with PF_5,[159] whereas 1,2-anhydro derivatives can be activated with $ZnCl_2$.[160-162] Leaving groups that follow both direct and remote activation pathways, depending on the activation conditions, will be discussed in Section 1.5.

1.4. Remote Activation

A majority of leaving groups that have been introduced in the past two-three decades are promoted via the remote activation pathway. Two limiting cases are presented in Scheme 1.7 although there are other examples that do not fall within either of these generic representations. Unique activation modes for these novel protecting groups also called for extensive studies and many remote activation pathways have been subjected to extended mechanistic studies. Many departed aglycones have been structurally elucidated, which could serve as sustaining evidence for the anticipated activation pathways.



Scheme 1.7. Remote Activation of Leaving Groups for Glycosylation: Focus on the Activated Species and the Departed Aglycone

1.4.a. Glycosyl Esters

Anomeric esters are relatively common glycosyl donors because of their ease of preparation and chemical stability. Activation of anomeric acetates was first demonstrated by Helferich,[163] wherein β-D-glucose pentaacetate was glycosidated with phenol in the presence of either $ZnCl_2$ or toluenesulfonic acid. Following general considerations, it is assumed that the electrophile interacts with the carbonyl oxygen leading to the reactive intermediate (Scheme 1.8a).[45] Over time various promoter systems have been developed for the activation of glycosyl ester donors. For instance, Mukaiyama *et al*. demonstrated the use of a combination of trimethylsilyl iodide and phosphine oxide as the promoter for the activation of glycosyl acetate donors.[164] The main drawback of this approach is that ordinary esters require harsh reaction conditions and stoichiometric amounts of strong Lewis acids. In this respect, glycosyl esters capable

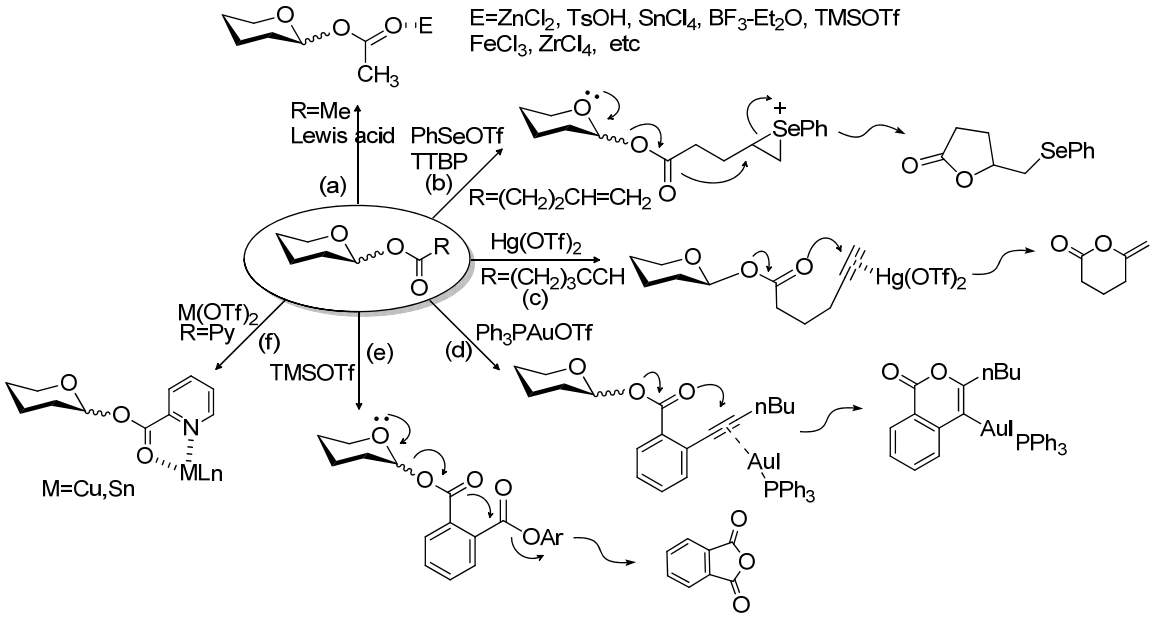
of the remote activation, via assisted cleavage protocol, offers further advantage by allowing the use of mild promoters or even conduct reactions under catalytic conditions.

Kunz[165] and Fraser-Reid[166] concomitantly investigated glycosyl pentenoate donors. Similar to that of *O*-pentenyl glycosides (*vide infra*), the 4-pentenoyl leaving group can also be activated via the remote olefin moiety. In this case, electrophile-induced lactonization takes place, and this product differs from the THF derivative obtained as a result of *O*-pentenyl group departure. Both activations can be stimulated using IDCP or NIS/TfOH, which acts as a source of an iodonium ion that adds to the double bond followed by γ-lactonization. Essentially the same reaction principle is followed when a pentenoyl moiety is activated with phenylselenyl trifluromethanesulfonate (PhSeOTf) as depicted in Scheme 1.8b.[167,168] Activation of pentenoyl leaving group can be also affected using 1,3-dithian-2-yl-tetrafluoroborate.[165]

A similar approach was explored with glycosyl hex-5-ynoate, wherein activation readily occurred in the presence of 5 mol % of $Hg(OTf)_2$. The suggested reaction pathway was proven by characterization of the departed aglycone as δ-methylene-δ-lactone (6-methylenetetrahydro-2*H*-pyran-2-one, Scheme 1.8c).[169] It has been proposed that during the activation, π-complexation of $Hg(OTf)_2$ with the terminal alkyne results in the formation of a vinyl mercuric lactone which, upon protonation, generates the oxonium species. The latter undergoes demercuration, hence regenerating the catalyst, $Hg(OTf)_2$. A similar reaction pathway was determined for the activation of pent-4-ynoate in which the leaving group departed as 5-methylenedihydrofuran-2(3*H*)-one in $Hg(OTf)_2$-3TMU promoted glycosylations or, its regioisomeric product, 5-methylfuran-2(3*H*)-one in $Hg(OTf)_2$-promoted reactions.[170] This mechanism is consistent with prior studies by

the Nishizawa group where the lactone**,** upon reaction of ω-alkynoic acids with catalytic amount of tetramethylurea (TMU) with complex of mercuric(II) trifluoromethanesulfonate, was isolated.

Yu *et al*. brought essentially the same principle a step forward by demonstrating that glycosyl ortho-alkynylbenzoates can be activated with catalytic amount of a gold(I) complex, such as $Ph_3PAuOTf$.[171-175] The activated intermediate, isochromen-4-yl-gold(I) complex, was isolated and studied by spectroscopic as well as X-ray diffraction methods (Scheme 1.8d).[176] This essential piece of information provided a more detailed understanding of the proposed catalytic cycle for the activation of the leaving group and regeneration of the catalyst.



Scheme 1.8. Activation of Glycosyl Esters

Kim *et al*. reported use of glycosyl phthalate donors[177] in the glycosylation reactions wherein the *p*-bromophenyl substituted leaving group was proven the most reactive.[178] The activation was affected using TMSOTf as a promoter and the structure

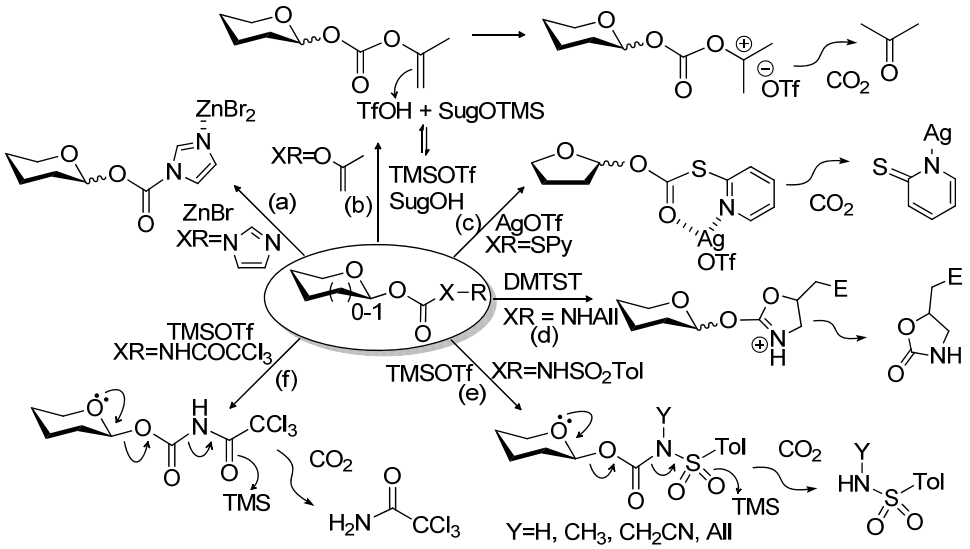
of the departed aglycone (phthalic anhydride) has been confirmed (Scheme 1.8e). Another noteworthy approach, the use of 2-pyridinecarboxylates, was investigated by Kobayashi and co-workers.[179] Thus, it was determined that these leaving groups can be activated using copper(II) or tin(II) triflates. The fact that these donors cannot be activated in the presence of other Lewis acids, including BF_3-etherate and TMSOTf, suggest the viability of the proposed bidentate coordination to carbonyl oxygen and the nitrogen (Scheme 1.8f).[179] Further indication on the possibility of this postulate derives from the fact that isomeric 4-pyridinecarboxylate was unreactive in the presence of $Cu(OTf)_2$.

1.4.b. Glycosyl Carbonates and Carbamates

Rearrangement of glycosyl carbonates, SugOC(=O)OR, into the corresponding glycosides (SugOR) or orthoesters under pyrolysis conditions was proven possible and has been known for long time. However, since these approaches do not involve the formal activation of the leaving group the reader shall be referred to the original manuscripts.[180-182] Ford and Ley explored glycosyl (1-imidazolyl)carbonates wherein it was anticipated that the leaving group departure is facilitated by chelation of zinc bromide to the N-3 of the ring (Scheme 1.9a).[183] However, glycosidation of these compounds was only effective in the refluxing solvents (ether or CH_2Cl_2).

One of the first attempts for the controlled glycosylation at low temperature (-25 ^oC) was reported by Sinay, wherein remote isopropenyl-mediated displacement in the presence of TMSOTf via *in situ* generation of TfOH was executed (Scheme 1.9b).[184] Hanessian and coworkers introduced thiopyridyl carbonate (TOPCAT) donors, which

were assumed to undergo activation via chelation of Lewis acid such as AgOTf with thiopyridyl nitrogen and either sulfur[185] or, more likely, carbonyl carbon (Scheme 1.9c).[59,186]



Scheme 1.9. Glycosyl Carbonates and Carbamates

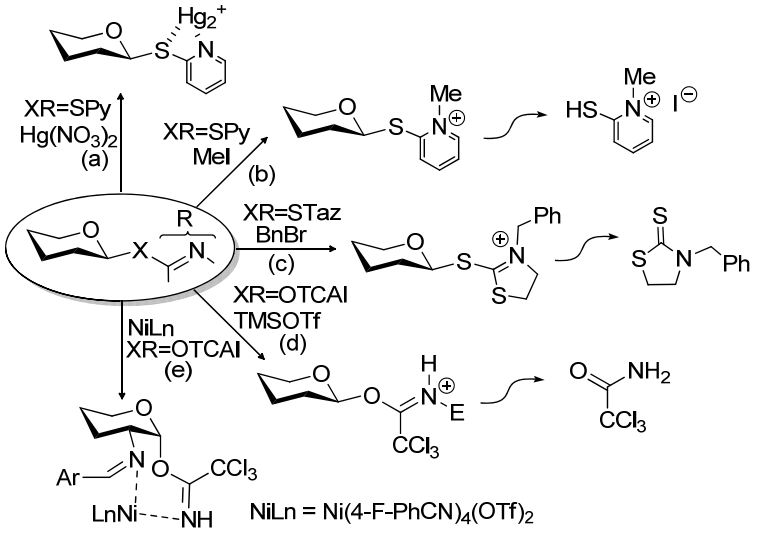
Glycosyl carbamates, SugOC(=O)NHR, have also been investigated and displayed excellent glycosyl donor properties. For instance, activation of *N*-allyl carbamoyl leaving group was assumed to follow similar mechanistic pathway as that of anomeric alkenoic esters. Thus, glycosylation reactions using promoters like DMTST, IDCP, methyl bis-methylthiosulfonium hexachloroantimonate (TMTSB) were thought to result in cyclization of the anomeric leaving group as shown in Scheme 1.9d.[187] Activation of *N*-sulfonylcarbamates was achieved by using various activators including TfOH, TMSOTf, $Yb(OTf)_3$, etc. It was proposed that reaction of these electrophilic promoters with the glycosyl donor results in a loss of CO_2 and sulfonamide as shown in Scheme 1.9e.[188] Trichloroacetyl carbamates on reaction with TMSOTf were theorized to

undergo remote activation resulting in the formation of trichloroacetamide with the loss of CO_2 (Scheme 1.9f).[189,190]

1.4.c. *O*/*S*-Glycosyl Imidates

Hanessian *et al*. investigated 2-pyridyl, 2-pyrimidyl and 2-imidazolinyl thioimidates as glycosyl donors that can be activated either using an acid catalyst or by using metal-based electrophilic promoter.[138] The acid catalyzed activation was achieved by using methanesulfonic acid, *p*-TsOH, etc. For metal ion-based activation, $AgNO_3$ as well as $Hg(NO_3)_2$ is employed, wherein the activation was demonstrated by coordination of the leaving group with the metal ion (Scheme 1.10a).[138] Mereyala and co-workers further studied this glycosylation methodology; the activation of 2-pyridyl thioimidates was accomplished with methyl iodide as a promoter.[191] It was anticipated that the activation of 2-pyridyl thioglycosides involves initial reaction with the electrophile such as methyl iodide to give *N*-methyl quaternary thiopyridinium glycoside (Scheme 1.10b). To support this mechanistic pathway, the authors isolated *N*-methyl 2-thiopyridone from this reaction.[191] Other glycosyl thioimidates such as SBox or SBiz were shown to undergo direct activation (*vide supra*). However, Demchenko *et.al* showed that the activation of *S*-thiazolinyl (STaz) glycosyl donor takes place via the remote nitrogen.[140] The reactions were performed with STaz glycosyl donors and a standard acceptor in the presence of benzyl bromide as a promoter. The departed aglycone was isolated and investigated by X-ray crystallography to determine that the benzyl group is present on the nitrogen, hence suggesting the remote activation pathway (Scheme 1.10c). Likewise, when a more powerful alkylating agent is used such as methyl triflate, it resulted in the

methylated aglycone with methyl group present at the nitrogen. The reactions were monitored by HPLC to eliminate the impact of tautomerization of products. The differential pathway for the activation of SBox and STaz leaving groups were exploited to develop a fully orthogonal activation, as discussed below.[140]



Scheme 1.10. Glycosyl *S*- and *O*-Imidates

Schmidt and coworkers introduced *O*-glycosyl trichloroacetimides (TCAI),[192] which were shown to have excellent glycosyl donor properties and became one of the most widespread glycosyl donors for chemical synthesis of glycosides and oligosaccharides.[193] Typical glycosylation with trichloroacetimidates requires catalytic amounts of Lewis acid such as trimethylsilyl trifluromethanesulfonate (TMSOTf) or boron trifluoride etherate (BF_3-Et_2O), but many other activators have been also tested.[193] It is generally assumed that the activation is initiated by coordination of a Lewis acid to the nitrogen of the imidoyl leaving group, which results in the formation of trichloroacetamide (Scheme 1.10d).[194] Since the basicity of the latter is lower than that of the imidate, the Lewis acid is released and becomes available for the next catalytic cycle.

To the best of our knowledge, this viable rationale for the activation of trichloroacetimidates is yet to be proven. Another interesting method for the activation glycosyl trichloroacetimidates employs a nickel-based catalyst, $Ni(p\text{-}FPhCN)_4(OTf)_2$, a concept developed by Nguyen and co-workers using 2-amino-2-deoxysugars.[195,196] One possible activation pathway involves coordination of the nickel catalyst with the benzylidene substituted nitrogen at C-2 and the nitrogen of the anomeric trichloroacetimidate leaving group forming a seven membered cyclic intermediate (Scheme 1.10e). Upon the leaving group departure, the ligand is exchanged between nucleophile and the trichloroacetamide, which results in the exit of the latter and regeneration of the Ni-catalyst. Another viable pathway is the coordination of the Ni-catalyst with the nitrogen of the trichloroacetimidate leaving group only.[197]

Yu[188] and subsequently, Iadonisi[189] demonstrated the use of *N*-phenyl trifluoroacetimidates (PTFAI) as glycosyl donors that can be activated in the presence of a catalytic amount of a Lewis acid. Since their initial studies, this new type of leaving group has become a very versatile class of glycosyl donors for glycoside and oligosaccharide synthesis both in solution and using polymer supports. Various promoter systems have been investigated and include TMSOTf,[188] I_2-Et_3SiH,[198] $Yb(OTf)_3$,[199-201] TBSOTf,[202] $Bi(OTf)_3$,[203] etc.[204] The activation mode of these compounds is still to be determined.[205,206] It is possible, similarly to that of their trichloroacetimidoyl counterparts, the activation takes place via the remote nitrogen atom. *N*-Phenyl trifluorothioacetimidates were also investigated, although the study of their activation mode has not yet emerged, [207] it was observed that glycosyl trifluoroacetimidates were less reactive as compared to their trichloro counterpart,[201,208] which probably is due to the

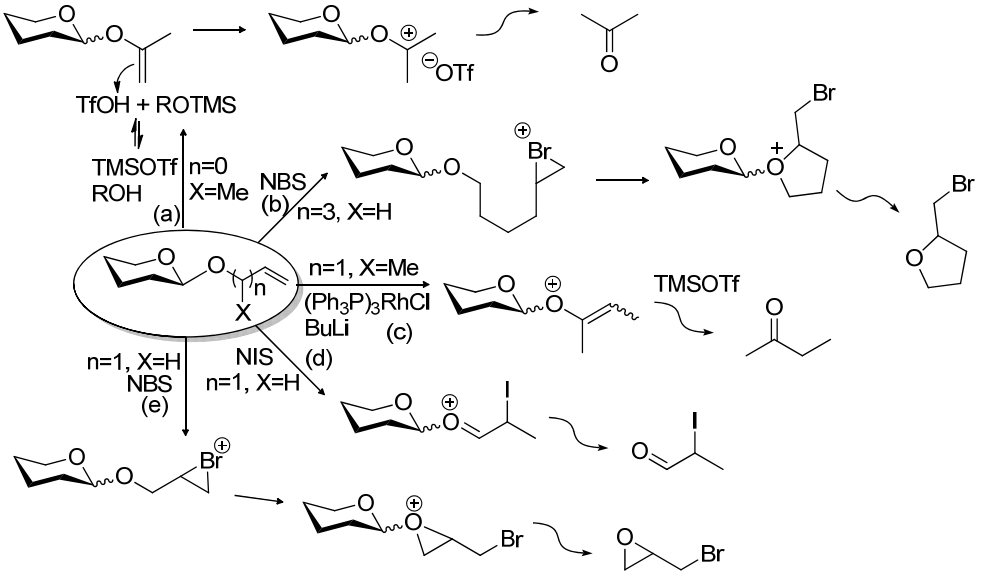
lower basicity of the nitrogen in trifluoroacetimidates. This stems from the presence of a *N*-substituent as well as the small conformational changes caused by the trifluoromethyl group,[208] and was proven by direct activation of TCAI donors over acceptors equipped with the anomeric PTFAI moiety.[205] A related glycosyl thioformimidate derivative was also introduced and tested.[209-212]

1.4.d. Alkenyl Glycosides

Early attempts in this field included isopropenyl glycosides reported by Sinay.[184] It was suggested that TMSOTf promoter first reacts with a glycosyl acceptor producing TfOH that protonates the double bond generating an unstable cationic species that gets readily displaced by the nucleophile (Scheme 1.11a). In 1988, Fraser-Reid *et al*. introduced the *n*-pentenyl group as a leaving group at the anomeric center of the glycosyl donor.[213] The first studies involved the activation with *N*-bromosuccinimide (NBS), although the best results were achieved with the use of an iodonium ion source; IDCP or NIS/TfOH. This reaction possibly proceeds via the initial interaction of the electrophile "X^+" with the olefin moiety to give a cyclic halonium ion. The leaving group departure is then assisted by cyclization via the anomeric oxygen and departs as halomethyltetrahydrofuran (Scheme 1.11b).

Boons *et al.* investigated 2-buten-2-yl glycosides as glycosyl donors, which were obtained by isomerizing 3-buten-2-yl glycosides using Wilkinson's catalyst and a base such as DABCO or *n*-BuLi. Activation of these glycosyl donors was achieved by using TMSOTf as a promoter and it is likely that the aglycone departs as butanone (Scheme 1.11c). This two-step activation served as a basis for an elegant active/latent

glycosylation strategy.[214-216] Wang and coworkers demonstrated the use of allyl glycosides as glycosyl donors.[217] The method involves prior isomerization of allyl glycoside to prop-1-enyl glycoside with $[Ir(COD)(PMePh_2)_2]PF_6$.[217] The activation of this prop-1-enyl glycoside was then achieved by using NIS at room temperature (Scheme 1.11d). This two-stage activation strategy was then applied to the synthesis of tetrasaccharide of *Bacillus anthracis exosporium*.[218] Taneja *et al.* developed alternative activation conditions of the anomeric allyl group using a combination of NBS and a catalytic amount of Lewis acid, such as $Zn(OTf)_2$.[219] It was proposed that the activation of the allylic group starts with initial formation of bromonium ion on reaction with NBS, which then departs as epibromohydrin (Scheme 1.11e).



Scheme 1.11. Alkenyl Glycosides

1.4.e. Other Leaving Groups for Remote Activation

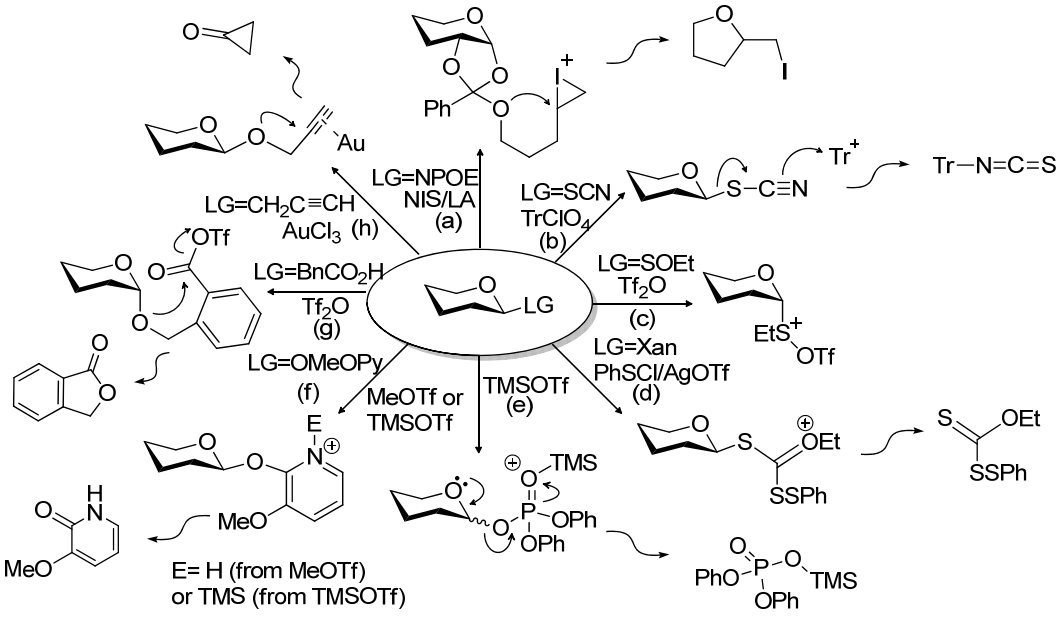
Orthoesters have been used as glycosyl donors for 1,2-*trans* glycosylation. Early studies focused on the investigation of *O*-alkyl orthoesters, which, however, often

produce by-products derived from the glycosylation of the departed *O*-alkyl moiety rather than the intended glycosyl acceptor.[220] A more recent study questioned the viability of the initially anticipated remote activation pathway and presented solid evidence for the activation taking place at the anomeric oxygen.[221] Many modifications have been made over the years and thioorthoesters,[222,223] cyanoethylidene,[224-226] and, more recently, *O*-pentenyl orthoesters (NPOE) have emerged.[227-229] Although it is very likely that the activation of thioorthoesters with thiophilic reagents and cyanoethylidene with triphenylmethylium perchlorate ($TrClO_4$)[159] follows a remote activation pathway, so far it has been confirmed only for NPOE. Thus, NIS/BF_3-Et_2O[230] NIS/$Yb(OTf)_2$[231,232] promoted activation of *O*-pentenyl moiety of the orthoester would lead to the furanylium ion that departs and 2-iodomethyltetrahydrofuran (Scheme 1.12a).

A variety of leaving groups based on the anomeric sulfur atom have been developed beyond thioglycosides and thioimidates discussed previously. For instance, Kochetkov *et al*. introduced 1,2-*trans* glycosyl thiocyanates as glycosyl donors for the highly stereoselective 1,2-*cis* glycosylation.[233,234] The reaction between a glycosyl thiocyanate donor and triphenylmethylated acceptor was performed in the presence of catalytic $TrClO_4$. Also isolated was trityl isothiocyanate which serves an indication of the remote activation pathway depicted in Scheme 1.12b.[233] It was assumed that the reaction proceeds via a concerted push-pull mechanism. It is possible that activation of glycosyl thiocyanates with TMSOTf[235] or AgOTf[236] allows for the glycosylation of typical hydroxylated acceptors which follow a similar activation pathway via a remote site. One of the most common methods for the activation of sulfoxides is with Tf_2O that trifluoromethanesulfonates the sulfoxide oxygen (Scheme 1.12c),[237] although alternative

activation conditions have been also developed and include: Tf_2O/DTBMP,[238] TMSOTf,[239] molecular iodine,[240] dicyclopentadienyl zirconium dichloride and silver perchlorate,[241] lanthanum and ytterbium triflates[242]

Glycosyl phenyl sulfones and glycosyl 2-pyridyl sulfones have also been used as glycosyl donors in glycosylation reactions.[243] Ley *et al.* utilized $MgBr_2$-etherate in THF for the activation of glycosyl phenyl sulfones,[244] whereas Lowary demonstrated the utility of $Sm(OTf)_3$ for the activation of 2-pyridyl sulfones for the synthesis of furanosides.[245] The activation via remote site is likely, although exact nature of the activation is yet to be determined.



Scheme 1.12. Miscellaneous Glycosyl Donors Involved in Remote Activation

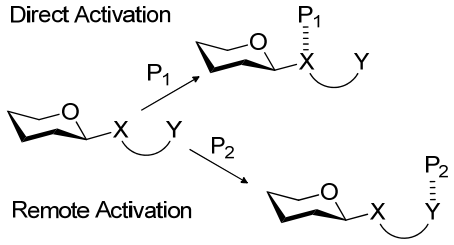
Glycosyl xanthates have also been utilized as glycosyl donors. Activation of these donors can be achieved by using DMTST,[246] $Cu(OTf)_2$,[247] MeSOTf,[248] etc. Also activation by single electron transfer in the presence of tris(4-bromophenyl)ammoniumyl hexachloroantimonate (TBPA), similarly to that of thioglycosides, has been shown to

activate xanthates efficiently.[137] A compelling mechanistic rationale has been presented as a result of phenylsulfenyl triflate (from PhSCl/AgOTf) promoted activation of xanthates that was assumed to proceed via the remote sulfur.[249] The anticipated disulfide derivative depicted in Scheme 1.12d was isolated from the reaction mixture and characterized by spectral methods.

The investigation of glycosyl phosphates and related compounds as glycosyl donors were pioneered by Hashimoto *et al.*in which they report the first use of diphenyl phosphate as an anomeric leaving group.[250,251] In recent years, glycosyl phosphates have become very valuable glycosyl donors for solution and solid-phase glycosylation, predominately thanks to extensive studies by Seeberger *et al.* [252-259] Activation of glycosyl phosphates can be achieved using TMSOTf as a promoter,[250] or alternatively using protic acids such as TfOH or TsOH in combination with TMS-protected acceptor.[254] Further, BF_3-Et_2O and $LiClO_4$ were shown to be effective promoter systems for the activation of glycosyl phosphates.[260] Mechanism for the activation of glycosyl phosphates has not been investigated, but it is predicted that the interaction with a Lewis acid (or sialylation) takes place at the remote phosphoryl oxygen as shown in Scheme 1.12e.[261]

O-Glycosides are not very common glycosyl donors beyond alkenyl derivatives, but a number of other concepts have been investigated and were shown to be viable alternatives to other methods. For instance, Hanessian *et al*. introduced 3-methoxy-2-pyridyl (MOP) glycosides as effective glycosyl donors that can be activated using various promoter systems including TMSOTf,[185] MeOTf,[22] TfOH, $Cu(OTf)_2$,[59] etc. It was proposed that the activation takes place remotely at the pyridyl nitrogen as depicted in

Scheme 1.12f.[22,262] Schmidt and co-workers also investigated various *O*-hetaryl glycosyl donors and demonstrated that heterocyclic *O*-glycosyl imidates that have electron-withdrawing groups, either as substituents or as components of the ring, are efficient glycosyl donors.[263] Kim and coworkers introduced 2-carboxybenzyl (CB) glycoside as a glycosyl donor. The activation of CB was achieved by using the combination of triflic anhydride and di-tert-butyl-4-methylpyridine (DTBMP).[264] The reaction proceeds through initial formation of a triflate derivative of CB, which undergoes lactonization resulting in the expulsion of a phthalide lactone (Scheme 1.12g). Propargyl glycosides have also been introduced as new promising glycosyl donors for chemical glycosylation.[21,265] It has been demonstrated that when promoted with 3 mol. % of $AuCl_3$, the aglycone departs as methyleneoxirane that rearranges into cyclopropanone (Scheme 1.12h).[265]



Scheme 1.13. Glycosyl Donors with Bidentate Reactivity

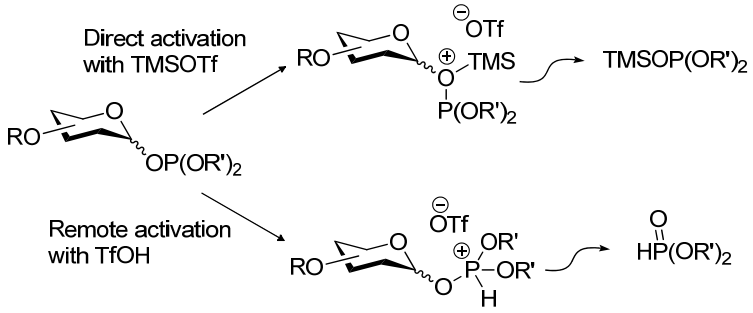
1.5. Bidentate Activation: Leaving Groups That Allow for Both Direct and Remote Activations

Various leaving groups were shown to follow either direct or remote activation pathway, but not both. Leaving groups that allow for the activation via both direct and remote activation sites have also been identified (Scheme 1.13). The utility of these

glycosyl donors can be envisaged for oligosaccharide synthesis wherein the activation mode can be flexibly changed by switching the promoter.

1.5.a. Glycosyl phosphites

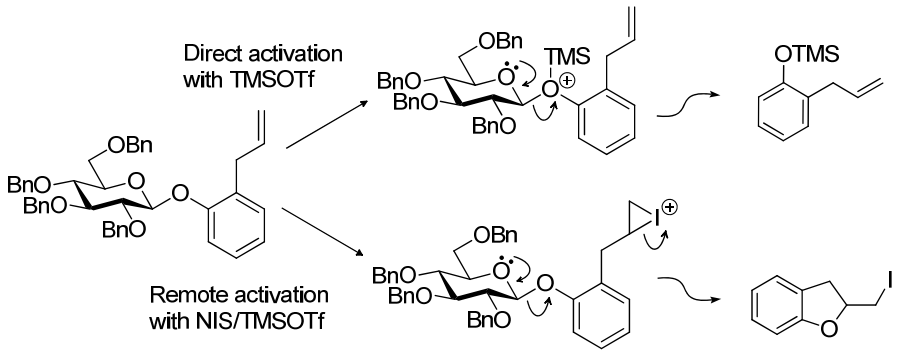
Schmidt *et al.*[250,251] and Wong *et al.*[266,267] independently introduced glycosyl phosphites as effective glycosyl donors.[268,269] Glycosyl phosphites can be activated using various promoter systems including TfOH, Tf_2O, TMSOTf, $ZnCl_2$, BF_3-Et_2O, etc.[270-272] It was proposed that the activation of glycosyl phosphites takes place via two different reaction mechanisms. First, upon interaction with Lewis acid (e.g. TMSOTf), direct activation mode takes place as shown in Scheme 1.14. Resultantly, the positive charge is formed on the anomeric oxygen leading to the enhanced leaving group ability. Kondo *et al*. have investigated this mechanism and found experimental evidence for the formation of a trimethylsilyl dibenzyl phosphite.[270] Second, protic acids (e.g. TfOH), activate the leaving group by protonating the phosphorus atom, which also leads to a straightforward departure of the phosphite leaving group as dialkyl hydrogen phosphite.[261,273]



Scheme 1.14. Two Pathways for the Activation of Glycosyl Phosphites

1.5.b. *o*-Allylphenyl Glycosides

Recently, *ortho*-allylphenyl (AP) was introduced as a novel and versatile leaving group by Hung *et al*.[274] and Demchenko *et.al*.[275] It was demonstrated that the activation of this leaving group could be achieved via direct or remote activation pathway by using a site-specific promoter. It was observed that on reaction with TMSOTf the leaving group departs as (*o*-allylphenoxy)trimethylsilane indicating anomeric oxygen to be the activation site (Scheme 1.15). However, when NIS/TMSOTf was used, the activation was observed to take place at the remote allyl moiety. The iodonium ion attacks the allyl group resulting in a epiiodonium intermediate which is then attacked by the anomeric oxygen and the AP leaving group departs in the form of 2-iodomethyl-2,3-dihydrobenzofuran. Both intermediates were isolated and identified using spectral methods.



Scheme 1.15. Two Pathways for the Activation of *o*-Allylphenyl Glycosides

1.6. Implications in Oligosaccharide Synthesis

Many new leaving groups have been developed in a search of new methods for chemical glycosylation to achieve high yields and complete stereocontrol. However, a single-step glycosylation is only one of the challenges researchers working on

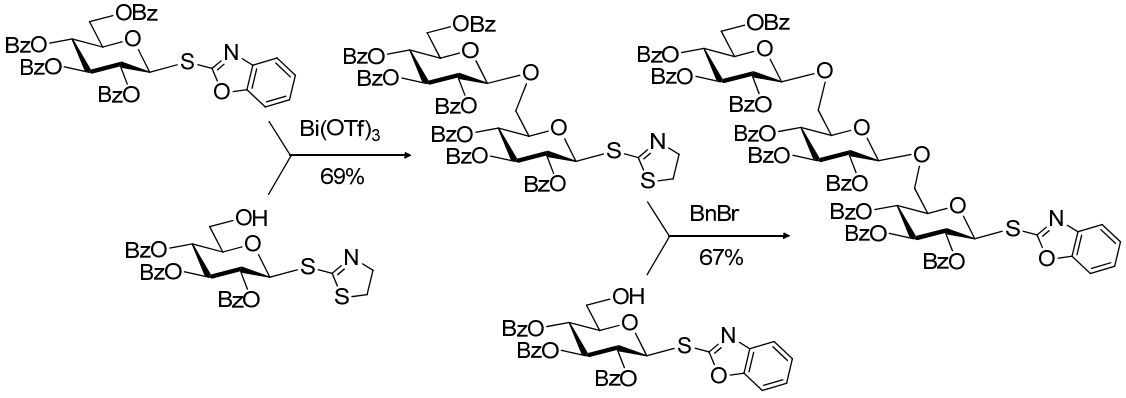
oligosaccharide synthesis face. Traditional approaches for the synthesis of oligosaccharides are lengthy and require conversion of the disaccharide intermediate into suitable glycosyl donors or acceptors of the second generation, etc. Such additional manipulations decrease the efficiency of the oligosaccharide assembly and a number of strategies to streamline oligosaccharide synthesis have already emerged.[276] Recent strategies for expeditious oligosaccharide synthesis are typically based on the sequential multi-step activation of a series of building blocks and Nicolaou's selective activation,[106] Fraser-Reid's armed-disarmed approach,[277] Danishefsky's glycal assembly,[278] Ogawa's orthogonal technique,[279,280] Roy's[281] and Boons'[214] active-latent concept, Wong's and Ley's programmable strategies,[282-285] Huang's preactivation approach[118,286-288] are only few such strategies to mention. Major strategies for oligosaccharide assembly, their advantages and drawbacks have been recently overviewed.[276]

Many advanced strategies that streamline oligosaccharide assembly by minimizing or even eliminating leaving or protecting group manipulations between coupling steps are based either on chemoselective or on selective activation of leaving groups.[276] For example, in accordance with the Fraser-Reid's armed-disarmed approach, electronically activated (armed) glycosyl donor is chemoselectively activated over deactivated (disarmed) glycosyl acceptor bearing the same type of a leaving group.[289,290] The resulting disaccharide can then be activated further using a more potent promoter. Among known strategies based on selective activation of different leaving groups,[276] orthogonal concept introduced by Kanie, Ito, and Ogawa is arguably the most advantageous.[291,292] Unfortunately, the application of this relatively simple concept to large oligosaccharide is still limited, so is the number of leaving groups compatible with

orthogonal activation. Traditionally, different classes of leaving groups have been used for orthogonal activation. The classic variation of the orthogonal activation route introduced by Ogawa *et al.* involves building blocks bearing *S*-phenyl and fluoro leaving groups.[279] In the recent years, the improved understanding of the activation pathways of different leaving groups allowed for development of more flexible approaches that will be discussed below.

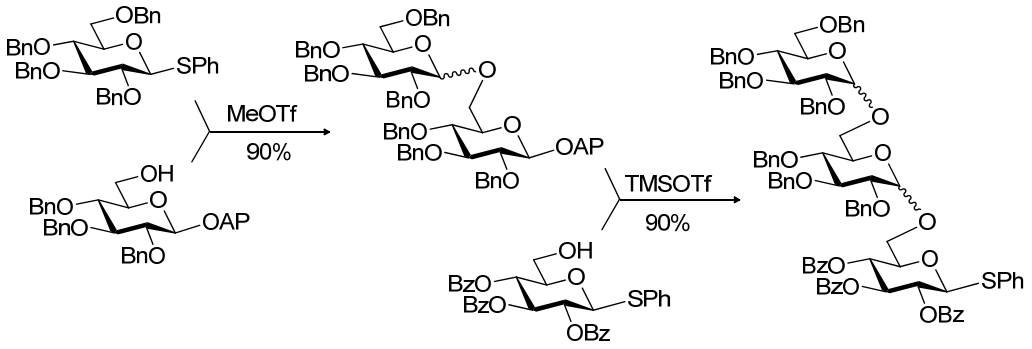
1.6.a. Direct vs. Remote Activation of Thioimidates: Orthogonality of SBox vs. STaz

The mechanistic studies conducted for understanding the activation of SBox and STaz thioimidates formed the base for the development of oligosaccharide synthetic strategy.[293] Mechanistic studies showed that the selective activation is based on the different activation modes of these leaving groups (*vide infra*). SBox glycosides can be selectively activated with $Cu(OTf)_2$[294] or $Bi(OTf)_3$[140] over the STaz leaving group. STaz leaving group, which is typically very stable towards a majority of thiophilic activation conditions, can also be selectively activated over SBox, but requires activation with benzyl bromide or methyl iodide.



Scheme 1.16. Trisaccharide Synthesis Using Orthogonality of SBox and STaz

Thus, it was discovered that preferential glycosidation of a given thioimidoyl leaving group is not simply determined by the strength of the promoter. Instead, the type of activation – direct (for SBox) vs. indirect (for STaz) – plays the key role. Resultantly, the activation of SBox donor over STaz acceptor in the presence of $Bi(OTf)_3$ afforded the corresponding disaccharide. In turn, the STaz leaving group of the disaccharide could be activated over the SBox acceptor in the presence of BnBr to give a trisaccharide as shown in Scheme 1.16.[293]



Scheme 1.17. Trisaccharide Synthesis Using Orthogonality of SPh and OAP

1.6.b. Direct activation of thioglycosides vs. remote activation of allylphenyl glycosides

The bidentate nature of allylphenyl (OAP) leaving group that allows for activation at remote as well as direct site was exploited in the development of the synthetic route for the trisaccharide. In this study, the orthogonality of allylphenyl glycosides and phenyl thioglycosides was demonstrated. Thus, selective activation of *S*-phenyl donor over glycosyl acceptor equipped with the anomeric OAP moiety was successfully accomplished in the presence of MeOTf. The resulting disaccharide was then activated

over *S*-phenyl acceptor in the presence of TMSOTf to afford the corresponding trisaccharide in a high yield (Scheme 1.17).

1.7. Conclusions and outlook

Development of stereoselective methods for chemical glycosylation and expeditious strategies for the oligosaccharide synthesis has always been the prime focus of studies in the field of glycosciences. Knowledge of the activation pathway followed by different leaving groups can be extremely helpful in making oligosaccharides synthesis more efficient. The mechanistic studies to understand the activation pathways of various leaving groups are still limited. With this chapter we have made an effort to shed light on the mechanistic studies that helped in getting a clear idea about the activation of different leaving groups. Further investigations of different leaving groups and their activation pathways can be very helpful for the advancement of the field of glycosciences.

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CHAPTER 2

Glycosyl Alkoxythioimidates as Complementary Building Blocks for Chemical Glycosylation

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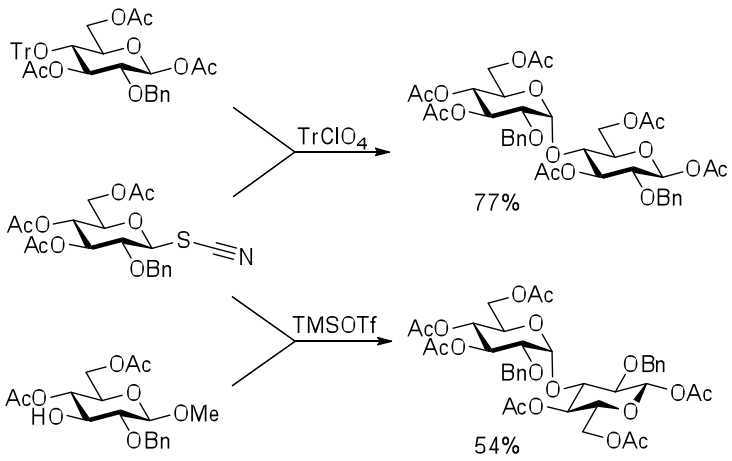
Ranade S C, Kaeothip S, Demchenko A V. " Glycosyl Alkoxythioimidates as Complementary Building Blocks for Chemical Glycosylation", Organic Letters, 2010, 12, 5628-5631.

2.1. Introduction

The stereocontrolled introduction of glycosidic linkages[1,2] is arguably the most challenging aspect in the synthesis of oligosaccharides[3-9] and glycoconjugates.[10-12] A broad variety of factors is known to have a profound effect on the stereoselectivity outcome of the chemical glycosylation.[13] Although a typical glycosylation reaction follows the unimolecular mechanism with the rate-determining step being the attack of the glycosyl acceptor on the intermediate formed as a result of the leaving group departure;[14,15] the effect of a leaving group is important. The belief that the nature of the leaving group itself may also have an influence on the anomeric stereoselectivity led to the development of a myriad of glycosyl donors.[2] However, it is not always clear whether this effect is a result of a bimolecular, close-ion-pair displacement mechanism, or others. For instance, glycosyl thiocyanates were introduced two decades ago as very effective glycosyl donors for 1,2-cis glycosylations.[16,17] Various hexose and pentose 1,2-trans thiocyanate glycosyl donors were found to provide challenging 1,2-cis glycosides[18] with complete stereoselectivity. While tritylated acceptors were used in most of the reported transformations, a procedure involving unprotected hydroxyl was also developed.[19] These two typical examples of glycosylation using the thiocyanate methodology are illustrated in Scheme 2.1. A major drawback of this technique is modest yields obtained during both the synthesis of glycosyl thiocyanates and their glycosidations. The modest yields are typically due to the propensity of thiocyanates to isomerize into the corresponding stable isothiocyanates.



Scheme 2.1. Reaction of a Glycosyl Thiocyanate with 4-O-Trityl and 3-Hydroxy Glycosyl Acceptors.

Our laboratory has been investigating glycosyl thioimidates, and the synthesis of the S-benzoxazolyl (SBox)[20-22] and S-thiazolinyl (STaz)[23,24] derivatives and their application as glycosyl donors has been reported. Undoubtedly, thioimidates have some structural similarity with thiocyanates. However, how these two methodologies compare in glycosylations remained unclear. Therefore, we decided to investigate these two structurally related classes of glycosyl donor by performing comparative side-by-side investigations. For this purpose, we obtained glycosyl donors **2.1a** (SCN) and **2.1b** [25] (SBox) and performed direct comparative couplings with glycosyl acceptor **2.2**.[26]

2.2. Results and Discussion

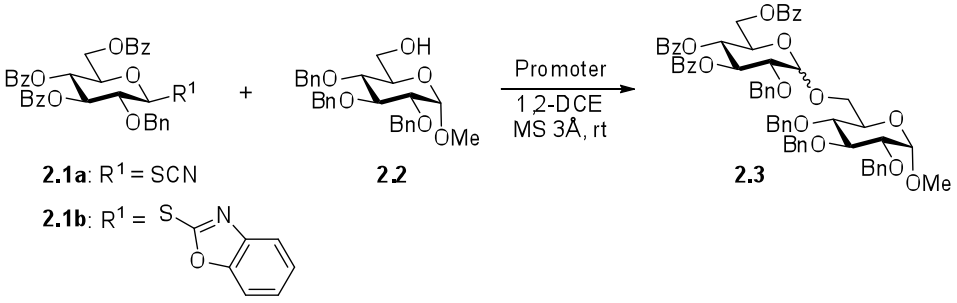
Silver(I) triflate (AgOTf) that was found to be a very efficient promoter for activating a variety of thioimidates studied in our laboratory,[27,28] was similarly effective with both thiocyanate **2.1a** and SBox **2.1b** glycosyl donors. The disaccharide **2.3** was isolated in around 80% yield (entries 1 and 2, Table 2.1). Relatively low stereoselectivity

obtained in the glycosidation of thiocyanate **2.1a** was not surprising in light of our recent observation that the stereoselectivity may greatly depend on the nature of the protecting groups used for masking hydroxyl groups of the glycosyl acceptor.[29]

Methyl triflate, very commonly used for the activation of thioglycosides[30] and thioimidates[31] was virtually ineffective in the case of thiocyanate **2.1a**, whereas glycosidation of SBox donor **2.1b** was much more efficient (entries 3 and 4). Conversely, copper(II) triflate, which is too mild an activator to activate SBox glycoside **2.1b** with the 2-Bn-tri-Bz superdisarming protective group pattern,[25] was rather effective with glycosyl thiocyanate. Thus, $Cu(OTf)_2$- promoted glycosidation of **2.1a** afforded disaccharide **2.3** in 95% yield and good stereoselectivity α/β = 9/1 (entry 5). The results summarized in Table 2.1 indicate potential orthogonality of these two classes of glycosyl donors, however, we anticipate that the application of thiocyanates in orthogonal-like oligosaccharide synthesis[32] will be cumbersome due to their general instability.

