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# New Catalytic Reactions in Carbohydrate Chemistry

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By

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# ABSTRACT


## New Catalytic Reactions in Carbohydrate Chemistry

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Carbohydrates or sugars are some of the most diverse and abundant biological molecules. They are involved in a multitude of processes in the body such as fertilization, cell-cell communication, and cancer metathesis. Because of these vital functions, the study of sugars is rapidly growing field. The field however is limited due to the complex nature of sugars which results in difficulties in obtaining large quantities for study.

Protecting group manipulation is a large emphasis area in carbohydrate chemistry due to the need to selectively protect different functional groups of each molecule during synthesis. Catalytic and selective cleavage of protecting groups is a growing area in the field of carbohydrates as current methods are time-consuming and require large excess of reagents. Picoloyl ester is becoming a common protecting group due to its ability to provide a powerful stereodirecting effect in glycosylation reaction. Chapter 2 details the development of a new catalytic approach to remove the picoloyl group in a highly chemoselective manner.

Protecting group manipulation is only one part of carbohydrate synthesis. New catalytic methods for glycosylation, a fundamental reaction for connecting two sugar

units, are also needed. Chapter 3 describes our recent discovery that catalytic $FeCl_3$ can efficiently activate glycosyl chloride to produce disaccharides in respectable yields in 30 min – 16 h. Chapter 4 further elaborates upon the topic of chemical glycosylation. Described herein is the application of a cooperative $Ag_2O$ and triflic acid catalysis to glycosidation of glycosyl chlorides. Fast reaction times and nearly quantitative yields are the main traits of this method.

Lastly, Chapter 5 combines findings described in the previous chapters into the development of a new superior platform for oligosaccharide synthesis. Currently used strategies for oligosaccharide synthesis are time consuming, inefficient, and may lead to low yields of oligosaccharides. By combining the catalytic picoloyl group cleavage and activation of glycosyl chlorides using $FeCl_3$ we developed a reverse orthogonal synthetic strategy which combined protecting group cleavage and activation of glycosyl donors in one step. We then showcased how efficiently this concept works for the rapid assembly of oligosaccharide sequences.

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# LIST OF ABBREVIATIONS

Å .....Ångström

Ac .....Acetyl

$Ac_2O$.....Acetic anhydride

AcCl …… Acetyl chloride

AcOH .....Acetic acid

$Ag_2O$ .....Silver(I) oxide

$AgClO_4$ ….....Silver perchlorate

AgOTf .....Silver(I) trifluoromethanesulfonate

All ….....Allyl

$BF_3 \cdot OEt_2$ .....Boron trifluoride etherate

$BH_3$•THF.....Borane tetrahydrofuran complex

Bn .....Benzyl

BnBr .....Benzyl bromide

$Br_2$ .....Bromine

BuLi.....Butyl lithium

$Bu_3SnH$ .....Tributyltin(IV) hydride

$Bu_2SnO$ .....Dibutyltin(IV) oxide

Bz .....Benzoyl

BzCl.....Benzoyl chloride

$CaH_2$ .....Calcium hydride

$CDCl_3$ .....Deuterated chloroform

$CD_3OD$ .....Deuterated methanol

$CHCl_3$ .....Chloroform

$CH_2Cl_2$ or DCM .....Dichloromethane

$CH_3COCH_3$ .....Acetone

$ClCH_2CH_2Cl$ .....1,2-Dichloroethane

$(COCl)_2$.....Oxalyl chloride

$Cu(OAc)_2$.....Copper(II) acetate

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

d .....Doublet

dd .....Doublet of doublets

DIPEA or *i*-$Pr_2NEt$ .....*N*,*N*-Diisopropylethylamine

DMAP .....4-Dimethylaminopyridine

DMC .....2-Chloro-1,3-dimethylimidazolinum chloride

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

EDC .....1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide

Et .....Ethyl

$Et_2O$ .....Diethyl ether

EtOAc..... Ethyl acetate

EtOH..... Ethanol

$Et_3SiH$..... Triethylsilane

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

Fmoc.....Fluorenylmethoxycarbonyl

FPyr.....*N*-Formylpyrrolidine

h ..... Hour(s)

HCl .....Hydrogen chloride

HMDS ..... Hexamethyldisilazane

$H_2O$.....Water

$H_2O_2$ .....Hydrogen peroxide

$H_2NNH_2$ $H_2O$ .....Hydrazine hydrate

HR-ESI MS .....High Resolution Electrospray Ionization mass spectrometry

Hz .....Hertz

$I_2$ .....Iodine

IBO..... Isobutylene oxide

IPA..... Isopropenyl acetate

k .....Kilo

$KHF_2$.....Potassium bifluoride

$K_2SO_4$.....Potassium Sulfate

Lev.....Levulinoyl

M .....Molar

m ..... Multiplet

Me ..... Methyl

MeCN ..... Acetonitrile

$Me_2EtSiH$.....Dimethylethylsilane

$MeNO_2$ ..... Nitromethane

MeOH ..... Methanol

min ..... Minute(s)