SNea **2.4c** can be prepared from benzobromoglucose directly, but in our hands higher overall yield was obtained from acetobromoglucose followed by sequential deacetylation-benzoylation. The SNea leaving group has been specifically designed to represent a hybrid structure bridging between simple acyclic thiocyanate **2.4a** and cyclic SBox glycoside **2.4b**. In addition, comparison of the SBox and SNea leaving groups could serve as a useful toolkit for studying whether the cyclic structure of thioimidates previously investigated in our laboratory[28] and by others[31] is truly crucial for the successful activation/application of this class of glycosyl donors.

Table 2.1. Comparative Studies of Glycosyl Thiocyanate **2.1a** and *S*-Benzoxazolyl Glycoside **2.1b**



Entry	Donor	Promoter (equiv)[a]	Time (h)	Yield (%) of disaccharide 2.3 (α/β ratio)
1	**2.1a**	AgOTf (1.2)	48	80 (3/1)
2	**2.1b**	AgOTf (1.2)[b]	48	79 (3.4/1)
3	**2.1a**	MeOTf (1.2)	48	Traces
4	**2.1b**	MeOTf (1.2)	48	76 (3.2/1)
5	**2.1a**	$Cu(OTf)_2$ (1.2)	1	95 (9.0/1)
6	**2.1b**	$Cu(OTf)_2$ (1.2)	48	Traces

[a] - Intentionally, only a slight excess of promoter has been used in these reactions to gain a better control of the reaction rate;

[b] - Completed in 15 min (86%) with 3 equiv. of promoter

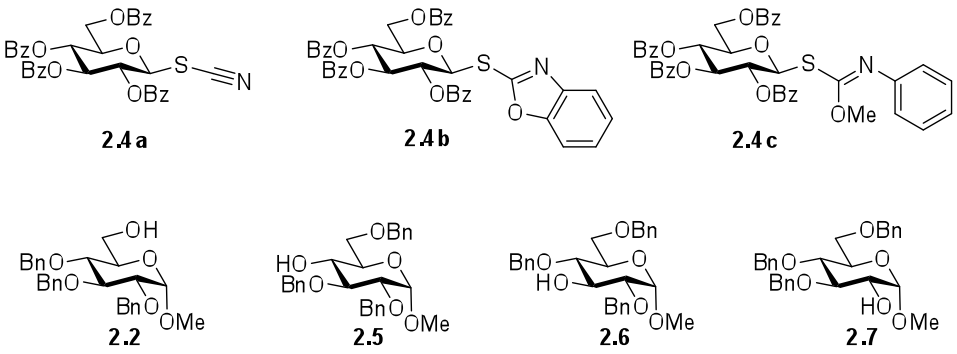


Figure 2.1. Glycosyl Donors **2.4a-2.4c** and Acceptors **2.2, 2.5-2.7** Used for the Comparative Studies

These comparative studies began with the investigation of per-benzoylated thiocyanate **2.4a**. We found that this derivative can be smoothly activated under a variety of reaction conditions also common for the activation of thioimidates (Table 2.2). With the exception of the MeOTf-promoted glycosidation that required 22 h to complete (entry 1), reactions with all other activators investigated were completed in less than 10 min (entries 2-4). The disaccharide **2.8** was obtained with consistently very good to excellent yields (82-95%), hence offering a variety of new effective pathways for the activation of glycosyl thiocyanates, which is significant since previously developed protocols suffered from very modest yields. The fact that per- benzoylated thiocyanate **2.4a** actually reacts in the presence of MeOTf can be explained by its significantly more reactive nature in comparison to that of its superdisarmed counterpart **2.1a**. The SBox glycoside **2.4b** performed very similarly (entries 5-8), although most reactions, except those promoted with MeOTf (entry 5), were notably slower than the respective reactions with thiocyanate **2.4a**. The $Cu(OTf)_2$-promoted reaction required 3 equiv. of the promoter to proceed with acceptable rate and good yield (entry 8). Strikingly, SNea carbamothioate **2.4c** reacted somewhat differently than either thiocyanate **2.4a** or SBox glycoside **2.4b**. First,

glycosidations of **2.4c** in the presence of either MeOTf or AgOTf as promoters were virtually ineffective (entries 9 and 10), whereas both **2.4a** and **2.4b** reacted readily. Second, although the reaction of **2.4c** required 3 equiv. of $AgBF_4$, it reached completion in 15 min (entry 11), similarly to that of thiocyanate **2.4a**, whereas glycosidation of SBox **2.4b** required 3.5 h. Third, $Cu(OTf)_2$ was particularly effective allowing the disaccharide **2.8** in 90% yield in 1 h (entry 12) even in the presence of a very slight excess of the promoter. These studies were extended to the evaluation of secondary glycosyl acceptors **2.5**-**2.7**.[33-35] All glycosylations readily afforded the target disaccharides **2.9**-**2.11**[24,36] in good yields (see entries 13-15).

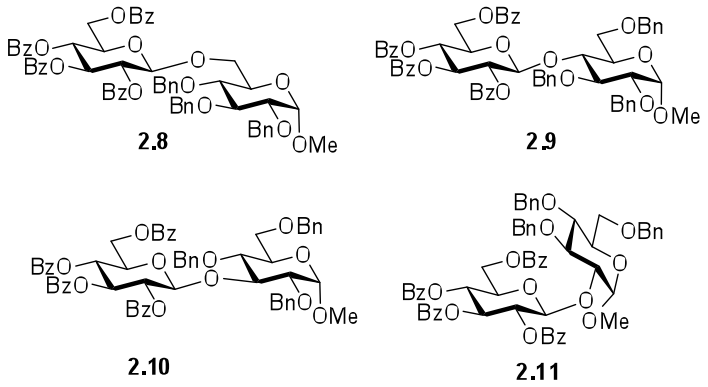
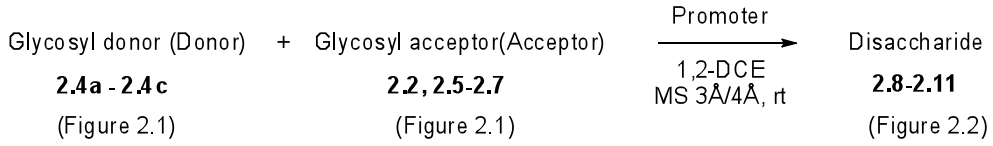


Figure 2.2: Structure of Disaccharides **2.8-2.11**

Overall, the reactivity pattern of benzoylated carbamothioate **2.4c** is very similar to that of the superdisarmed thiocyanate **2.1a** observed earlier (Table 2.1). This led us to postulate that SNea leaving group reacts similarly to that of the SCN, but it is somewhat less reactive and its activation requires more powerful conditions and/or longer reaction time (compare for example results depicted in entries 4 and 12, Table 2.2). It is possible that the SNea moiety follows a remote activation pathway,[37] similar to that of thiocyanates (via the nitrogen atom),[38] while SBox glycosides were found to be activated

Table 2.2. Comparative Studies of Per-Benzoylated Glycosyl Thiocyanate **2.4a**, SBox Glycoside **2.4b** and SNea Carbamothioate **2.4c**.



Entry	Donor	Acceptor	Promoter (equiv)	Time	Disaccharide (yield)
1	**2.4a**	**2.2**	MeOTf (1.2)	22 h	**2.8** (84%)
2	**2.4a**	**2.2**	AgOTf (1.2)	5 min	**2.8** (82%)
3	**2.4a**	**2.2**	$AgBF_4$ (1.2)	5 min	**2.8** (95%)
4	**2.4a**	**2.2**	$Cu(OTf)_2$ (1.2)	10 min	**2.8** (87%)
5	**2.4b**	**2.2**	MeOTf (1.2)	6 h	**2.8** (94%)
6	**2.4b**	**2.2**	AgOTf (1.2)	30 min	**2.8** (88%)
7	**2.4b**	**2.2**	$AgBF_4$ (1.2)	3.5 h	**2.8** (91%)
8	**2.4b**	**2.2**	$Cu(OTf)_2$ (1.2 or 3.0)	24 h	**2.8** (35 or 85%)
9	**2.4c**	**2.2**	MeOTf (1.2 or 3.0)	24 h	**2.8** (traces or 12%)
10	**2.4c**	**2.2**	AgOTf (1.2 or 3.0)	24 h	**2.8** (traces of 32%)
11	**2.4c**	**2.2**	$AgBF_4$ (1.2 or 3.0)	24 h	**2.8** (25 or 55%)
12	**2.4c**	**2.2**	$Cu(OTf)_2$ (1.2 or 3.0)	1 h	**2.8** (90 or 91%)
13	**2.4c**	**2.5**	$Cu(OTf)_2$ (3.0)[a]	1 h	**2.9** (78%)
14	**2.4c**	**2.6**	$Cu(OTf)_2$ (3.0)[a]	1 h	**2.10** (74%)
15	**2.4c**	**2.7**	$Cu(OTf)_2$ (3.0)[a]	1 h	**2.11** (75%)

[a] - Slower reaction (24 h) and lower yields were observed with 1.2 equiv of promoter

directly via the sulfur atom[21,39] similarly to that of the conventional alkyl/aryl thioglycosides (Figure 2.3).

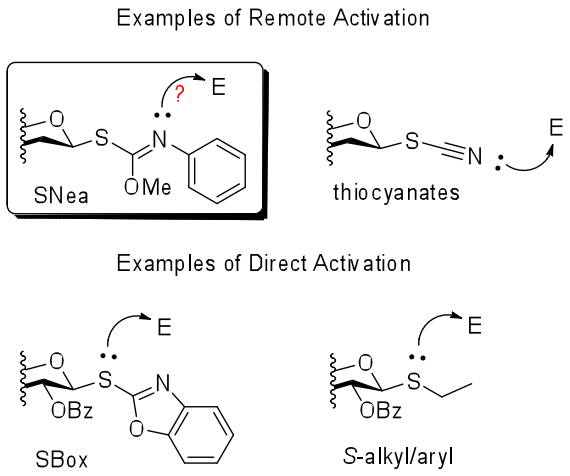
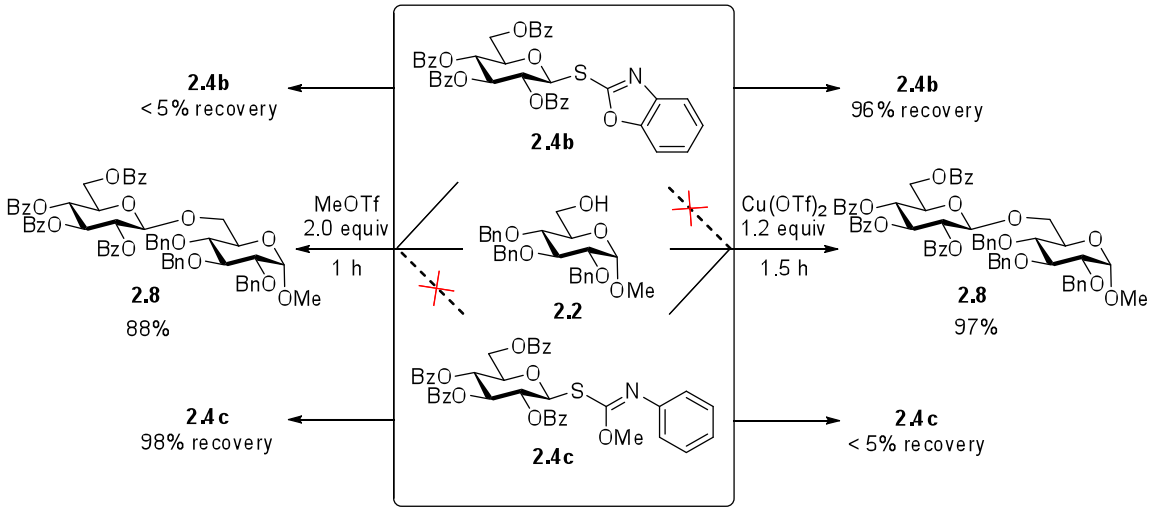


Figure 2.3. Direct vs. Remote Activation Pathways

In comparison to the SBox glycosyl donor **2.4b**, SNea derivative **2.4c** may be considered fully orthogonal: the SBox leaving group was promoted much faster in the presence of MeOTf, whereas $Cu(OTf)_2$ was found to be significantly more effective for the activation of SNea carbamothioate. The anticipated orthogonality of the SBox vs SNea derivatives has been evaluated in the direct competition experiments depicted in Scheme 2.2. In these reactions, two glycosyl donors **2.4b** and **2.4c** were allowed to compete for one glycosyl acceptor **2.2**. Upon consumption of the acceptor, the products were separated, and the unreacted glycosyl donor was recovered. The differentiation of the SBox and SNea building blocks was found to be very effective in both directions. First, MeOTf-promoted competition experiment led to the formation of disaccharide **2.8** in 88%. In this case, 98% of SNea glycosyl donor **2.4c** could be recovered, while only

traces of SBox glycoside **2.4b** were remaining. Second, the $Cu(OTf)_2$-promoted competition experiment led to the formation of disaccharide **2.8** in 97% yield. In this case, 96% of SBox glycosyl donor **2.4b** could be recovered while only traces of SNea carbamothioate **2.4a** were present. These results clearly serve as an indication for the highly selective nature of these orthogonal activations.



Scheme 2.2. Competitive Glycosylations Involving Differentiation of two Glycosyl Donors, SBox **2.4b** vs. SNea **2.4c**

2.3. Conclusions

As a part of a program dealing with the investigation of glycosyl donors with S-C-N generic leaving group structure, we described the comparative studies of glycosyl thiocyanates vs. *S*-benzoxazolyl glycosides. To gain a better insight into the reactivity mode of these structurally similar glycosyl donors react, we designed a bridging structure, SNea carbamothioate, which were found to react similarly to the SCN derivatives. Higher stability of the SNea carbamothioate allowed for the investigation of

their proposed orthogonality with the SBox glycosides. Further studies of these promising new glycosyl donors in the context of expeditious oligosaccharide synthesis via effective selective or orthogonal activation strategies are currently underway in our laboratory.

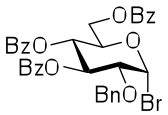
2.4. Experimental Section

2.4.1. 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. Methanol was dried by refluxing with magnesium methoxide, distilled and stored under argon. Acetonitrile and pyridine were dried by refluxing with CaH_2 and then distilled and stored over molecular sieves (3 Å). Acetone was dried by refluxing with K_2CO_3 and then distilled and stored over molecular sieves (3 Å). KSCN was dried *in vacuo* at 150 ^{o}C for 24 h. 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 was co-evaporated with toluene (3 x 10 mL) and dried *in vacuo* for 2-3 h directly prior to application. $Cu(OTf)_2$ was dried *in vacuo* for 1-2 h before using for glycosylation. Optical rotations were measured at 'Jasco P-1020' polarimeter. ^{1}H-n.m.r. spectra were recorded in $CDCl_3$ at 300 MHz, ^{13}C-NMR spectra were recorded in $CDCl_3$ at 75 MHz (Bruker Avance). HRMS determinations were made with the use of

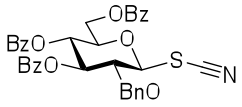
JEOL MStation (JMS-700) Mass Spectrometer, matrix *m*-nitrobenzyl alcohol, with NaI as necessary.

3,4,6-Tri-O-benzoyl-2 *O*-benzyl-α-D-glucopyranosyl bromide (2.12).



A solution of acetyl bromide (4 mL, 54.29 mmol) and methanol (2.1 mL, 54.29 mmol) in dichloromethane (25 mL) was added to a solution of 1,3,4,6-tetra-O-benzoyl-2-O-benzyl-D-glucopyranose[40] (2.3 g, 3.393 mmol) in dichloromethane (15 mL) at 0 ^{o}C. The resulting reaction mixture was stirred for 2 h at 0 ^{o}C and then washed with water (15 mL), sat. aq. $NaHCO_3$ (15 mL), and water (3 x 15 mL). The organic layer was separated, dried with $MgSO_4$, concentrated in *vacuo* and dried to afford the title compound in 78% (1.7 g) yield, which was used directly in subsequent synthesis of **2.1a**. Spectral data of **2.12** was the same as reported previously.[41]

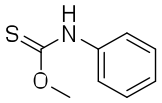
3,4,6-Tri-O-benzoyl-2 *O*-benzyl-β-D-glucopyranosyl thiocyanate (2.1a).



The title compound was obtained in accordance with the method reported previously.[38] 18-Crown-6 (85 mg, 0.3 mmol) and KSCN (312 mg, 3.0 mmol) were added to a stirred solution of bromide **2.12** (690 mg, 1.0 mmol) in dry acetone (2.6 mL) and the reaction mixture was stirred under argon for 2.5 h at rt. After that, the mixture was diluted with acetone (20 mL), the solid was filtered off, rinsed with acetone (3 x 5 mL) and the combined filtrate was concentrated *in vacuo*. The residue was purified by column

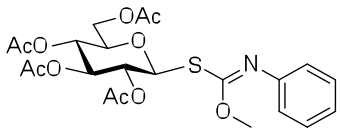
chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the title compound as a white foam in 65% (434.5 mg) yield. Analytical data for **2.1a**: R_f = 0.48 (ethyl acetate/hexanes, 3/7, v/v); $[\alpha]_D^{22}$ 21.1 (c = 0.9, $CHCl_3$); ^{1}H n.m.r.: δ, 4.14 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 4.24 (m, 1H, $J_{5,6a}$ = 5.0, $J_{5,6b}$ = 2.9 Hz, H-5), 4.56 (dd, 1H, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.68 (dd, H-6b), 4.83 (dd, 2H, ^{2}J = 10.7 Hz, CH_2Ph), 4.94 (d, 1H, $J_{1,2}$ = 9.3 Hz, H-1), 5.70 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.93 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 7.27-8.12 (m, 25H, aromatic) ppm; ^{13}C n.m.r.: δ, 62.9, 68.9, 75.4, 75.9, 77.1, 79.1, 84.3, 108.5, 128.5 (x 3), 128.6 (x 2), 128.61 (x 2), 128.7 (x 6), 128.9, 129.6, 129.9 (x 2), 130.0 (x 4), 133.3, 133.6, 136.3, 165.3, 165.6, 166.2 ppm, HR-FAB MS$[M+Na]^+$ calcd for $C_{35}H_{29}NO_8SNa^+$ 646.1512, found 646.1501.

***O*-Methyl phenylcarbamothioate.**



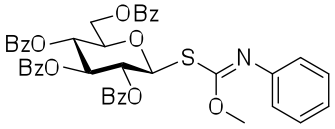
A solution of NaOMe in methanol (1M, 22.2 mL) was added to phenyl isothiocyanate (1.7 mL, 14.7 mmol) and the resulting mixture was stirred for 15 min at rt. After that, conc. HCl was added till the pH ~ 4-5. The resulting white precipitate was filtered off and the filtrate was concentrated *in vacuo*. The crude residue containing the title compound was used directly in subsequent reactions with glycosyl bromides. The analytical data of the title compound were the same as described previously.[42]

2,3,4,6-Tetra *O*-acetyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (2.13).



O-Methyl phenylcarbamothioate (HSNea, 61 mg, 0.364 mmol) and NaOH (9.7 mg, 0.243 mmol) were added to a stirring solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide[43] (100 mg, 0.243 mmol) in dry acetonitrile (1.2 mL) and the resulting reaction mixture was stirred for 1 h at rt. After that, the solid was filtered off and filtrate was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 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 the title compound as white foam in 60% (73.3 mg) yield. Analytical data for **2.13**: R_f = 0.42 (ethyl acetate/hexanes, 3/7, v/v); $[\alpha]_D^{25}$ -1.9 (c = 1, $CHCl_3$); ^{1}H-n.m.r.: δ, 1.99, 2.01, 2.03, 2.09 (4s, 12H, 4 x $COCH_3$), 3.77 (m, 1H, $J_{5,6a}$ = 2.3 Hz, $J_{5,6b}$ = 4.7 Hz, H-5), 4.01 (s, 3H, OCH_3), 4.14 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.25 (dd, 1H, H-6b), 4.99 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 5.07 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.22 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 5.24 (dd, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 6.83-7.27 (m, 5H, aromatic) ppm; ^{13}C n.m.r.: δ, 20.7 (x 3), 20.9, 56.8, 62.2, 68.2, 69.9, 74.1, 76.3, 81.4, 121.5 (x 2), 124.4, 129.3 (x 2), 146.3, 154.5, 169.3, 169.5, 170.4, 170.8 ppm; HR-FAB MS$[M+Na]^+$ calcd for $C_{22}H_{27}NO_{10}SNa^+$ 520.1253, found 520.1263.

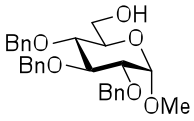
2,3,4,6-Tetra *O*-benzoyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (2.4c).



A solution of NaOMe in methanol (1M, ~0.1 mL) was added dropwise to a solution of thiocarbamate **2.12** (72 mg, 0.145 mmol) in methanol (1.0 mL) until pH ~ 9 was reached and the resulting reaction mixture was kept for 1 h at rt. After that, Dowex (H^+) was added till pH ~ 7, the resin was filtered off and washed successively with methanol (5 x 5 mL). The combined filtrate was concentrated *in vacuo* and dried. The residue was dissolved in pyridine (1 mL) and benzoyl chloride (0.1 mL, 0.87 mmol) was added dropwise at 0 ^oC under argon. The external cooling was removed, the reaction mixture was allowed to warm to rt and stirred for 4 h total. After that, methanol (1 mL) was added, the volatiles were evaporated *in vacuo*, and the residue was co-evaporated with toluene (3 x 5 mL). The resulting residue was diluted with dichloromethane (100 mL) and washed with 1N aq. HCl (25 mL), water (25 mL), sat. aq. $NaHCO_3$ (25 mL), and water (3 x 25 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 the title compound as a white foam in 83% (90 mg) yield. Analytical data for **2.4c**: R_f = 0.37 (ethyl acetate/toluene, 1.5/8.5, v/v); $[\alpha]_D^{21}$ 0.35 (c = 1, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.90 (s, 3H, OCH_3), 4.25 (m, 1H, $J_{5,6a}$ = 5.7 Hz, $J_{5,6b}$ = 2.9 Hz, H-5), 4.49 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.64 (dd, 1H, H-6b), 5.54 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 5.62 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 5.64 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.95 (dd, $J_{3,4}$ = 9.2 Hz, H-3), 6.72-8.06 (m, 25H, aromatic) ppm; ^{13}C-n.m.r.: δ, 56.8, 63.4, 69.6,

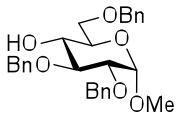
70.6, 74.3, 77.4, 81.9, 121.5 (x 2), 124.2, 128.5 (x 2), 128.6 (x 6), 128.7 (x 2), 128.9 (x 2), 129.1, 129.2 (x 2), 129.8, 129.9 (x 3), 130.0 (x 3), 133.4, 133.5, 133.6, 133.7, 146.3, 154.5, 165.1, 165.4, 165.9, 166.3 ppm; HR-FAB MS[M+Na]$^+$ calcd for $C_{42}H_{35}NO_{10}SNa^+$ 768.1879, found 768.1896.

Methyl 2,3,4-tri *O*-benzyl-α-D-glucopyranoside (2.2).



Analytical data for **2.2**: 1H n.m.r.: δ, 1.69 (s, 1H, OH), 3.33 (s, 3H, OCH_3), 3.45-3.52 (m, 2H, H-2, 4), 3.59-3.76 (m, 3H, H-5, 6a, 6b), 3.98 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.53 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.59-4.65 (m, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.75-4.87 (m, 3H, CH_2Ph), 4.96 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 7.21-7.34 (m, 15H, aromatic) ppm; ^{13}C n.m.r.: δ, 55.12, 61.76, 70.55, 73.33, 74.93, 77.24, 79.82, 81.83, 98.01, 127.42, 127.68, 127.74, 127.76 (x 3), 127.83 (x 2), 127.92 (x 2), 128.20 (x 2), 128.27 (x 4), 137.87, 138.48 ppm.

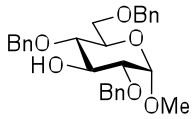
Methyl 2,3,6-tri *O*-benzyl-α-D-glucopyranoside (2.5).



Analytical data for **2.5**: ^1H n.m.r.: δ, 3.34 (s, 3H, OCH_3), 3.52 (dd, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 3.56-3.69 (m, 4H, H-4, 5, 6a, 6b), 3.74 (dd, 1H, $J_{3,4}$ = 9 Hz, H-3), 4.52 (dd, 2H, ^2J = 12.2 Hz, CH_2Ph), 4.59 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.63-4.75 (m, 3H, CH_2Ph), 4.96 (d, 1H, ^2J = 11.4 Hz, ½ CH_2Ph), 7.22-7.22 (m, 15H, aromatic) ppm; ^{13}C n.m.r.: δ, 55.36,

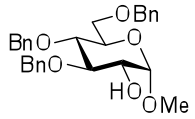
69.57, 70.02, 70.80, 73.28, 73.69, 75.55, 79.71, 81.59, 98.32, 127.80 (x 3), 128.02, 128.14, 128.18 (x 2), 128.31 (x 2), 128.54 (x 2), 128.66 (x 2), 128.77 (x 2), 138.19, 138.24, 138.99 ppm.

Methyl 2,4,6-tri *O*-benzyl-α-D-glucopyranoside (2.6).



Analytical data for **2.6**: R_f = 0.35 (ethylacetate/toluene, 2/8, v/v), $[\alpha]_D^{27}$ +36.0 (c = 1, $CHCl_3$); ^{1}H n.m.r.: δ, 3.29 (s, 3H, OCH_3), 3.36 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.51 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 3.58-3.7 (m, 3H, H-5,6a,6b), 4.02 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 4.41-4.68 (m, 6H, H-1, CH_2Ph), 4.79 (d, 1H, ^{2}J = 11.2 Hz, ½ CH_2Ph), 7.15-7.33 (m, 15H, aromatic). ^{13}C n.m.r.: δ, 55.21, 68.51, 69.65, 73.11, 73.54, 73.63, 74.60, 77.29, 79.51, 97.60, 127.73, 127.76, 127.91 (x 2), 127.99 (x 2), 128.13, 128.17 (x 2), 128.42 (x 4), 128.61 (x 2), 137.94, 138.01, 138.45 ppm.

Methyl 3,4,6-tri *O*-benzyl-α-D-glucopyranoside (2.7).



Analytical data for **2.7**: ^{1}H n.m.r.: δ, 2.12 (d, 1H, OH), 3.43 (s, 3H, OCH_3), 3.62-3.80 (m, 6H, H-2, 3, 4, 5, 6a, 6b), 4.49 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1), 4.53 (d, 1H, ½ CH_2Ph), 4.65 (d, ^{2}J = 12.1 Hz, ½ CH_2Ph), 4.81-4.93 (m, 4H, ^{2}J = 11.2 Hz, CH_2Ph), 7.14-7.30 (m, 15H, aromatic) ppm. ^{13}C n.m.r.: δ, 55.32, 68.60, 70.54, 73.03, 73.64, 75.48, 77.60, 83.38,

99.53, 127.84, 127.97 (x 2), 128.03 (x 5), 128.51 (x 4), 128.57 (x 3), 138.05, 138.30, 138.79 ppm.

General procedures for glycosylation

In the presence of MeOTf (Method A). A mixture of a glycosyl donor (0.04 mmol), glycosyl acceptor (0.032 mmol), and freshly activated molecular sieves (3Å, 90 mg) in 1,2-dichloroethane (0.5 mL) was stirred under argon at rt for 1.5 h. MeOTf (10 μL, 0.08 mmol) was added and the reaction mixture was stirred at rt for 22-48 h. After that, the solid was filtered off and the filtrate was washed successively with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 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 the corresponding disaccharide.

In the presence of AgOTf (Method B): A mixture of glycosyl donor (0.04 mmol), glycosyl acceptor (0.032 mmol), and freshly activated molecular sieves (3Å, 90 mg) in 1,2-dichloroethane (0.5 mL) was stirred under argon for 1.5 h. AgOTf (12.3 mg, 0.048 mmol) was added and the reaction mixture was stirred for 24 h. Upon completion, the solid was filtered off and the filtrate was washed with $NaHCO_3$ (5 mL) and water (3 x 5 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.

In the presence of $AgBF_4$ (Method C): A mixture of glycosyl donor (0.04 mmol), glycosyl acceptor (0.032 mmol), and freshly activated molecular sieves (3Å, 90 mg) in 1,2-dichloroethane (0.5 mL) was stirred under argon for 1.5 h. $AgBF_4$ (9.3 mg, 0.048 mmol) was added and the reaction mixture was stirred for 5 min - 24 h. Upon completion, the solid was filtered off and the filtrate was washed with $NaHCO_3$ (5 mL) and water (3 x 5 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.

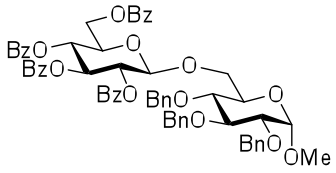
In the presence of $Cu(OTf)_2$ (Method D): A mixture of glycosyl donor (0.04 mmol), glycosyl acceptor (0.032 mmol), and freshly activated molecular sieves (4Å, 90 mg) in 1,2-dichloroethane (0.5 mL) was stirred under argon for 1.5 h. $Cu(OTf)_2$ (17 mg, 0.048 mmol) was added and the reaction mixture was stirred for 10 min - 24 h. Upon completion, the solid was filtered off and the filtrate was washed with $NaHCO_3$ (5 mL) and water (3 x 5 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.

General Procedure for Competitive Glycosylations

A mixture of glycosyl donor **2.4b** (47 mg, 0.0645 mmol), glycosyl donor **2.4c** (48 mg, 0.0645 mmol), glycosyl acceptor **2.2** (20 mg, 0.043 mmol), and freshly activated molecular sieves (4Å for $Cu(OTf)_2$ or 3Å for MeOTf-promoted reactions, 140 mg) in 1,2-dichloroethane (1 mL) was stirred under argon at rt for 1h. $Cu(OTf)_2$ (28 mg, 0.0774

mmol) or MeOTf (16 μL, 0.129 mmol) was added and the resulting reaction mixture was stirred at rt. The reaction was monitored by TLC (ethyl acetate / toluene, 1/4, v/v); upon disappearance of the glycosyl acceptor **2.2** (1-1.5 h), the solid was filtered off, rinsed with CH_2Cl_2 (3 x 5 mL), and the combined filtrate was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 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 (ethyl acetate – hexanes gradient elution) to afford disaccharide **2.8** in 88-97% yield and unreacted glycosyl donors.

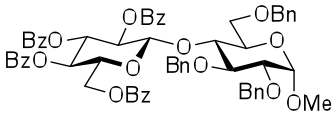
Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (2.8).



This compound was synthesized by Method D from glycosyl donor **2.4c** (30 mg, 0.04 mmol) and glycosyl acceptor **2.2** (15 mg, 0.032 mmol) in 90% (30.2 mg) yield. Analytical data for **2.8**: ^{1}H n.m.r.: δ, 3.22 (s, 3H, OCH_3), 3.35-3.45 (m, 2H, H-4, 2), 3.70-3.78 (m, 2H, H-5, 6a), 3.89 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.08-4.17 (m, 2H, H-6b, 5'), 4.29 (d, 1H, ^{2}J = 11.1 Hz, ½ CH_2Ph), 4.49-4.55 (m, 3H, H-1, 6a', 6b'), 4.58-4.64 (m, 2H, CH_2Ph), 4.67-4.76 (m, 2H, CH_2Ph), 4.83 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.90 (d, 1H, ^{2}J = 10.9 Hz, ½ CH_2Ph), 5.6 (dd, 1H, $J_{2',3'}$ = 9.6 Hz, H-2'), 5.68 (dd, 1H, $J_{4',5'}$ = 9.7 Hz, H-4'), 5.9 (dd, 1H, $J_{3',4'}$ = 9.6 Hz, H-3'), 7.1-7.91 (m, 35H, aromatic) ppm. ^{13}C n.m.r.: 55.04, 63.27, 68.33, 69.48, 69.80, 71.82, 72.22, 72.88, 73.41, 74.74, 75.58, 77.41, 79.76, 81.91, 97.97, 101.35, 127.50 (x 3), 127.64, 127.92 (x 3), 128.16 (x 3), 128.45 (x 3), 128.48 (x

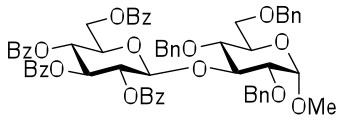
6), 128.76 (x 3), 129.10, 129.18, 129.57, 129.75, 129.78 (x 3), 129.85 (x 4), 129.95 (x 2), 133.15, 133.18, 133.30, 133.48, 138.17, 138.21, 138.81, 164.96, 165.20, 165.20, 165.88, 166.15 ppm.

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (2.9).



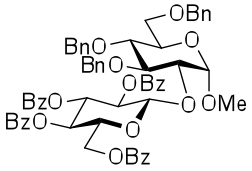
This compound was synthesized by Method D from glycosyl donor **2.4c** (30 mg, 0.04 mmol) and glycosyl acceptor **2.5** (15 mg, 0.032 mmol) in 78% (26.1 mg) yield. Analytical data for **2.9**: R_f = 0.58 (ethyl acetate/ hexane, 1/1, v/v), $[\alpha]_D^{27}$ +4.3 (c = 1, $CHCl_3$),^{1}H n.m.r.: δ, 3.20 (s, 3H, OCH_3), 3.34-3.46 (m, 3H, H-2, 5, 6a), 3.62-3.63 (m, 2H, H-5', 6b), 3.85 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 3.91 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 4.21 (dd, 1H, $J_{6a',6b'}$ = 12.1, $J_{5',6a'}$ = 4.9 Hz, H-6a'), 4.28 (d, 1H, ^{2}J = 12.1 Hz, ½ CH_2Ph), 4.34 (dd, 1H, $J_{5',6b'}$ = 3.0 Hz, H-6b'), 4.48-4.54 (m, 2H, H-1, ½ CH_2Ph), 4.66-4.76 (m, 4H, CH_2Ph), 5.02 (d, 1H, $J_{1',2'}$ = 11.2 Hz, H-1'), 5.41 (dd, 1H, $J_{3',4'}$ = 8.9 Hz, H-3'), 5.44-5.60 (m, 2H, H-2', 4'), 7.09-7.89 (m, 35H, aromatic) ppm; 13C n.m.r.: δ, 55.49, 63.28, 67.68, 69.59, 69.98, 71.96, 72.37, 73.29, 73.71, 73.76, 77.41, 78.89, 80.09, 98.62, 100.55, 127.29, 127.55 (x 3), 127.89, 128.19 (x 4), 128.42 (x 4), 128.48 (x 5), 128.54 (x 2), 128.59 (x 2), 128.97, 129.02 (x 3), 129.17, 129.74, 129.81 (x 2), 129.88 (x 5), 133.11, 133.31, 133.49, 133.51, 138.01, 138.46, 138.46, 138.41, 164.96, 165.24, 165.87, 166.11 ppm.

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (2.10).



This compound was synthesized by Method D from glycosyl donor **2.4c** (30 mg, 0.04 mmol) and glycosyl acceptor **2.6** (15 mg, 0.032 mmol) in 74% (24.9 mg) yield. Analytical data for **2.10**: R_f = 0.4 (ethyl acetate/ toluene, 1.5/7.5, v/v), $[\alpha]_D^{27}$ -12.8 (c = 1, $CHCl_3$), ^{1}H-n.m.r.: δ, 3.14 (s, 3H, OCH_3), 3.25 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.44-3.58 (m, 4H, H-4, 5, 6a, 6b), 4.03-4.07 (m, 2H, H-5', ½ CH_2Ph), 4.19 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.25-4.48 (m, 6H, H-3, 6a', CH_2Ph), 4.56 (d, 1H, $J_{6a',6b'}$ = 12.2 Hz, H-6a'), 5.04 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 5.43 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1'), 5.57 (dd, 1H, $J_{2',3'}$ = 9.7 Hz, H-2'), 5.63 (dd, 1H, $J_{4',5'}$ = 9.7 Hz, H-4'), 5.86 (dd, 1H, $J_{3',4'}$ = 9.6 Hz, H-3'), 7.0-7.94 (m, 35H, aromatic) ppm; ^{13}C n.m.r.: δ, 55.19, 63,46, 68.59, 69.71, 70.05, 72.08, 72.68, 73.32, 73.66, 74.01, 75.07, 75.58, 79.51, 80.97, 97.84, 101.19, 127.62, 127.88, 128.07 (x 2), 128.14 (x 2), 128.25 (x 4), 128.29 (x 2), 128.38 (x 2), 128.46 (x 2), 128.54 (x 4), 128.64 (x 2), 128.67 (x 2), 128.99, 129.57, 129.79, 129.89 (x 2), 129.99 (x 4), 130.03 (x 2), 133.07, 133.39, 133.46, 133.54, 138.04, 138.11, 138.66, 165.34, 165.43, 166.02, 166.28 ppm; HR-FAB MS$[M+Na]^+$ calcd for $C_{62}H_{58}O_{15}Na^+$ 1065.3673, found 1065.3673.

Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (2.11).



This compound was synthesized by Method D from glycosyl donor **2.4c** (30 mg, 0.04 mmol) and glycosyl acceptor **2.7** (15 mg, 0.032 mmol) in 75% (25.4 mg) yield. Analytical data for **2.11**: R_f = 0.27 (ethyl acetate/hexane, 3/7, v/v), $[\alpha]_D^{24}$ +29.1 (c = 1, $CHCl_3$); ^{1}H n.m.r.: δ, 3.27(s, 3H, OCH_3), 3.54-3.68 (m, 4H, H-4, 5, 6a, 6b), 3.73 (dd, 1H, $J_{2,3}$ = 9.7Hz, H-2), 3.85 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 4.08 (m, 1H, H-5'), 4.32-4.42 (m, 4H, H-6b', CH_2Ph), 4.49-4.57 (m, 3H, CH_2Ph), 4.64 (dd, 1H, $J_{6a',6b'}$ = 12.2, $J_{5',6a'}$ = 2.9 Hz, H-6a'), 4.97 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 5.09 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1'), 5.61-5.67 (m, 2H, H-4', 2'), 5.83 (dd, 1H, $J_{3',4'}$ = 9.6 Hz, H-3'), 6.87-7.98 (m, 35H, aromatic) ppm; ^{13}C n.m.r.: δ, 55.49, 63.07, 68.77, 69.68, 70.04, 72.19, 72.51, 73.47, 73.72, 75.11, 75.45, 77.98, 81.07, 82.07, 99.77, 102.61, 127.32, 127.42 (x 3), 127.74, 127.88, 127.96 (x 3), 128.09 (x 2), 128.28 (x 2), 128.42 (x 4), 128.58 (x 3), 128.66 (x 3), 128.94, 129.08, 129.64, 129.93 (x 2), 130.01 (x 2), 130.07 (x 2), 133.21, 133.40 (x 2), 133.68, 138.23, 138.36, 138.69, 142.09, 142.35, 142.60, 165.22, 165.38, 166.02, 166.26 ppm.

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CHAPTER 3

Chemical Glycosylation via Tunable SNea Glycosyl Thiocarbamates

3.1. Introduction

Structural complexity of carbohydrates makes these natural compounds attractive and challenging targets for many synthetic chemists. Complex carbohydrates are typically found in nature in the form of oligosaccharides and glycoconjugates and are involved in many life-sustaining and life-threatening processes.[1] In spite of the abundance of complex carbohydrates in nature, their isolation and purification is cumbersome. Chemical and enzymatic synthesis is also challenging, and many past and ongoing research efforts have been directed to improve synthetic strategies to obtain oligosaccharides with high efficiency and yields. The outcome of chemical glycosylation reaction is dependent on a variety of factors which include the structure of glycosyl donor, glycosyl acceptor, activator, solvent, temperature, pressure etc.[2] Different aspects and components of the glycosyl donor, such as the structure of the leaving group, the nature of protecting groups, conformation, configuration, etc. all may have a profound effect on stability and reactivity of glycosyl donors and often affect the outcome of glycosylation.

The effect of neighboring protecting groups on reactivity of glycosyl donors and stereoselectivity of their glycosidation has been noticed long time ago.[3] More recent study by Fraser-Reid and co-workers generalized the accumulated knowledge and served as the basis for the development of a so-called “armed-disarmed” strategy for oligosaccharide synthesis.[4] This strategy exploits differential properties of protecting groups and the effect that protecting groups have on the reactivity of the anomeric leaving groups. Thus, it was noticed that ester-type protecting groups can reduce the reactivity of building blocks equipped with the anomeric *n*-pentenyl leaving group.

Hence, acylated building block is called “disarmed” in comparison to its alkylated, “armed” counterpart. Resultantly, armed glycosyl donor could be activated over the disarmed glycosyl acceptor offering a useful concept for chemoselective oligosaccharide assembly. The armed-disarmed strategy has been exploited in a number of ways, and a variety of protecting group-based chemoselective approaches have emerged as its extension. These more recent adjustments of the classic strategy include torsional deactivation,[5-7] tunable reactivity,[8] programmable,[9] deactivation by a single remote moiety,[10,11] inverse armed-disarmed,[12,13] conformationally superarmed,[14-17] electronically superarmed/superdisarmed,[18-21] etc.[22]

While the electronic effect of protecting groups on the reactivity of glycosyl donors has been investigated in a variety of ways, the electronic effects originated from the leaving group are much less explored. Roy and co-workers were amongst the first to observe the differential reactivity of electronically activated *p*-(*N*-acetamido)phenyl thioglycoside versus electronically deactivated *p*-nitrophenyl counterpart. This discovery led to the development of a practical and efficient strategy for oligosaccharide synthesis termed active-latent strategy.[23] The active-latent concept was further extended by Fraser-Reid,[24] Boons,[25] Kim,[26,27] and others,[28-30] but, to the best of our knowledge, only Roy’s original approach relies on the reactivity differentiation by electronic properties of the leaving group.

Along similar lines, Kahne *et al.* demonstrated the difference in reactivity depending on the nature of the substituent at the *para*-position of phenyl sulfoxides.[31] In this study, the reactivity was observed to decrease in the following order: OMe > H > NO_2. The difference in the reactivity was utilized for a one-pot synthesis of Ciclamycin 0

trisaccharide via selective activation. Similar observations of electronic effect originated from various substituents on the leaving group have been reported by van Boom and co-workers,[32] Hanessian et al.,[33] and Hasty et al.[34]

Previously, we designed and explored the reactivity of a novel glycosyl alkoxythioimidate donor (SNea, Figure 3.1).[35] We were intrigued by the discrepancy of results obtained with the SNea donor and structurally similar *S*-benzoxazolyl (SBox) donor. The activation profile seemed so drastically different that this allowed us to develop an orthogonal-like activation[36] of building blocks equipped with SNea and SBox leaving groups.[35] On the other hand, comparative studies between glycosyl thiocyanate and glycosyl SNea donors showed that the activation conditions for these two glycosyl donors are similar.[35] Earlier mechanistic investigations indicated that the SBox leaving group tends to be activated via the anomeric sulfur[37] (direct activation pathway like in alkyl/aryl thioglycosides)[38] regardless of the activation condition chosen. This suggests that glycosyl SNea donors may follow the remote activation pathway as seen in case of glycosyl thiocyanates (Figure 3.1).[39,40]

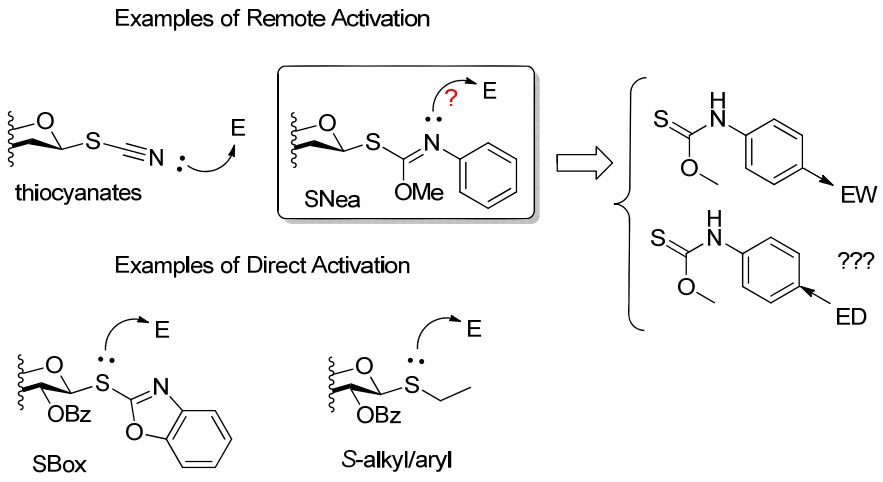


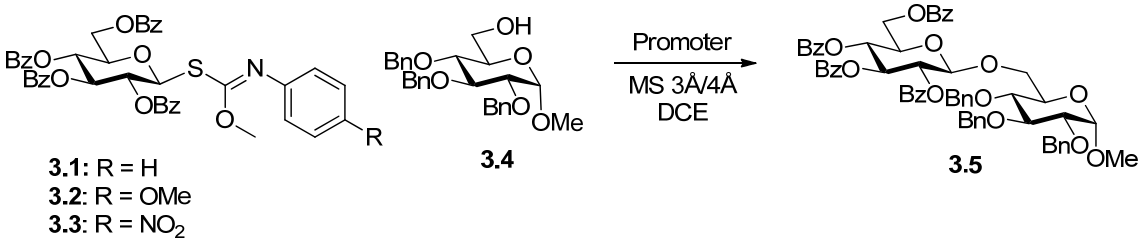
Figure 3.1. Direct vs. Remote Activation of Leaving Groups, Possible Electronic Effects

To test this hypothesis we performed a comparison study involving a series of building blocks modified with electron-withdrawing and electron-donating substituents at the phenyl group of SNea leaving group. We anticipated that the presence of these substituents would have a direct effect on the relative nucleophilicity of the nitrogen atom. Conversely, the effect of such modification on the nucleophilicity of the anomeric sulfur atom would be weaker. Therefore, if the activation of the SNea moiety were indeed taking place via the nitrogen, such modifications may significantly impact the reactivity of the respective alkoxythioimidoyl leaving groups.

3.2. Results and Discussion

To test the hypothesis of the anticipated remote activation of the SNea leaving group, we obtained a series of glycosyl donors: standard SNea donor (**3.1**),[35] *p*-methoxy-SNea donor (**3.2**), and *p*-nitro-SNea donor (**3.3**, Table 3.1) using earlier established protocols.[35] In order to test the relative reactivity of a new series of glycosyl donors in glycosylation we chose a range of metal triflates that showed excellent results with glycosyl thioimidates and SNea donors in our previous studies.[41] Herein, we tested copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$), bismuth(III) trifluoromethanesulfonate ($Bi(OTf)_3$), and silver(I) trifluoromethanesulfonate (AgOTf). Glycosidation reactions of donor **3.1** with acceptor **3.4**[42] in the presence of $Cu(OTf)_2$ or $Bi(OTf)_3$ as promoters were very smooth and completed within 1 h. Resultantly, disaccharide **3.5** was isolated in 91% and 95% yields, respectively (entries 1 and 2, Table 3.1). AgOTf-promoted glycosylation reaction was even faster (30 min) and disaccharide **3.5** was obtained in 95% yield (entry 3, Table 3.1).

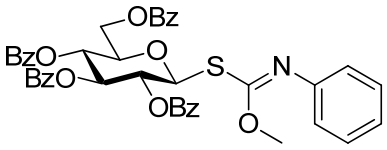
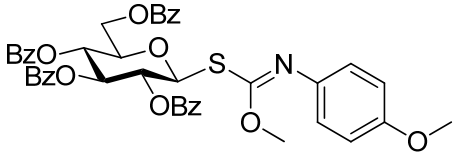
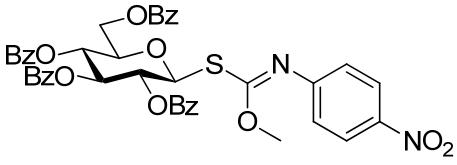
Table 3.1. Comparative Glycosidations of Glycosyl Donors **3.1**-**3.3** with Glycosyl Acceptor **3.4** in the Presence of Various Metal-Based Promoters



3.1: R = H
3.2: R = OMe
3.3: R = NO_2

3.4

3.5

Entry	Glycosyl Donor	Promoter (3 equiv)	Time	Yield of 3.5
1	 **3.1**	$Cu(OTf)_2$	1 h	91%
2	**3.1**	$Bi(OTf)_3$	1 h	95%
3	**3.1**	AgOTf	30 min	95%
4	 **3.2**	$Cu(OTf)_2$	2 h	86%
5	**3.2**	$Bi(OTf)_3$	10 min	93%
6	**3.2**	AgOTf	30 min	97%
7	 **3.3**	$Cu(OTf)_2$	2 h	90%
8	**3.3**	$Bi(OTf)_3$	2 h	71%
9	**3.3**	AgOTf	24 h	< 10%

Encouraged by this strong performance of SNea donor **3.1**, we turned our attention to investigating the modified donors. When *p*-methoxy donor **3.2** was reacted with glycosyl acceptor **3.4** in the presence of $Cu(OTf)_2$, a similar result to that obtained with standard donor **3.1** was obtained. The glycosidation required a slightly longer time (2 h for **3.2** vs. 1 h for **3.1**) and afforded disaccharide **3.5** in 86% yield (entry 4, Table 3.1). In case of $Bi(OTf)_3$, the reaction was much fasted and completed within 10 min (1 h for **3.1**) to give disaccharide **3.5** in 93% yield (entry 5, Table 3.1). AgOTf-promoted reaction gave 97% of disaccharide **3.5** in 30 min, which was practically the same reaction time as that recorded for SNea donor **3.1**. Resultantly, disaccharide **3.5** was isolated in 97% yield (entry 6, Table 3.1). As a whole, these comparative glycosylations showed that both SNea **3.1** and *p*-methoxy-SNea **3.2** thiocarbamates are excellent glycosyl donors for chemical glycosylation. *p*-Methoxy-SNea derivative **3.2** showed slightly enhanced reactivity in the presence of $Cu(OTf)_2$ and was significantly more reactive in the presence of $Bi(OTf)_3$.

In case of the reaction of *p*-nitro-SNea donor **3.3** with glycosyl acceptor **3.4** in the presence of $Cu(OTf)_2$ disaccharide **3.5** was formed in 90% yield showing somewhat insignificant deviation in reactivity (entry 7, Table 3.1). The reaction of *p*-nitro-SNea donor **3.3** with acceptor **3.4** in the presence of $Bi(OTf)_3$ gave disaccharide **3.5** in 71% yield (entry 8) in 1 h, similar to that of glycosidation of the standard SNea donor **3.1**. Interestingly, donor **3.3** reacted very slowly in the presence of AgOTf, and even after 24 h only trace amount of disaccharide **3.5** was obtained (entry 9).

Since the results of activations of different leaving groups with metal triflates were inconclusive, we wanted to look into the mode of activation that, in principle, could

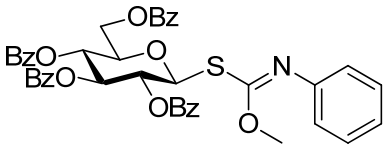
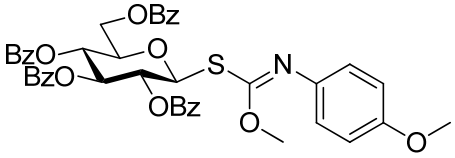
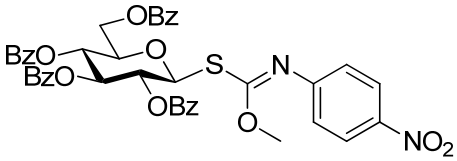
be established by determining the structure of departed aglycones. Although we had had some prior success,[43] elucidation of exact mode of activation using metal-based promoters is cumbersome. This is because upon departure, thioimidoyl leaving groups often result in the formation of metal inclusion polymers $(\text{-M-S-C=N-})_n$, which are very cumbersome to characterize.[43] Therefore, in order to gain a reliable insight into the activation mode of alkoxythioimidates, we turned our attention towards studying alternative activation pathways. Promoters used for this extended study included methyl trifluoromethanesulfonate (MeOTf), *N*-iodosuccinimide/ trifluoromethane sulfonic acid (NIS/TfOH) and trimethylsilyl trifluoromethanesulfonate (TMSOTf). These reaction conditions were proven successful for determining activation pathways of SBox (MeOTf),[43] STaz (MeOTf, BnBr),[44] SBiz (BnBr),[34] SEt (MeOTf),[38] and ortho-allylphenyl (TMSOTf and NIS/TfOH)[45] leaving groups. We also included molecular iodine (I_2) into the list of promoters to be tested due to our fruitful experience with differentiating armed vs. superarmed levels of reactivity of various thioglycosides and thioimidates using these reaction conditions.[21]

With this new set of promoters, we were bound to deepen our understanding of the activation modes and relative reactivities of glycosyl donors **3.1-3.3**. The progress of all side-by-side experiments was monitored by TLC, and the reactions were quenched as soon as the acceptor disappeared. To maintain standard comparison between different glycosyl donors, the incomplete reactions, as judged by TLC, were stopped after 24 h. Previously, we have shown that glycosyl SNea donor **3.1** reacts quite sluggishly in the presence of 3 equiv. of MeOTf.[35] Indeed, reaction of donor **3.1** with glycosyl acceptor **3.4** was practically ineffective, and even after 24 h afforded disaccharide **3.5** in only 12%

yield (entry 1, Table 3.2). The activation of SNea donor **3.1** was also ineffective in the presence of iodine, wherein no traces of the anticipated product **3.5** were detected (entry 2). SNea donor **3.1** was much more reactive in the presence of NIS/TfOH or TMSOTf; these reactions completed in 3-3.5 h. However, but disaccharide **3.5** was formed in modest yields of 45% or 65%, respectively due to high rates of competing hydrolysis, as judged by accumulation of the corresponding hemiacetal derivative (entries 3 and 4, Table 3.2). Thus, none of these non-metallic electrophilic promoters offered a reliable activation pathway for glycosidation of SNea donor **3.1** at the ambient temperature. Lowering the reaction temperature allowed to control the competing hydrolysis and afforded disaccharide **3.5** in a higher yield. This results, however, cannot be compared with all other experiments performed at room temperature and, hence, is not shown.

Encouragingly, *p*-methoxy-SNea donor **3.2** was significantly more reactive than its non-substituted SNea counterpart **3.1**. Both MeOTf and molecular iodine, which were practically ineffective with donor **3.1**, promoted glycosidations of glycosyl donor **3.2** with acceptor **3.4**. These reactions were still rather slow and incomplete even after 24 h, but disaccharide **3.5** was obtained in 62% and 43% yield, respectively (entries 5 and 6). NIS/TfOH-promoted reaction was very fast and completed in 30 min, but again yielded disaccharide **3.5** in a modest yield of 48% due to the competing hydrolysis (entry 7). Similar reaction time was recorded for glycosidation of donor **3.2** with acceptor **3.4** in the presence of TMSOTf, but this reaction was much cleaner and afforded disaccharide **3.5** in 90% yield (entry 8).

Table 3.2. Comparative Glycosidations of Donors **3.1**-**3.3** with Acceptor **3.4** in the Presence of Various Electrophilic and Thiophilic Promoters

Entry	Donor	Promoter[a]	Time	Yield of 3.5
1	 **3.1**	MeOTf	24 h	12%
2	**3.1**	I_2	24 h	NR[b]
3	**3.1**	NIS/TfOH	3.5 h	45%
4	**3.1**	TMSOTf	3 h	65%
5	 **3.2**	MeOTf	24 h	62%
6	**3.2**	I_2	24 h	43%
7	**3.2**	NIS/TfOH	30 min	48%
8	**3.2**	TMSOTf	30 min	95%
9	 **3.3**	MeOTf	24 h	10%
10	**3.3**	I_2	24 h	<10%
11	**3.3**	NIS/TfOH	15 min	85%
12	**3.3**	TMSOTf	1 h	85%

[a] 2 equiv. of TMSOTf and 3 equiv. of all other promoters have been used

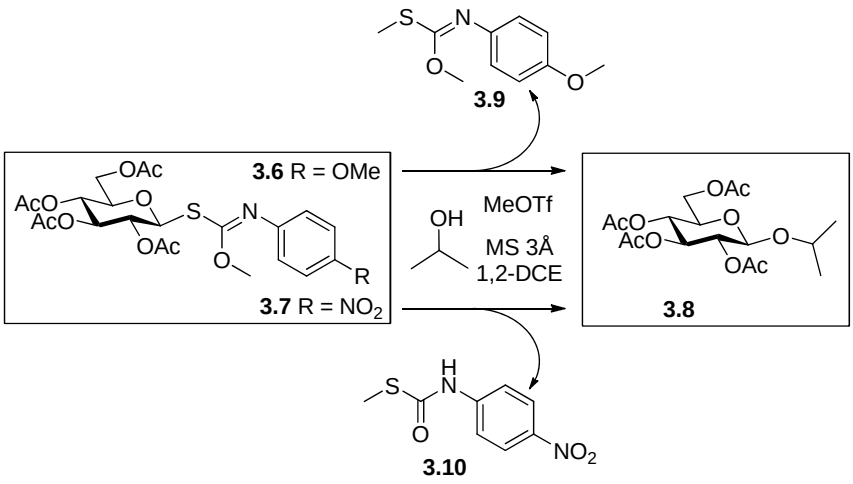
[b] NR : no reaction

Similarly to our earlier observations made with metal triflates, p-methoxy donor **3.2** showed over-all higher reactivity than that of its unmodified SNea counterpart **3.1** in the presence of non-metallic promoters. While in a series of metal triflates, only $Bi(OTf)_3$ showed significant level of differentiation between the reactivity of donors **3.1** and **3.2**, practically every non-metallic electrophilic promoter was much more effective with p-methoxy-SNea donor **3.2**, as surveyed in Table 3.2.

Having completed the comparison of donors **3.1** and **3.2**, we turned our attention to studying *p*-nitro-SNea donor **3.3**. When donor **3.3** reacted with acceptor **3.4** in the presence of MeOTf, the reaction was found to be very sluggish, similar to that of SNea donor **3.1**. As a result, disaccharide **3.5** was isolated in a very modest yield of 10% (entry 9, Table 3.2). A similar observation was made in case of molecular iodine; the reaction was very slow and gave only traces of disaccharide **3.5**, even after 24 h (entry 10, Table 3.2). However, in case of NIS/TfOH, the reaction proceeded rather fast and completed in 15 min affording disaccharide **3.5** in 85% yield (entry 11, Table 3.2). A similar result was obtained in the TMSOTf-promoted glycosylation that took 1 h to afford disaccharide **3.5** in 85% yield (entry 12, Table 3.2).

From results obtained during the comparative study it is clear that a notable difference in reactivity can be achieved upon modification of the structure of the leaving group. Next, we extend results obtained in glycosylation promoted with MeOTf to investigating the mechanistic profile of this reaction. A range of experiments were performed to determine the activation mode of these leaving groups during the glycosylation reaction. For this model mechanistic study we obtained acetylated *p*-methoxy-SNea (**3.6**) and *p*-nitro-SNea (**3.7**) donors, which were reacted with isopropanol

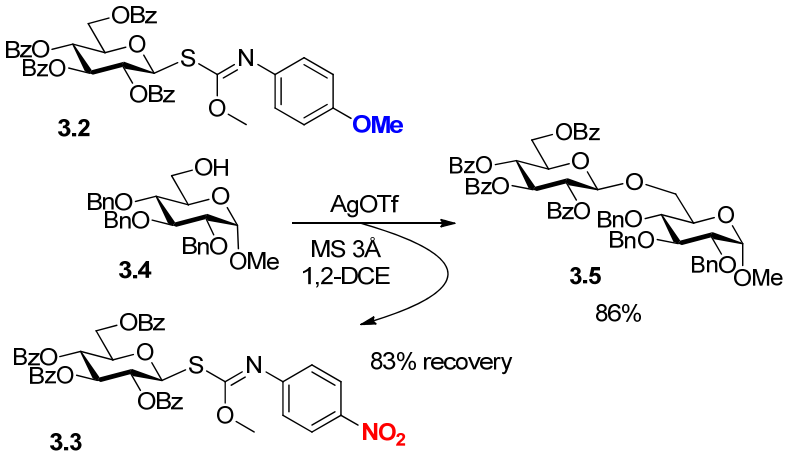
as the glycosyl acceptor (Scheme 3.1). These reactions were monitored by TLC and upon disappearance of the glycosyl donor, the reaction mixture was concentrated *in vacuo*. After that, all components of the reaction have been isolated by column chromatography. Glycosidation of *p*-methoxy-SNea donor **3.6** afforded isopropyl glycoside **3.8**;[46,47] also isolated was the departed aglycone that was found to be methylated at sulfur, *O,S*-dimethyl (4-methoxyphenyl)carbonimidothioate (**3.9**). Glycosidation of *p*-nitro-SNea donor **3.7** afforded isopropyl glycoside **3.8**. Also isolated was the departed aglycone that was found to be also methylated at sulfur, *S*-methyl (4-nitrophenyl)carbamothioate (**3.10**). The identity of compounds **3.9** and **3.10** was proven by spectral methods.



Scheme 3.1. Mechanism of Activation of Alkoxythioimidates **3.6** and **3.7** with MeOTf

Initially, it was anticipated that the activation of the SNea leaving group would take place via the remote activation pathway. In this case, the presence of electron-donating or electron-withdrawing substituents would directly affect the nucleophilicity of the nitrogen atom and hence affect the overall reactivity of the leaving group. However, our mechanistic study showed that both *p*-methoxy-SNea and *p*-nitro-SNea leaving

groups seems to undergo the direct activation pathway. This indicates that the presence of an electron-donating substituent at the remote *para*-position of the *N*-phenyl ring can also affect the nucleophilicity of the anomeric sulfur. Consequently, due to the presence of the distant electron donating substituent, *p*-methoxy-SNea leaving group is activated much more efficiently in comparison with its SNea and *p*-nitro-SNea counterparts. To test the viability of this key observation and gain a more reliable evidence of differential reactivity of glycosyl donors **3.2** and **3.3**, a competitive glycosylation reaction depicted in Scheme 3.2 was planned.



Scheme 3.2. Competitive Glycosylation Involving Two Glycosyl Donors with Different Reactivity **3.2** and **3.3**.

In this experiment, glycosyl donors **3.2** and **3.3** were set to compete against each other for a limited amount of glycosyl acceptor **3.4**, a protocol that became standard in our laboratory to perform direct comparison of reactivity levels of different building blocks.[19,35,45] Since the greatest degree of differentiation was achieved with AgOTf as the promoter (Table 3.1), we chose to apply these reaction conditions. Upon addition of AgOTf, the reaction between donors **3.2** and **3.3** and glycosyl acceptor **3.4** proceeded

smoothly to give disaccharide **3.5** in 86% yield (Scheme 3.2). Also recovered was the unreacted glycosyl donor **3.3**, which was isolated in 83% yield. These results confirm that the *p*-methoxy-SNea donor **3.2** is indeed significantly more reactive in the presence of AgOTf than its *p*-nitro-SNea counterpart **3.3**.

3.3. Conclusions

Structural modifications of SNea leaving group involving change of substituents that express different electronic effects led to a better understanding of how the reactivity of glycosyl donors can be modified by changing the structure of their leaving groups. Mechanistic studies involving the isolation of departed aglycones were indicative of the activation of both *p*-methoxy-SNea and *p*-nitro-SNea leaving groups via the anomeric sulfur. The presence of an electron donating substituent (*p*-methoxy) has a strong effect on the nucleophilicity of the distant sulfur atom that becomes more susceptible towards the attack of thiophilic reagents. This key observation allowed to differentiate the reactivity levels of *p*-methoxy-SNea vs. *p*-nitro-SNea and even unmodified SNea leaving groups. The reactivity difference observed in the series of SNea leaving groups is sufficient to be exploited in expeditious oligosaccharide synthesis via selective activation strategies.

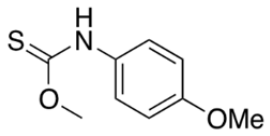
3.4. Experimental Section

3.4.1. General Remarks

The reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). Detection of compounds was achieved using UV light and by charring with 10% sulfuric

acid in methanol. Purification by column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh). Removal of solvents was achieved *in vacuo* at < 40 ^{o}C using rotary evaporators. CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled from CaH_2 directly before using for the reactions. Methanol was dried by refluxing with magnesium methoxide, distilled and stored under argon. Pyridine and acetonitrile were dried by refluxing with CaH_2, distilled and stored over molecular sieves (3 Å). Molecular sieves (3 Å and 4 Å) used for reactions were crushed and activated *in vacuo* at 390 ^{o}C during 8 h at first and then for 2-3 h at 390 ^{o}C prior to application. AgOTf was co-evaporated with toluene (3 x 10 mL) and dried *in vacuo* for 2-3 h prior to using in reactions. Optical rotations were measured using '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 noted otherwise. HRMS determinations were made with the use of JOEL MStation (JMS-700) Mass spectrometer, matrix *m*-nitrobenzyl alcohol, with NaI as necessary.

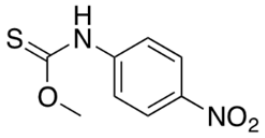
_O_-Methyl (4-methoxyphenyl)carbamothioate.



A 1M solution of NaOMe in methanol (9.1 mL) was added to the flask containing *p*-methoxyphenyl isothiocyanate (0.8 mL, 6.05 mmol) and the resulting mixture was stirred for 15 min at rt. Then, conc. aq. HCl (~5 mL) was added till the pH ~ 4-5. The resulting precipitate was filtered off and rinsed successively with methanol. The combined filtrate (~100 mL) was concentrated *in vacuo*. The residue containing the title compound was used directly in subsequent transformations. Analytical data for the title compound: R*f* =

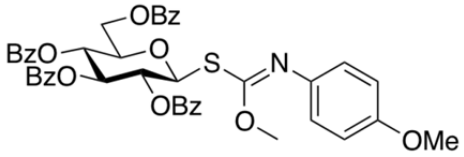
0.57 (ethyl acetate/hexanes, 3/7, v/v); ^{1}H-n.m.r.: δ, 3.81 (s, 1H, OCH_3), 4.12 (s, 1H, OCH_3), 6.87 (dd, 2H, aromatic), 7.16 (dd, 2H, aromatic), 7.41 (br. s, 1H, NH) ppm; ^{13}C n.m.r.: δ, 55.7, 58.9, 114.4 (x 2), 124.2, 126.2, 130.0, 157.6, 189.7 ppm; HR-FAB MS $[M]^+$ calcd for $C_9H_{11}NO_2S^+$ 197.0510, found 197.0510.

_O_-Methyl (4-nitrophenyl)carbamothioate.



A 1M solution of NaOMe in methanol (16.5 mL) was added to the flask containing *p*-nitrophenyl isothiocyanate (2.0 g, 11.1 mmol) and the resulting mixture was stirred for 15 min at rt. Then, conc. aq. HCl (~5 mL) was added till the pH ~ 4-5. The resulting precipitate was filtered off and rinsed successively with methanol. The combined filtrate (~100 mL) was concentrated *in vacuo*. The residue containing the title compound was used directly in subsequent transformations. The analytical data of the title compound were essentially the same as described previously.[48]

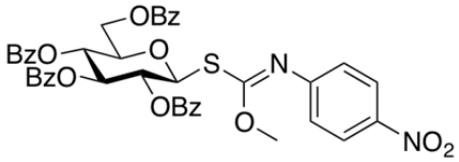
_S_-(2,3,4,6-Tetra-_O_-benzoyl-β-D-glucopyranosyl) _O_-methyl (4-methoxyphenyl) carbonimidothioate (3.2).



O-Methyl (4-methoxyphenyl)carbamothioate (1.1 g, 5.69 mmol) and KOH (212 mg, 3.79 mmol) were added to a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl

bromide[49] (2.5 g, 3.79 mmol) in dry acetonitrile (30 mL) and the resulting mixture was stirred for 2.5 h at rt. After that, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with sat. aq. $NaHCO_3$ (15 mL) and water (3 x 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 22% yield (650 mg) as a white foam. Analytical data for **3.2**: R_f = 0.6 (ethyl acetate/toluene, 1/9, v/v); $[\alpha]_D^{30}$ -7.4 (c = 1, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.76 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.25 (m, 1H, $J_{5,6a}$ = 2.9 Hz, $J_{5,6b}$ = 5.7 Hz, H-5), 4.48 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.64 (dd, 1H, H-6b), 5.53 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 5.61 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 5.64 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.94 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 6.64-7.91 (m, 24H, aromatic) ppm; ^{13}C n.m.r.: δ, 55.4, 56.6, 63.2, 69.4, 70.5, 74.1, 77.2, 81.7, 144.3 (x 2), 122.3 (x 2), 128.3 (x 2), 128.4 (x 6), 128.5 (x 2), 128.7, 128.9, 129.6, 129.8 (x 3), 129.9 (x 3), 133.2, 133.3, 133.4, 133.5, 139.3, 154.4, 156.4, 164.9, 165.1, 165.7, 166.1 ppm; HR-FAB MS$[M+Na]^+$ calcd for $C_{43}H_{37}NO_{11}SNa^+$ 798.1985, found 798.1977.

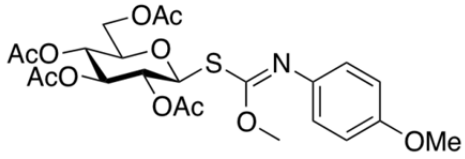
_S_-(2,3,4,6-Tetra-_O_-benzoyl-_β_-D-glucopyranosyl) _O_-methyl (4-nitrophenyl) carbonimidothioate (3.3).



Sodium salt of *O*-methyl (4-nitrophenyl)carbamothioate (0.426 g, 1.82 mmol) and 15-crown-5 (30.4 μL, 0.15 mmol) were added to a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-

glucopyranosyl bromide[49] (1.0 g, 1.52 mmol) in dry acetonitrile (10.0 mL) and the resulting reaction mixture was stirred for 45 min at rt. After that, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~50 mL) was washed with sat. aq. $NaHCO_3$ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 47% yield (560 mg) as a white foam. Analytical data for **3.3**: R_f = 0.63 (ethyl acetate/toluene, 1/9, v/v); $[\alpha]_D^{30}$ -18.2 (c = 1, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.94 (s, 3H, OCH_3), 4.31 (m, 1H, $J_{5,6a}$ = 2.8 Hz, $J_{5,6b}$ = 5.6 Hz, H-5), 4.54 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.69 (dd, 1H, H-6b), 5.56–5.63 (m, 2H, H-1, H-2), 5.70 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 6.01 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 6.83–8.10 (m, 24H, aromatic) ppm; ^{13}C n.m.r.: δ, 57.2, 63.2, 69.4, 70.5, 74.0, 76.9, 82.0, 122.1 (x 2), 125.2 (x 2), 128.5 (x 2), 128.6 (x 3), 128.7 (x 5), 128.8 (x 2), 129.7, 129.9 (x 3), 130.1 (x 3), 133.5, 133.6, 133.8, 133.9, 144.4, 152.6, 155.8, 165.1, 165.3, 165.9, 166.2 ppm; HR-FAB MS$[M+Na]^+$ calcd for $C_{42}H_{34}N_2O_{12}SNa^+$ 813.1730, found 813.1724.

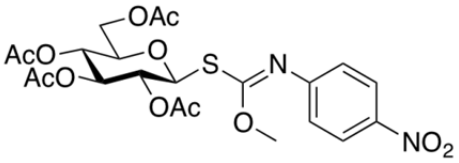
_S_-(2,3,4,6-Tetra-_O_-acetyl-β-D-glucopyranosyl) _O_-methyl (4-methoxyphenyl) carbonimidothioate (3.6).



O-Methyl (4-methoxyphenyl)carbamothioate (1.2 g, 5.84 mmol) and NaOH (194 mg, 4.87 mmol) were added to a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl

bromide[50] (2.0 g, 4.87 mmol) in dry acetonitrile (30 mL) and the resulting reaction mixture was stirred for 1.5 h at rt. After that, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with sat. aq. $NaHCO_3$ (25 mL) and water (3 x 25 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 35% yield (897 mg) as a white foam. Analytical data for **3.6**: R_f = 0.48 (ethyl acetate/hexanes, 2/3, v/v), $[\alpha]_D^{30}$ -2.3 (c = 1, $CHCl_3$), ^{1}H n.m.r.: δ, 1.99, 2.01, 2.02, 2.09 (4 s, 12H, 4 x $COCH_3$), 3.75 (m, 1H, $J_{5,6a}$ = 2.4 Hz, $J_{5,6b}$ = 4.8 Hz, H-5), 3.78 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.13 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.25 (dd, 1H, H-6b), 4.99 (dd, 1H, $J_{2,3}$ = 9.1 Hz, H-2), 5.03 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.20–5.27 (m, 2H, H-3, H-1), 6.74–6.84 (m, 4H, aromatic) ppm; ^{13}C n.m.r.: δ, 20.8 (x 3), 20.9, 55.6, 56.8, 62.1, 68.2, 69.9, 74.1, 76.2, 81.4, 114.5 (x 2), 122.5 (x 2), 139.4, 154.6, 156.6, 169.3, 169.5, 170.3, 170.8 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{23}H_{29}NO_{11}SNa^+$ 550.1359, found 550.1371

_S_-(2,3,4,6-Tetra-_O_-acetyl-β-D-glucopyranosyl) _O_-methyl (4-nitrophenyl) carbonimidothioate (3.7).



O-Methyl (4-nitrophenyl)carbamothioate (1.2 g, 5.84 mmol) and NaOH (194 mg, 4.87 mmol) were added to the a stirring solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[50] (2.0 g, 4.87 mmol) in dry acetonitrile (30 mL) and the resulting reaction

mixture was stirred overnight (16 h) at rt. After that, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with sat. aq. $NaHCO_3$ (25 mL) and water (3 x 25 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound as white foam in 61% yield (1.6 g) as a pale-yellow foam. Analytical data for **3.7**: R_f = 0.61 (ethyl acetate/hexanes, 2/3, v/v) $[\alpha]_D^{30}$ 11.8 (c = 1, $CHCl_3$), ^{1}H n.m.r.: δ, 2.00, 2.02, 2.03, 2.10 (4s, 12H, 4 x $COCH_3$), 3.78 (m, $J_{5,6a}$ = 2.3 Hz, $J_{5,6b}$ = 5.4 Hz, H-5), 4.03 (s, 3H, OCH_3), 4.14 (dd, 1H, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.25 (dd, 1H, H-6b), 5.01 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 5.05 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.25 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 5.25 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 6.91-6.96 (m, 2H, aromatic), 8.14-8.18 (m, 2H, aromatic) ppm; ^{13}C n.m.r.: δ, 20.8 (x 3), 20.9, 57.3, 68.1, 69.6, 73.9, 76.4, 81.5, 122.1 (x 2), 125.3 (x 2), 144.5, 152.6, 155.7, 169.3, 169.5, 170.3, 170.8 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{22}H_{26}N_2O_{12}SNa^+$ 565.1104, found 565.1106.

General Glycosylation Procedures:

Method A – Activation with $Cu(OTf)_2$

A mixture of the glycosyl donor (0.038 mmol), glycosyl acceptor (0.03 mmol), and freshly activated molecular sieves (4Å, 90 mg) in $ClCH_2CH_2Cl$ (0.5 mL) was stirred under argon for 1.5 h at rt. $Cu(OTf)_2$ (41.3 mg, 0.114 mmol) was added and the resulting mixture was stirred for 1-2 h (see Table 3.1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5

mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford disaccharide **3.5**.

Method B – Activation with $Bi(OTf)_3$

A mixture containing glycosyl donor (0.038 mmol), glycosyl acceptor (0.03 mmol) and freshly activated molecular sieves (3Å, 90 mg) in $ClCH_2CH_2Cl$ (0.5 mL) was stirred under argon for 1.5 h at rt. $Bi(OTf)_3$ (74.8 mg, 0.114 mmol) was added and the reaction mixture was stirred for 10 min - 2 h (see Table 3.1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **3.5**.

Method C – Activation with AgOTf

A mixture containing glycosyl donor (0.038 mmol), glycosyl acceptor (0.03 mmol) and freshly activated molecular sieves (3Å, 90 mg) in $ClCH_2CH_2Cl$ (0.5 mL) was stirred under argon for 1.5 h at rt. Freshly activated AgOTf (29.3 mg, 0.114 mmol) was added and the reaction mixture was stirred for 30 min - 24 h (see Table 3.1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off and rinsed successively with CH_2Cl_2. The filtrate (~25 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$ and

concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **3.5**.

Method D – Activation with MeOTf

A mixture containing glycosyl donor (0.038 mmol), glycosyl acceptor (0.03 mmol) and freshly activated molecular sieves (3Å, 90 mg) in $ClCH_2CH_2Cl$ (0.5 mL) was stirred under argon for 1.5 h at rt. MeOTf (14.2 μL, 0.114 mmol) was added and the reaction mixture was stirred for 24 h (see Table 3.1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 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 the disaccharide **3.5**.

Method E – Activation with molecular I_2

A mixture containing glycosyl donor (0.025 mmol), glycosyl acceptor (0.02 mmol) and freshly activated molecular sieves (3Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h at rt. Iodine (19.3 mg, 0.076 mmol) was added and the reaction mixture was stirred for 24 h (see Table 3.1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with 10% $Na_2S_2O_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The

residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **3.5**.

Method F – Activation with NIS/TfOH

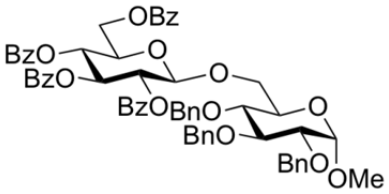
A mixture containing glycosyl donor (0.025 mmol), glycosyl acceptor (0.02 mmol) and freshly activated molecular sieves (4Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h at rt. NIS (17.1 mg, 0.076 mmol) and TfOH (0.7 μL, 0.007 mmol) were added and the reaction mixture was stirred for 15 min – 3.5 h (see Table 3.1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2 (25 mL), the solid was filtered-off and rinsed with CH_2Cl_2. The filtrate was washed with 10% $Na_2S_2O_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **3.5**.

Method G – Activation with TMSOTf

A mixture containing glycosyl donor (0.025 mmol), glycosyl acceptor (0.02 mmol) and freshly activated molecular sieves (4Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h at rt. TMSOTf (9.0 μL, 0.05 mmol) was added and the reaction mixture was stirred for 30 min - 3 h (see Table 3.1) at rt. After that, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off and then rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated

in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution) to afford the disaccharide **3.5**.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (3.5).



The title compound was synthesized as described in Tables 3.1 and 3.2. For example, the synthesis from glycosyl donor **3.2** (0.038 mmol) and glycosyl acceptor **3.4** (0.03 mmol) using Method A allowed the title compound in 91% yield. Analytical data for **3.5** was essentially the same as reported previously.[51]

Aglycone isolation

***O,S*-Dimethyl (4-methoxyphenyl)carbonimidothioate (3.8)**

The title compound was isolated by column chromatography from the reaction mixture resulted from MeOTf-promoted glycosylation between **3.6** and isopropanol. Analytical data for **3.8**: R_f = 0.62 (ethyl acetate/toluene, 0.5/9.5, v/v), ^{1}H n.m.r.: δ, 2.34 (s, 3H, SCH_3), 3.79 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.82-6.86 (m, 4H, aromatic) ppm; ^{13}C n.m.r.: δ, 13.7, 55.6, 56.3, 114.5 (x 2), 122.7 (x 2), 140.8, 156.3, 159.4 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{10}H_{13}NO_2S$ 211.0667, found 211.0663.

***S*-Methyl (4-nitrophenyl)carbamothioate (3.9).**

The title compound was isolated by column chromatography from the reaction mixture resulted from glycosylation between **3.6** and isopropanol in as white solid. Complete analytical data for **3.9** were reported previously.[52] ^{1}H n.m.r.: δ, 2.27 (s, 3H, SCH_3), 7.59-7.62 (m, 2H, aromatic), 8.06-8.09 (m, 2H, aromatic) ^{13}C n.m.r.: δ, 12.4, 119.6 (x 2), 126.1 (x 2), 144.3, 146.4, 169.1 ppm

Competitive Glycosylation between Glycosyl Donor 3.2 and 3.3.

A mixture of glycosyl donor **3.2** (40 mg, 0.05 mmol), glycosyl donor **3.3** (41 mg, 0.05 mmol), glycosyl acceptor **3.4** (19.5 mg, 0.04 mmol), and freshly activated molecular sieves (3 Å, 120 mg) in 1,2-dichloroethane (0.8 mL) was stirred under argon for 1 h at rt. AgOTf (40 mg, 0.16 mmol) was added and the resulting mixture was stirred for 1.5 at rt. At this time point, glycosyl acceptor **3.4** had been completely consumed as indicated by TLC (ethyl acetate/toluene, 1/9, v/v). The solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~50 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – toluene gradient elution) to afford disaccharide **3.5** in 86% yield. Also isolated was unreacted glycosyl donor **3.3** (83 % yield).

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CHAPTER 4

Investigation of Cyclic Thioimidates and Their Acyclic Analogs

4.1. Introduction

Oligosaccharide synthesis[1-4] has always challenged organic chemists due to the intricacies involved in the formation of glycosidic bonds.[5,6] A variety of factors are known to have a substantial effect on the outcome of the glycosylation reaction.[7] Amongst these, structural features of the glycosyl donor including protecting groups, leaving groups, stereochemistry, conformation, etc. may significantly affect the outcome of the glycosylation reaction by influencing the reactivity of the donor.[8-10] Many different classes of glycosyl donors equipped with various leaving groups have been synthesized and tested.[6] Even minor structural modifications of the leaving group, steric hindrance, and electronic factors have been shown to have an effect on the reactivity of the glycosyl donor and could have a significant effect on the overall outcome of the glycosylation reaction. Along with basic studies, a variety of useful strategies for expeditious oligosaccharide synthesis based on these differences in reactivity have emerged.[3] Features of leaving groups, such as the presence of a specific functional group providing electronic or steric effects, may considerably alter the activation profile of glycosyl donors.[11-13]

For over a decade, our laboratory has been interested in glycosyl thioimidates, a relatively new class of glycosyl donors for chemical glycosylation.[14-16] Among a range of derivatives investigated, *S*-benzoxazolyl (SBox, **4.1**, Figure 4.1) glycosides have been studied most extensively.[17-20] This study was inspired by earlier work conducted by Mukaiyama who introduced *S*-benzothiazolyl (SBaz, **4.2**) glycosides,[21] building blocks that also have application in glycoside and oligosaccharide synthesis.[22-24] Very recently, our laboratory reported that structurally similar *S*-benzimidazolyl (SBiz, **4.3**) glycosides

are also promising building blocks of this class.[25] Practically all glycosyl thioimidate donors gave excellent results in glycosylations and were shown to be compatible with various strategies for oligosaccharide synthesis.[16,24,26-30] Although some deviation in the activation profile has been noticed, the effect of the heteroatom in the five-membered aromatic ring, the only structural difference amongst the three leaving groups, remained elusive.[22,24] Hence, a direct comparison of a range of structurally related glycosyl thioimidates as donors in glycosylations appealed to us as an important research venue. The focus of the study disclosed herein is to investigate the reactivity pattern of thioimidoyl leaving groups equipped with various heteroatoms, nitrogen, oxygen, or sulfur. We expected this study to improve our understanding of the features of the leaving group that might be critical to their reactivity in glycosylation reactions. Consequently, this will enhance our ability to use glycosyl thioimidates as building blocks for expeditious oligosaccharide synthesis.

4.2. Results and discussion

To gain a better insight into the reactivity profile of a series of structurally similar glycosyl donors, we obtained per-benzoylated SBox (**4.1**),[19] SBaz (**4.2**),[22] and SBiz (**4.3**)[25] derivatives in accordance with reported procedures. With glycosyl donors **4.1**-**4.3** in hand, we performed comparative side-by-side glycosylation reactions using standard glycosyl acceptor **4.4**[31] and a variety of promoters. Previously, it has been demonstrated that metal triflate-based promoters including $Cu(OTf)_2$, $Bi(OTf)_3$, and AgOTf can be very efficiently utilized for the activation of glycosyl thioimidates in glycosylation.[22,24,32] MeOTf has also been shown to activate both thioglycosides and thioimidates quite

effectively.[15,33] The progress of all side-by-side experiments was monitored by TLC, and the reactions were quenched upon consumption of the glycosyl acceptor. To maintain standard comparison between different glycosyl donors, the incomplete reactions, as judged by TLC, were stopped after 24 h.

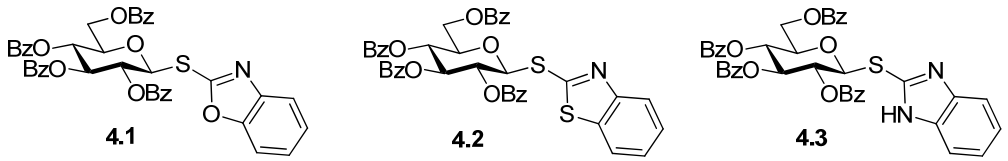


Figure 4.1. Structures of Glycosyl Donors **4.1**-**4.3** Equipped with Cyclic Thioimidoyl Leaving Groups

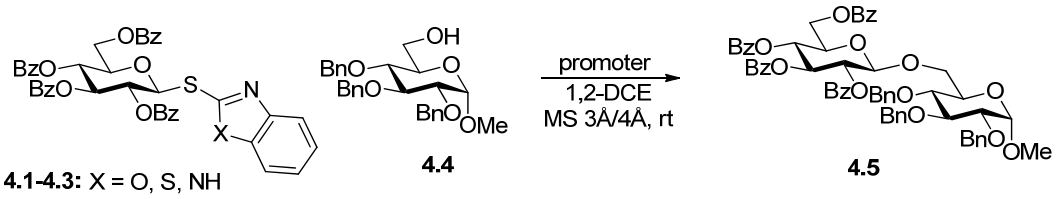
As mentioned in Chapter 2, the reaction of SBox donor **4.1** with glycosyl acceptor **4.4** in the presence of $Cu(OTf)_2$ was completed in 24 h and gave disaccharide **4.5** in 85% yield (entry 1, Table 4.1). $Bi(OTf)_3$ was also effective as a promoter for activating glycosyl donor **4.1** giving disaccharide **4.5** in 97% yield in 1 h (entry 2). AgOTf-promoted reaction of glycosyl donor **4.1** with acceptor **4.4** gave disaccharide **4.5** in 97% yield in 30 min (entry 3). Reaction with TMSOTf was completed within 2 h to give disaccharide **4.5** in 67% yield (entry 4). The moderate yield obtained in the latter experiment is arguably due to a high rate of the competing hydrolysis of glycosyl donor **4.1**. Finally, MeOTf also activated donor **4.1** quite efficiently to give disaccharide **4.5** in 95% yield within 1 h (entry 5). All these results were consistent with those reported previously for glycosidation of SBox derivatives.[17,18,24,30,34-36]

The analog containing endocyclic sulfur, SBaz glycoside **4.2** exhibited an overall decrease in reactivity when the same set of promoters, under essentially the same reactions conditions as those for the activation of SBox donor **4.1**, were used. The

activation of SBaz donor was very sluggish with $Cu(OTf)_2$ and only traces of disaccharide **4.5** were detected (<10%, entry 6). $Bi(OTf)_3$-promoted reaction was completed within 4 h to give disaccharide **4.5** in 93% yield (entry 7). Activation using 3 equiv. of AgOTf gave disaccharide **4.5** in 89% yield within 15 min (entry 8), which was the only case wherein the activation of SBaz donor **4.2** was faster than that of SBox donor **4.1**. SBaz donor **4.2** reacted very slowly in the presence of TMSOTf to give only trace amounts of disaccharide **4.5**, even after 24 h (entry 9). MeOTf on the other hand, activates SBaz very efficiently to give disaccharide **4.5** in 84% yield in 2 h.[23] These results indicate an overall lower reactivity of SBaz donor **4.2** than its SBox counterpart **4.1** under a variety of activation conditions, which is consistent with our previous observations.[22,24]

We then moved to investigating the nitrogen containing analog, SBiz glycoside **4.3**. Upon activation with the same set of promoters, we observed a notable drop in reactivity, as compared to the results obtained with both SBox and SBaz glycosyl donors, **4.1** and **4.2**, respectively. Thus, the reaction of SBiz glycosyl donor **4.3** with glycosyl acceptor **4.4** in the presence of $Cu(OTf)_2$ was very sluggish and gave disaccharide **4.5** in only 22% yield after 24 h (entry 11). It was previously reported that this reaction is able to proceed further and gives disaccharide **4.5** in 83% yield after 144 h.[25] We then determined that neither $Bi(OTf)_3$ nor TMSOTf are able to activate glycosyl donor **4.3** (entries 12 and 14). AgOTf was again the most effective promoter and gave disaccharide **4.5** in 86% yield (entry 13). This reaction was completed in 2 h. MeOTf also activated SBiz donor **4.3**, but the reaction was still incomplete after 24 h, which was reflected in a modest yield of 67% for disaccharide **4.5** (entry 15).

Table 4.1. Comparative Activation of Glycosyl Donors **4.1-4.3**

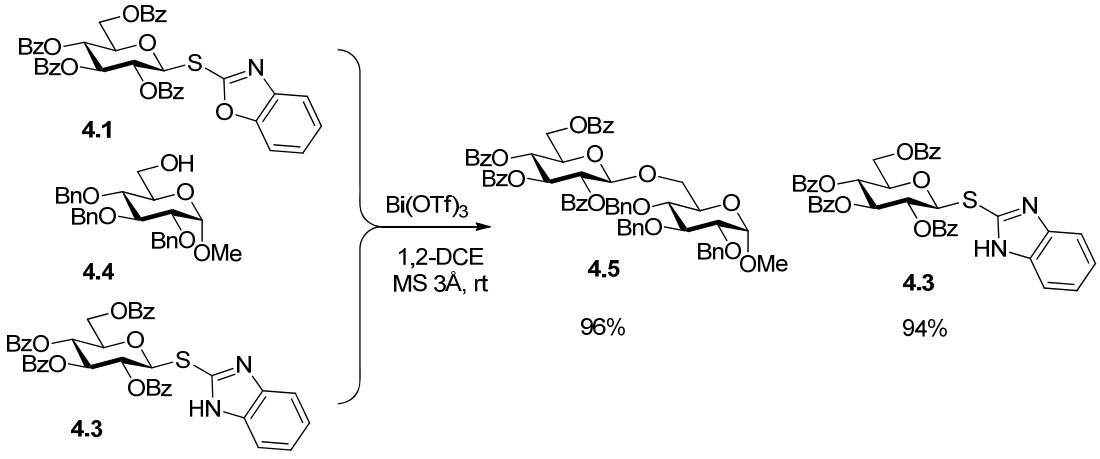


Entry	Donor	Promoter[a]	Time	Yield of disaccharide 4.5
1	**4.1**	$Cu(OTf)_2$	24 h	85%
2	**4.1**	$Bi(OTf)_3$	1 h	97%
3	**4.1**	AgOTf	30 min	97%
4	**4.1**	TMSOTf	2 h	67%
5	**4.1**	MeOTf	1 h	95%
6	**4.2**	$Cu(OTf)_2$	24 h	<10%
7	**4.2**	$Bi(OTf)_3$	4 h	93%
8	**4.2**	AgOTf	15 min	89%
9	**4.2**	TMSOTf	24 h	<10%
10	**4.2**	MeOTf	2 h	84%
11	**4.3**	$Cu(OTf)_2$	24 h	22%
12	**4.3**	$Bi(OTf)_3$	24 h	NR[b]
13	**4.3**	AgOTf	2 h	86%
14	**4.3**	TMSOTf	24 h	NR[b]
15	**4.3**	MeOTf	24 h	67%

[a] - 2 equiv. of TMSOTf and 3 equiv. of all other promoters have been used

[b] - NR: no reaction

To gain a better insight into the difference in reactivity, we decided to set up direct competitive glycosylation experiments. The purpose of these test reactions is to allow two glycosyl donors *i.e.* **4.1** and **4.3** (1.5 equiv. each) compete for a limited quantity (1 equiv.) of glycosyl acceptor **4.4**. We chose $Bi(OTf)_3$ as the most suitable promoter for this competition experiment because our preliminary study showed prompt activation of SBox donor **4.1** and practically no activation of SBiz donor **4.3**. On addition of $Bi(OTf)_3$, disaccharide **4.5** was obtained in 96% yield within 1 h and the unreacted SBiz glycosyl donor **4.3** was recovered in 94% yield. This result unambiguously demonstrates that SBox glycosyl donor **4.1** is significantly more reactive than its SBiz counterpart **4.3** in glycosylations promoted with $Bi(OTf)_3$.