MS ..... Molecular sieves

MW .....Molecular weight

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

Na .....Sodium

$NaCNBH_3$ .....Sodium cyanoborohydride

NaH .....Sodium hydride

$NaHCO_3$ .....Sodium bicarbonate

NaOH ..... Sodium hydroxide

NaOMe ..... Sodium methoxide

Nap ..... Naphthyl

$Na_2S_2O_3$ .....Sodum thiosulfate

NBS ..... *N*-Bromosuccinimide

NMR ..... Nuclear magnetic resonance

NPhth .....Phthalimido

$PBr_3$ ..... Phosphorus tribromide

$PCl_5$ ..... Phosphorus tetrachloride

Pd/C .....Palladium on carbon

Ph ..... Phenyl

$Ph_2SO$ ..... Diphenyl sulfoxide

$Ph_3PO$ ..... Triphenylphosphine oxide

Pico ..... Picoloyl

PivCl ..... Pivaloyl chloride

pMB ..... *p*-Methoxybenzyl

ppm ..... Parts per million

Py .....Pyridine

R*f*..... Retention factor

rt ..... Room temperature

s ..... Singlet

SBox .....*S*-Benzoxazolyl

SEt ..... Ethylthio

$SnCl_2$ ..... Tin(II) chloride

$SnCl_4$ ..... Tin(IV) chloride

$SOCl_2$ ..... Thionyl Chloride

SPh ..... Phenylthio

SPh-Cl ..... 4-Chlorophenylthio

STol ..... 4-Methylphenylthio

t ..... Triplet

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

TBACN ..... Tetra-*n*-butyl ammonium cyanide

TBAI ..... Tetra-*n*-butyl ammonium iodide

TBDMS or TBS ..... *tert*-Butyldimethylsilyl

TBDPS ..... *tert*-Butyldiphenylsilyl

TBDMSiH ..... *tert*-Butyldimethylsilane

TCT.....Trichlorotriazine

*tert*-BuOH.....*tert*-Butanol

TFA ..... Trifluoroacetic acid

$Tf_2O$ .....Trifluoromethanesulfonic (triflic) anhydride

TfOH ..... Trifluoromethanesulfonic (triflic) acid

THF .....Tetrahydrofuran

$TiCl_4$.....Titanium(IV) Chloride

TLC ..... Thin layer chromatography

TMS .....Trimethylsilyl

TMSI.....Trimethylsilyl iodide

TMSOTf ..... Trimethylsilyl trifluoromethanesulfonate

TPPO ..... Triphenylphosphine oxide

TsOH ..... *p*-Toluenesulfonic acid

TTMPP ..... Tris(2,4,6-trimethoxyphenyl)phosphine

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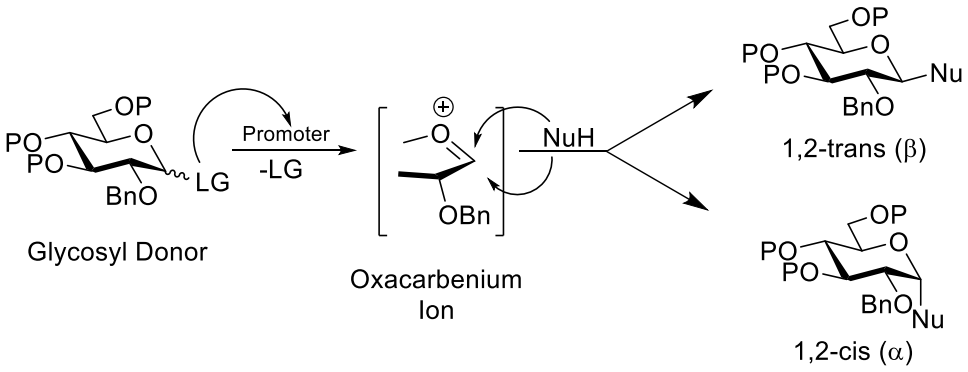
# CHAPTER 1

## Synthesis and Reactions of Glycosyl Chlorides and Iodides

## 1.1. Introduction

The development of stereoselective glycosylation methods and efficient strategies for the synthesis of complex carbohydrates is critical for the field of glycosciences. Significant improvements of the disaccharide synthesis have emerged with the introduction of various glycosylation methods. While certain methods allow solving particular challenges associated with stereoselective glycosylation, no method can do it all.