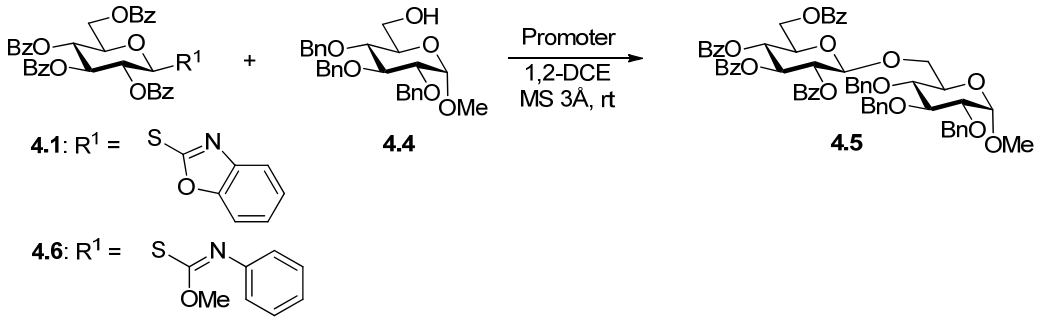


Scheme 4.1. Competitive Glycosylation of Glycosyl Donors **4.1** and **4.3**

These promising results stimulated us to pursue the study of the effect of changing the heteroatom in a series of acyclic leaving groups based on glycosyl alkoxythioimidate (SNea) derivatives reported earlier by our group.[36] This leaving group was originally designed as a bridging structure bearing features of both simple acyclic thiocyanates and cyclic SBox glycosides. In particular, a very unexpected change in the

reactivity profile was observed between cyclic SBox glycosyl donor **4.1** and its acyclic SNea counterpart **4.6** (Table 4.2). Interestingly, by simple change from $Cu(OTf)_2$ to MeOTf activation, an orthogonal character of SBox donor **4.1** and SNea donor **4.6** was observed. Thus, $Cu(OTf)_2$ –mediated activation of SBox donor **4.1** was very sluggish while SNea donor **4.6** was promptly glycosidated in 1 h giving disaccharide **4.5** in 90% yield. Conversely, MeOTf-promoted activation of SBox donor **4.1** was smoothly driven to completion in 6 h, whereas practically no glycosidation of SNea donor **4.6** was detected.[36] All preliminary evaluations have been performed in the presence of 1.2 equiv. of the promoter. This allowed for totally independent activation of one leaving group over another that could be achieved simply by switching the promoter.

Table 4.2. Comparative Studies of SBox Glycoside **4.1** and Glycosyl SNea Donor **4.6.**



Entry	Donor	Promoter (1.2 equiv)	Time	Yield of disaccharide 4.5
1	**4.1**	$Cu(OTf)_2$	24 h	35%
2	**4.6**	$Cu(OTf)_2$	1 h	90%
3	**4.1**	MeOTf	6 h	94%
4	**4.6**	MeOTf	24 h	<10%

With the purpose of evaluating acyclic leaving groups in mind, we obtained a range of novel glycosyl donors **4.7-4.9** depicted in Figure 4.2. It should be noted that *O*-, *S*-, or *N*-ethyl moiety rather than methyl moiety like in the SNea leaving group was chosen for the convenience and feasibility of the synthesis of all three analogs. A comparative test experiment of SNea donor **4.6** and its *O*-ethyl counterpart **4.7** showed an insignificant decrease in reactivity (results are not shown).

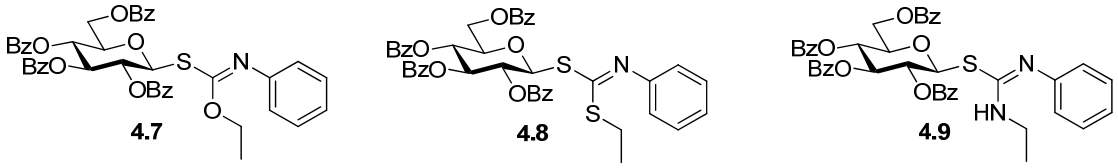


Figure 4.2. A Series of New Glycosyl Donors **4.7-4.9** Equipped with Acyclic Leaving Groups**.**

With these new glycosyl donors in hand, we began our comparative studies using the same promoters as those used for comparing the reactivity of cyclic glycosyl donors **4.1**-**4.3**. $Cu(OTf)_2$-promoted glycosidation of *O*-ethyl thioimidate donor **4.7** with glycosyl acceptor **4.4** provided disaccharide **4.5** in 85% in 7.5 h (entry 1, Table 4.3). Reaction in the presence of $Bi(OTf)_3$ was faster (4.5 h) and gave disaccharide **4.5** in 81% yield (entry 2). AgOTf and TMSOTf were not as effective as promoters; these reactions were incomplete after 24 h and afforded disaccharide **4.5** in 44% and 33% yield, respectively (entries 3 and 4). MeOTf was practically ineffective in case of donor **4.7** and only traces of disaccharide **4.5** have been detected (entry 5).

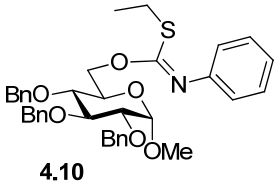
When *S*-ethyl thioimidate donor **4.8** was reacted with glycosyl acceptor **4.4** in the presence of these promoters we found some overall drop of reactivity (except reaction in the presence of bismuth(III) triflate) in comparison to that of its *O*-ethyl counterpart **4.7**.

Table 4.3. Comparative Studies of Acyclic Glycosyl Thioimidates **4.7-4.9**.

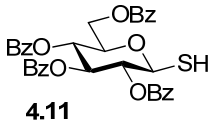
Entry	Donor	Promoter[a]	Time	Yield of disaccharide 4.5
1	**4.7**	$Cu(OTf)_2$	7.5 h	85%
2	**4.7**	$Bi(OTf)_3$	4.5 h	81%
3	**4.7**	AgOTf	24 h	44%
4	**4.7**	TMSOTf	24 h	33%
5	**4.7**	MeOTf	24 h	<10%
6	**4.8**	$Cu(OTf)_2$	24 h	80%
7	**4.8**	$Bi(OTf)_3$	3.5 h	88%
8	**4.8**	AgOTf	45 min	9%[b]
9	**4.8**	TMSOTf	24 h	25%
10	**4.8**	MeOTf	24 h	23%
11	**4.9**	$Cu(OTf)_2$	24 h	<10%
12	**4.9**	$Bi(OTf)_3$	24 h	NR[c]
13	**4.9**	AgOTf	24 h	67%
14	**4.9**	TMSOTf	24 h	NR[c]
15	**4.9**	MeOTf	24 h	27%

[a] - 2 equiv. of TMSOTf and 3 equiv. of all other promoters have been used

[b] – The following compounds were isolated as the major products:



4.10



4.11

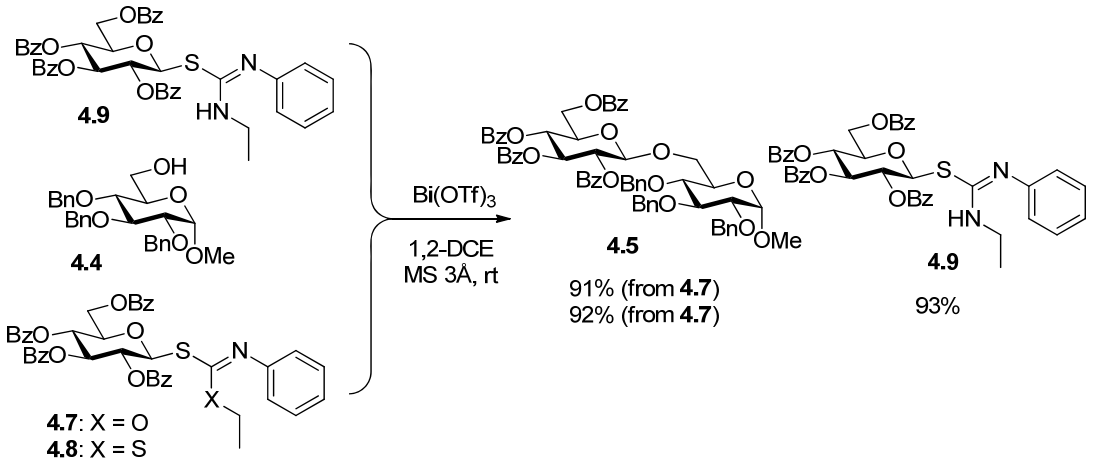
[c] - NR: no reaction

Thus, glycosylation in the presence of $Cu(OTf)_2$ afforded disaccharide **4.5** in 80% in 24 h (entry 6). The reaction clearly slowed down for the sulfur-containing analog as compared to oxygen-containing glycosyl donor **4.7** (7.5 h). The reaction promoted by $Bi(OTf)_3$ was slightly faster (3.5 h vs. 4.5 h for **4.7**) and yielded disaccharide **4.5** in 88% yield (entry 7). During the reaction in the presence of AgOTf, we observed rapid decomposition of *S*-ethyl thioimidate donor **4.8** and migration of the leaving group to the glycosyl acceptor to form compound **4.10** (Table 4.3 footnote) leaving 2,3,4,6-tetra-O-benzoyl-1-thio-β-D-glucopyranose **4.11**[37] as a by-product. Resultantly, disaccharide **4.5** was obtained in only 9% yield (entry 8). Reactions in the presence of TMSOTf and MeOTf were sluggish and afforded disaccharide **4.5** in 25 and 23%, respectively, after 24 h (entries 9 and 10).

Having performed the comparison of *O*-ethyl thioimidate donor **4.7** and *S*-ethyl thioimidate donor **4.8**, we turned to investigating their *N*-ethyl counterpart **4.9**. Similar to that of the previous observation made with cyclic leaving groups (*vide supra*), *N*-ethyl thioimidate donor **4.9** was found to be the least reactive in this series. Activation of glycosyl donor **4.9** was only effective with AgOTf, but was still incomplete within 24 h. Resultantly, disaccharide **4.5** was obtained in 67% yield (entry 13, Table 4.3). Reactions in the presence of $Cu(OTf)_2$ and MeOTf were sluggish and gave disaccharide **4.5** in <10% and 27% yield, respectively (entries 11 and 15). Additionally, neither $Bi(OTf)_3$ nor TMSOTf could activate donor **4.9** (entries 12 and 14).

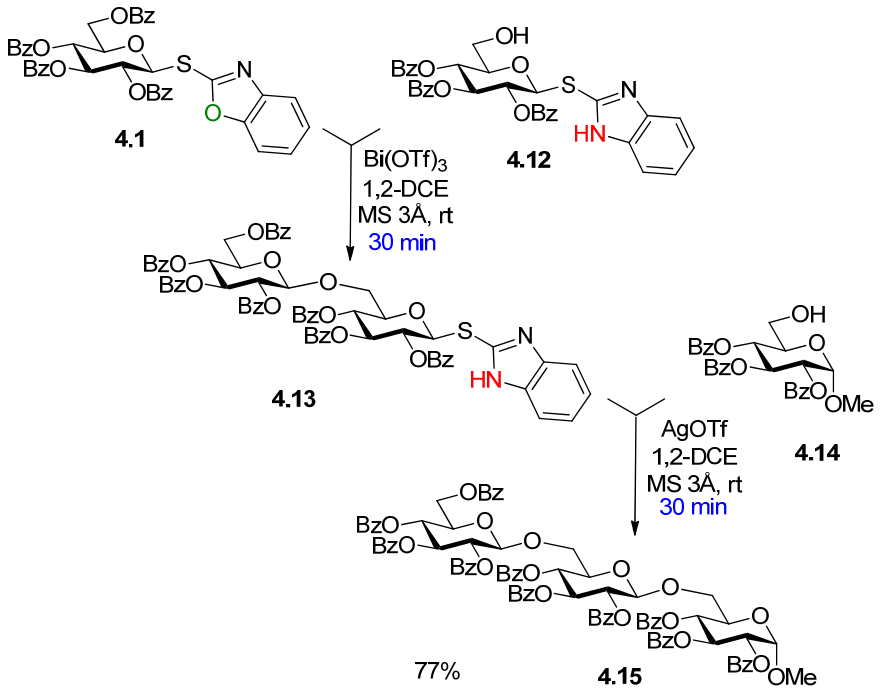
This notable difference in reactivity between *N*-ethyl thioimidoyl donor **4.9** and its *O*-ethyl and *S*-ethyl counterparts **4.7** and **4.8**, could be suitable for oligosaccharide synthesis via selective activation strategy.[38] The differentiation in the presence of $Bi(OTf)_3$ appealed to us as the best mode because both *O*-ethyl thioimidate donor **4.7** and

S-ethyl thioimidate donor **4.8** are smoothly activated under these reaction conditions (entries 2 and 7, respectively, Table 4.3), whereas *N*-ethyl donor **4.9** remains entirely intact (entry 12). To verify the viability of this observation, we performed direct competitive glycosylation reactions wherein two glycosyl donors (1.5 equiv. each) were competed against each other for a limited amount (1 equiv.) of glycosyl acceptor **4.4**. A competition experiment between *O*-ethyl thioimidate donor **4.7** and *N*-ethyl donor **4.9** in the presence of $Bi(OTf)_3$ resulted in the formation of disaccharide **4.5** in 91% yield within 4.5 h (Scheme 4.2). Unreacted glycosyl donor **4.9** was recovered in 93% yield confirming that practically no activation of **4.9** took place and the formation of disaccharide **4.5** should be credited to the activation of *O*-ethyl thioimidate donor **4.7**. A similar competition experiment was performed with *S*-ethyl thioimidate donor **4.8** and *N*-ethyl thioimidate donor **4.9** in the presence of $Bi(OTf)_3$. Resultantly, disaccharide **4.5** was obtained in 92% and the unreacted glycosyl donor **4.8** was again recovered in 93% yield (Scheme 4.2).



Scheme 4.2. Competitive Glycosylations of *O*/*S*-Ethyl Glycosyl Donors **4.7**/**4.8** vs. *N*-Ethyl Donor **4.9.**

The results obtained by comparing cyclic and acyclic analogs having different heteroatoms showed that the reactivity of the glycosyl donors **4.1**-**4.3** equipped with cyclic leaving groups followed a similar trend to that observed for their acyclic counterparts **4.7**-**4.9**. However, overall reactivity of the cyclic donors was somewhat higher, reactions were faster, cleaner, and disaccharide **4.5** was typically isolated in a higher yield. To emphasize our observations and test the applicability of different reactivity in oligosaccharide synthesis, we performed a one-pot sequential activation of building blocks equipped with different leaving groups.[39,40] For this purpose we obtained glycosyl acceptor **4.12** equipped with the SBiz anomeric moiety.



Scheme 4.3. One-Pot Synthesis of Trisaccharide **4.15**.

In the first step, SBox glycosyl donor **4.1** was reacted with SBiz glycosyl acceptor **4.12.** Upon addition of $Bi(OTf)_3$, the reaction was smoothly driven to completion in 30 min. At this time, disaccharide **4.13** was formed (the identity of this intermediate was

confirmed by its isolation from a separate experiment). Glycosyl acceptor **4.14** and AgOTf were then added to the same reaction flask (pot). Resultantly, trisaccharide **4.15** was obtained in 77% yield over the two coupling steps (Scheme 4.3).

4.3. Conclusion

In summary, we have demonstrated that the reactivity of thioimidate glycosyl donors is very sensitive to the change of heteroatom displaying the following reactivity trend in the presence of most of the promoters: O > S > N for both cyclic and acyclic leaving groups. The difference in the reactivity of these glycosyl donors was confirmed in direct competition experiments wherein two glycosyl donors were set to complete for one glycosyl acceptor. Additionally, a two-step one-pot selective activation was performed using SBox glycosyl donor and SBiz glycosyl acceptor resulting in the formation of a trisaccharide derivative.

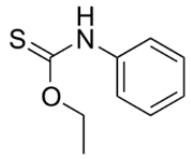
4.4. Experimental section

4.4.1. General remarks

The reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). Detection of compounds was carried out using UV light and by charring with 10% sulfuric acid in methanol. Purification by column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh). Removal of solvents was achieved *in vacuo* at < 40 ^{o}C using rotary evaporators. CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled from CaH_2 directly before using for the reactions. Methanol was dried by refluxing with magnesium methoxide, distilled and stored under argon. Pyridine and acetonitrile were dried by

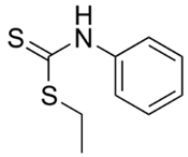
refluxing with CaH_2, distilled and stored over molecular sieves (3 Å). Molecular sieves (3 or 4 Å) used for reactions were crushed and activated *in vacuo* at 390 ^oC during 8 h at first and then for 2-3 h at 390 ^oC prior to each application. AgOTf was co-evaporated with toluene (3 x 10 mL) and dried *in vacuo* for 2-3 h prior to using in reactions. Optical rotations were measured using '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 JOEL MStation (JMS-700) Mass spectrometer, matrix *m*-nitrobenzyl alcohol, with NaI as necessary.

_O_-Ethyl phenylcarbamothioate



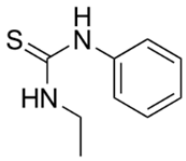
A 1M solution of NaOEt in ethanol (11.1 mL) was added to phenyl isothiocyanate (0.9 mL, 7.40 mmol) and the resulting mixture was stirred for 15 min at rt. After that, conc. aq. HCl was added until pH ~ 4-5. The resulting white precipitate was filtered off, rinsed with methanol and the combined filtrate (~50 mL) was concentrated *in vacuo*. The crude residue containing the title compound was used directly in subsequent reactions with glycosyl bromides (*vide infra*). The analytical data of the title compound were essentially the same as described previously.[41]

S-Ethyl phenylcarbamodithioate



NaH (ca. 60% dispersion in mineral oil; 528 mg, 0.02 mol was added to a solution of ethanethiol (1.6 mL, 0.02 mol) in THF (2.0 mL), and the resulting mixture was stirred for 10 min at rt. After that, phenyl isothiocyanate (1.6 mL, 0.02 mol) was added and the resulting mixture was stirred for 2 h at rt. After that, the reaction mixture was diluted with CH_2Cl_2 (~100 mL) and washed with sat. aq. $NaHCO_3$ (15 mL) and water (3 x 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 82% yield (3.6 g). Analytical data of the title compound is essentially the same as reported previously.[42]

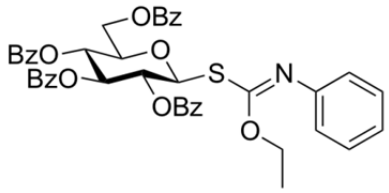
1-Ethyl-3-phenylthiourea



A solution of ethylamine in methanol (1.8 mL, 0.031 mol) was added to phenyl isothiocyanate (3.7 mL, 0.031 mol) and the resulting mixture was stirred for 30 min at 0 ^{o}C. After that, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford the title compound in 71% yield (3.9 g). Analytical data of the title compound is essentially the same as reported previously.[43]

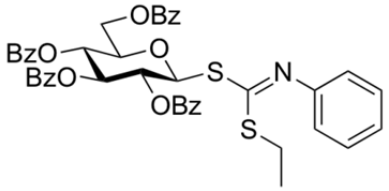
Synthesis of glycosyl donors

***S*-(2,3,4,6-Tetra-*O*-benzoyl-*β*-D-glucopyranosyl) *O*-ethyl phenylcarbonimidothioate (4.7)**



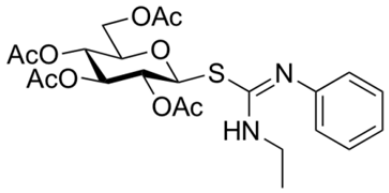
O-Ethyl phenylcarbamothioate (309 mg, 1.71 mmol) and KOH (64 mg, 1.14 mmol) were added to a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide[44] (750 mg, 1.14 mmol) in dry acetonitrile (9.0 mL) and the resulting mixture was stirred for 24 h at rt. After that, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with sat. aq. $NaHCO_3$ (20 mL) and water (3 x 20 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 56% yield (485 mg) as a white foam. Analytical data for **4.7**: R_f = 0.56 (ethyl acetate/toluene, 1/9, v/v); $[\alpha]_D^{30}$ 18.3 (c = 1, $CHCl_3$); ^{1}H-n.m.r.: δ, 1.38 (t, 3H, CH_2CH_3), 4.22 (m, 1H, $J_{5,6a}$ = 2.6 Hz, $J_{5,6b}$ = 5.7 Hz, H-5), 4.34 (m, 2H, CH_2CH_3), 4.50 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.64 (dd, 1H, H-6b), 5.52-5.62 (m, 3H, H-1, 2, 4), 5.94 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 6.71–8.06 (m, 25H, aromatic) ppm; ^{13}C n.m.r.: δ, 14.2, 63.2, 65.6, 69.5, 70.3, 74.2, 77.2, 81.9, 121.4 (x 2), 123.9, 128.3 (x 2), 128.4 (x 5), 128.5 (x 2), 128.6, 128.7, 128.9, 129.0 (x 2), 129.6, 129.7 (x 2), 129.8 (x 2), 129.9 (x 3), 133.2, 133.3, 133.4, 133.5, 146.3, 153.5, 164.9, 165.2, 165.8, 166.2 ppm; HR-FAB MS$[M+Na]^+$ calcd for $C_{43}H_{37}NO_{10}SNa^+$ 782.2036, found 782.2050.

***S*-(2,3,4,6-Tetra-*O*-benzoyl-*β*-D-glucopyranosyl) *S*-ethyl phenylcarbonimidothioate (4.8)**



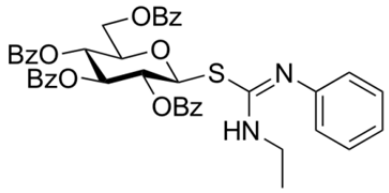
S-Ethyl phenylcarbamodithioate (336 mg, 1.71 mmol) and KOH (64 mg, 1.14 mmol) were added to a stirring solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (750 mg, 1.14 mmol) in dry acetonitrile (9.0 mL) and the resulting mixture was stirred under argon for 2.5 h at rt. After that, the solid was filtered off and washed successively with dichloromethane. The combined filtrate (~100 mL) was washed with sat. aq. $NaHCO_3$ (20 mL) and water (3 x 20 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 75% yield (663 mg) as a white foam. Analytical data for **4.8**: R_f = 0.60 (ethyl acetate/toluene, 1/9, v/v), $[\alpha]_D^{30}$ 66.3 (c = 1, $CHCl_3$), ^{1}H n.m.r.: δ, 1.22 (t, 3H, CH_2CH_3), 2.98 (m, 2H, CH_2CH_3), 4.33 (m, 1H, $J_{5,6a}$ = 2.2 Hz, $J_{5,6b}$ = 5.9 Hz, H-5), 4.51 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.67 (dd, 1H, H-6b), 5.59-5.74 (m, 2H, H-2, H-4), 5.99 (dd, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 6.76-8.10 (m, 25H, aromatic) ppm; H-1 appears to be suppressed in the ^{1}H n.m.r; ^{13}C n.m.r.: δ, 26.8, 63.5, 69.5 (x 2), 70.3, 74.4, 77.4, 82.9, 120.3 (x 2), 124.4, 128.5 (x 5), 128.6 (x 2), 128.7 (x 2), 128.8, 128.9, 129.0, 129.1 (x 2), 129.8, 129.9 (x 2), 130.0 (x 4), 130.1 (x 2), 133.3, 133.5, 133.6, 133.7, 149.2, 163.4 (x 2), 165.9, 166.4 ppm. HR-FAB MS $[M+Na]^+$ calcd for $C_{43}H_{37}NO_9S_2Na^+$ 798.1808, found 798.1792.

***S*-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl) *N*-ethyl phenylcarbonimidothioate (4.16)**



1-Ethyl-3-phenylthiourea (92 mg, 0.51 mmol) and BF_3-Et_2O (49 μL, 0.51 mmol) were added to a mixture of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (100 mg, 0.26 mmol) and molecular sieves (3Å, 128 mg) in dry CH_2Cl_2 (1.0 mL) and the resulting mixture was heated at reflux for 16 h. After that, the solid was filtered off and rinsed successively with dichloromethane. The combined filtrate (~50 mL) was washed with sat. aq. $NaHCO_3$ (15 mL) and water (3 x 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 93% yield (121 mg) as a white foam. Analytical data for **4.16**: R_f = 0.46 (ethyl acetate/hexanes, 1/1, v/v), $[\alpha]_D^{30}$ -13.5 (c = 1, $CHCl_3$), ^{1}H n.m.r.: δ, 1.21 (t, 3H, CH_2CH_3), 1.81, 1.92, 1.96, 2.04 (4 s, 12H, 4 x $COCH_3$), 3.38 (m, 2H, CH_2CH_3), 3.68 (m, 1H, $J_{5,6a}$ = 2.2 Hz, $J_{5,6b}$ = 5.1 Hz, H-5), 4.09 (dd, 1H, $J_{6a,6b}$ = 12.6 Hz, H-6a), 4.19 (dd, 1H, H-6b), 4.76 (br. s, 1H, H-1), 5.08 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 5.13 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 5.18 (dd, 1H, $J_{3,4}$ = 9.2, H-3), 6.70 (dd, 2H, aromatic), 6.90-6.95 (dd, 1H, aromatic), 7.12-7.17 (dd, 2H, aromatic) ppm; ^{13}C n.m.r.: δ, 14.8, 20.5, 20.6, 20.7, 20.8, 62.1, 67.9, 69.5, 73.6, 76.4, 82.8, 122.5 (x 2), 123.1, 128.7 (x 2), 149.6, 169.3, 169.4, 170.2, 170.6 ppm. HR-FAB MS $[M+Na]^+$ calcd for $C_{23}H_{30}N_2O_9SNa^+$ 533.1570, found 533.1563.

***S*-(2,3,4,6-Tetra-*O*-benzoyl-*β*-D-glucopyranosyl) *N*-ethyl phenylcarbonimidothioate (4.9)**



A 1M solution of NaOMe in methanol (~0.1 mL) was added dropwise to a solution of thiocarbamate **4.16** (120 mg, 0.24 mmol) in methanol (1.5 mL) until pH ~ 9 and the resulting mixture was kept for 20 min at rt. After that, the reaction mixture was neutralized with Dowex (H^+), the resin was filtered off and washed successively with methanol (5 x 5 mL). The combined filtrate (~100 mL) was concentrated *in vacuo* and dried. The residue was dissolved in pyridine (2.0 mL) and benzoyl chloride (0.1 mL, 0.96 mmol) was added dropwise under argon at 0 ^oC. The external cooling was removed, the reaction mixture was allowed to warm to rt, and stirred for 45 min total. After that, methanol (~1 mL) was added, the volatiles were removed *in vacuo*, and the residue was co-evaporated with toluene (3 x 5 mL). The resulting residue was diluted with CH_2Cl_2 (~100 mL) and washed with 1N aq. HCl (25 mL), water (25 mL), sat. aq. $NaHCO_3$ (25 mL), and water (3 x 25 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – toluene gradient solution) to afford the title compound in 86% yield (158 mg) as a white foam. Analytical data for **4.9**: R_f = 0.42 (ethyl acetate/toluene, 1.5/8.5, v/v), $[\alpha]_D^{30}$ 33.9 (c = 1, $CHCl_3$), ^{1}H n.m.r.: δ, 1.13 (t, 1H, CH_2CH_3), 3.33 (m, 2H, CH_2CH_3), 4.21 (m, 1H, $J_{5,6a}$ = 2.8 Hz, $J_{5,6b}$ = 5.8 Hz, H-5), 4.48 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.70 (dd, 1H, H-6b), 5.23 (br. s, 1H, H-1), 5.63–5.73 (m, 2H, H-4, H-2), 5.88 (dd,

1H, $J_{3,4}$ = 9.4 Hz, H-3), 6.69–8.08 (m, 25H, aromatic) ppm; ^{13}C n.m.r.: δ, 14.8, 63.1, 69.2, 70.3, 74.0, 77.0, 77.4, 83.3, 122.6, 128.6 (x 3), 128.7 (x 4), 128.8, 129.0, 129.6, 129.9 (x 4), 130.0 (x 3), 130.1 (x 3), 133.6 (x 2), 133.8, 165.2, 165.3, 165.8, 166.4 ppm; HR-FAB MS$[M+Na]^+$ calcd for $C_{43}H_{38}N2O_9SNa^+$ 781.2196, found 781.2190

General Glycosylation Procedures:

Method A – Activation with $Cu(OTf)_2$

A mixture of glycosyl donor (0.025 mmol), glycosyl acceptor (0.02 mmol), and freshly activated molecular sieves (4Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h. $Cu(OTf)_2$ (0.075 mmol) was added and the reaction mixture was stirred for 7.5 h – 24 h (see Tables) at rt. After that, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford disaccharide **4.5**.

Method B – Activation with $Bi(OTf)_3$

A mixture containing glycosyl donor (0.026 mmol), glycosyl acceptor (0.021 mmol) and freshly activated molecular sieves (3Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h. $Bi(OTf)_3$ (0.078 mmol) was added and the reaction mixture was stirred for 3.5 h - 24 h (see Tables) at rt. After that, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with

$MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford disaccharide **4.5**.

Method C – Activation with AgOTf

A mixture containing glycosyl donor (0.026 mmol), glycosyl acceptor (0.021 mmol) and freshly activated molecular sieves (3Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h. Freshly activated AgOTf (0.078 mmol) was added and the reaction mixture was stirred for 45 min - 24 h (see Tables) at rt. After that, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford disaccharide **4.5**.

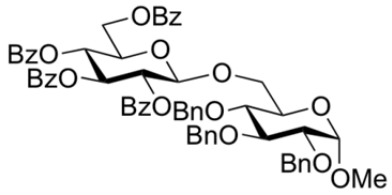
Method D – Activation with TMSOTf

A mixture containing glycosyl donor (0.026 mmol), glycosyl acceptor (0.021 mmol) and freshly activated molecular sieves (4Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h. TMSOTf (0.052 mmol) was added and the reaction mixture was stirred for 24 h (see Tables) at rt. After that, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford disaccharide **4.5**.

Method E – Activation with MeOTf

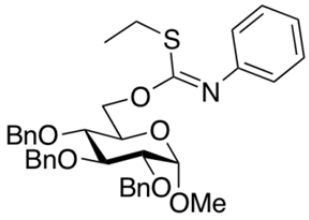
A mixture containing glycosyl donor (0.026 mmol), glycosyl acceptor (0.021 mmol) and freshly activated molecular sieves (3Å, 60 mg) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred under argon for 1.5 h. MeOTf (0.078 mmol) was added and the reaction mixture was stirred for 24 h (see Tables) at rt. After that, the solid was filtered-off and rinsed successively with CH_2Cl_2. The combined filtrate (~25 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford disaccharide **4.5**.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (4.5)



The title compound was synthesized by a variety of methods as listed in Tables 4.1 and 4.3. For example, the synthesis from glycosyl donor 4.1 (0.025 mmol) and glycosyl acceptor 4.4 (0.02 mmol) using method A allowed the title compound in 85% yield. Analytical data for **4.5** was essentially the same as reported previously.[45]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(*S*-ethyl phenylcarbamothioyl)-α-D-glucopyranoside (4.10)



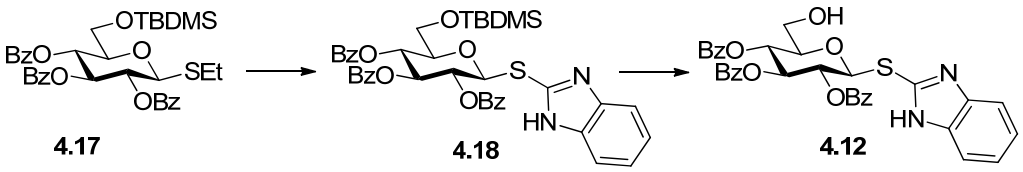
The title compound was formed as a byproduct in the reaction between glycosyl donor **4.8** (0.026 mmol) and glycosyl acceptor **4.4** (0.021 mmol) by Method C in 70% yield (9.8 mg) as a white foam. Analytical data for **4.10**: R_f = 0.47 (ethyl acetate/toluene, 1/9, v/v), ^{1}H n.m.r.: δ, 1.19 (t, 3H, CH_2CH_3), 2.80 (m, 2H, CH_2CH_3), 3.36 (s, 3H, OCH_3), 3.43-3.51 (m, 2H, H-2, 4), 3.91 (m, $J_{5,6a}$ = 1.9 Hz, $J_{5,6b}$ = 4.8 Hz, H-5), 4.00 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.44 (dd, 1H, $J_{6a,6b}$ = 11.7 Hz, H-6a), 4.52 (dd, 1H, H-6b), 5.24 (dd, 1H, $J_{1,2}$ = 3.1 Hz, H-1), 4.63 (d, 2H, CH_2Ph), 4.76-4.97 (m, 4H, CH_2Ph), 6.79 (d, 2H, aromatic), 6.99 (dd, 1H, aromatic), 7.04-7.34 (m, 17H, aromatic) ppm; ^{13}C n.m.r.: δ, 15.3, 25.4, 55.4, 67.6, 69.1, 73.7, 75.5, 76.2, 77.6, 80.2, 82.2, 98.3, 121.7 (x 2), 123.9, 128.0, 128.1, 128.2 (x 3), 128.3 (x 3), 128.4 (x 3), 128.7 (x 3), 129.1 (x 3), 138.1, 138.2, 138.7, 147.4, 158.3 ppm; HR-FAB MS[M+Na]$^+$ calcd for $C_{37}H_{41}NO_6SNa^+$ 650.2552, found 650.2462.

General Procedure for Competitive Glycosylations

A mixture of glycosyl donor A (0.064 mmol), glycosyl donor B (0.064 mmol), glycosyl acceptor **4.4** (0.043 mmol), and freshly activated molecular sieves (3 Å, 150 mg) in 1,2-dichloroethane (1.0 mL) was stirred under argon for 1.5 h at rt. $Bi(OTf)_3$ (126 mg, 0.192 mmol) was added and the resulting reaction mixture was stirred at rt for 1-4.5 h. The reaction was monitored by TLC (ethyl acetate / toluene, 1/9, v/v); upon disappearance of

glycosyl acceptor **4.4**, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~50 mL) was washed with sat. aq. $NaHCO_3$ (5 mL) and water (3 x 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – toluene gradient elution) to afford disaccharide **4.5**.

2-Benzimidazolyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (4.12)

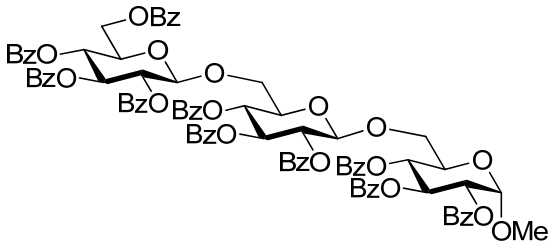


A mixture of ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside[46] (**4.17**, 1.25 g, 1.92 mmol) and activated molecular sieves (3 Å, 0.96 g) in CH_2Cl_2 (29 mL) was stirred under argon for 1 h at rt. A freshly prepared solution of Br_2 in CH_2Cl_2 (19 mL, 1/165, v/v) was added and the resulting mixture was stirred for 15 min at rt. After that, the solid was filtered off and rinsed successively with dichloromethane. The combined the filtrate (~200 mL) was concentrated *in vacuo* at rt. The crude residue was dissolved in dry acetone (25 mL), KSBiz (0.903 g, 4.8 mmol) and 18-crown-6 (0.10 g, 0.38 mmol) were added and the resulting mixture was stirred under argon for 16 h at rt. After that, the solid was filtered off and rinsed successively with dichloromethane. The combined the filtrate (~200 mL) was washed with 10% aq. NaOH (20 mL) and water (3 x 20 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-toluene gradient elution) to afford 2-benzimidazolyl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**4.18**, 0.971 g, 68%) as an off-

white foam. Analytical data for **4.18**: R_f = 0.49 (ethyl acetate/toluene, 3/17, v/v); $[\alpha]_D^{27}$ +4.1 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 0.00 (s, 6H, 2 x CH_3), 0.81 (s, 9H, $C(CH_3)_3$), 3.81-3.92 (m, 2H, H-6a, 6b), 4.04 (m, 1H, H-5), 5.45 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 5.56 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.59 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.94 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 7.14-7.93 (m, 20H, aromatic, NH) ppm; ^{13}C-n.m.r.: δ, -5.1, 18.6, 26.0 (x 3), 62.9, 69.0, 71.1, 74.1, 80.0, 83.9, 123.1, 128.5 (x 6), 128.6 (x 3), 128.7 (x 3), 128.8, 129.0, 130.0 (x 4), 130.1 (x 3), 133.5, 133.6, 133.8, 145.2, 165.2, 165.7, 165.9 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{40}H_{42}N_2O8SSiNa^+$ 761.2329, found 761.2334.

Tetrabutylammonium fluoride (1.35 mL, 1.35 mmol) was added to a solution of compound **4.18** (0.500 g, 0.67 mmol) in THF (5.0 mL) and the resulting 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 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 (0.376 g, 89 %) as a white amorphous solid. Analytical data for **4.12**: R_f = 0.46 (ethyl acetate/toluene, 2/3, v/v); $[\alpha]_D^{27}$ -66.4 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.83 (dd, 1H, $J_{6a,6b}$ = 12.6, H-6a), 3.96 (dd, 1H, H-6b), 4.05 (m, 1H, $J_{5,6a}$ = 6.0, $J_{5,6b}$ = 1.8 Hz, H-5), 5.27 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 5.48 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.56 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 6.01 (dd, 1H, $J_{3,4}$ = 9.5, H-3), 7.18-8.09 (m, 20H, aromatic, NH) ppm; ^{13}C-n.m.r.: δ, 61.4, 69.3, 71.4, 73.7, 77.4, 79.6, 83.4, 128.5 (x 3), 128.6, 128.7 (x 7), 128.8, 129.9 (x 3), 130.1 (x 3), 130.2 (x 2), 133.6, 133.9, 143.6, 165.9 (x 2), 166.0 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{34}H_{29}N_2O_8S$ 625.1639, found 625.1635.

Methyl *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (4.15).



A mixture of glycosyl donor **4.1** (50 mg, 0.068 mmol), glycosyl acceptor **4.12** (33.7 mg, 0.054 mmol) and molecular sieves (3 Å, 150 mg) in 1,2-dichloroethane (0.8 mL) was stirred under argon for 1.5 h at rt. $Bi(OTf)_3$ (133.9, 0.204 mmol) was added and the resulting mixture was stirred for 30 min at rt. Upon formation of the intermediate disaccharide **4.13**, glycosyl acceptor **4.14** (21.8 mg, 0.043 mmol) and AgOTf (41.6 mg, 0.162 mmol) were added and the resulting mixture was stirred for 30 min at rt. After that, the reaction mixture was diluted with dichloromethane, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~50 mL) was washed with water (10 mL), sat. $NaHCO_3$ (10 mL), and water (3 x 10 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 77% yield (51.5 mg) as a white foam. Analytical data for trisaccharide **4.15** were essentially the same as previously reported.[47]

Analytical data for **2-benzimidazolyl *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (4.13)**: R_f = 0.25 (ethyl acetate/ toluene, 1/9, v/v); $[\alpha]_D^{27}$ +37.4 (c = 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ, 3.57-4.05 (m, 2H, H-6a,

6b), 4.05-4.19 (m,2H, H-5, 5'), 4.28 (dd, 1H, $J_{5',6a'}$ = 4.8 Hz, $J_{6a',6b'}$ = 12.3 Hz, H-6a'), 4.62 (dd, 1H, $J_{5',6b'}$ = 3.1 Hz, H-6b'), 5.00 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 5.20 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 5.36 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.48 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.56 (dd, 1H, $J_{2',3'}$ = 7.8 Hz, H-2'), 5.61 (dd, 1H, $J_{4',5'}$ = 9.7 Hz, H-4'), 5.87 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.93 (dd, 1H, $J_{3',4'}$ = 9.5 Hz, H-3'), 7.20-7.93 (m, 39H, aromatic) ppm; ^{13}C-n.m.r.: δ, 62.7, 68.3, 69.4, 69.5, 70.7, 72.1, 72.6, 72.7, 73.7, 77.9, 84.3, 101.5, 128.4 (x 3), 128.5 (x 4), 128.6 (x 10), 128.7 (x 2), 128.8 (x 4), 128.9 (x 2), 129.0 (x 2), 129.4, 129.7 (x 2), 129.9 (x 5), 130.0 (x 4), 130.1 (x 2), 130.2 (x 2), 133.4 (x 2), 133.6, 133.7, 133.8 (x 2), 144.6, 165.3 (x 2), 165.5, 165.7, 165.8, 165.9, 166.3 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{68}H_{54}N_2O_{17}S$ 1225.3041, found 1225.3068.