**Scheme 1.1. General glycosylation reaction representation**




For the synthesis of disaccharides, monosaccharide building blocks are coupled together by means of the glycosylation reaction, arguably the most important and challenging reaction in carbohydrate chemistry.[1] Typical chemical glycosylation involves the nucleophilic displacement of the leaving group (LG) on the glycosyl donor with the hydroxyl moiety of the glycosyl acceptor (Scheme 1.1). The remaining hydroxyls (or other functional moieties) of both units are temporarily masked with protecting groups. There are many complexities to consider when depicting the mechanism of the glycosylation reaction,[2,3] and often a clear delineation between $S_N1$ and $S_N2$ nucleophilic substitution reactions is obscured.[4]

Various factors such as temperature, pressure, structure, conformation, solvent,

promoter, steric hindrance, or leaving group can affect the stereoselectivity of glycosylation.[5] Some of these factors influence the stereoselectivity dramatically, others only to certain extent. Undoubtedly, the leaving group is one of the major players in this respect. As a result, a number of glycosyl donors have been developed.[6,7] However, even the most commonly used halides, O-trichloroacetimidates, or alkyl/aryl thioglycosides have their limitations. First introduced in glycosylation, glycosyl halides remain prominent glycosyl donors, and recent advances are expected to provide further enhancement of their utility in synthesis.

This Chapter summarizes recent advances made in the area of the disaccharide and oligosaccharide synthesis using glycosyl halides as donors. In particular, we will focus our discussion on glycosyl chlorides as the most pertinent compounds to the topic of this dissertation, and glycosyl iodides as the least explored glycosyl donors of this class. A brief overview of fluorides and bromides commonly used in synthesis will also be presented.

### 1.2. Overview of Common Glycosyl Halides (Bromides and Fluorides)

The classic Koenigs–Knorr methodology for glycoside synthesis implies the use of glycosyl bromides (and chlorides) as glycosyl donors.[8-10] Traditional approach makes use of insoluble silver oxide or silver carbonate as acid scavengers. The Helferich modification involves the use of mercury salts as relatively active yet toxic promoters.[11] Although nowadays, these classic approaches are mainly used the synthesis of simple glycosides, a number of successful applications for the di- and higher saccharide synthesis is available.[12] More reactive activators have been introduced over the years, among these a partially soluble silver triflate is most commonly used in a combination

with a base for synthesis.[13,14] The *in-situ* anomerization procedure, so called *"halide ion catalyzed glycosidation reactions"* by Lemieux and co-workers has been successfully applied to the synthesis of 1,2-cis-glycosides from reactive glycosyl bromides.[15] Bromides obtained from thioglycosides with $Br_2$ in situ have been also used in a variety of applications.[16] Activations of glycosyl halides in the presence of a Lewis acid or other promoters are also known.[6]

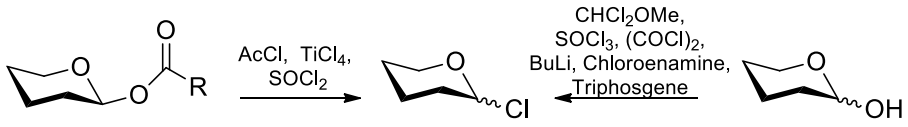
Glycosyl fluorides were introduced by Mukaiyama who demonstrated that an α-glucosyl fluoride could be activated in the presence of $SnCl_2$ and $AgClO_4$ to afford glycosides with excellent yields.[17] This glycosylation approach has become very popular due to advantageous features of fluorides as glycosyl donors discovered: accessibility, greater stability over their bromide and chloride counterparts, unique activation conditions, in versatility in oligosaccharide synthesis.[18,19] Among the most effective application of glycosyl fluorides is Nicolaou's two-stage activation procedure,[20] and the *orthogonal glycosylation strategy* developed by Ogawa and co-workers.[21] Glycosyl fluorides can be activated in the presence of a number of other activating systems; overall, these potent glycosyl donors are widely used for the introduction of various glycosidic linkages.[22] Amongst these is a simple and efficient activation with TfOH, a method that offers further experimental advantages.[23]

### 1.3. Glycosyl Chlorides

For the first time glycosyl chlorides were synthesized from free glucose by the treatment with acetyl chloride (AcCl) by Colley.[24,25] Expanding on the early work by Colley, others have also used AcCl for the synthesis of glycosyl chlorides of other sugar series.[26,27] Subsequently, more general methods have been developed for the synthesis of

glycosyl chlorides. Most commonly, glycosyl chlorides are prepared from two anomeric groups, either an ester protecting group such as acetate or hemiacetal (Scheme 1.2). Selected reagents suitable for converting anomeric esters into glycosyl chlorides include $TiCl_4$,[28] $SOCl_2$,[29] and $PCl_5$.[30] Representative reagents used in the synthesis of chlorides from hemiacetals include $CHCl_2OMe$,[31,32] $SOCl_2$,[33] oxalyl chloride,[34-36] *n*-BuLi and $ClPO(OPh)_2$,[37] chloroenamine,[38] and triphosgene.[39] Evidently, many if not all of these reactions use harsh and/or toxic reagents.

**Scheme 1.2. Synthesis of glycosyl chlorides using ethers and hemiacetals**



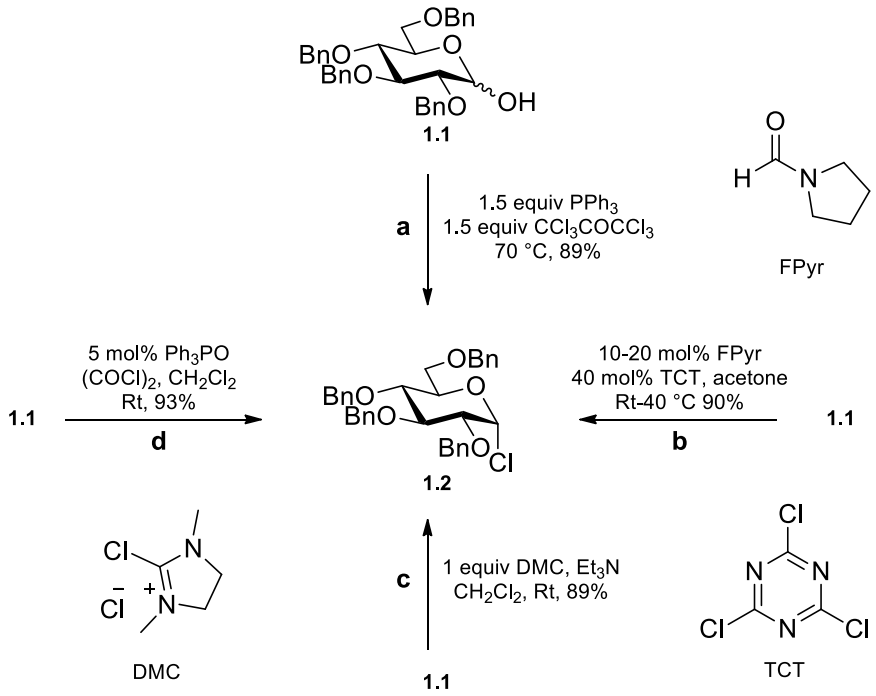

### 1.3.1. Recent Advances in the Synthesis of Glycosyl Chlorides

Finding new methods to avoid some of these harsh conditions, toxicity, and heavy metals has been a vibrant area of study in recent years. In 2017, Iadonisi[40] developed a solvent-free method for the synthesis of a variety of glycosyl chlorides (Scheme 1.3a). Using triphenyl phosphine and hexachloroacetone at 70 °C, this method produced the corresponding glycosyl chloride **1.2** in 45 minutes in moderate to high yields from the hemiacetal derivative **1.1**. These conditions were applied to many sugar series including mannose, galactose, and fucose giving high yields (80%+) in most cases. These conditions did perform poorly with some nitrogen-containing sugars such as glucosamine only giving a yield of 44%.

Huy and Filbrich[41] have recently developed a method for the synthesis of glycosyl chlorides from the corresponding hemiacetal derivatives using as little as 34 mol % of

trichlorotriazine (TCT) as a source of stoichiometric chlorine. Thus, reaction of hemiacetal **1.1** with TCT in the presence of 10-20 mol % of *N*-formylpyrrolidine (FPyr) at 40 °C produced glycosyl chloride **1.2** in 90% yield (Scheme 1.3b). These conditions were shown to work both with sugar substrates such as glucose and fructose and on aliphatic alcohols.

**Scheme 1.3. New methods for the synthesis of glycosyl chlorides**




In 2018, Judeh *et al.*[42] introduced chlorinating agent 2-chloro-1,3-dimethylimidazolinum chloride (DMC) that was applied to the synthesis of glycosyl chlorides. Using stoichiometric DMC in the presence of triethylamine converted hemiacetal **1.1** into the corresponding glycosyl halide **1.2** in 15-30 min in 89% yield (Scheme 1.3c). This reaction worked very well for a variety of sugars (glucose, mannose, galactose) giving 80-95% yield in most cases. The developed conditions were found to be compatible with many commonly used protecting groups such as acetates, silyl ethers,

and acetals.