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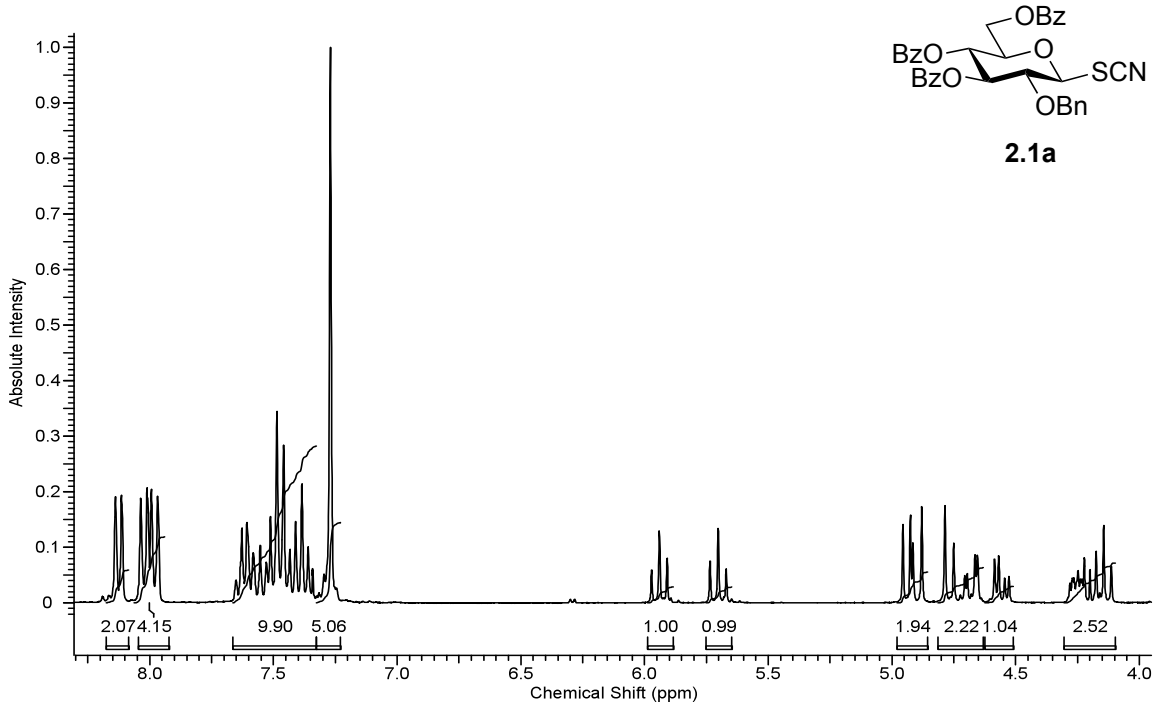
CHAPTER 5

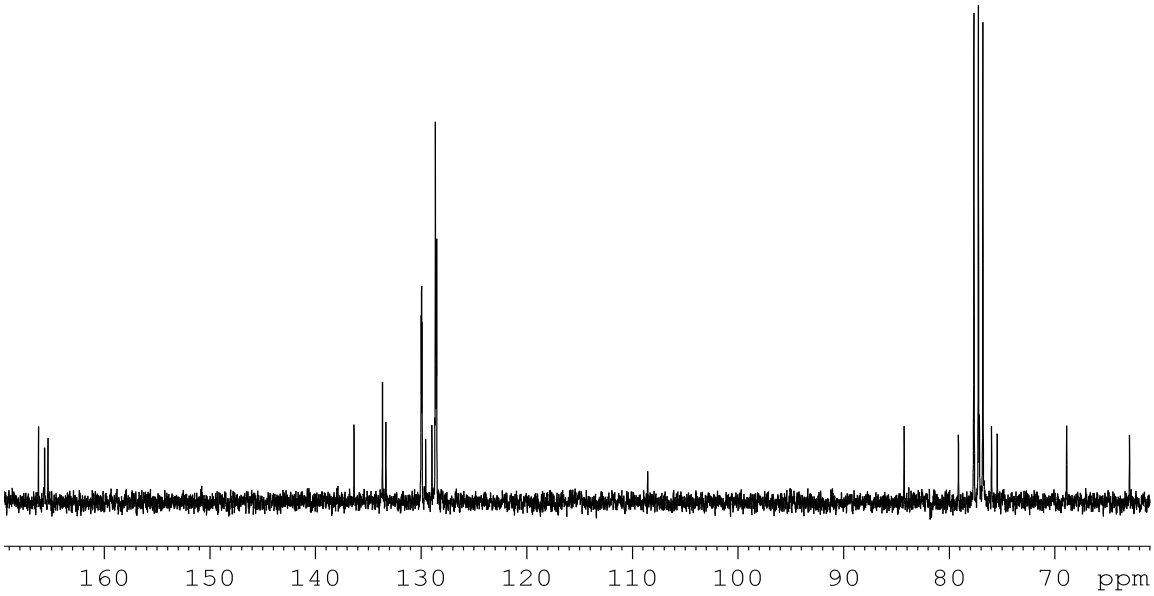
Appendix

Selected NMR Spectral and X-Ray Crystallography Data



$CDCl_3$ at 300 MHz

Figure A-1: ^{1}H NMR spectrum of 3,4,6-Tri-*O*-benzoyl-2-*O*-benzyl-β-D-glucopyranosyl thiocyanate (**2.1a**)



$CDCl_3$ at 75 MHz

Figure A-2: ^{13}C NMR spectrum of 3,4,6-Tri *O*-benzoyl-2 *O*-benzyl-β-D-glucopyranosyl thiocyanate (**2.1a**)

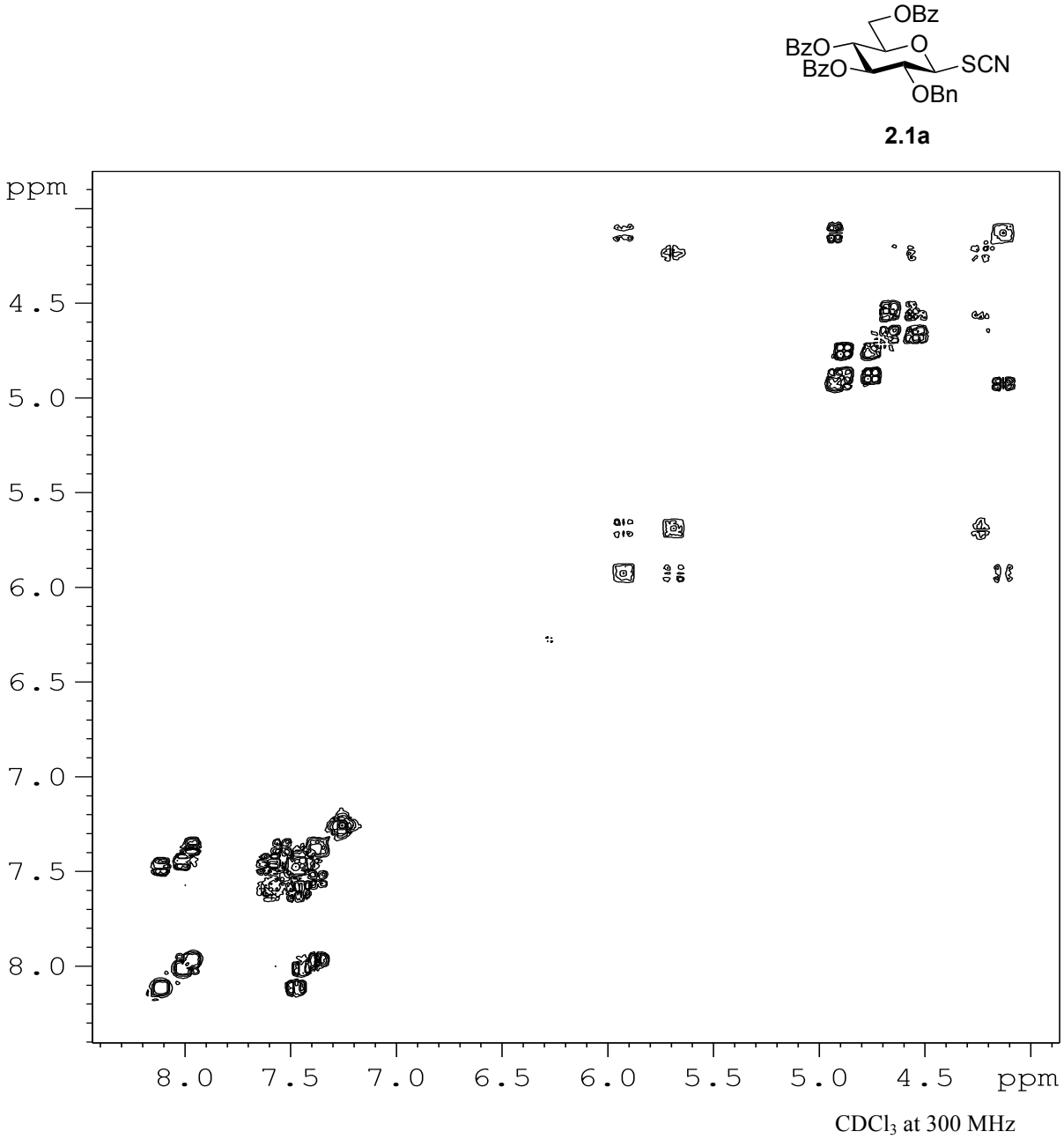
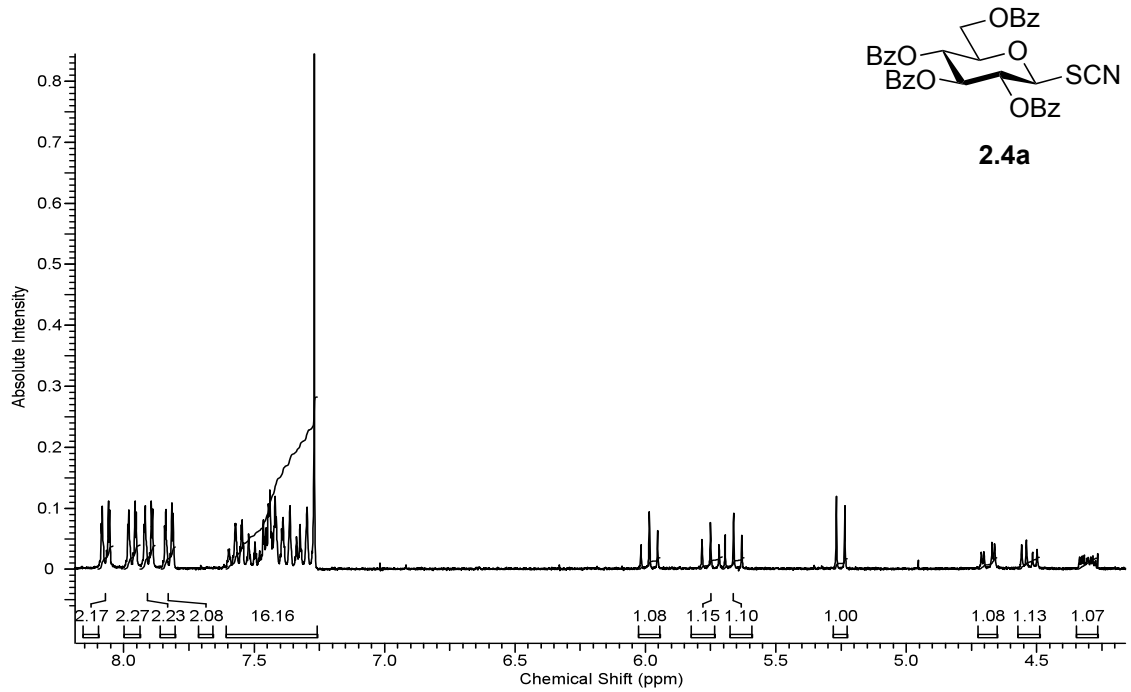
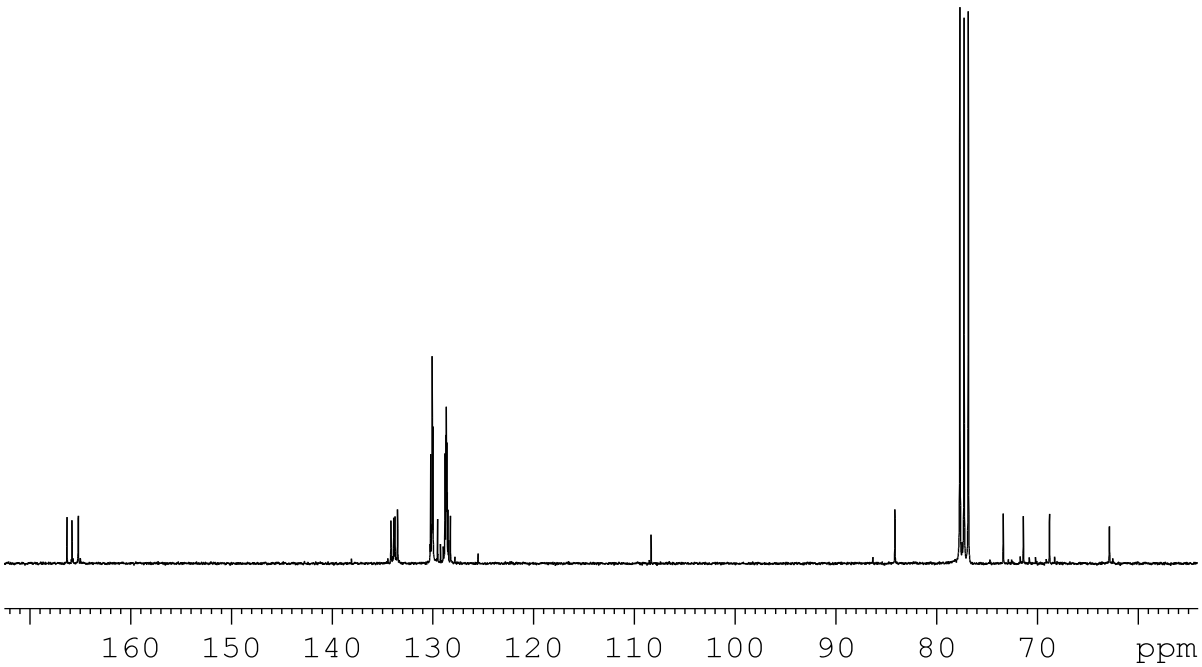


Figure A-3: 2-D NMR COSY spectrum of 3,4,6-Tri *O*-benzoyl-2 *O*-benzyl-β-D-glucopyranosyl thiocyanate (**2.1a**)



$CDCl_3$ at 300 MHz

Figure A-4: ^{1}H NMR spectrum of 2,3,4,6-Tetra *O*-benzoyl-β-D-glucopyranosyl thiocyanate **(2.4a)**



$CDCl_3$ at 300 MHz

Figure A-5: ^{13}C NMR spectrum of 2,3,4,6-Tetra *O*-benzoyl-β-D-glucopyranosyl thiocyanate **(2.4a)**

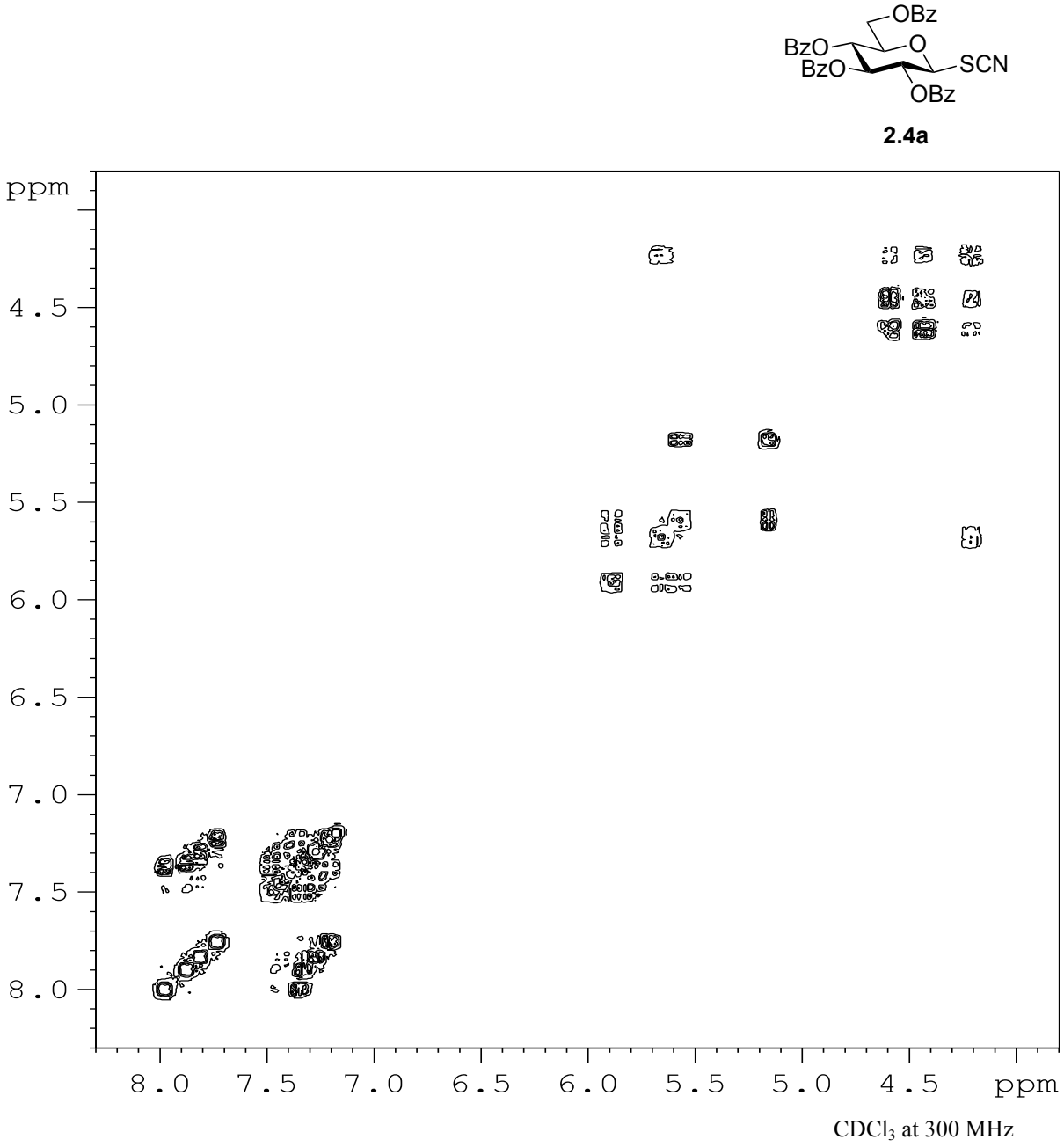


Figure A-6: 2-D NMR COSY spectrum of 2,3,4,6-Tetra *O*-benzoyl-β-D-glucopyranosyl thiocyanate **(2.4a)**

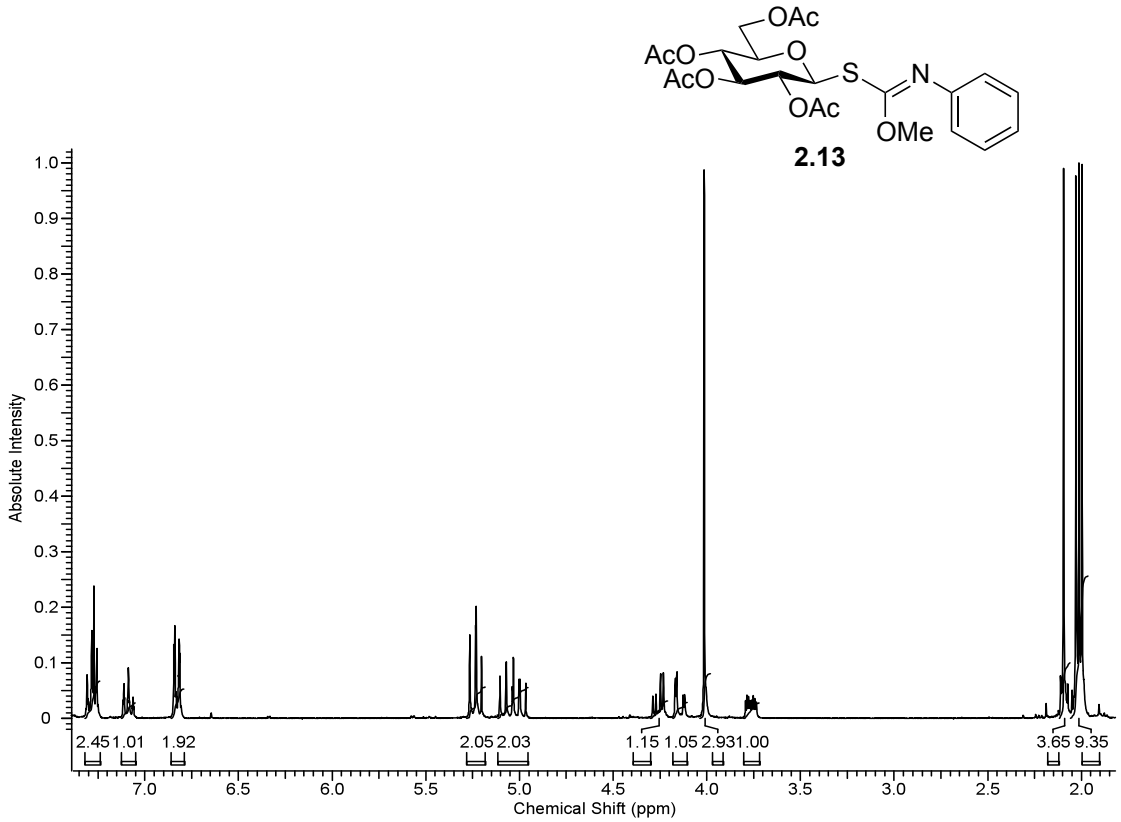


Figure A-7: ^{1}H NMR spectrum of 2,3,4,6-Tetra *O*-acetyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (**2.13**)

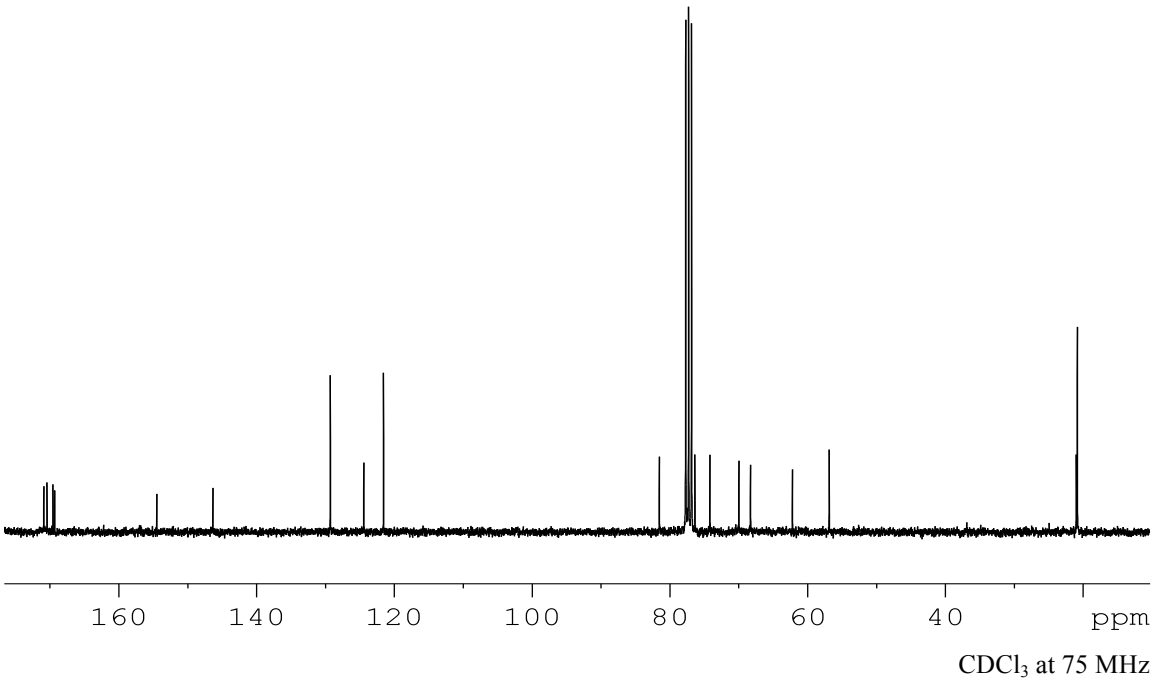


Figure A-8: ^{13}C NMR spectrum of 2,3,4,6-Tetra *O*-acetyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (**2.13**)

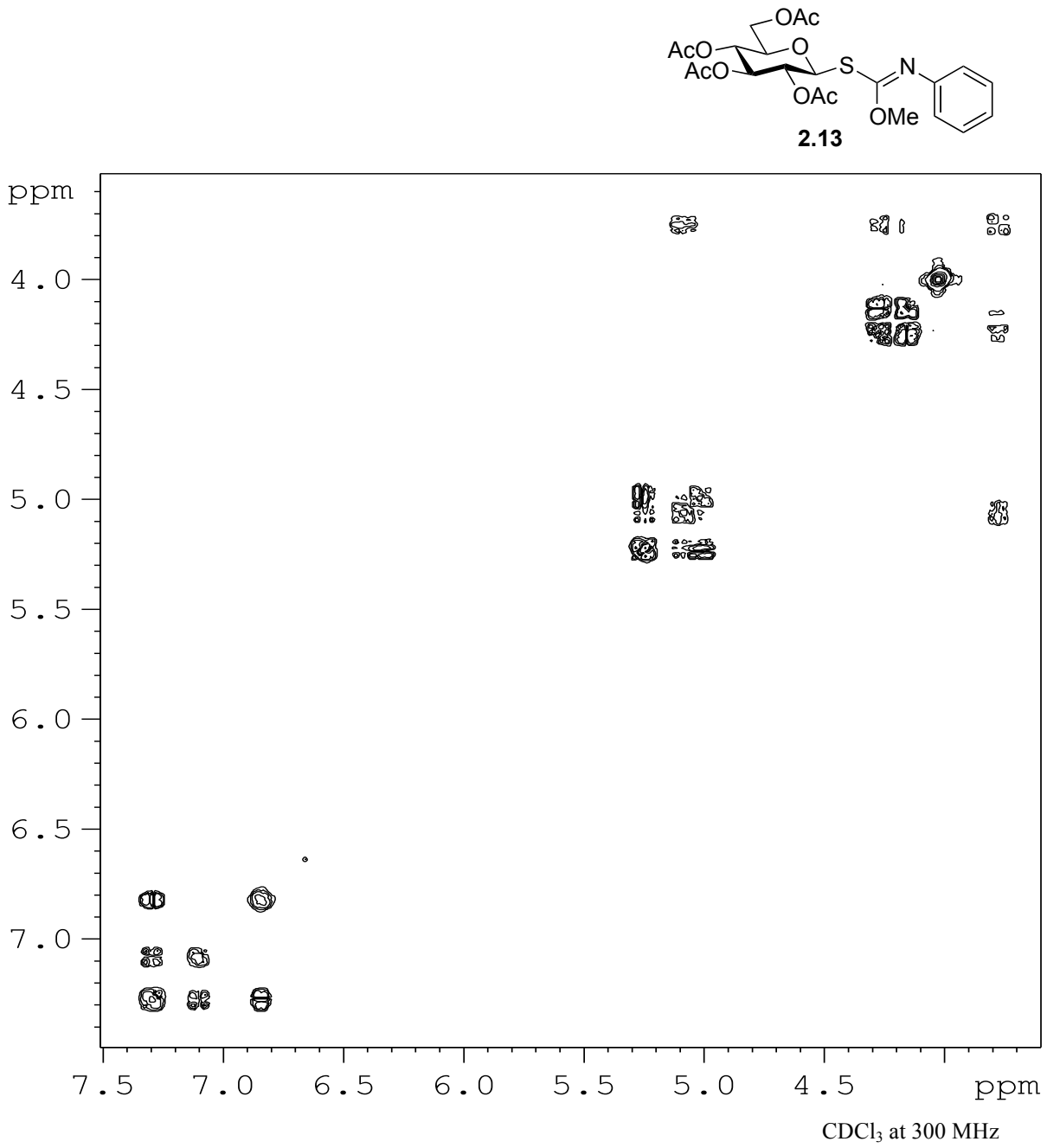


Figure A-9: 2-D NMR COSY spectrum of 2,3,4,6-Tetra *O*-acetyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (**2.13**)

Table 1. Crystal data and structure refinement for 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-glucopyranosyl-O-methyl phenylcarbamothioate **2.13**.

Identification code	v110rt/LB4Pg106	
Empirical formula	C_{22} H_{27} N O_{10} S	
Formula weight	497.51	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.5778(6) Å	a= 90°.
	b = 14.1056(16) Å	b= 98.808(4)°.
	c = 16.6334(19) Å	g = 90°.
Volume	1293.3(3) $Å^3$	
Z	2	
Density (calculated)	1.278 Mg/m^3	
Absorption coefficient	0.177 mm^{-1}	
F(000)	524	
Crystal size	0.62 x 0.13 x 0.03 mm^3	
Theta range for data collection	1.90 to 25.10°.	
Index ranges	$-6\leq h\leq 6$, $-16\leq k\leq 16$, $-19\leq l\leq 19$	
Reflections collected	24563	
Independent reflections	4575 [R(int) = 0.0697]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9956 and 0.8974	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4575 / 1 / 322	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0563, wR2 = 0.1294	
R indices (all data)	R1 = 0.0852, wR2 = 0.1442	
Absolute structure parameter	0.05(13)	
Largest diff. peak and hole	0.263 and -0.191 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for avd110. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	7130(2)	7904(1)	2528(1)	56(1)
O(1)	6772(5)	9745(2)	2614(2)	50(1)
O(2)	7229(9)	11193(3)	1563(2)	91(1)
O(3)	10038(13)	12303(5)	1663(4)	141(2)
O(4)	3120(5)	11456(2)	3557(2)	46(1)
O(5)	6043(6)	12527(2)	3943(2)	58(1)
O(6)	3927(4)	9890(2)	4685(2)	40(1)
O(7)	-78(6)	9849(4)	4654(2)	79(1)
O(8)	3282(5)	8172(2)	3717(2)	45(1)
O(9)	6237(6)	7246(2)	4363(2)	59(1)
O(10)	5294(9)	8596(3)	1124(2)	93(2)
N(1)	7363(10)	7227(3)	1041(2)	75(1)
C(1)	5388(9)	10599(3)	2647(3)	46(1)
C(2)	4881(8)	10716(3)	3521(3)	38(1)
C(3)	3726(7)	9827(3)	3814(2)	40(1)
C(4)	4973(7)	8926(3)	3617(3)	40(1)
C(5)	5421(9)	8933(3)	2745(3)	49(1)
C(6)	6881(11)	11394(3)	2381(3)	63(1)
C(7)	8988(18)	11659(5)	1299(5)	103(3)
C(8)	9420(20)	11333(8)	502(5)	172(5)
C(9)	3937(9)	12342(3)	3802(3)	48(1)
C(10)	1860(9)	12995(3)	3824(3)	60(1)
C(11)	1891(8)	9875(3)	5022(3)	45(1)
C(12)	2486(9)	9898(4)	5931(3)	53(1)
C(13)	4126(8)	7378(3)	4112(3)	41(1)
C(14)	2091(9)	6724(3)	4198(3)	55(1)
C(15)	6603(10)	7869(4)	1443(3)	60(1)
C(16)	5480(50)	8676(18)	279(15)	117(10)
C(16')	4250(50)	8610(20)	209(12)	126(11)

C(17)	8764(11)	6459(4)	1403(3)	64(1)
C(18)	7846(13)	5561(5)	1310(4)	87(2)
C(19)	9277(19)	4785(5)	1625(6)	119(3)
C(20)	11592(17)	4934(6)	2018(5)	107(2)
C(21)	12478(15)	5833(5)	2118(4)	95(2)
C(22)	11088(12)	6587(5)	1811(4)	77(2)

Table 3. Bond lengths [Å] and angles [°] for avd110.

S(1)-C(15)	1.784(4)
S(1)-C(5)	1.802(5)
O(1)-C(5)	1.407(5)
O(1)-C(1)	1.436(5)
O(2)-C(7)	1.311(9)
O(2)-C(6)	1.432(6)
O(3)-C(7)	1.194(9)
O(4)-C(9)	1.370(5)
O(4)-C(2)	1.441(5)
O(5)-C(9)	1.191(5)
O(6)-C(11)	1.342(5)
O(6)-C(3)	1.438(4)
O(7)-C(11)	1.174(5)
O(8)-C(13)	1.347(5)
O(8)-C(4)	1.448(5)
O(9)-C(13)	1.202(5)
O(10)-C(15)	1.322(6)
O(10)-C(16)	1.43(3)
O(10)-C(16')	1.544(19)
N(1)-C(15)	1.237(6)
N(1)-C(17)	1.415(7)
C(1)-C(6)	1.502(7)
C(1)-C(2)	1.532(6)
C(1)-H(1)	0.9800
C(2)-C(3)	1.523(6)
C(2)-H(2)	0.9800

C(3)-C(4)	1.509(6)
C(3)-H(3)	0.9800
C(4)-C(5)	1.509(6)
C(4)-H(4)	0.9800
C(5)-H(5)	0.9800
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-C(8)	1.459(10)
C(8)-H(8A)	0.9600
C(8)-H(8B)	0.9600
C(8)-H(8C)	0.9600
C(9)-C(10)	1.485(6)
C(10)-H(10A)	0.9600
C(10)-H(10B)	0.9600
C(10)-H(10C)	0.9600
C(11)-C(12)	1.497(6)
C(12)-H(12A)	0.9600
C(12)-H(12B)	0.9600
C(12)-H(12C)	0.9600
C(13)-C(14)	1.486(6)
C(14)-H(14A)	0.9600
C(14)-H(14B)	0.9600
C(14)-H(14C)	0.9600
C(16)-H(16A)	0.9600
C(16)-H(16B)	0.9600
C(16)-H(16C)	0.9600
C(16')-H(16D)	0.9600
C(16')-H(16E)	0.9600
C(16')-H(16F)	0.9600
C(17)-C(18)	1.367(8)
C(17)-C(22)	1.380(8)
C(18)-C(19)	1.407(11)
C(18)-H(18)	0.9300
C(19)-C(20)	1.372(11)
C(19)-H(19)	0.9300
C(20)-C(21)	1.362(11)

C(20)-H(20)	0.9300
C(21)-C(22)	1.368(9)
C(21)-H(21)	0.9300
C(22)-H(22)	0.9300

C(15)-S(1)-C(5)	102.4(2)
C(5)-O(1)-C(1)	111.9(3)
C(7)-O(2)-C(6)	115.9(5)
C(9)-O(4)-C(2)	118.4(3)
C(11)-O(6)-C(3)	118.7(3)
C(13)-O(8)-C(4)	118.8(3)
C(15)-O(10)-C(16)	109.7(10)
C(15)-O(10)-C(16')	120.6(11)
C(16)-O(10)-C(16')	26.1(19)
C(15)-N(1)-C(17)	122.9(4)
O(1)-C(1)-C(6)	106.8(4)
O(1)-C(1)-C(2)	107.7(3)
C(6)-C(1)-C(2)	113.0(4)
O(1)-C(1)-H(1)	109.8
C(6)-C(1)-H(1)	109.8
C(2)-C(1)-H(1)	109.8
O(4)-C(2)-C(3)	105.0(3)
O(4)-C(2)-C(1)	110.1(3)
C(3)-C(2)-C(1)	111.3(3)
O(4)-C(2)-H(2)	110.1
C(3)-C(2)-H(2)	110.1
C(1)-C(2)-H(2)	110.1
O(6)-C(3)-C(4)	107.7(3)
O(6)-C(3)-C(2)	107.4(3)
C(4)-C(3)-C(2)	113.1(3)
O(6)-C(3)-H(3)	109.5
C(4)-C(3)-H(3)	109.5
C(2)-C(3)-H(3)	109.5
O(8)-C(4)-C(5)	108.8(3)
O(8)-C(4)-C(3)	105.3(3)
C(5)-C(4)-C(3)	110.7(3)

O(8)-C(4)-H(4)	110.6
C(5)-C(4)-H(4)	110.6
C(3)-C(4)-H(4)	110.6
O(1)-C(5)-C(4)	109.0(3)
O(1)-C(5)-S(1)	108.2(3)
C(4)-C(5)-S(1)	111.0(3)
O(1)-C(5)-H(5)	109.5
C(4)-C(5)-H(5)	109.5
S(1)-C(5)-H(5)	109.5
O(2)-C(6)-C(1)	107.1(4)
O(2)-C(6)-H(6A)	110.3
C(1)-C(6)-H(6A)	110.3
O(2)-C(6)-H(6B)	110.3
C(1)-C(6)-H(6B)	110.3
H(6A)-C(6)-H(6B)	108.6
O(3)-C(7)-O(2)	123.1(6)
O(3)-C(7)-C(8)	124.3(8)
O(2)-C(7)-C(8)	112.6(8)
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
O(5)-C(9)-O(4)	122.1(4)
O(5)-C(9)-C(10)	127.5(4)
O(4)-C(9)-C(10)	110.4(4)
C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
O(7)-C(11)-O(6)	124.4(4)
O(7)-C(11)-C(12)	125.0(4)
O(6)-C(11)-C(12)	110.6(4)

C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
O(9)-C(13)-O(8)	123.3(4)
O(9)-C(13)-C(14)	126.3(4)
O(8)-C(13)-C(14)	110.4(4)
C(13)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(13)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
N(1)-C(15)-O(10)	124.4(4)
N(1)-C(15)-S(1)	123.3(4)
O(10)-C(15)-S(1)	112.3(4)
O(10)-C(16)-H(16A)	109.5
O(10)-C(16)-H(16B)	109.5
O(10)-C(16)-H(16C)	109.5
O(10)-C(16')-H(16D)	109.5
O(10)-C(16')-H(16E)	109.5
H(16D)-C(16')-H(16E)	109.5
O(10)-C(16')-H(16F)	109.5
H(16D)-C(16')-H(16F)	109.5
H(16E)-C(16')-H(16F)	109.5
C(18)-C(17)-C(22)	119.0(6)
C(18)-C(17)-N(1)	119.3(6)
C(22)-C(17)-N(1)	121.7(5)
C(17)-C(18)-C(19)	119.9(7)
C(17)-C(18)-H(18)	120.1
C(19)-C(18)-H(18)	120.1
C(20)-C(19)-C(18)	119.8(8)
C(20)-C(19)-H(19)	120.1
C(18)-C(19)-H(19)	120.1

C(21)-C(20)-C(19)	119.9(8)
C(21)-C(20)-H(20)	120.0
C(19)-C(20)-H(20)	120.0
C(20)-C(21)-C(22)	120.2(7)
C(20)-C(21)-H(21)	119.9
C(22)-C(21)-H(21)	119.9
C(21)-C(22)-C(17)	121.2(6)
C(21)-C(22)-H(22)	119.4
C(17)-C(22)-H(22)	119.4

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for avd110. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	81(1)	45(1)	42(1)	-8(1)	7(1)	16(1)
O(1)	61(2)	37(2)	55(2)	-3(2)	22(1)	1(2)
O(2)	152(4)	71(3)	62(2)	-5(2)	55(3)	-28(3)
O(3)	209(7)	122(5)	112(4)	4(4)	87(4)	-54(5)
O(4)	42(2)	30(2)	67(2)	-5(1)	10(1)	2(1)
O(5)	49(2)	38(2)	92(2)	-5(2)	20(2)	-8(2)
O(6)	39(2)	37(2)	45(2)	0(1)	12(1)	-1(1)
O(7)	40(2)	114(3)	85(3)	-20(3)	15(2)	-6(2)
O(8)	41(2)	32(2)	62(2)	3(1)	5(1)	-4(1)
O(9)	49(2)	46(2)	83(2)	13(2)	12(2)	6(2)
O(10)	151(4)	75(3)	46(2)	0(2)	-9(2)	31(3)
N(1)	113(4)	70(3)	44(2)	-15(2)	13(2)	6(3)
C(1)	60(3)	29(2)	49(3)	2(2)	9(2)	-1(2)
C(2)	39(3)	34(2)	43(2)	-2(2)	9(2)	0(2)
C(3)	40(2)	36(2)	44(2)	-2(2)	8(2)	-1(2)
C(4)	35(2)	27(2)	58(3)	-3(2)	10(2)	-1(2)
C(5)	58(3)	36(2)	53(3)	-8(2)	8(2)	-3(2)
C(6)	102(4)	43(3)	48(3)	-3(2)	28(3)	-7(3)

C(7)	169(8)	65(4)	91(5)	6(4)	73(5)	1(5)
C(8)	273(13)	168(10)	104(6)	0(6)	119(8)	-13(9)
C(9)	48(3)	37(2)	62(3)	-1(2)	18(2)	1(2)
C(10)	62(3)	33(3)	88(3)	0(3)	18(3)	8(2)
C(11)	37(2)	27(2)	73(3)	-6(2)	16(2)	-2(2)
C(12)	66(3)	44(3)	53(3)	-2(2)	20(2)	-1(2)
C(13)	44(3)	30(2)	51(3)	2(2)	11(2)	8(2)
C(14)	50(3)	46(3)	69(3)	12(2)	6(2)	-6(2)
C(15)	87(4)	50(3)	39(2)	-4(3)	-1(2)	4(3)
C(16)	180(30)	84(12)	67(11)	24(9)	-49(14)	50(14)
C(16')	150(20)	190(20)	22(7)	-22(9)	-37(10)	52(18)
C(17)	84(4)	66(4)	48(3)	-17(3)	25(3)	1(3)
C(18)	104(5)	72(4)	87(5)	-24(3)	19(4)	-13(4)
C(19)	174(8)	47(4)	149(7)	-11(5)	69(7)	7(5)
C(20)	122(6)	97(6)	102(5)	9(5)	20(5)	36(6)
C(21)	108(6)	84(5)	96(5)	-15(4)	23(4)	15(4)
C(22)	88(5)	70(4)	78(4)	-14(3)	24(3)	-1(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for avd110.

	x	y	z	U(eq)
H(1)	3852	10549	2274	55
H(2)	6387	10865	3885	46
H(3)	2010	9802	3573	48
H(4)	6497	8839	3989	48
H(5)	3866	8944	2380	59
H(6A)	6044	11994	2405	75
H(6B)	8433	11432	2734	75
H(8A)	8559	11731	87	258
H(8B)	8871	10691	419	258
H(8C)	11129	11363	475	258
H(10A)	2442	13585	4068	91
H(10B)	738	12714	4138	91
H(10C)	1056	13109	3280	91
H(12A)	1055	10055	6158	80
H(12B)	3714	10367	6091	80
H(12C)	3071	9287	6126	80
H(14A)	1539	6424	3685	83
H(14B)	782	7076	4367	83
H(14C)	2638	6250	4599	83
H(16A)	7155	8684	211	175
H(16B)	4713	9253	67	175
H(16C)	4684	8146	-10	175
H(16D)	3239	8068	77	189
H(16E)	5557	8605	-105	189
H(16F)	3306	9179	88	189
H(18)	6279	5463	1040	104
H(19)	8655	4173	1566	143
H(20)	12556	4422	2215	128
H(21)	14034	5935	2397	114
H(22)	11721	7197	1878	93

Table 6. Torsion angles [°] for avd110.

C(5)-O(1)-C(1)-C(6)	-172.0(4)
C(5)-O(1)-C(1)-C(2)	66.3(4)
C(9)-O(4)-C(2)-C(3)	142.0(4)
C(9)-O(4)-C(2)-C(1)	-98.0(4)
O(1)-C(1)-C(2)-O(4)	-169.1(3)
C(6)-C(1)-C(2)-O(4)	73.2(5)
O(1)-C(1)-C(2)-C(3)	-53.1(5)
C(6)-C(1)-C(2)-C(3)	-170.8(4)
C(11)-O(6)-C(3)-C(4)	-117.0(4)
C(11)-O(6)-C(3)-C(2)	120.9(4)
O(4)-C(2)-C(3)-O(6)	-76.5(4)
C(1)-C(2)-C(3)-O(6)	164.5(3)
O(4)-C(2)-C(3)-C(4)	164.9(3)
C(1)-C(2)-C(3)-C(4)	45.8(5)
C(13)-O(8)-C(4)-C(5)	105.5(4)
C(13)-O(8)-C(4)-C(3)	-135.8(4)
O(6)-C(3)-C(4)-O(8)	77.5(4)
C(2)-C(3)-C(4)-O(8)	-164.0(3)
O(6)-C(3)-C(4)-C(5)	-165.1(3)
C(2)-C(3)-C(4)-C(5)	-46.6(4)
C(1)-O(1)-C(5)-C(4)	-68.5(4)
C(1)-O(1)-C(5)-S(1)	170.8(3)
O(8)-C(4)-C(5)-O(1)	171.4(3)
C(3)-C(4)-C(5)-O(1)	56.2(4)
O(8)-C(4)-C(5)-S(1)	-69.5(4)
C(3)-C(4)-C(5)-S(1)	175.3(3)
C(15)-S(1)-C(5)-O(1)	-78.1(4)
C(15)-S(1)-C(5)-C(4)	162.4(3)
C(7)-O(2)-C(6)-C(1)	-162.7(6)
O(1)-C(1)-C(6)-O(2)	61.3(5)
C(2)-C(1)-C(6)-O(2)	179.6(4)
C(6)-O(2)-C(7)-O(3)	-9.8(12)
C(6)-O(2)-C(7)-C(8)	172.9(7)
C(2)-O(4)-C(9)-O(5)	4.0(6)

C(2)-O(4)-C(9)-C(10)	-178.2(4)
C(3)-O(6)-C(11)-O(7)	-3.0(7)
C(3)-O(6)-C(11)-C(12)	177.1(4)
C(4)-O(8)-C(13)-O(9)	-2.7(6)
C(4)-O(8)-C(13)-C(14)	176.2(4)
C(17)-N(1)-C(15)-O(10)	179.9(5)
C(17)-N(1)-C(15)-S(1)	-0.9(8)
C(16)-O(10)-C(15)-N(1)	-16.3(14)
C(16')-O(10)-C(15)-N(1)	10.0(17)
C(16)-O(10)-C(15)-S(1)	164.4(13)
C(16')-O(10)-C(15)-S(1)	-169.2(15)
C(5)-S(1)-C(15)-N(1)	-175.9(5)
C(5)-S(1)-C(15)-O(10)	3.3(5)
C(15)-N(1)-C(17)-C(18)	115.9(6)
C(15)-N(1)-C(17)-C(22)	-67.6(8)
C(22)-C(17)-C(18)-C(19)	-0.5(9)
N(1)-C(17)-C(18)-C(19)	176.1(6)
C(17)-C(18)-C(19)-C(20)	-0.4(11)
C(18)-C(19)-C(20)-C(21)	1.4(11)
C(19)-C(20)-C(21)-C(22)	-1.6(11)
C(20)-C(21)-C(22)-C(17)	0.7(10)
C(18)-C(17)-C(22)-C(21)	0.3(8)
N(1)-C(17)-C(22)-C(21)	-176.2(5)

Projection view with 25% thermal parameters- disorder C atoms omitted:

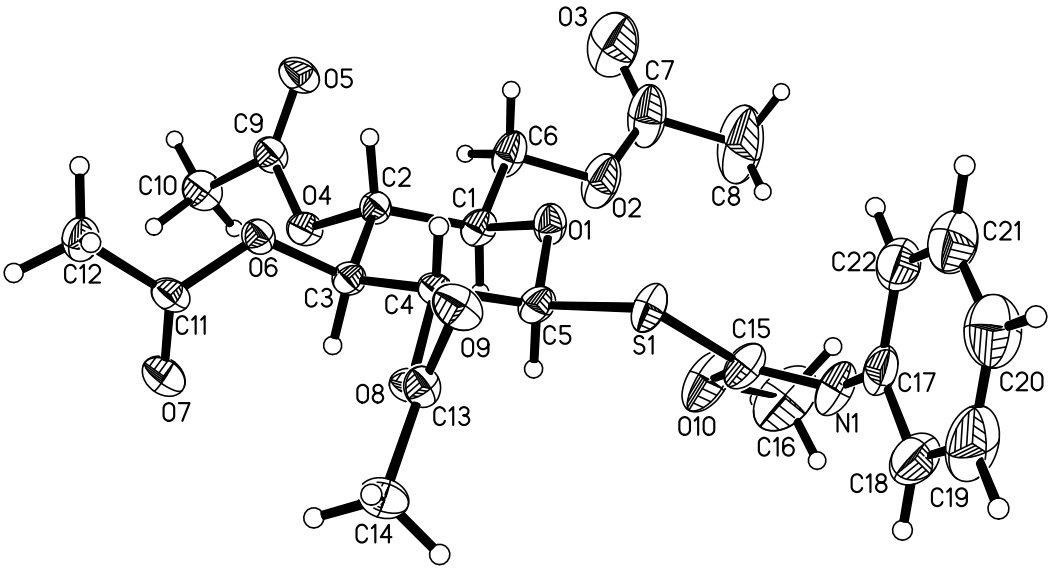
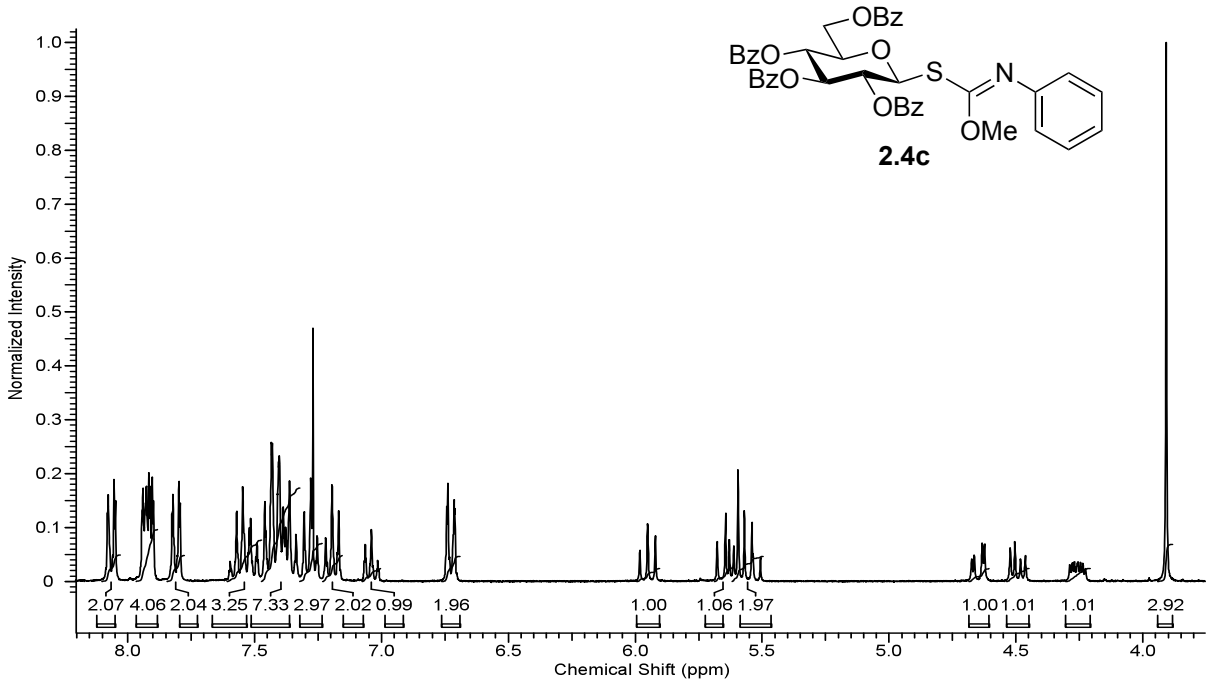
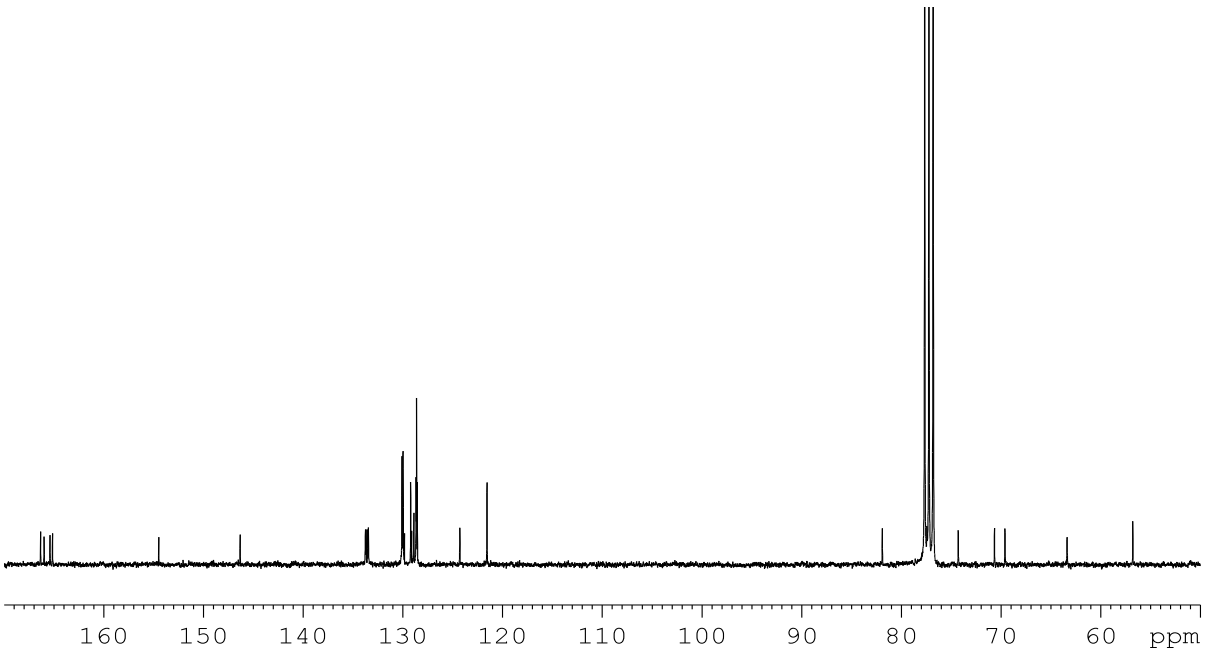