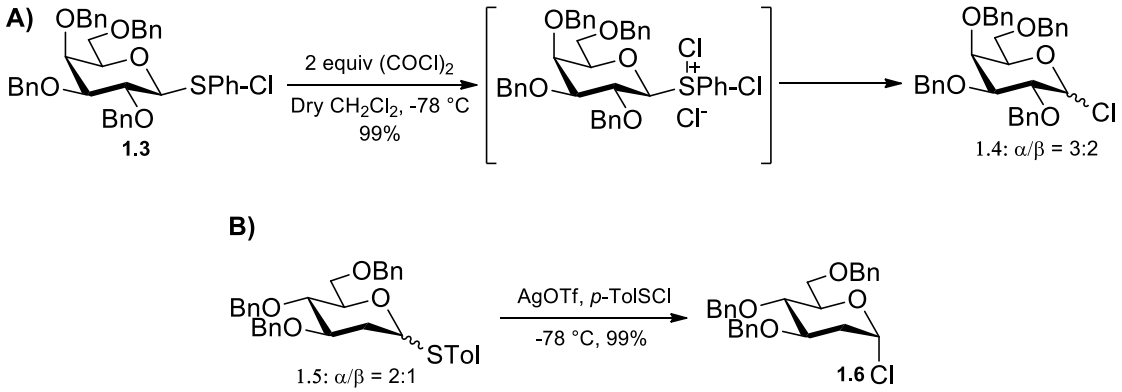
McGarrigle *et al*.[43] found that catalytic Appel conditions using 5 mol % $Ph_3PO$ and 1.5 equiv $(COCl)_2$ are also capable of chlorinating hemiacetals (Scheme 1.3d). Using these conditions, chloride **1.2** can be synthesized from hemiacetal **1.1** in 93% yield. While this protocol worked well for glucose, most other sugars such as mannose, galactose, and 2-deoxyglucose gave lower yields between 67-79%. Glucosamine and galactosamine derivatives performed the worst giving mixtures of products.

One major disadvantage with the synthesis of glycosyl chlorides is the requirement to go through intermediacy of an anomeric ester group or hemiacetal derivative. Most carbohydrate syntheses today involve thioglycosides. Thioglycosides have many advantages such as being stable allowing for protecting group manipulations and can be stored for long periods of time. Conversion from thioglycosides to glycosyl chlorides previously involved a two-step protocol with the first step being hydrolysis of the anomeric thioglycoside to the hemiacetal. The first direct conversion of thioglycosides to glycosyl chlorides was reported by Sugiyama and Diakur in 2000.[44] This was affected by the reaction of 4-chlorophenylthio derivative **1.3** with oxalyl chloride in dichloromethane. The reaction was found to proceed through intermediacy of a glycosyl halosulfonium salt (Scheme 1.4a). The latter is unstable and it quickly heterolyzes into the corresponding glycosyl chloride **1.4**. The resulting glycosyl chlorides could then be isolated in high yields (90%+) or subsequent glycosylations could be carried out directly, using crude chlorides. While this protocol reduces the need to conduct the two-step protocol, it still uses harsh reaction conditions. The scope of the reaction is currently limited to the use of 4-chlorophenylthio glycosides as starting

materials.

In 2013, Verma and Wang[45] used stoichiometric *p*-TolSCl in the presence of catalytic AgOTf to convert 2-deoxy thioglycoside **1.5** containing the *p*-tolylthio (STol) leaving group into the corresponding chloride **1.6** (Scheme 1.4b). These reaction conditions removed the need for oxalyl chloride resulting in much milder reaction conditions. Following the conversion, the corresponding chloride could be used for oligosaccharide assembly without further purification.

**Scheme 1.4. Direct synthesis of glycosyl chlorides from thioglycosides**

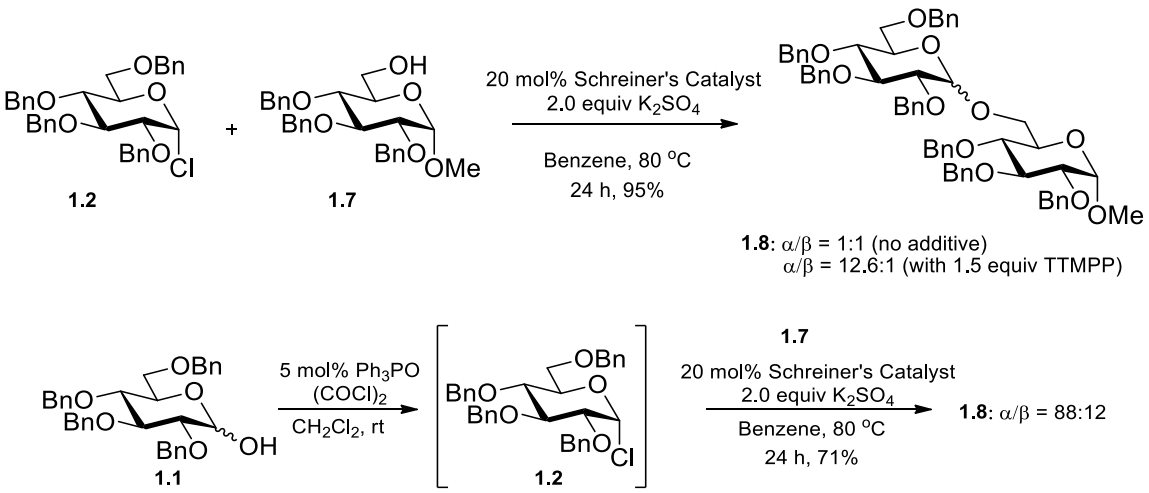



### 1.3.2. Activation of Glycosyl Chlorides in Glycosylation

Michael[46] in 1879 was the first to perform a glycosylation with glycosyl chlorides. Peracetylated glucosyl chloride was reacted with potassium phenoxide giving phenyl glucoside as the product. Then in 1901, the activation of glycosyl chlorides was performed by Koenigs-Knorr.[8] These reactions used insoluble silver(I) salts such as silver oxide or silver carbonate which were thought to act as an acid scavenger. Little was done to improve the activation of chlorides until 1949 when Helferich[11] introduced mercury salts as active promoters. While these methods can be used to synthesize oligosaccharides, mercury salts are very toxic and today are avoided.[12,47] Nevertheless, both of these methods have found utility in the synthesis of a variety of simple

glycosides. Partially soluble silver(I) triflate is an even more reactive promoter. It has successfully been used for less reactive glycosyl donors such as sialic acid chlorides.[13,14]

**Scheme 1.5. Glycosyl chloride activation using Schreiner's catalyst**




These classical methods were the state-of-the-art until recently, when new methods for the activation of glycosyl chlorides have emerged. The first new method was introduced by the Ye group in 2016.[48] Using a variety of benzylated glycosyl chlorides, 20 mol % of Schreiner's catalyst, and 2.0 equiv $K_2SO_3$ in benzene at 80 °C the respective disaccharides were produced in high yields (80%+). At first, these reactions were rather slow, required 24 h to complete, and the stereoselectivity was poor. Thus, glycosylation between glycosyl chloride donor **1.2** and primary acceptor **1.7** gave disaccharide **1.8** in 95% yield as an anomeric mixture (α/β = 1:1, Scheme 1.5). When the same reaction was carried out in the presence of 1.5 equiv of tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) as an additive, the anomeric stereoselectivity could be improved to a commendable α/β = 12.6:1. The improvement of stereoselectivity with TTMPP was seen throughout a series of glycosyl acceptors. Based on the NMR data, the authors theorized that TTMPP noncovalently interacted with the anomeric carbon from the β-face. This

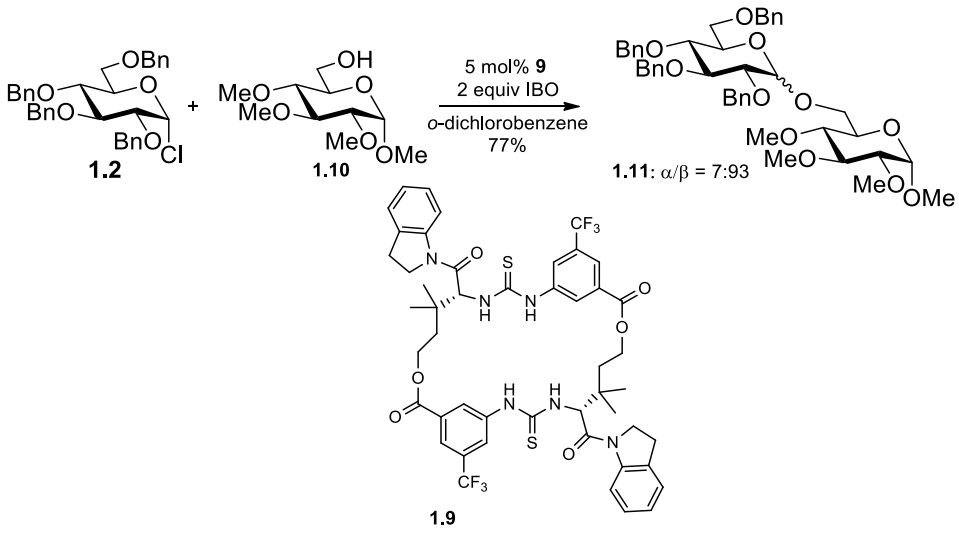
interaction directed the acceptors to attack from the opposite face giving rise to α-glycosides.