Figure A-10: X-Ray Crystal Structure of 2,3,4,6-Tetra *O*-acetyl-1-thio-β-D-glucopyranosyl *O*-methyl phenylcarbamothioate (**2.13**)



$CDCl_3$ at 300 MHz

Figure A-11: ^{1}H NMR spectrum of 2,3,4,6-Tetra-O-benzoyl-1-thio-β-D-glucopyranosyl-O-methyl phenylcarbamothioate (**2.4c**)



$CDCl_3$ at 75 MHz

Figure A-12: ^{13}C NMR spectrum of 2,3,4,6-Tetra-O-benzoyl-1-thio-β-D-glucopyranosyl-O-methyl phenylcarbamothioate (**2.4c**)

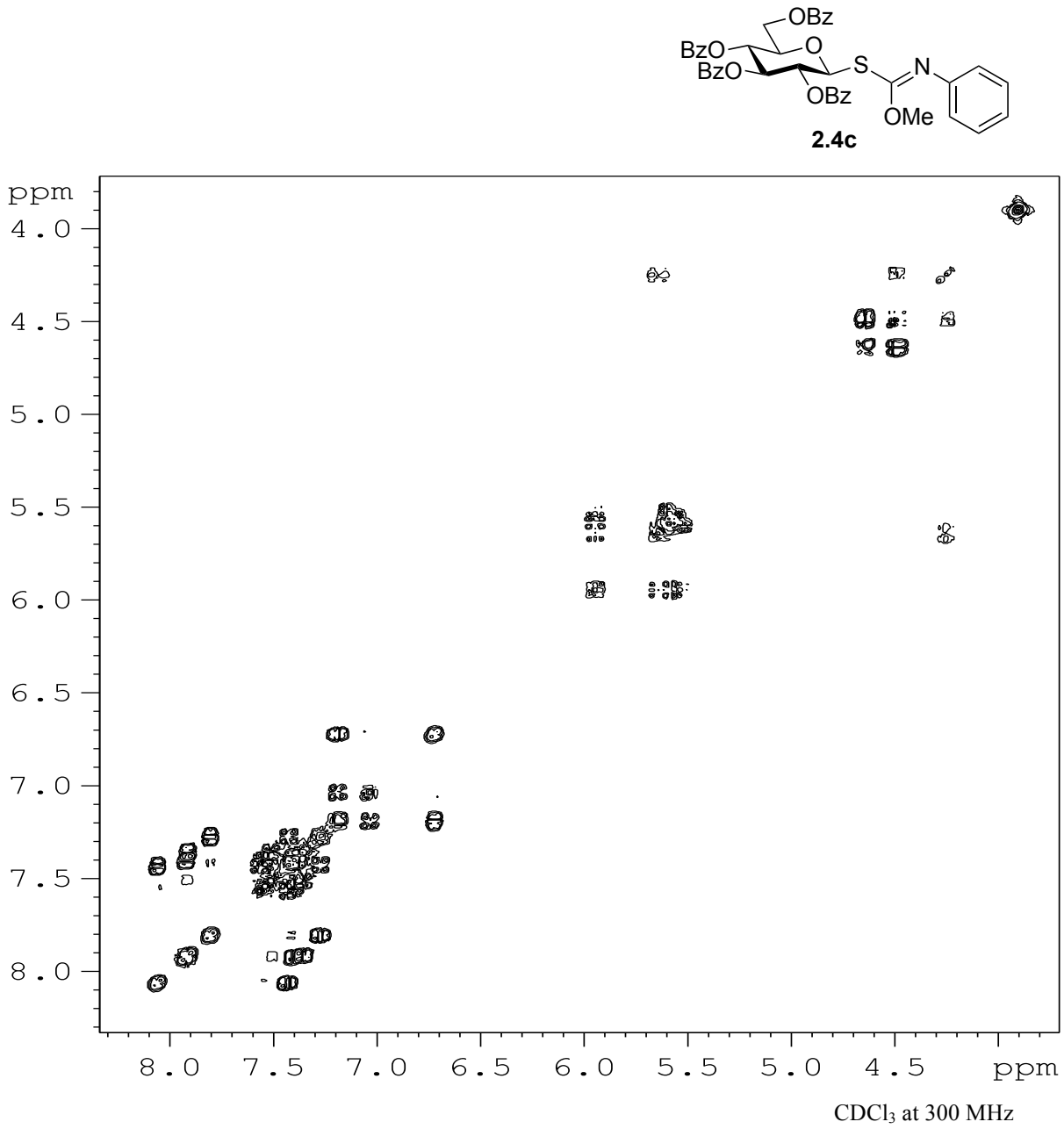
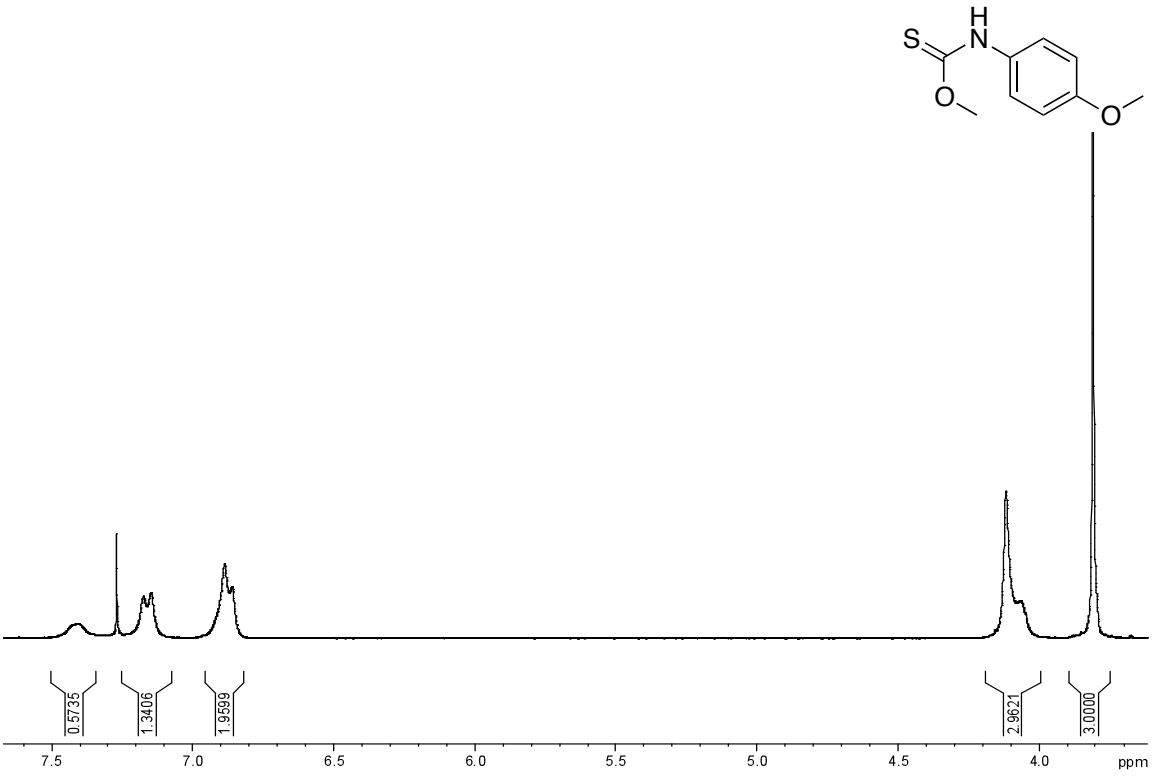
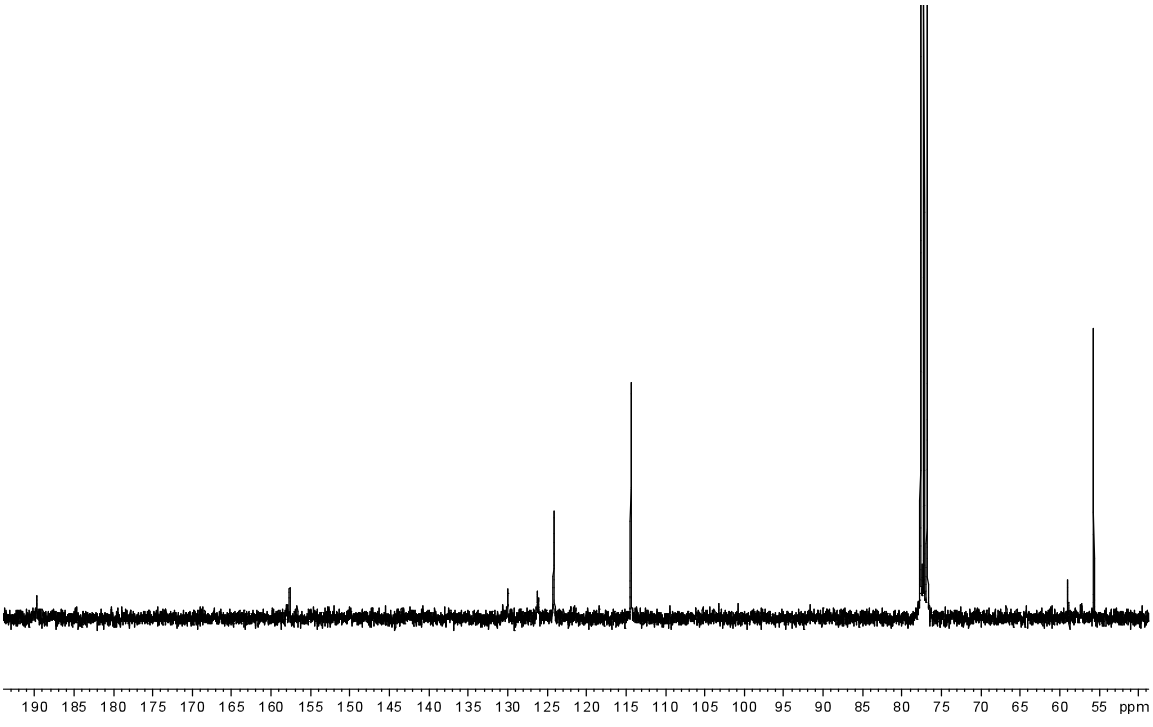


Figure A-13: 2-D NMR COSY spectrum of 2,3,4,6-Tetra-O-benzoyl-1-thio-β-D-glucopyranosyl-O-methyl phenylcarbamothioate (**2.4c**)



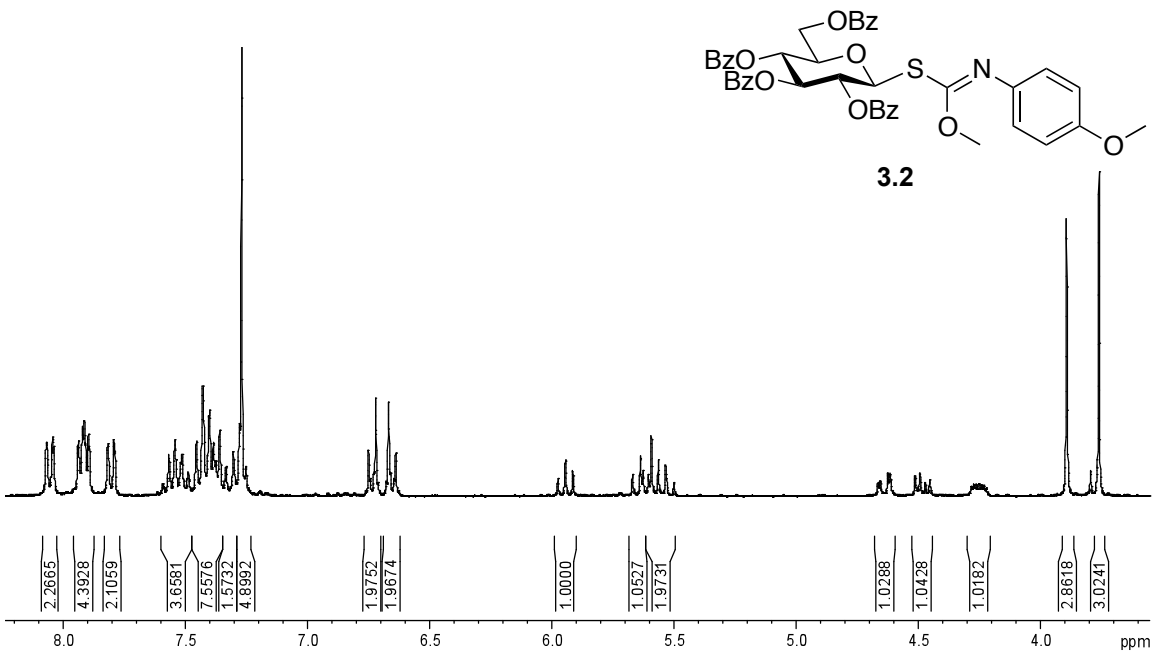
$CDCl_3$ at 300 MHz

Figure A-14: ^{1}H NMR spectrum of *O*-Methyl (4-methoxyphenyl)carbamothioate



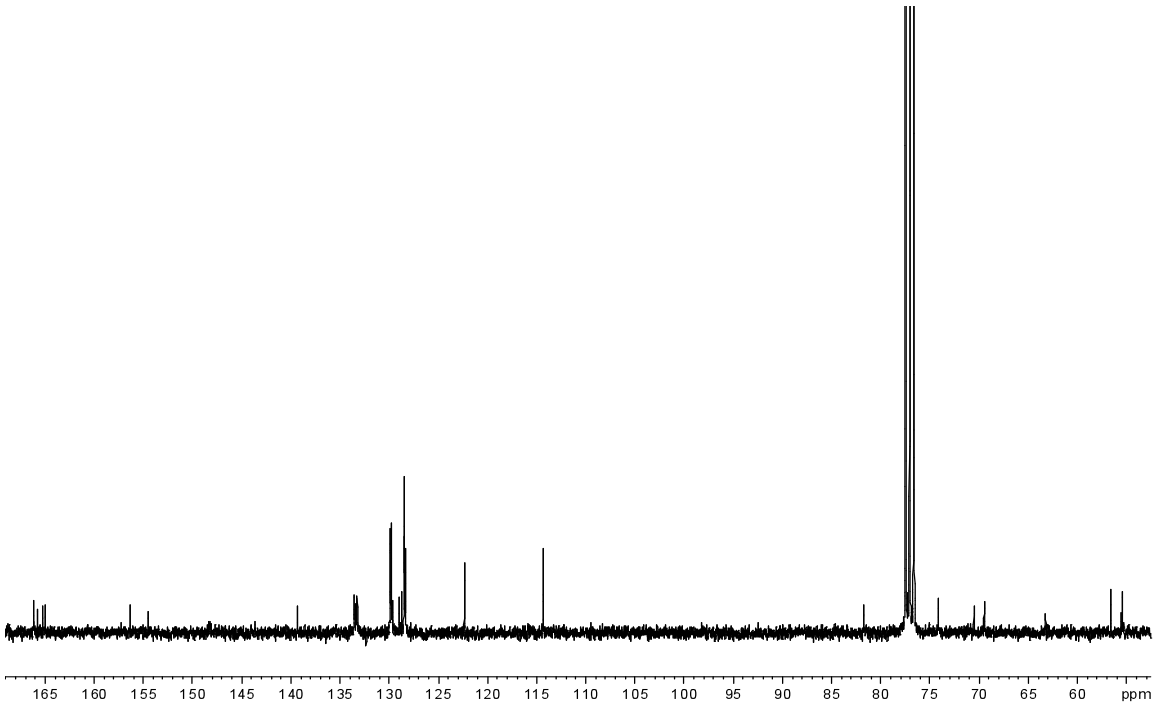
$CDCl_3$ at 75 MHz

Figure A-15: ^{13}C NMR spectrum of *O*-Methyl (4-methoxyphenyl)carbamothioate



$CDCl_3$ at 300 MHz

Figure A-16: ^{1}H NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *O*-methyl (4-methoxyphenyl)carbamothioate (**3.2**)



$CDCl_3$ at 75 MHz

Figure A-17: ^{13}C NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *O*-methyl (4-methoxyphenyl)carbamothioate (**3.2**)

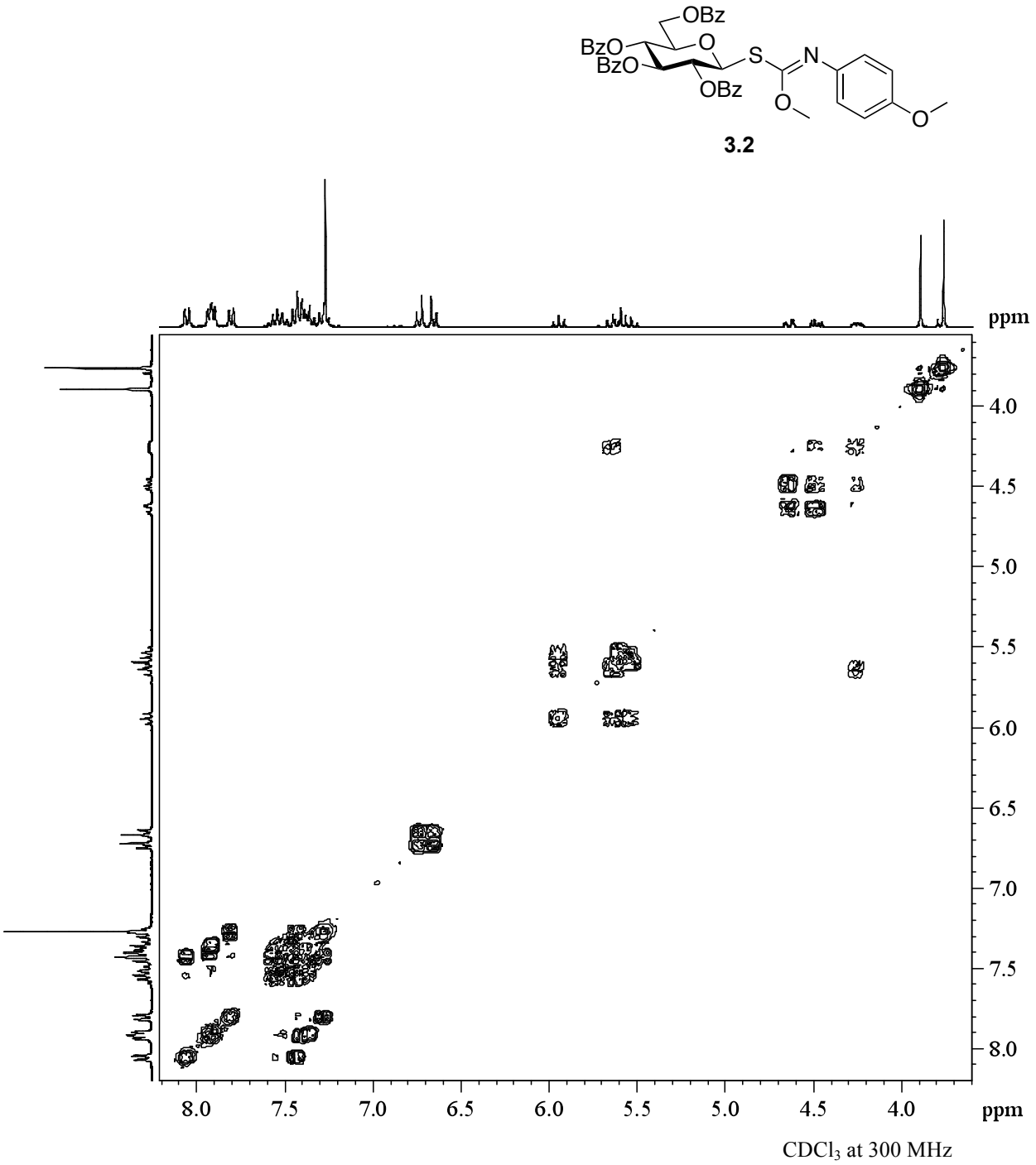
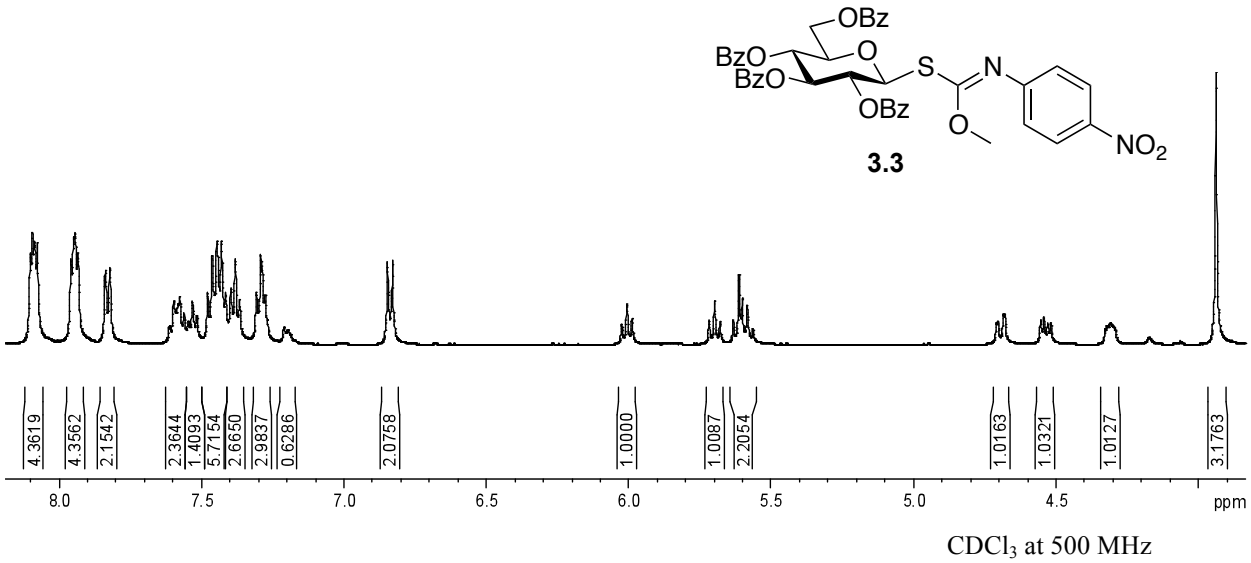
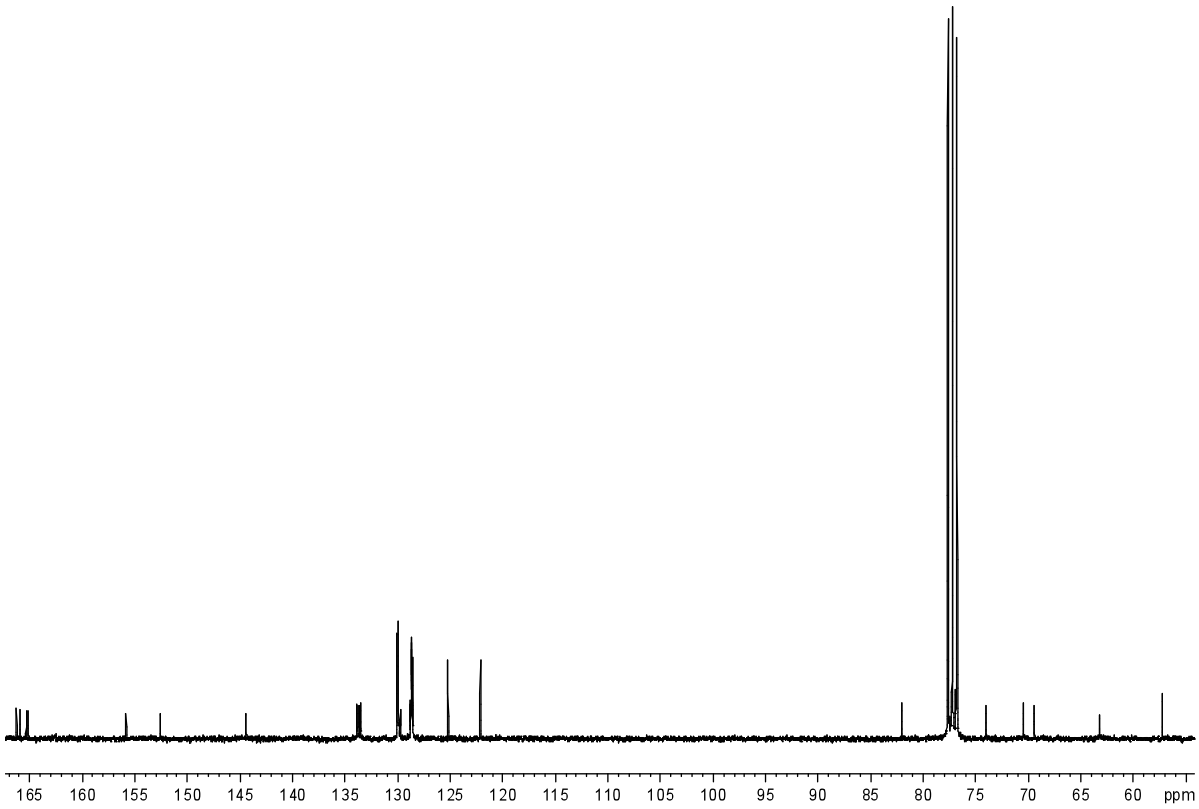


Figure A-18: 2-D NMR COSY spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *O*-methyl (4-methoxyphenyl)carbamothioate (**3.2**)



$CDCl_3$ at 500 MHz

Figure A-19: ^{1}H NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *O*-methyl (4-nitrophenyl)carbamothioate (**3.3**)



$CDCl_3$ at 75 MHz

Figure A-20: ^{13}C NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *O*-methyl (4-nitrophenyl)carbamothioate (**3.3**)

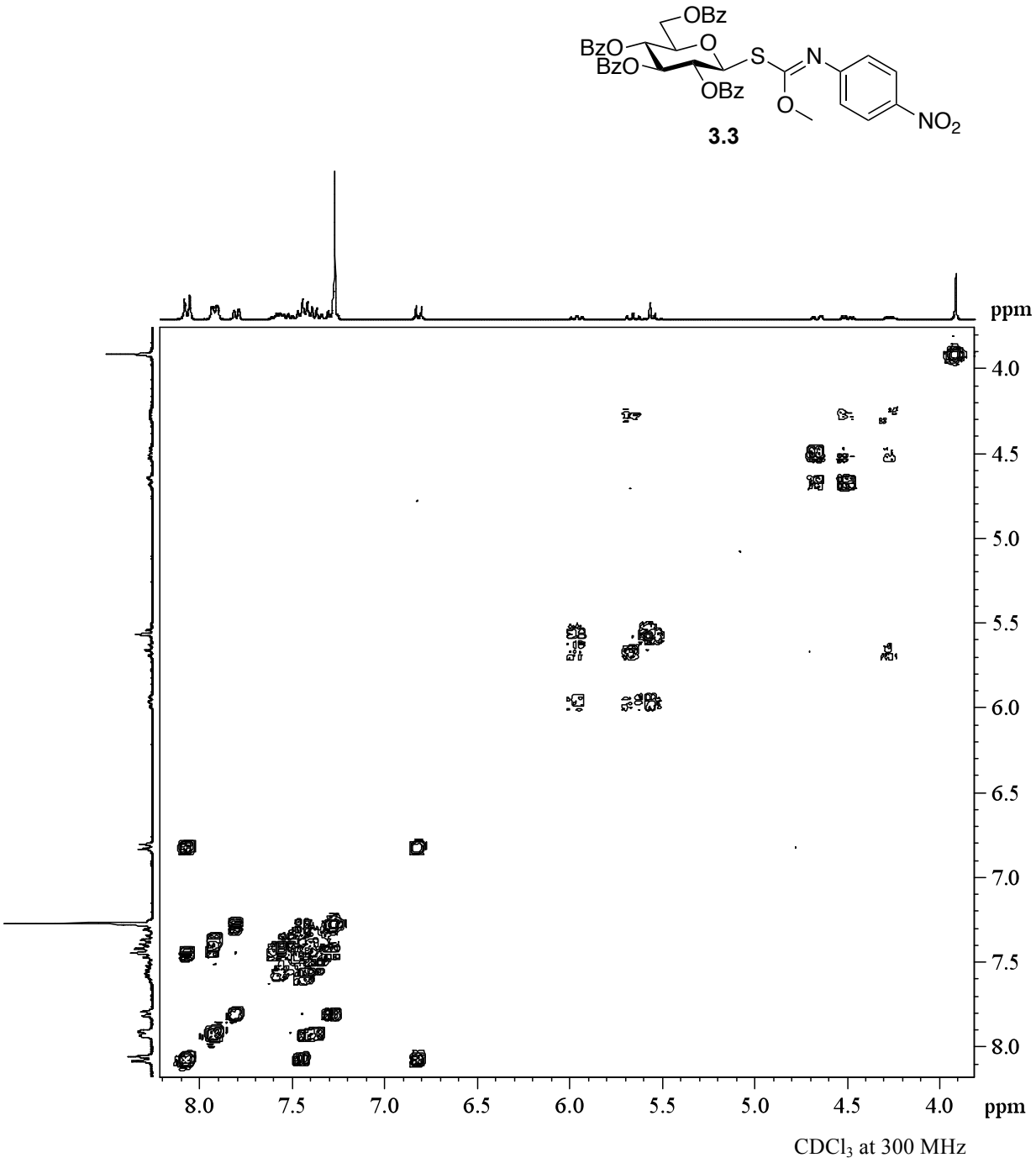


Figure A-21: 2-D NMR COSY spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *O*-methyl (4-nitrophenyl)carbamothioate (**3.3**)

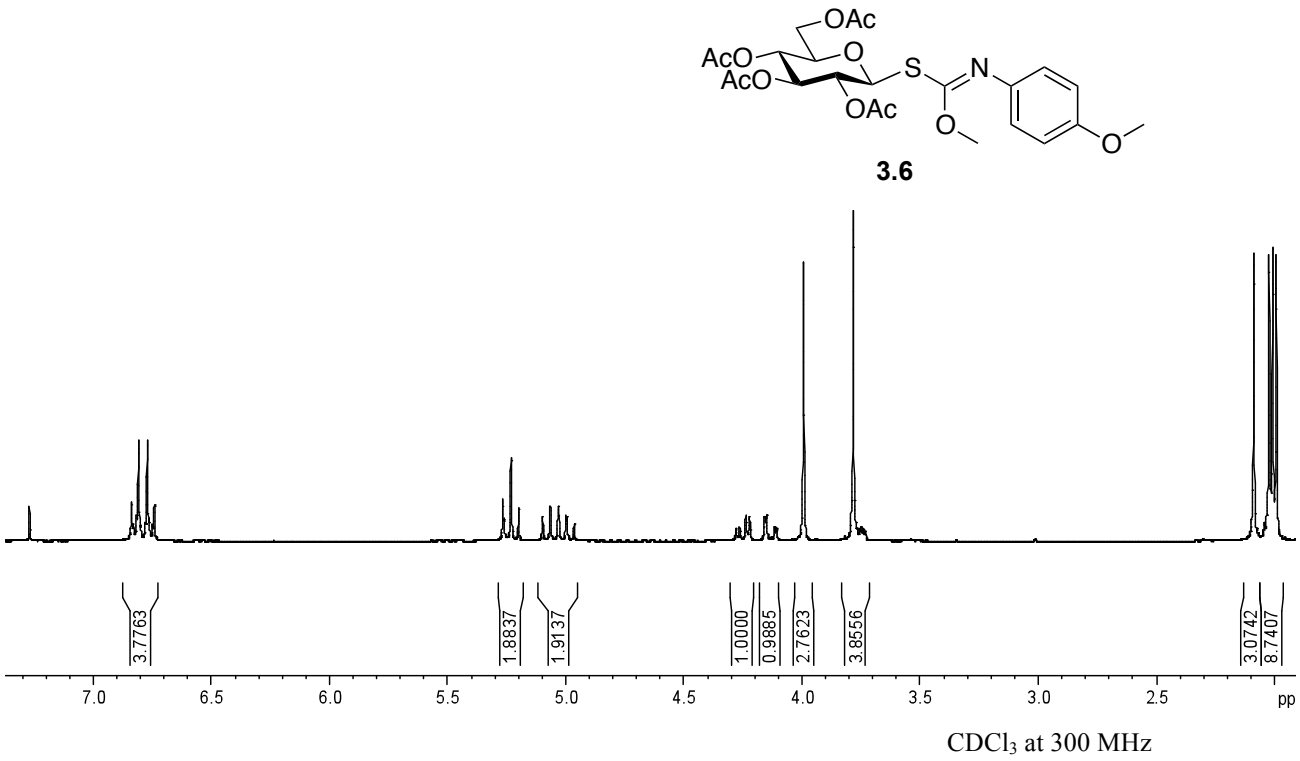


Figure A-22: ^{1}H NMR spectrum of 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-glucopyranosyl O-methyl (4-methoxyphenyl)carbamothioate (**3.6**)

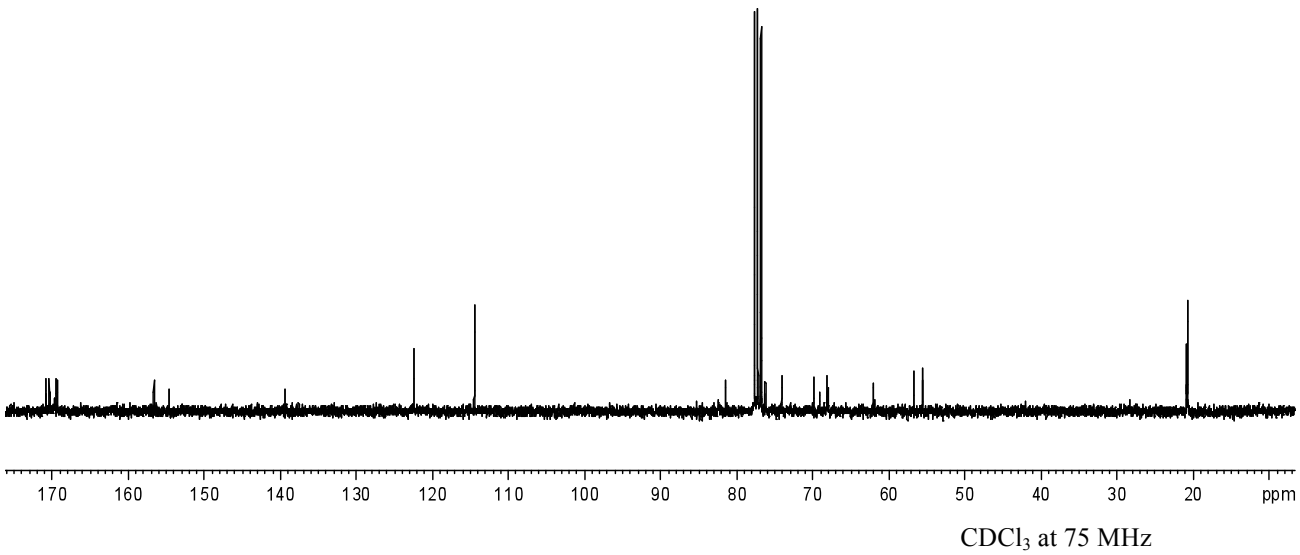


Figure A-23: ^{13}C NMR spectrum of 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-glucopyranosyl O-methyl (4-methoxyphenyl)carbamothioate (**3.6**)

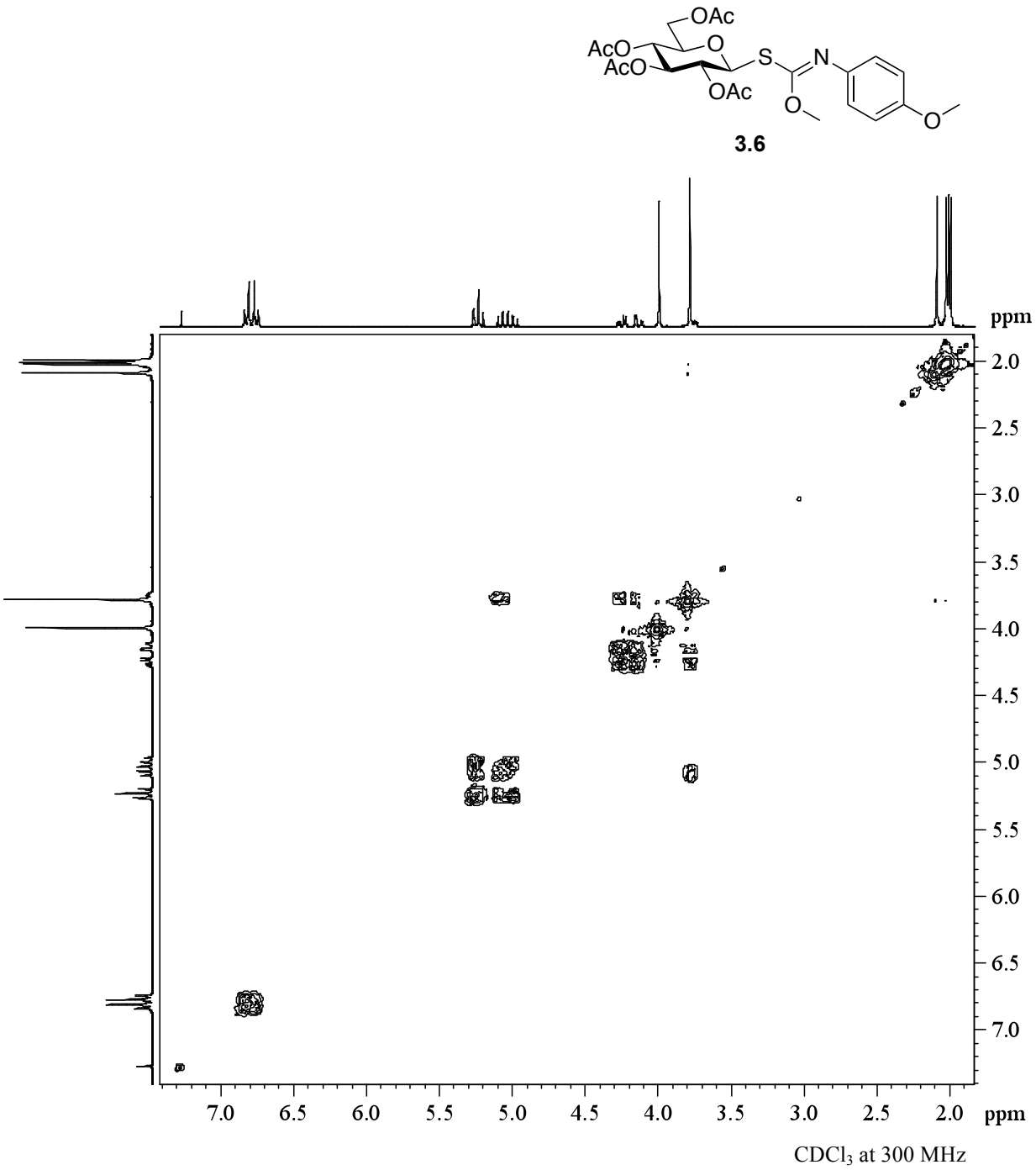


Figure A-24: 2-D NMR COSY spectrum of 2,3,4,6-Tetra-O-acetyl-1-thio-*β*-D-glucopyranosyl O-methyl (4-methoxyphenyl)carbamothioate (**3.6**)

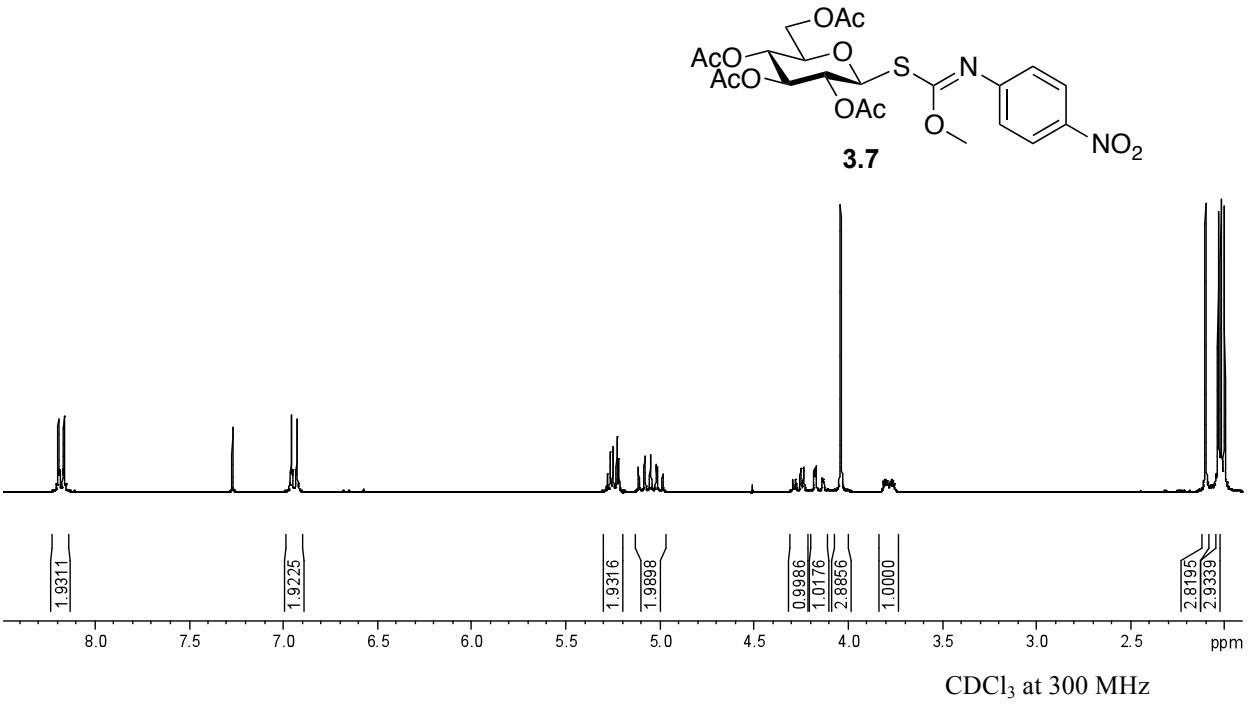


Figure A-25: ^{1}H NMR spectrum of 2,3,4,6-Tetra-*O*-acetyl-1-thio-*β*-D-glucopyranosyl *O*-methyl (4-nitrophenyl)carbamothioate (**3.7**)