In 2019, McGarrigle[43] applied the Appel conditions (vide supra) to the synthesis of glycosyl chlorides followed by their glycosidation in one pot. The treatment of hemiacetal **1.1** with $Ph_3PO$ and oxalyl chloride in dichloromethane produced glycosyl chloride **1.2**. Then glycosyl acceptor **1.7** was added *in situ* along with 20 mol % Schreiner's catalyst, 2.2 equiv $K_2CO_3$ and 20 mol % TTMPP (Ye's conditions, Scheme 1.5). This one-pot approach led to a decrease in yield of disaccharide **1.8** that was obtained in 71% yield (vs. 95% reported by Ye) with an anomeric ratio of α/β = 88:12.

The Jacobsen group developed thiourea catalyst **1.9**[49] which cooperatively activates both the glycosyl chloride donor and the glycosyl acceptor. The glycosyl chloride donor hydrogen bonds with the thiourea portion of catalyst **1.9**, which enhances its leaving group ability. At the same time, the incoming nucleophile is also activated by the catalyst by Lewis basic interactions with the carbonyl oxygen of the amide of the catalyst. The combination of these two activations by the catalyst leads to an $S_N2$-like displacement. These reactions were conducted in the presence of 5 mol % of **1.9**, 2 equiv of isobutylene oxide (IBO), which acts as an electrophilic trap for the departing HCl, in *o*-dichlorobenzene. Reacting donor **1.2** with acceptor **1.10** using the conditions above, gave disaccharide **1.11** in 77% yield (α/β = 7:93, Scheme 1.6). Other sugars showed similar yields and selectivity. To prove that these glycosylations undergo an $S_N2$-like displacement the authors also studied the glycosyl chloride configuration at the anomeric center. It was determined that an α-chloride leaving group gave primarily the β-linked product whereas a β-chloride gave a majority of the α-linked product. This trend was seen

throughout a series of glycosyl chlorides, showing that these reactions follow an $S_N2$-like displacement of the leaving group, without the formation of an oxacarbenium ion intermediate.

**Scheme 1.6. Glycosyl chloride activation using catalyst 1.9**



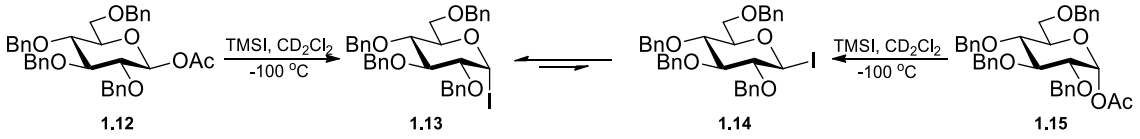

## 1.4. Glycosyl Iodides

The first synthesis of glycosyl iodides was reported by Fischer, who synthesized 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl iodide by reaction of per-*O*-acetylated glucose with HI.[50] Fischer also noted that the glycosyl iodide quickly reacted with methanol in the presence of silver carbonate to afford the methyl glycoside. The field did not have much growth until 1974 when Kronzer and Schuerch[51] discovered that the glycosylation of benzylated glucosyl bromides could be promoted by the addition of sodium iodide. These glycosylation reactions were performed under metal-free conditions and presumed to occur through the intermediacy of glycosyl iodides.

Shortly thereafter, Thiem and Meyer[52] reported that glycosyl iodides could be synthesized from a variety of precursors such as anhydrosugars, methyl glycosides, and peracetylated hexoses using TMSI. This discovery allowed for the synthesis of many

glycosyl iodide donors that for the first time became readily available. However, only acetylated glycosyl iodides were sufficiently stable to be fully characterized. Benzylated iodides were deemed too unstable and had to be synthesized and used in subsequent glycosylations *in situ*.[51] This was the case until Gervay *et al*. devised a technique to fully characterize benzylated glycosyl iodides by monitoring their formation in the presence of TMSI in $CD_2Cl_2$ at -100 °C in an NMR spectrometer (Scheme 1.7).[53] The authors found that the anomeric peaks appeared as a doublet at either 6.68 ppm for α-glycosyl iodide **1.13** or at 5.61 ppm for β-glycosyl iodide **1.14**. The ratios of these products depended on the configuration of the anomeric acetate in the substrates, α-acetate **1.15** or β-acetate **1.12**. Regardless of the initial configuration the iodide displaced the acetates in an $S_N2$-like manner. Following the displacement, anomerization of the β-iodide rapidly occurs to the thermodynamically stable α-iodide (Scheme 1.7).