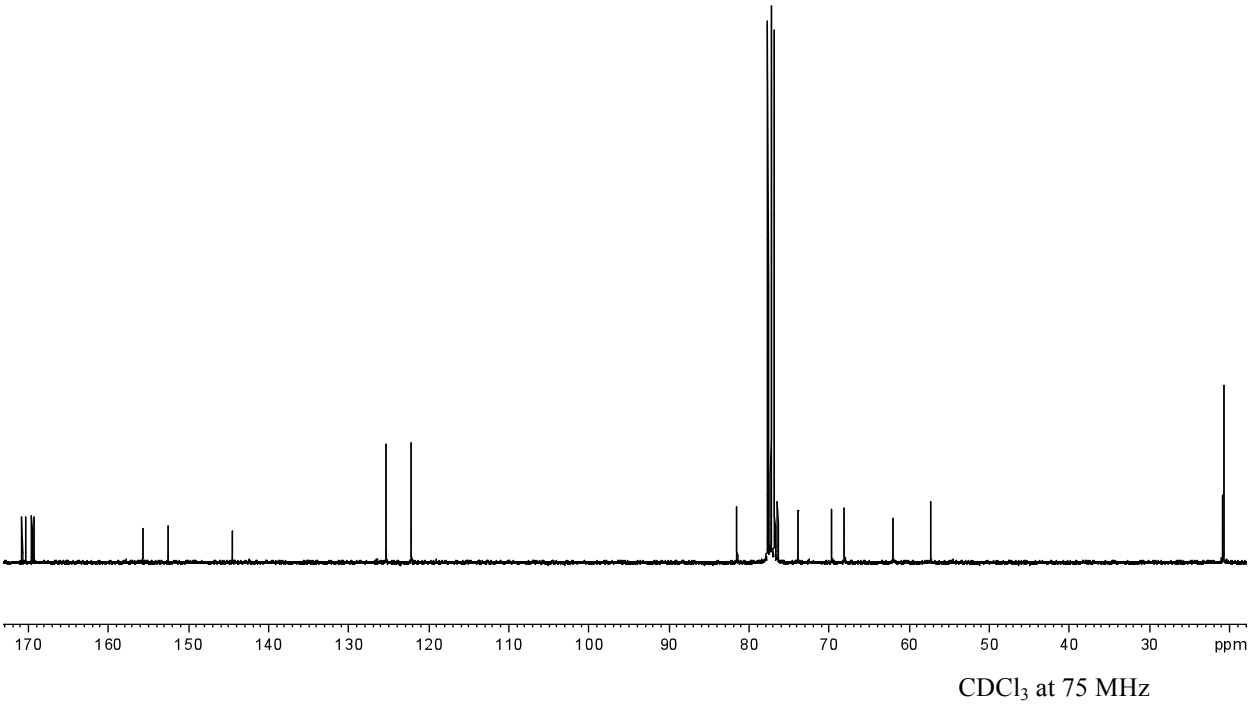


Figure A-26: ^{13}C NMR spectrum of 2,3,4,6-Tetra-*O*-acetyl-1-thio-*β*-D-glucopyranosyl *O*-methyl (4-nitrophenyl)carbamothioate (**3.7**)

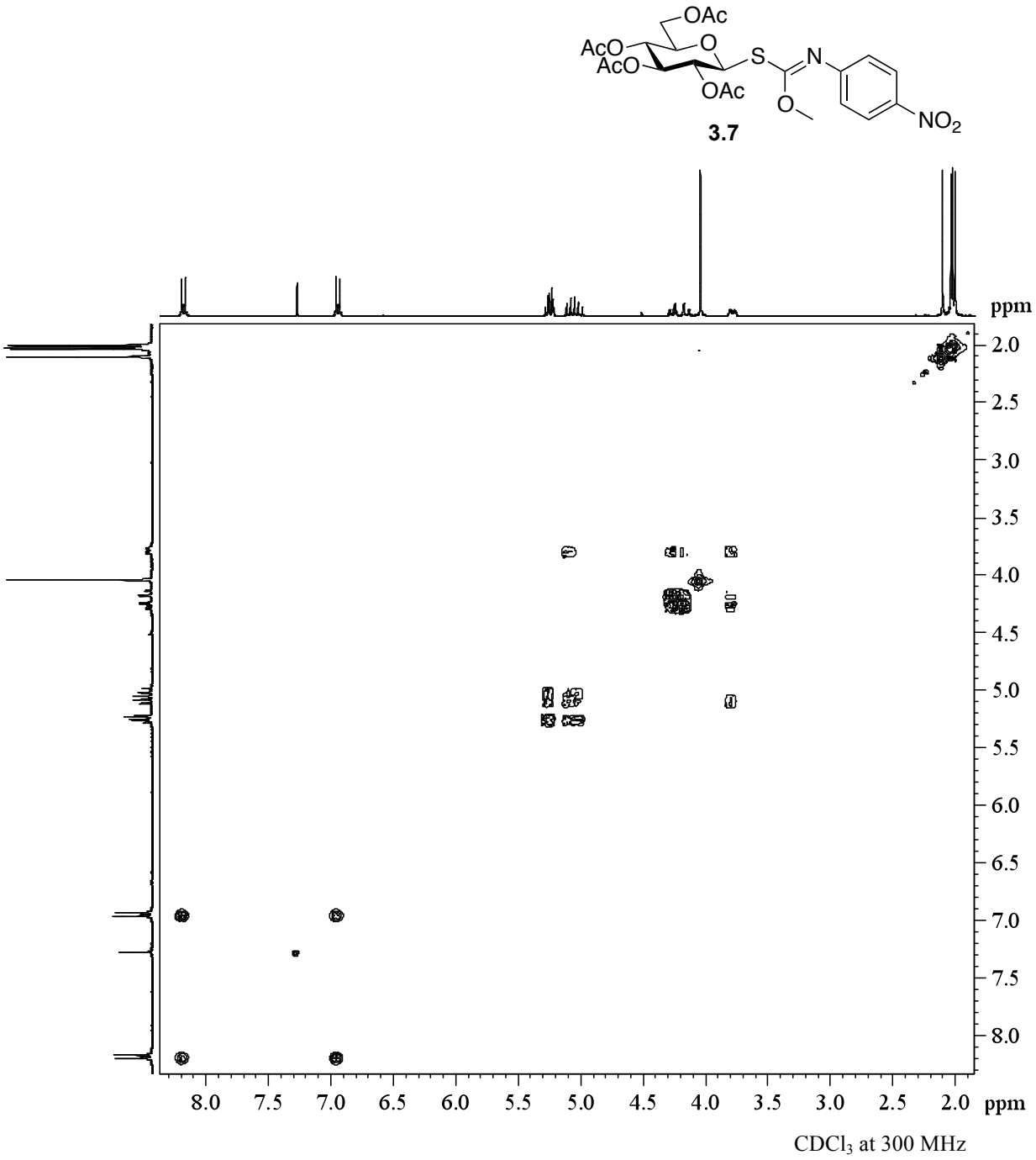
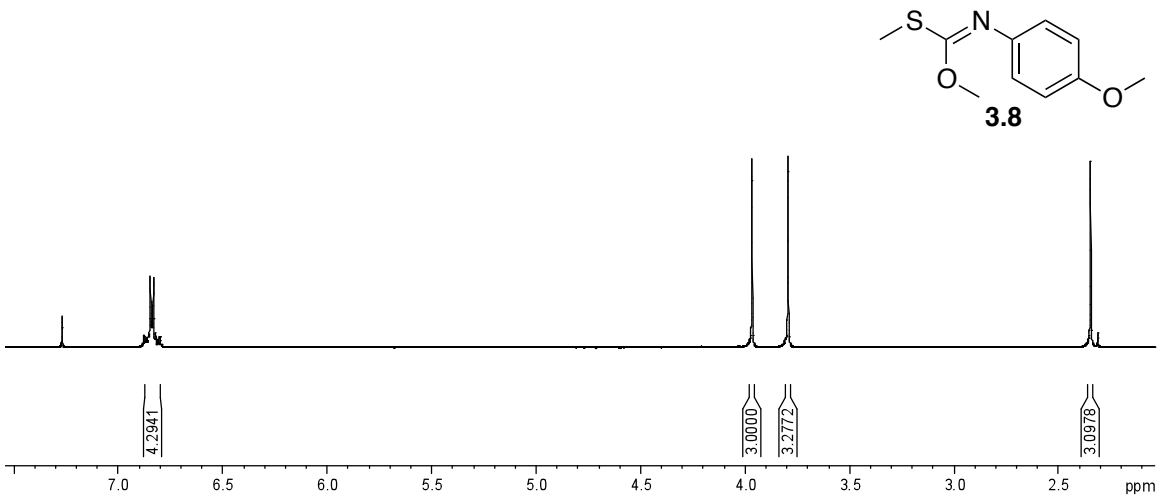
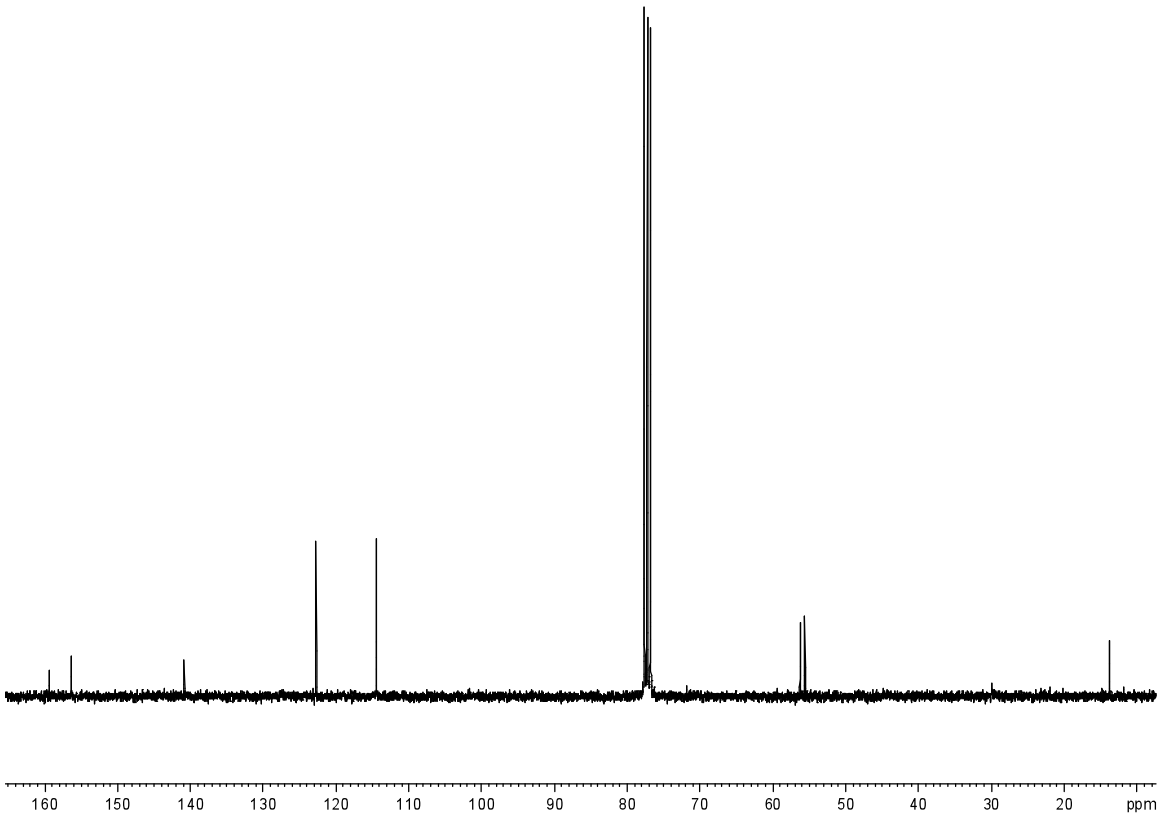


Figure A-27: 2-D NMR COSY spectrum of 2,3,4,6-Tetra-*O*-acetyl-1-thio-*β*-D-glucopyranosyl *O*-methyl (4-nitrophenyl)carbamothioate (**3.7**)



$CDCl_3$ at 300 MHz

Figure A-28: ^{1}H NMR spectrum of *O, S*-Dimethyl (4-methoxyphenyl)carbamothioate (**3.8**)



$CDCl_3$ at 75 MHz

Figure A-29: ^{13}C NMR spectrum of *O, S*-Dimethyl (4-methoxyphenyl)carbamothioate (**3.8**)

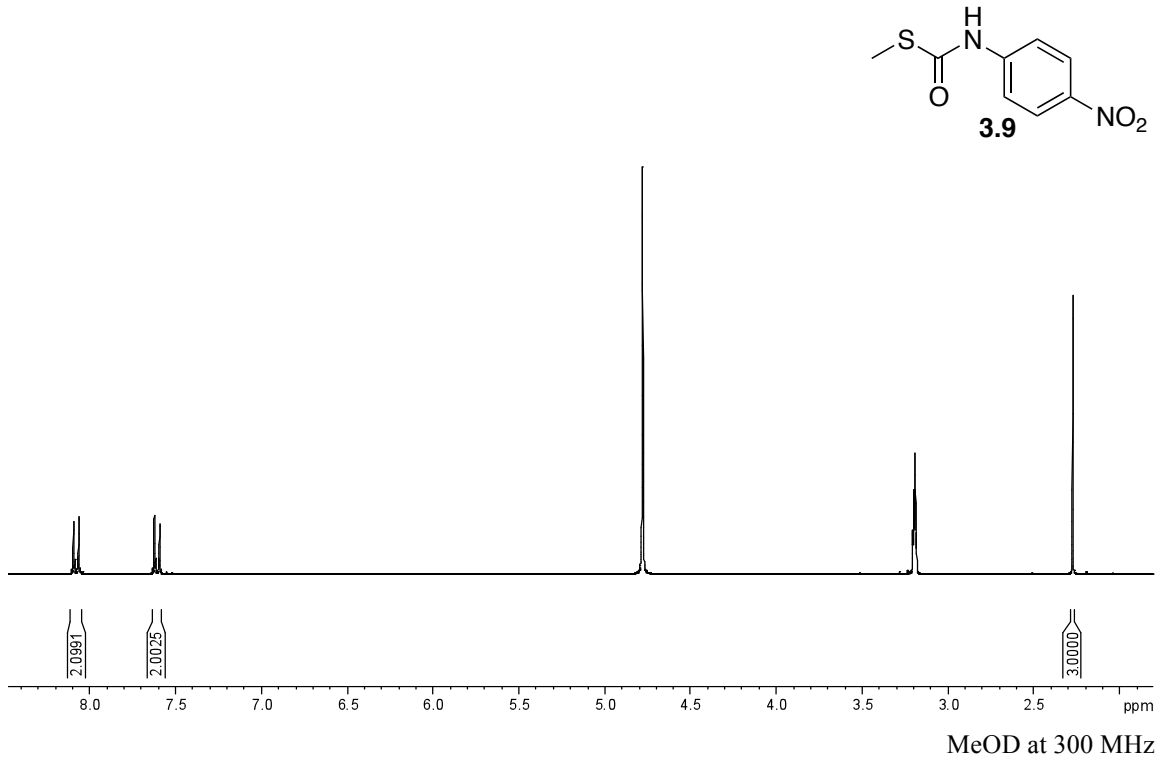


Figure A-30: ^{1}H NMR spectrum of *S*-Methyl (4-nitrophenyl)carbamothioate (**3.9**)

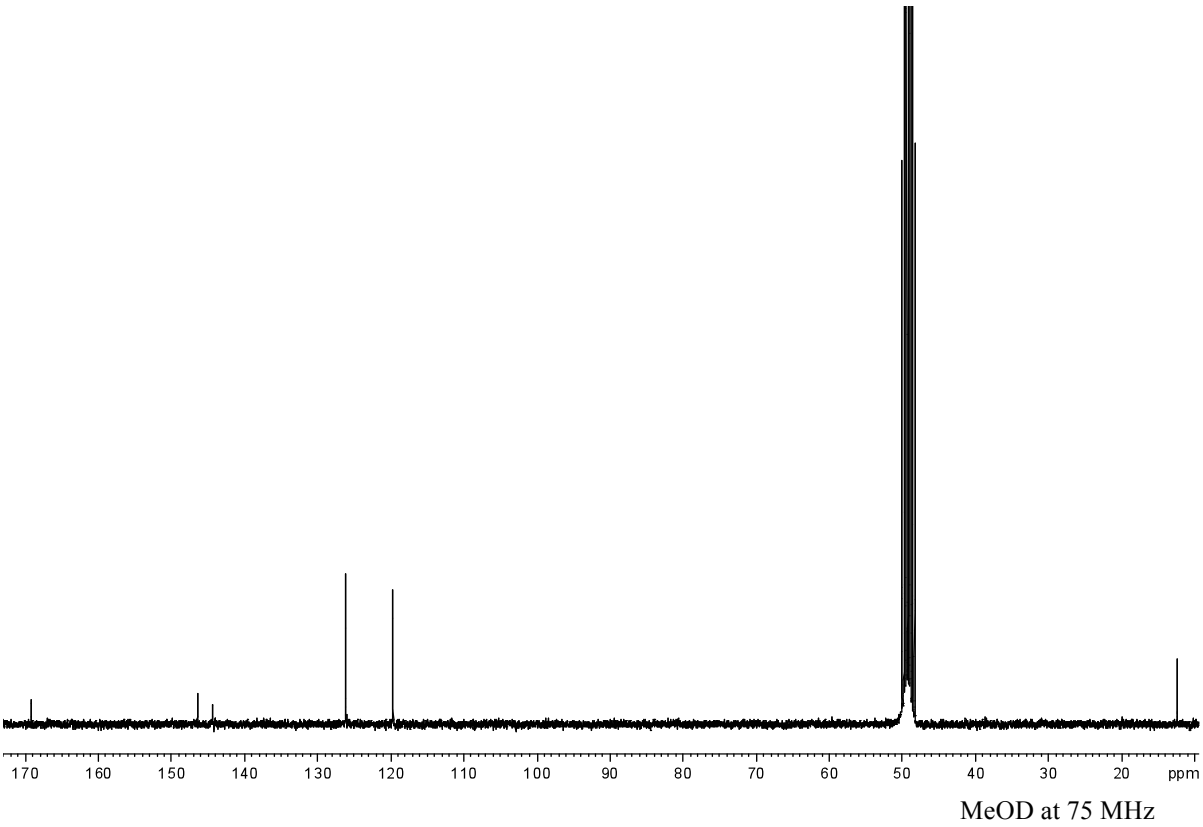


Figure A-31: ^{13}C NMR spectrum of *S*-Methyl (4-nitrophenyl)carbamothioate (**3.9**)

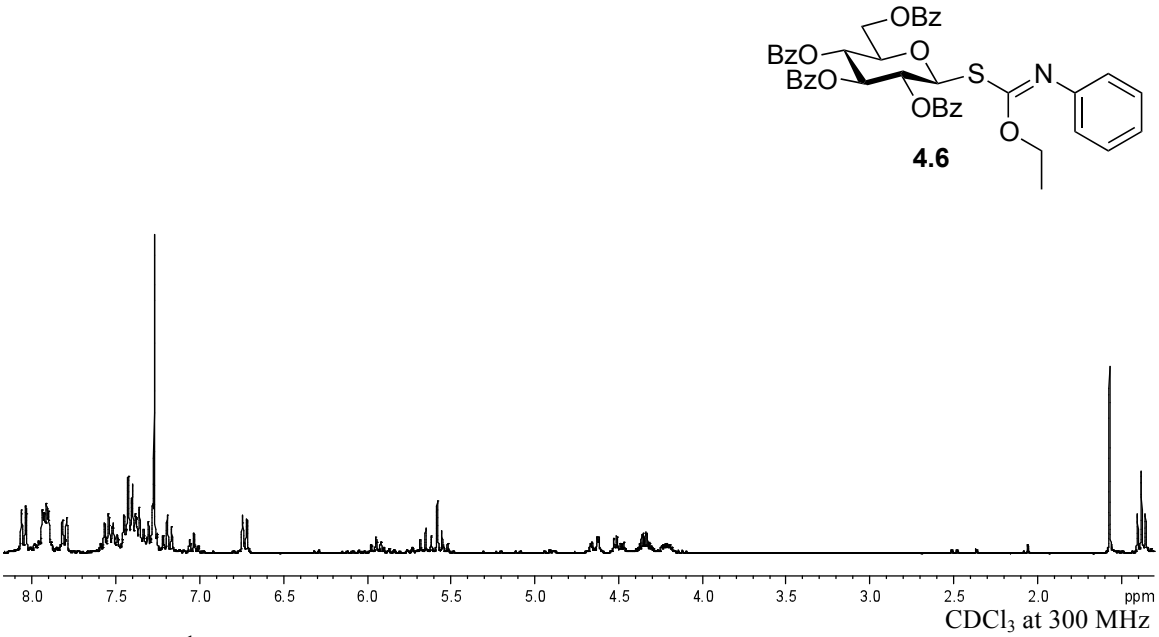


Figure A-32: ^{1}H NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *O*-ethyl phenylcarbamothioate (**4.6**)

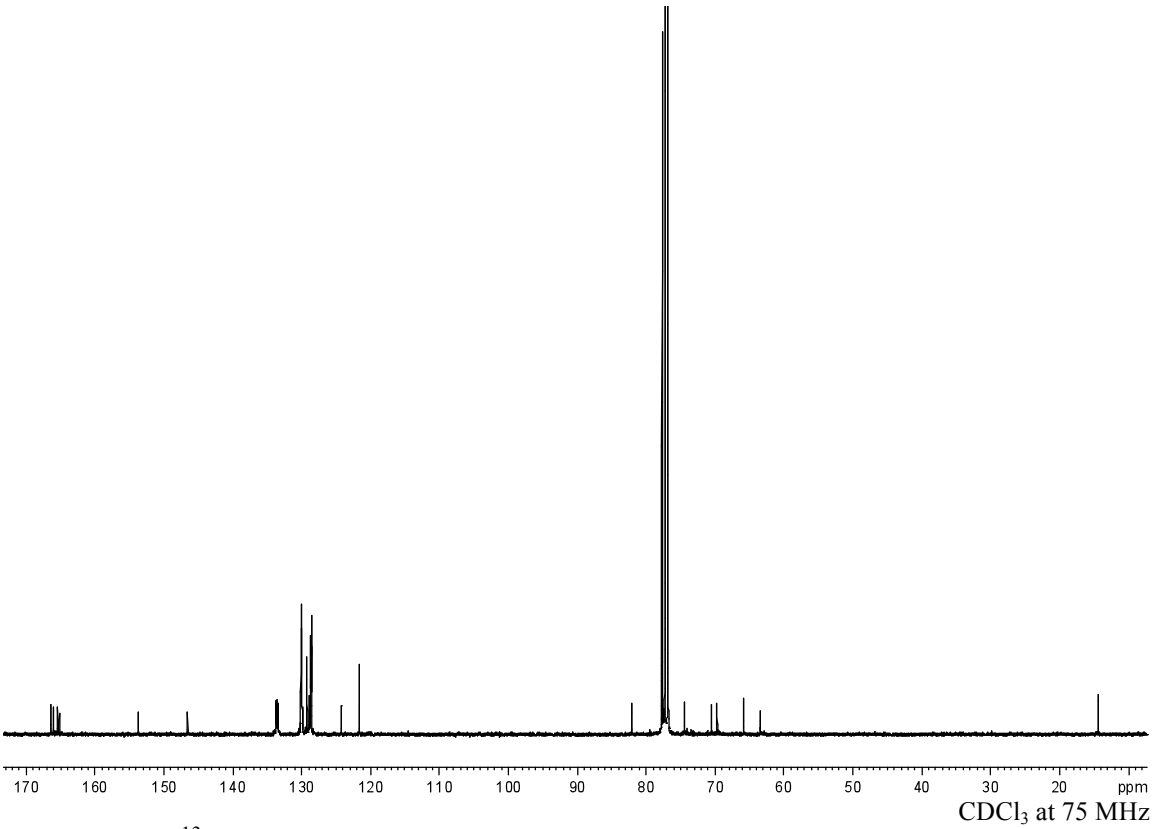


Figure A-33: ^{13}C NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *O*-ethyl phenylcarbamothioate (**4.6**)

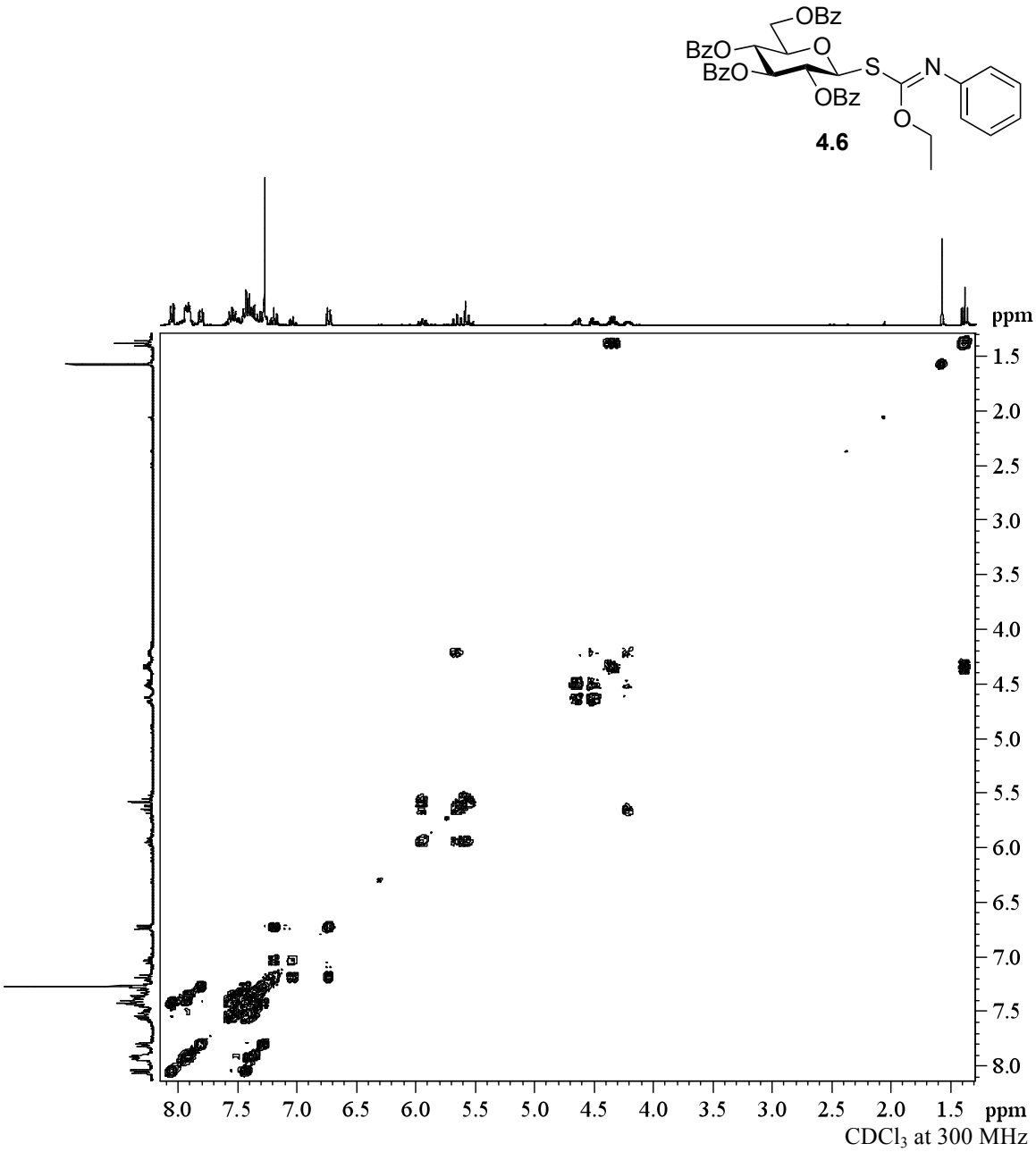
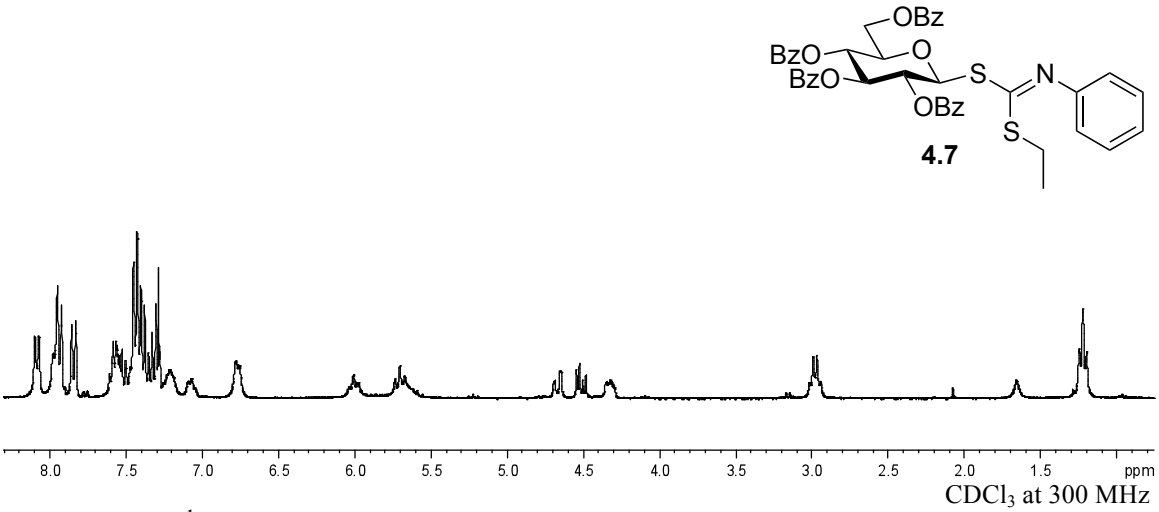
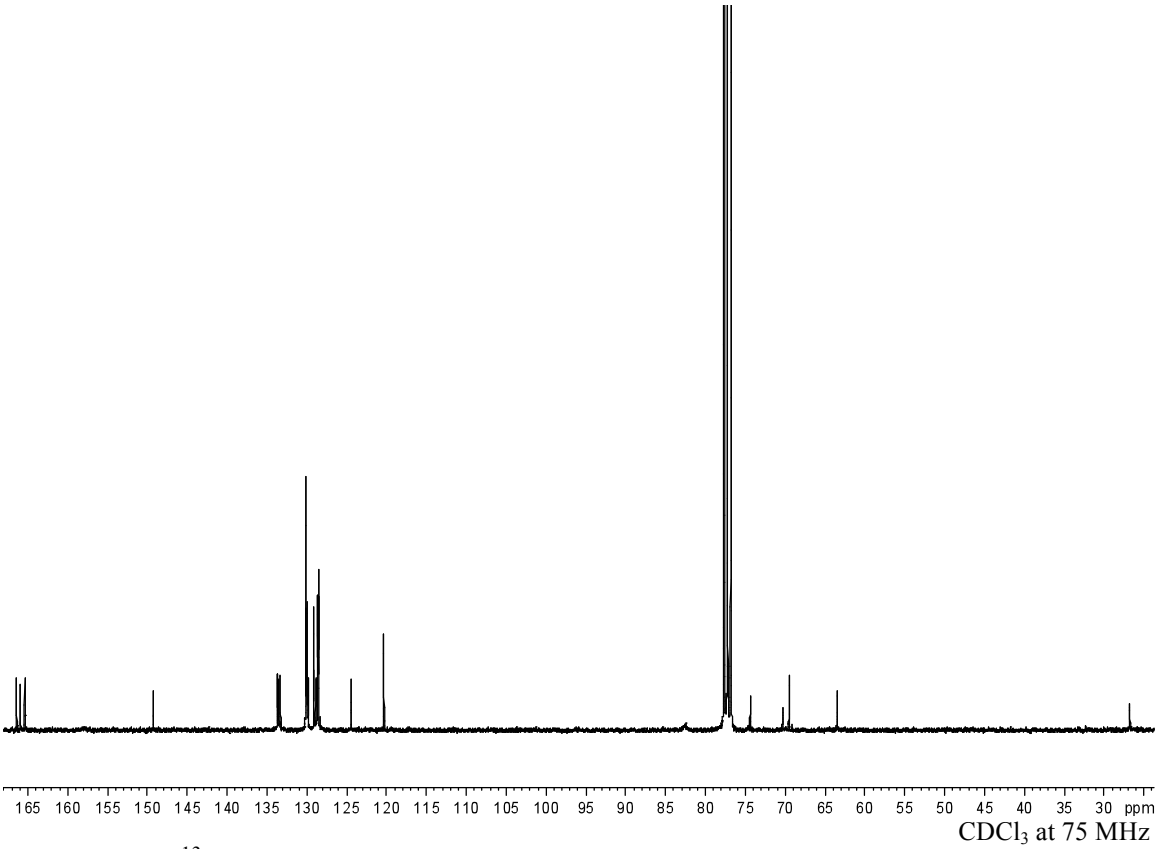


Figure A-34: 2-D NMR COSY spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *O*-ethyl phenylcarbamothioate (**4.6**)



$CDCl_3$ at 300 MHz

Figure A-35: ^{1}H NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl ethyl phenylcarbamodithioate (**4.7**)



$CDCl_3$ at 75 MHz

Figure A-36: ^{13}C NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl ethyl phenylcarbamodithioate (**4.7**)

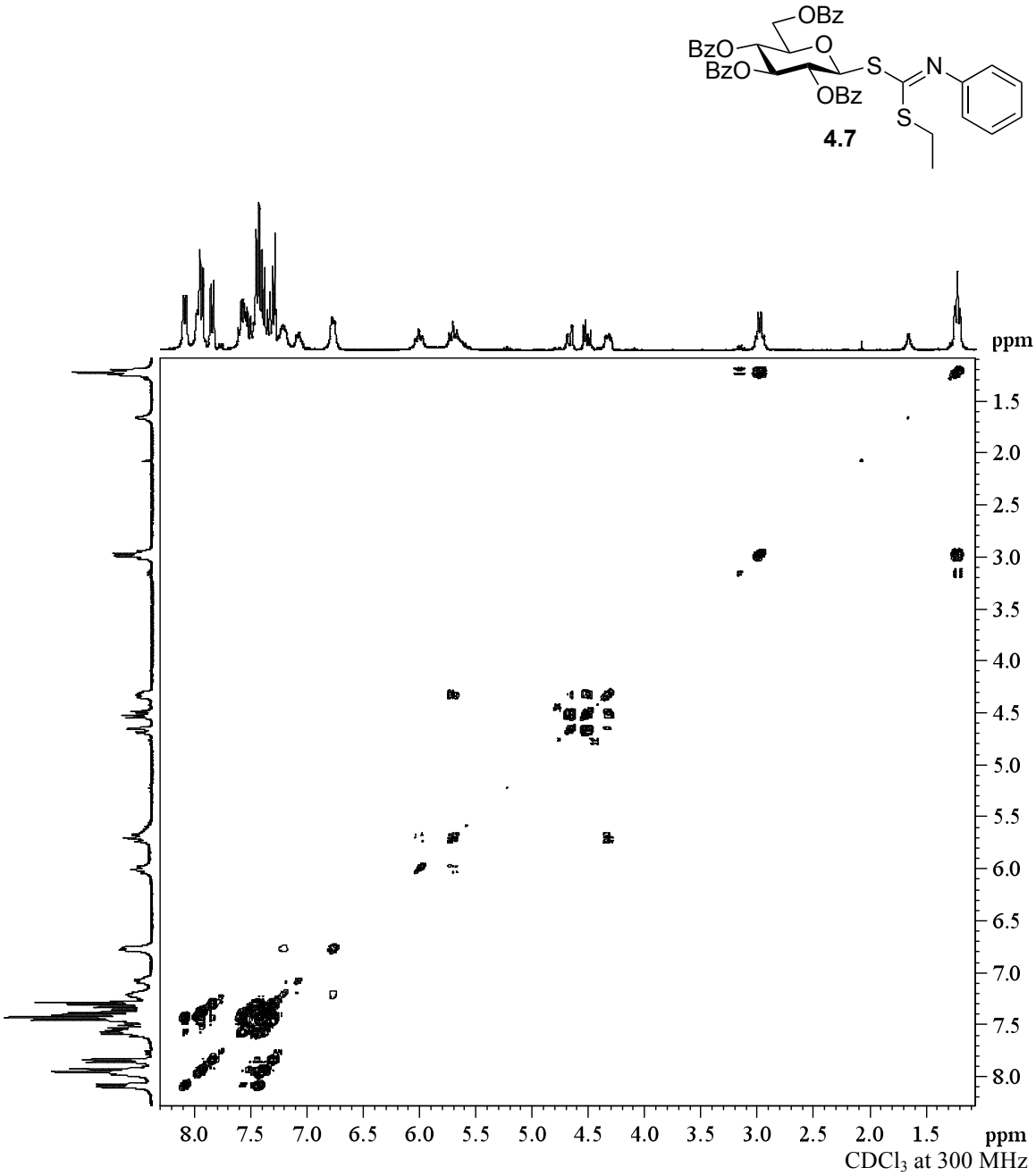
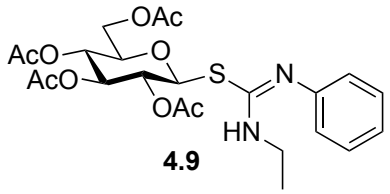
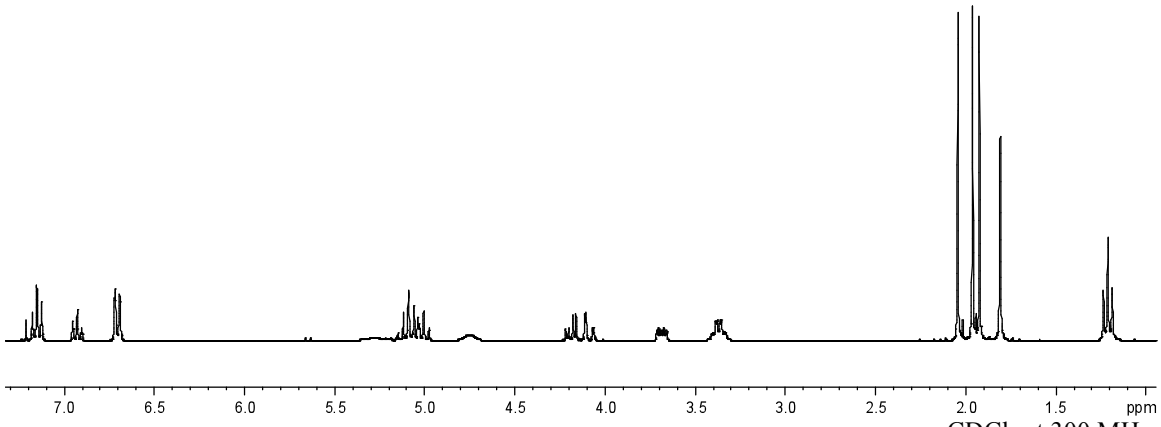


Figure A-37: 2-D NMR COSY spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl ethyl phenylcarbamodithioate (**4.7**)

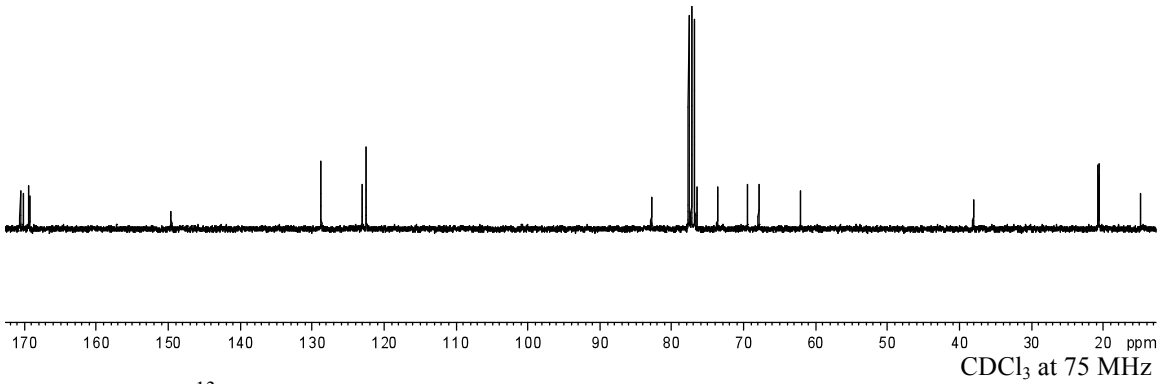


4.9



$CDCl_3$ at 300 MHz

Figure A-38: ^{1}H NMR spectrum of 2,3,4,6-Tetra-*O*-acetyl-1-thio-*β*-D-glucopyranosyl *NH*-ethyl phenylcarbamothioate (**4.9**)



$CDCl_3$ at 75 MHz

Figure A-39: ^{13}C NMR spectrum of 2,3,4,6-Tetra-*O*-acetyl-1-thio-*β*-D-glucopyranosyl *NH*-ethyl phenylcarbamothioate (**4.9**)

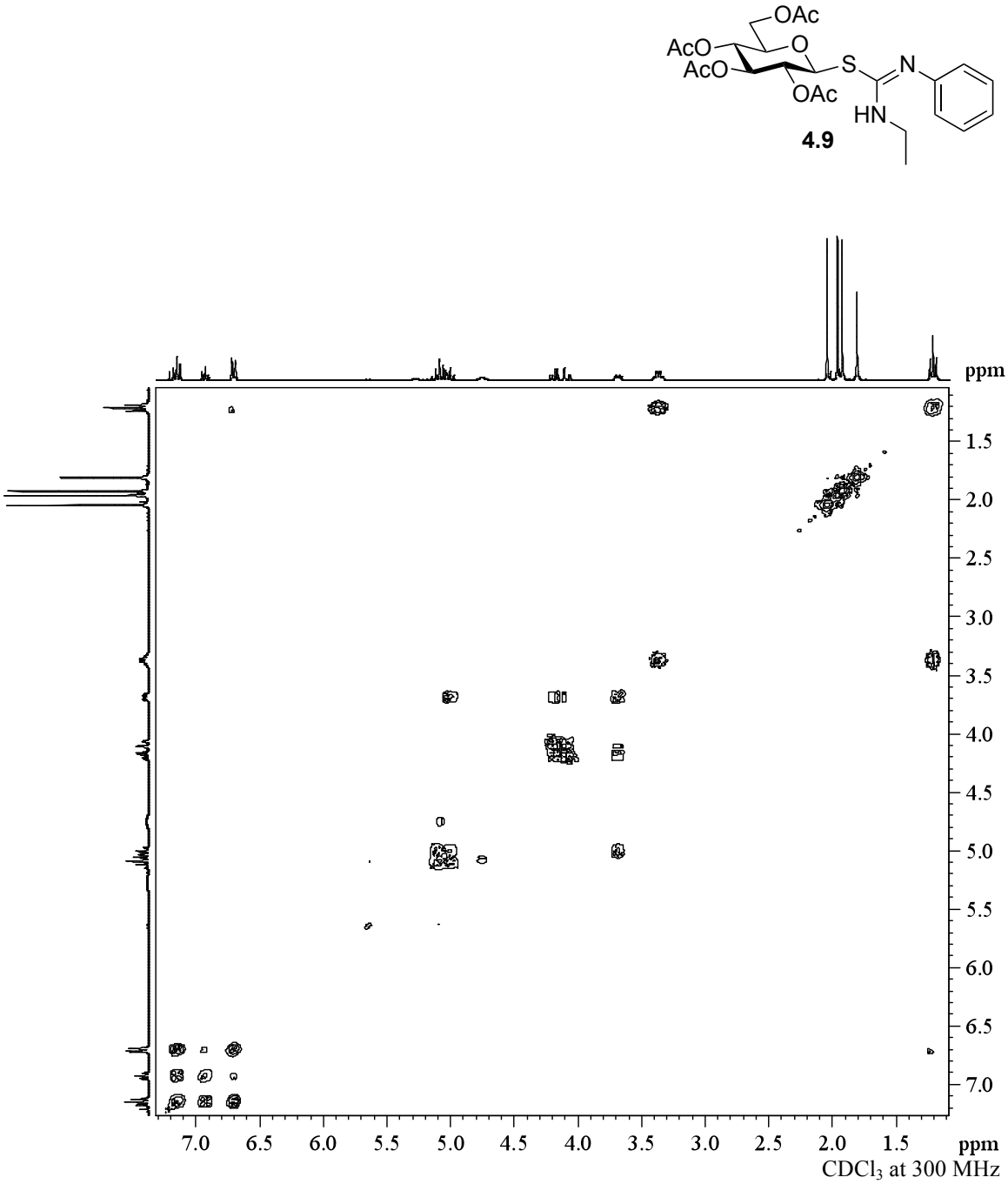


Figure A-40: 2-D NMR COSY spectrum of 2,3,4,6-Tetra-*O*-acetyl-1-thio-*β*-D-glucopyranosyl *NH*-ethyl phenylcarbamothioate (**4.9**)

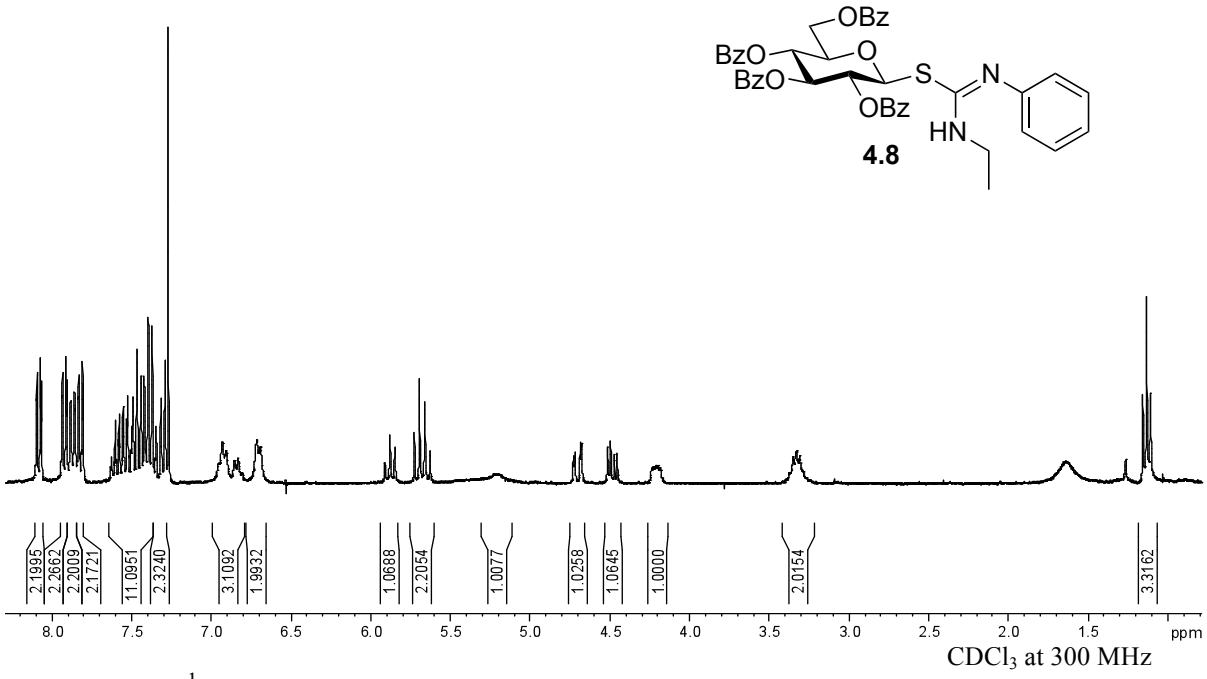


Figure A-41: ^{1}H NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *NH*-ethyl phenylcarbamothioate (**4.8**)

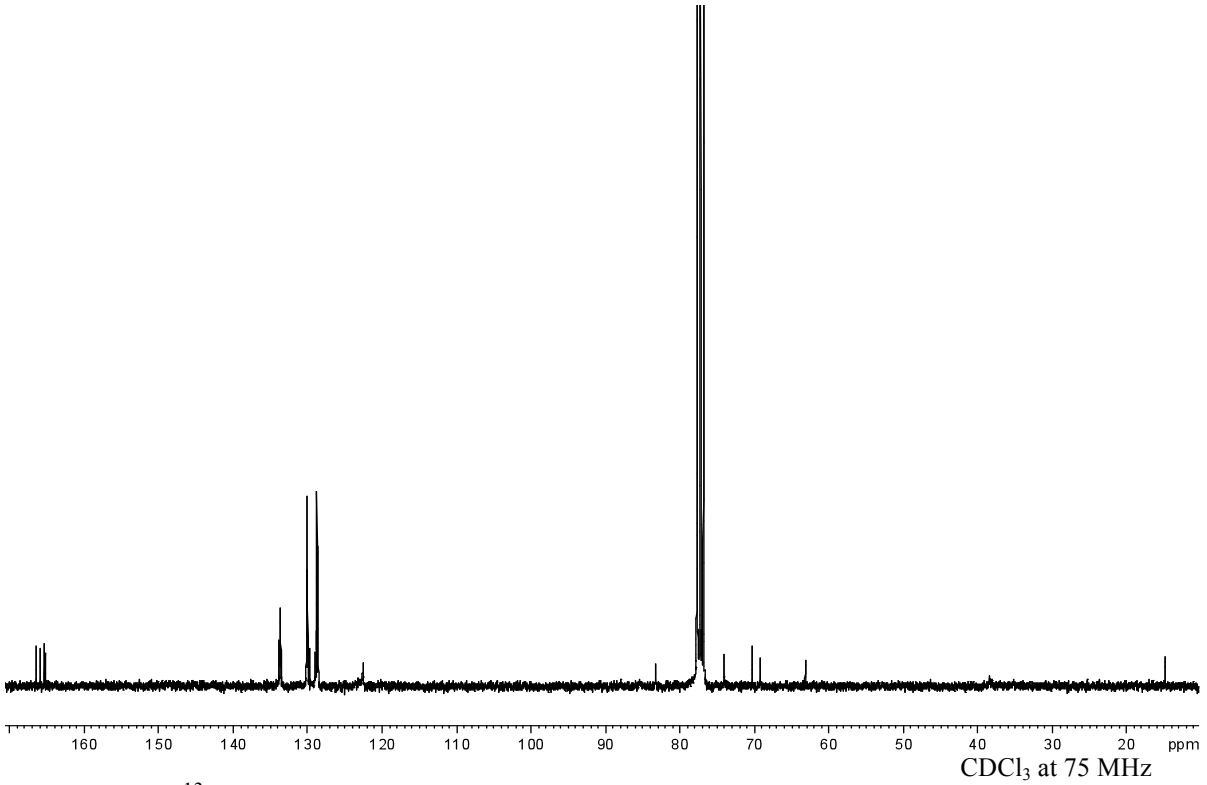


Figure A-42: ^{13}C NMR spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *NH*-ethyl phenylcarbamothioate (**4.8**)

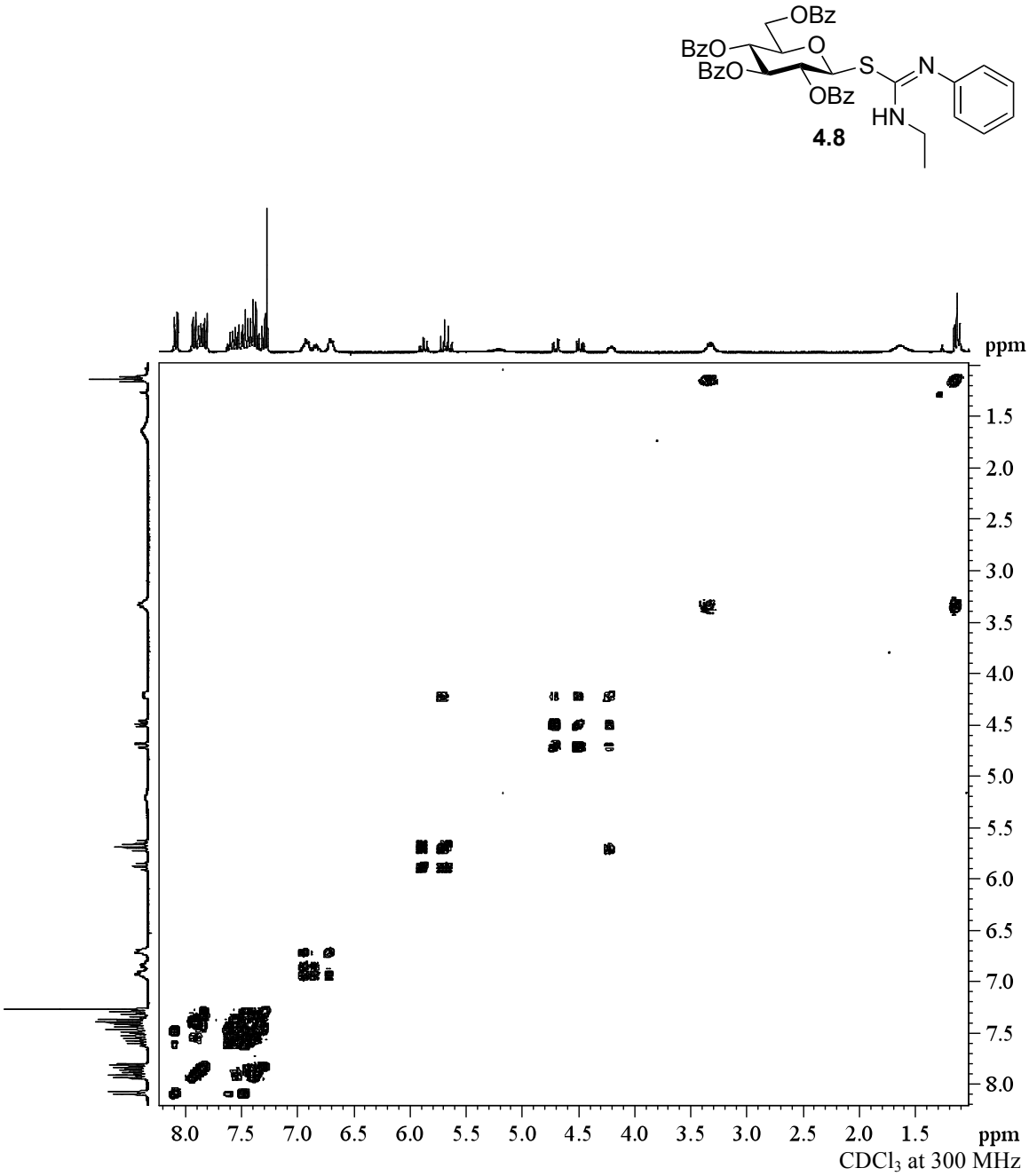
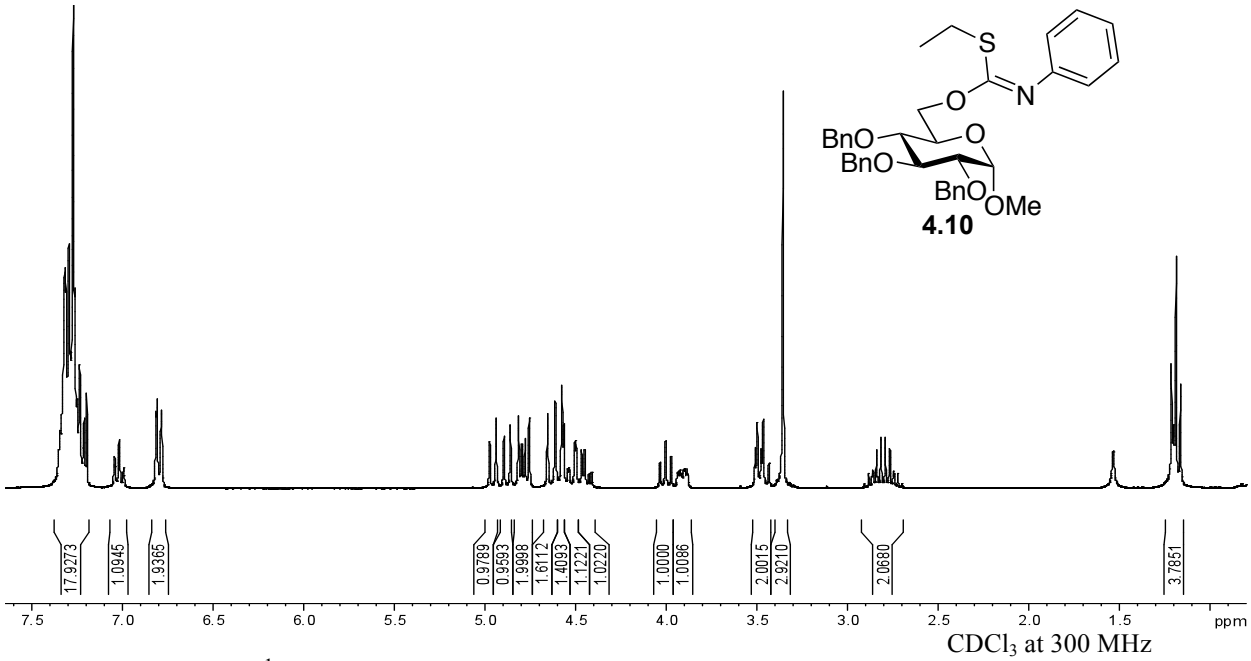
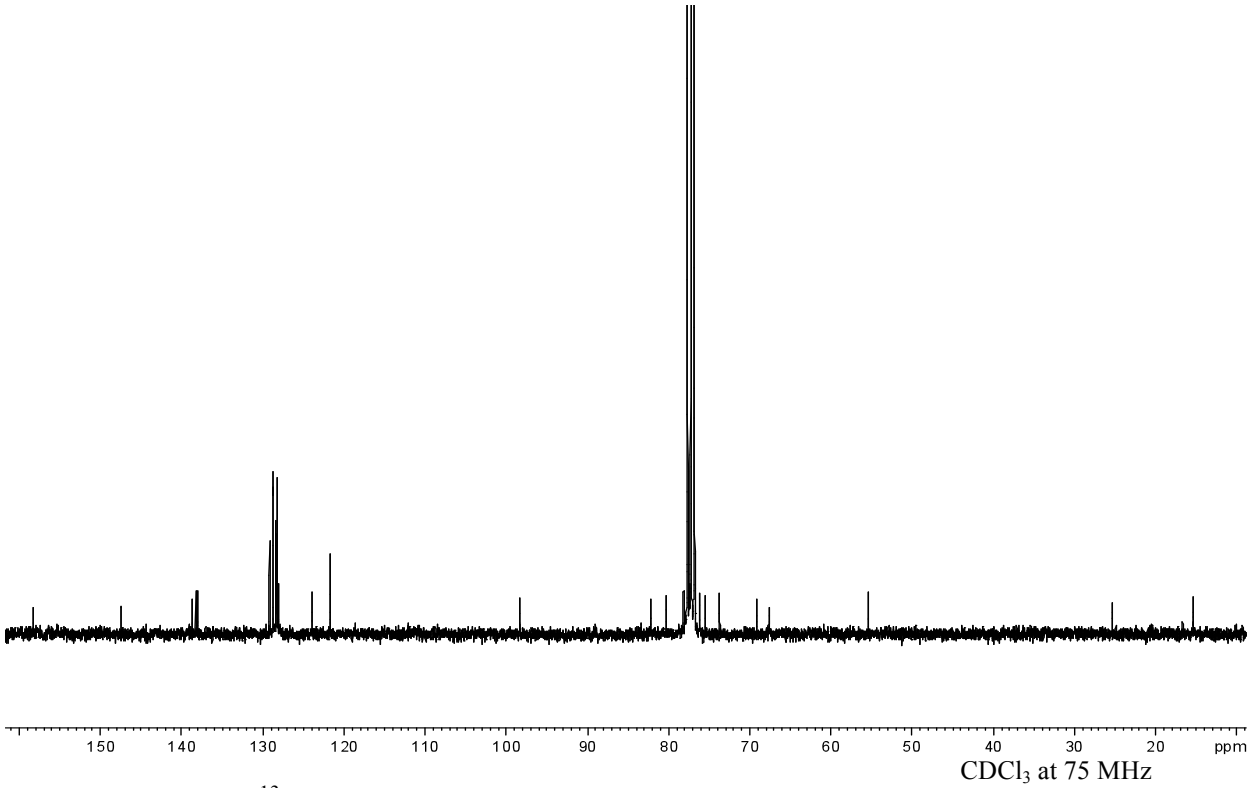


Figure A-43: 2-D NMR COSY spectrum of 2,3,4,6-Tetra-*O*-benzoyl-1-thio-*β*-D-glucopyranosyl *NH*-ethyl phenylcarbamothioate (**4.8**)



$CDCl_3$ at 300 MHz

Figure A-44: ^{1}H NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(*S*-ethyl) phenylcarbamothioate (**4.10**)



$CDCl_3$ at 75 MHz

Figure A-45: ^{13}C NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(*S*-ethyl) phenylcarbamothioate (**4.10**)

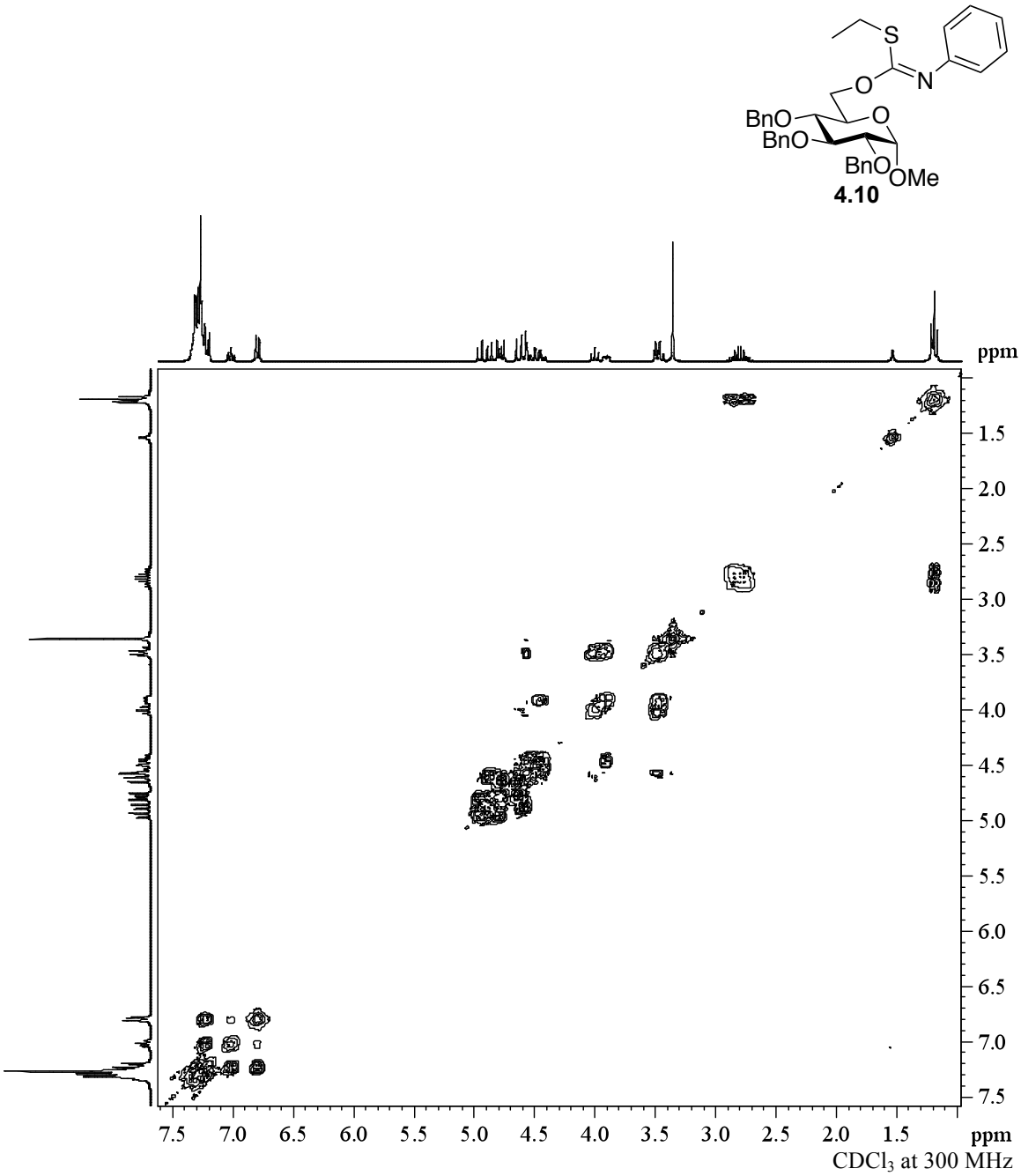
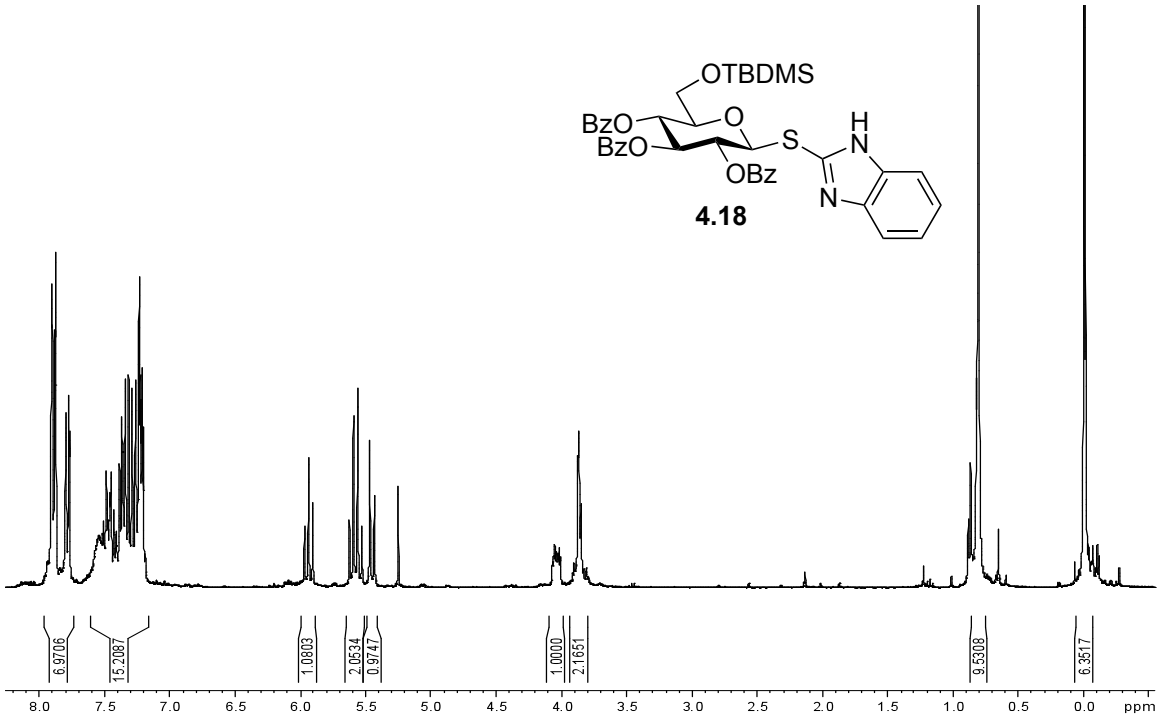
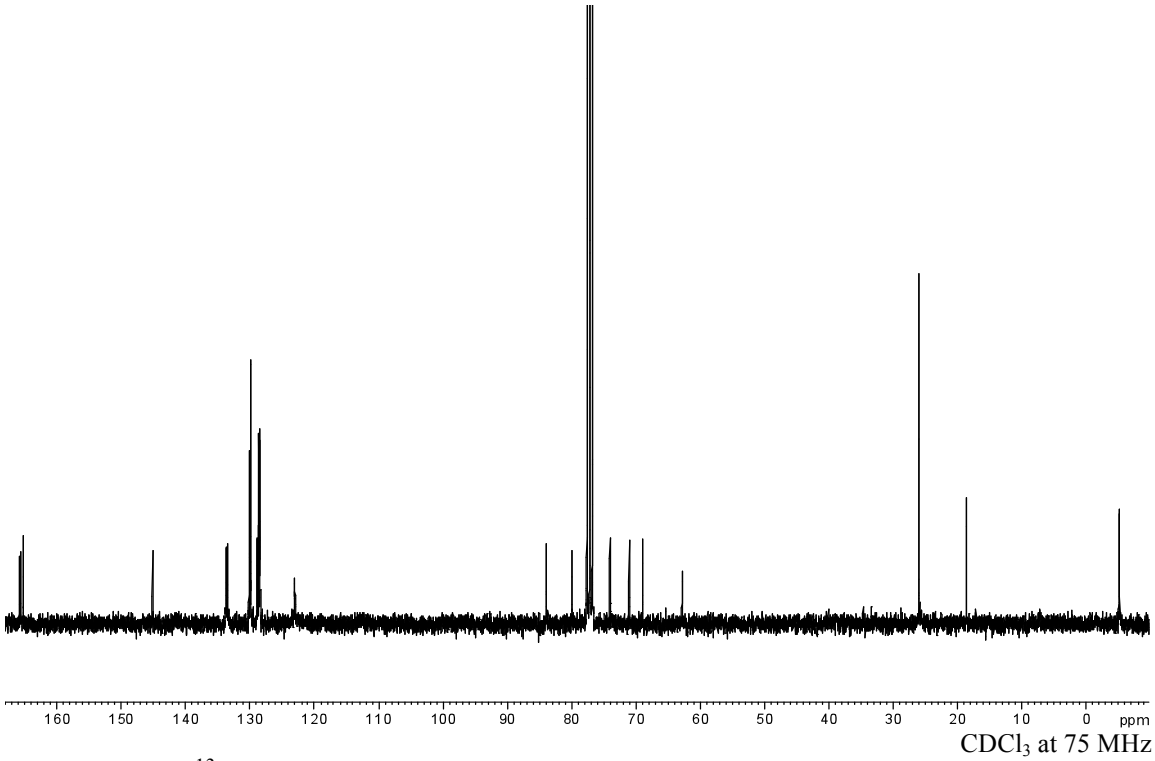


Figure A-46: 2-D NMR COSY spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(*S*-ethyl) phenylcarbamothioate (**4.10**)



$CDCl_3$ at 300 MHz

Figure A-47: ^{1}H NMR spectrum of 2-benzimidazolyl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**4.18**)



$CDCl_3$ at 75 MHz

Figure A-48: ^{13}C NMR COSY spectrum of 2-benzimidazolyl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**4.18**)

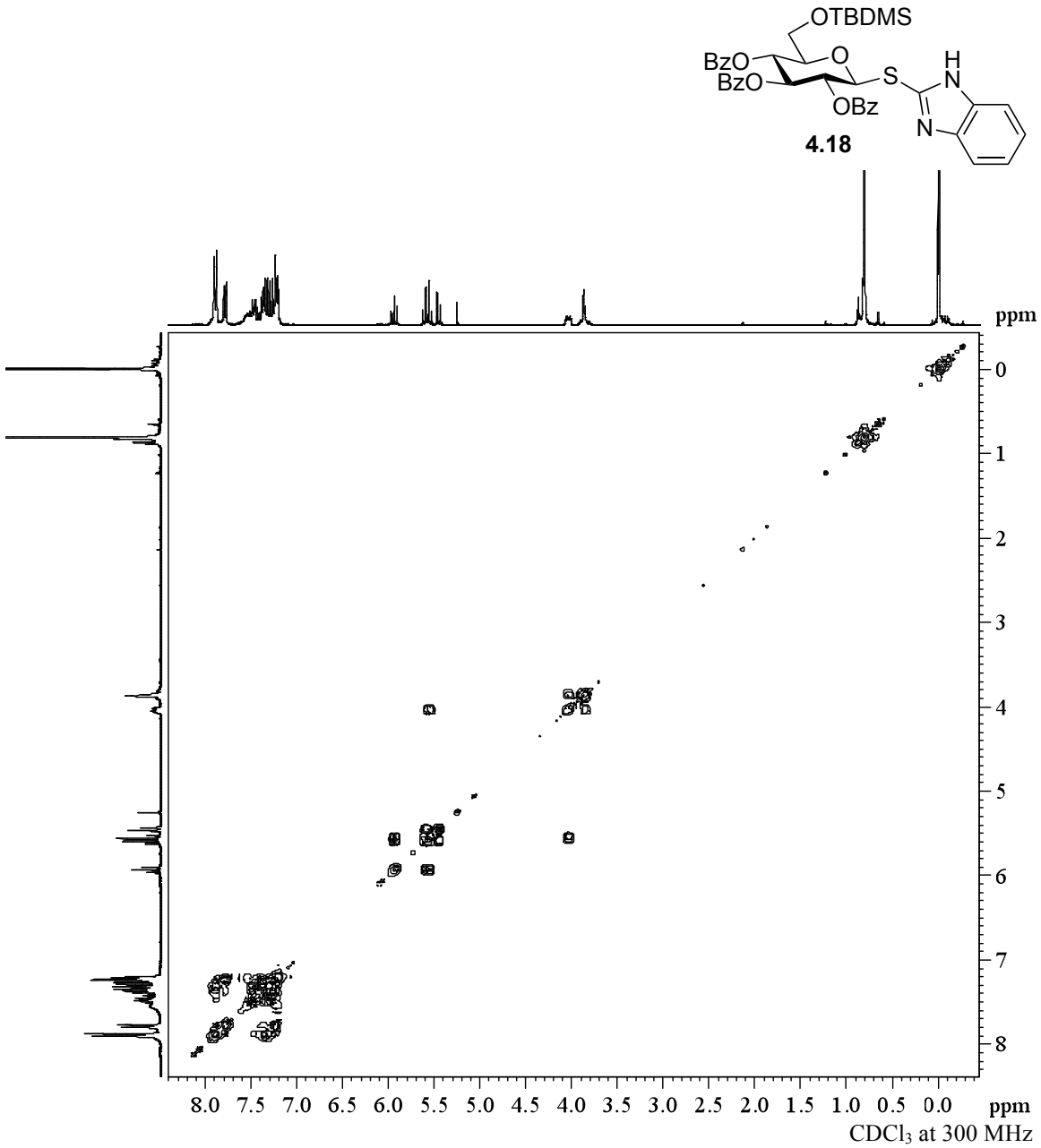


Figure A-49: 2-D NMR COSY spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(*S*-ethyl) phenylcarbamothioate 2-benzimidazolyl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**4.18**)

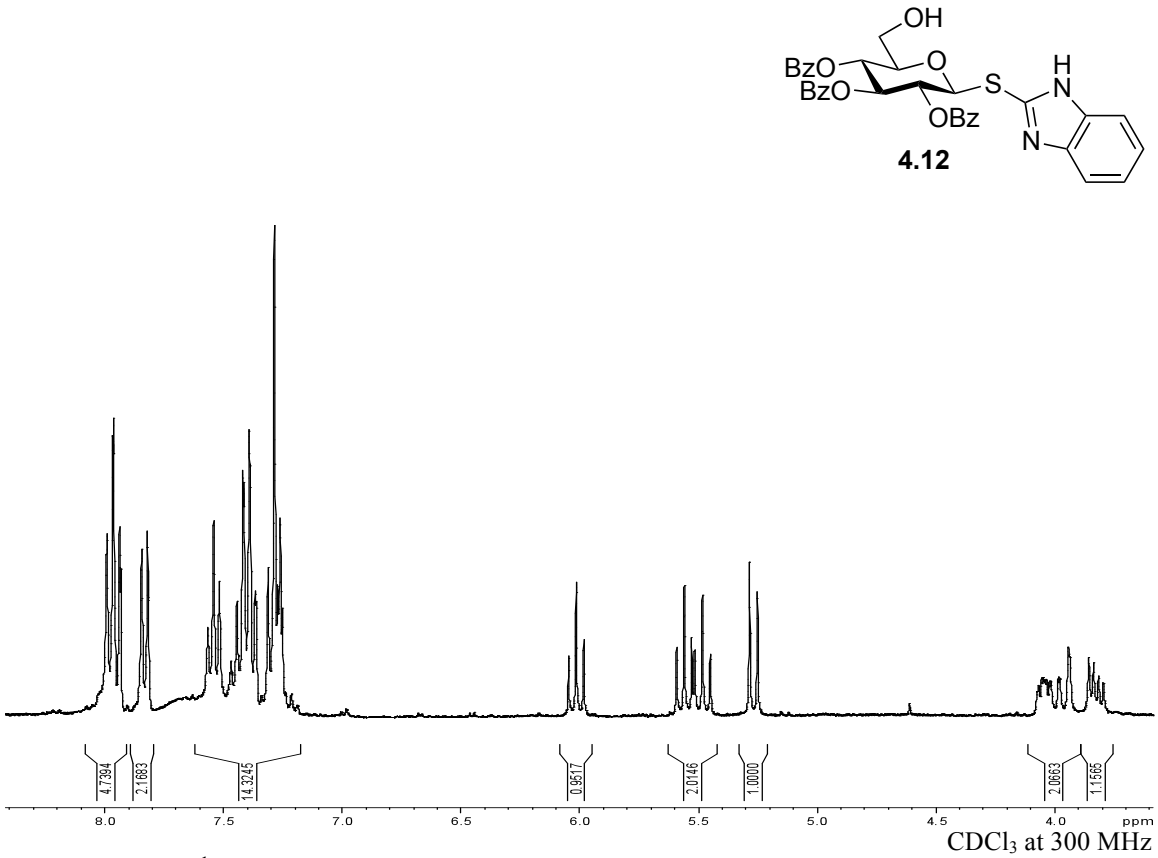


Figure A-50: ^{1}H NMR spectrum of 2-Benzimidazolyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.12**)

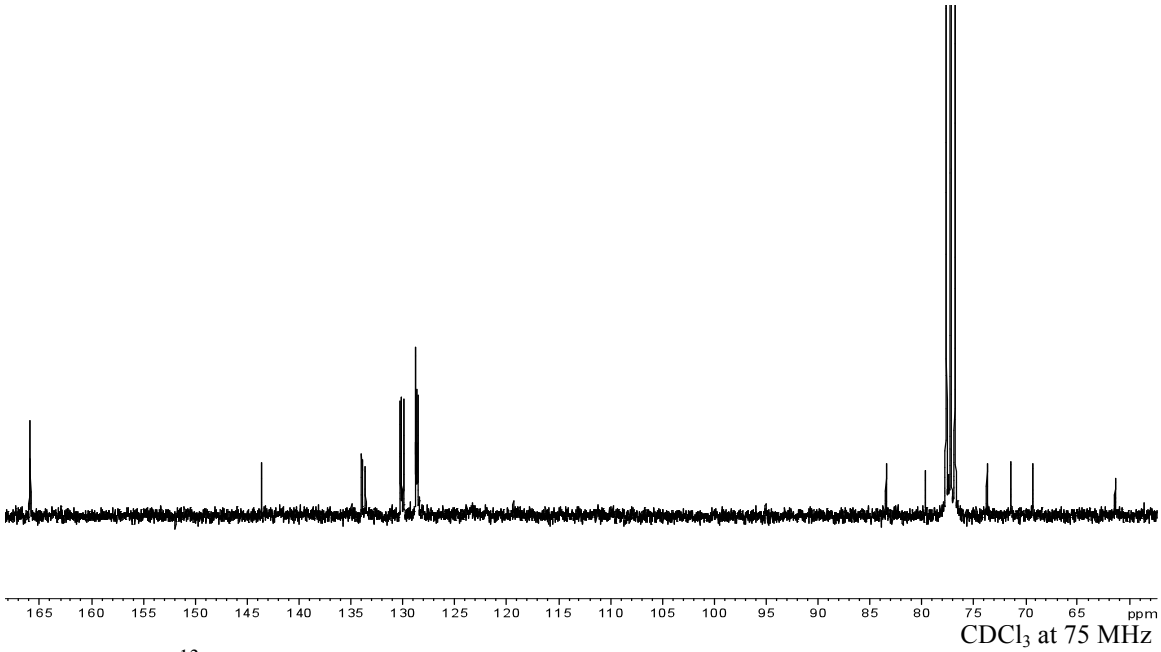


Figure A-51: ^{13}C NMR COSY spectrum of 2-Benzimidazolyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.12**)

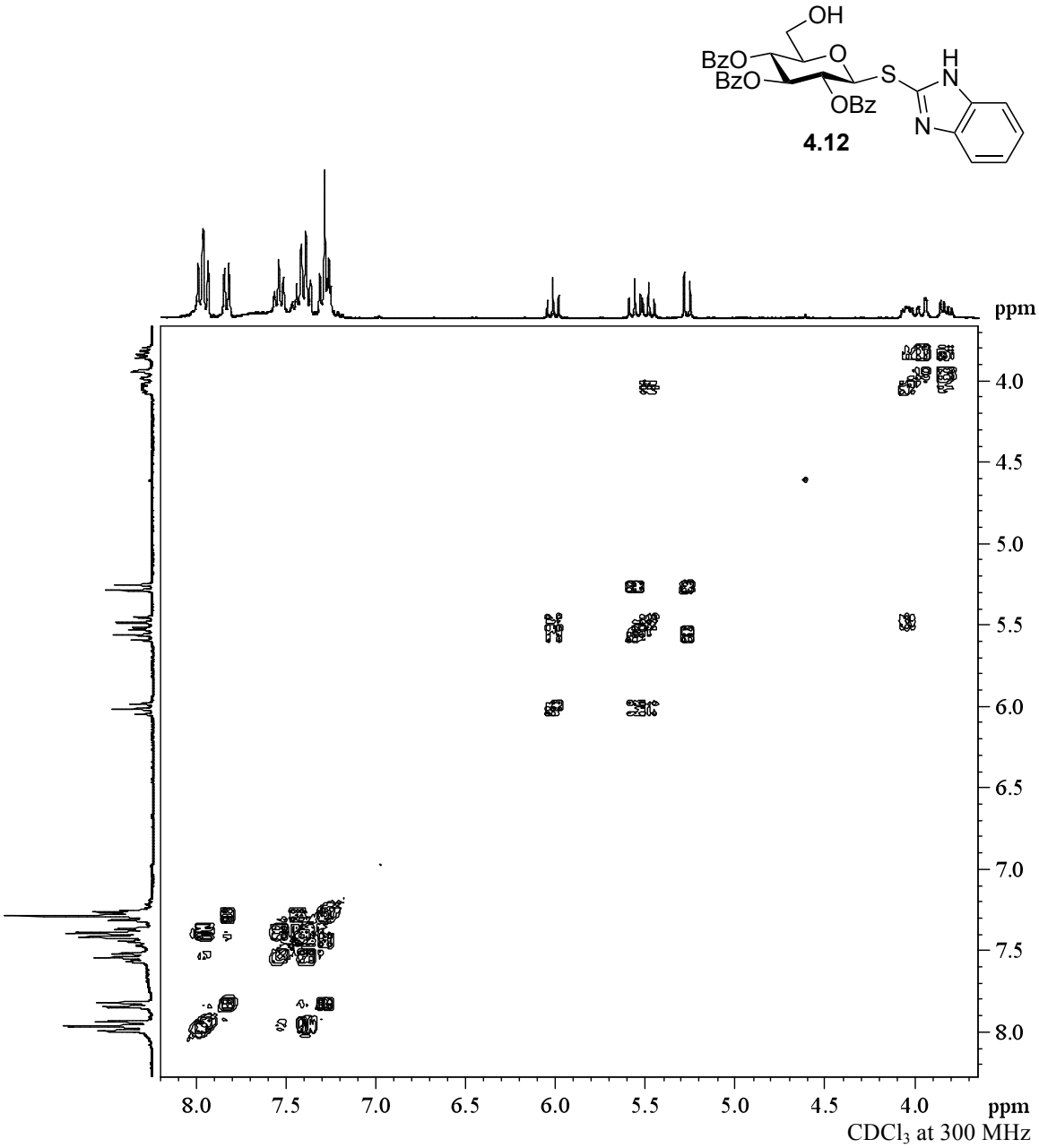
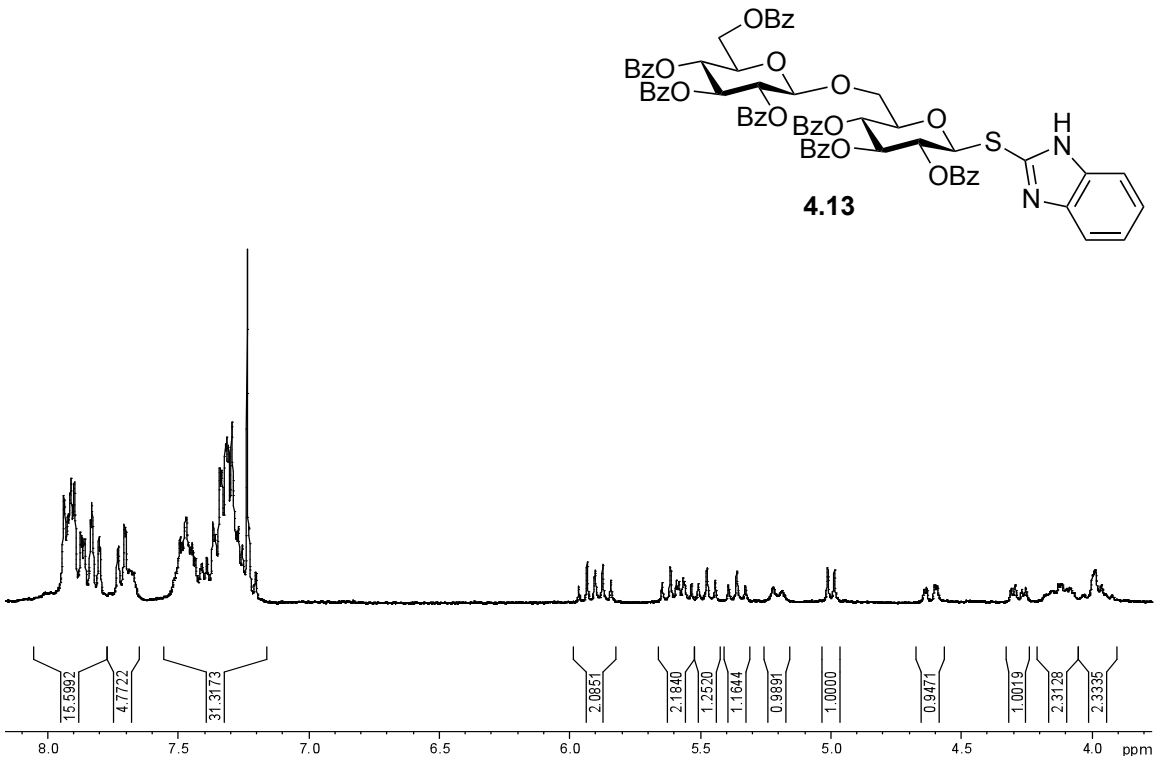
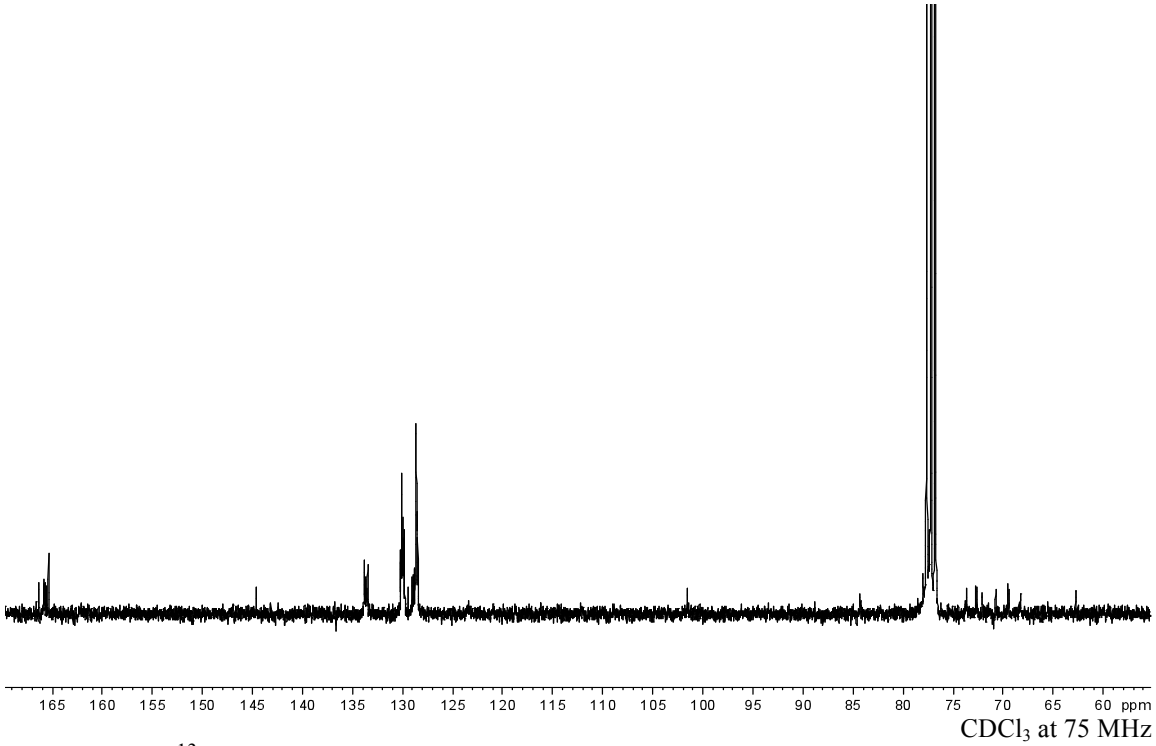


Figure A-52: 2-D NMR COSY spectrum of 2-Benzimidazolyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4.12**)



$CDCl_3$ at 300 MHz

Figure A-53: ^{1}H NMR spectrum of 2-benzimidazolyl *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**4.13**)



$CDCl_3$ at 75 MHz

Figure A-54: ^{13}C NMR COSY spectrum of 2-benzimidazolyl *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**4.13**)

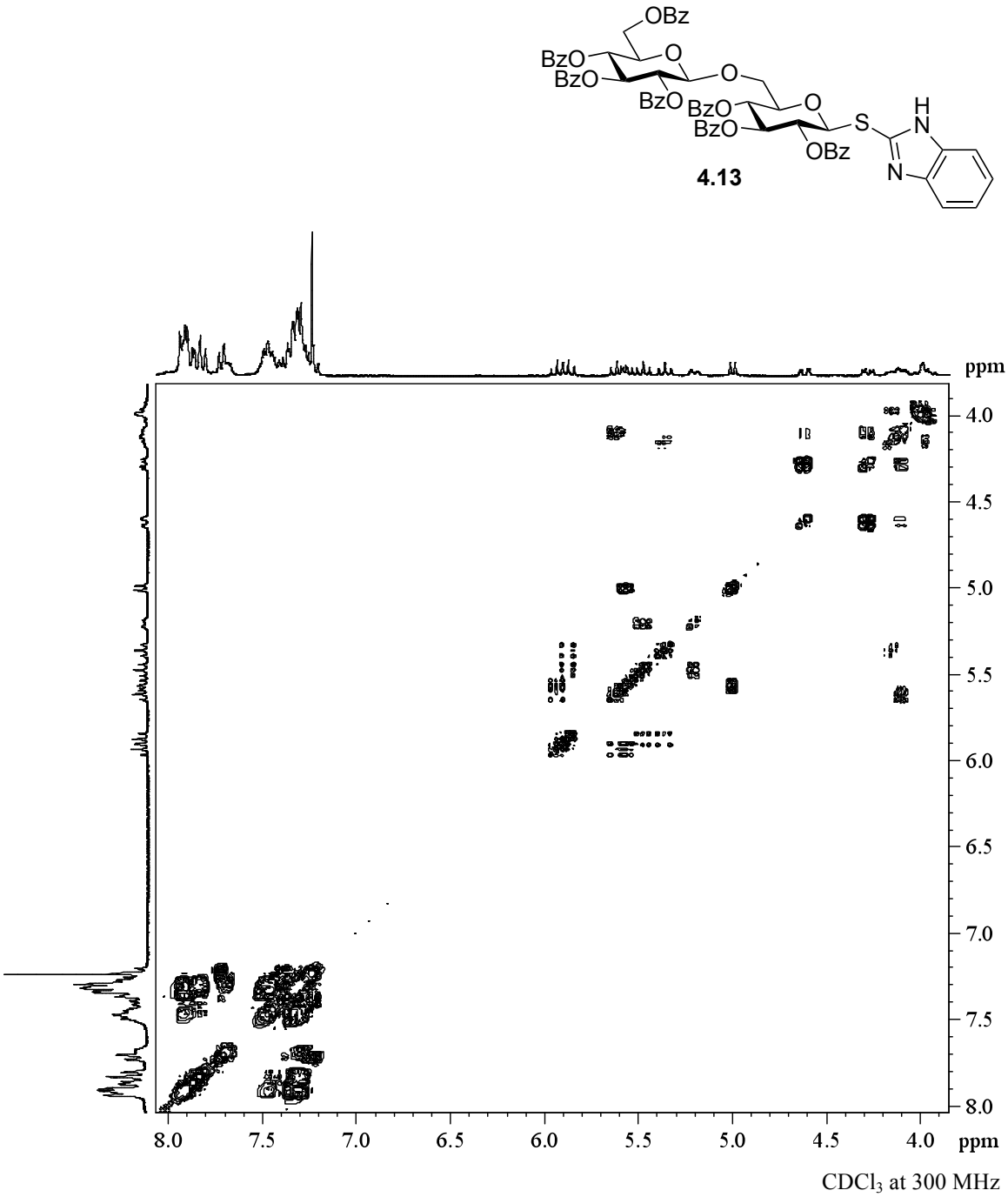


Figure A-55: 2-D NMR COSY spectrum of 2-benzimidazolyl *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**4.13**)