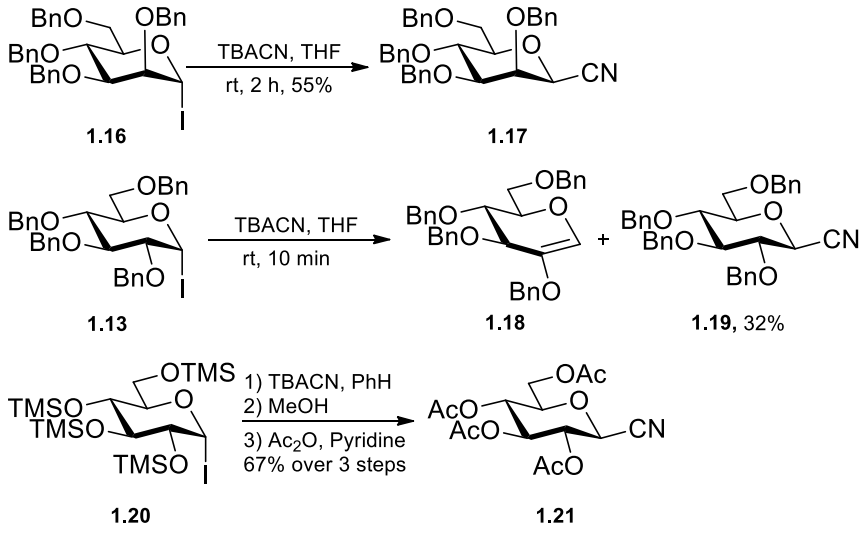
**Scheme 1.7. Anomerization of glycosyl iodides**




Following these first major mechanistic studies, glycosyl iodides found a much broader application in synthetic chemistry. This first started with C-glycosides showing that the reactions occur in an $S_N2$ like manner with direct displacement of the glycosyl iodide with the nucleophilic acceptor. Using tetrabutylammonium cyanide (TBACN) in THF and the armed α-mannosyl iodide **1.16**, the β-cyanoglycoside **1.17** could be obtained in a respectable yield (55%).[54] This worked well with the armed mannose iodide, however when using armed glucosyl iodide **1.13**, the major product was often E2 elimination **1.18** with 32% of the β-cyanoglycoside **1.19** (Scheme 1.8). Switching to a

fully protected glucose with TMS ethers **1.20**, however, allowed for the synthesis of the corresponding β-cyanoglucoside. This was accomplished using TBACN in toluene, followed by cleavage of the TMS groups with MeOH and subsequent acetylation using $Ac_2O$ in pyridine to give **1.21** in an overall yield of 67%. Similar C-glycoside formation was accomplished by using Grignard reagents in the synthesis of glycolipid BbGL2, as reported by Kulkarni and Gervay.[55]

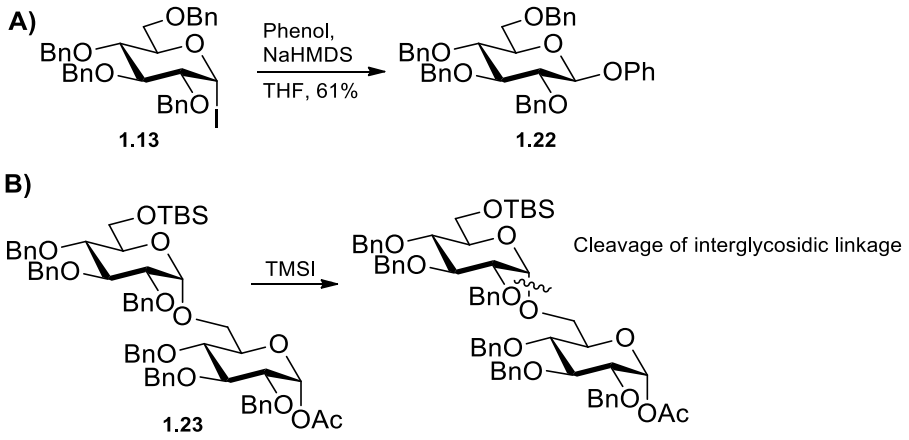
**Scheme 1.8. Synthesis of C-glycosides using glycosyl iodides**




O-Glycosides proved to be more difficult to synthesize however. When using small nucleophiles such as phenol with NaHMDS in THF, glycosyl iodide **1.13** can give phenol glycoside **1.22** in 61% yield (Scheme 1.9a). Other small nucleophiles such as sodium acetate or sodium tert-butoxide worked well giving complete β-stereoselectivity following direct displacement of the α-iodide.[56,57] However, when attempting to perform more complicated oligosaccharide synthesis proved difficult. Synthesis of the disaccharide proved to be straightforward, however, converting the disaccharide into the second-generation glycosyl donor was troublesome. During displacement of the O-acetyl anomeric group into the iodide donor **1.23**, cleavage of the interglycosidic bond has

occurred (Scheme 1.9b). This problem was solved by Lam and Gervay[58] by a simple addition of an acetate (or other electron-withdrawing) group at the C-6 position of the glycosyl donor. This modification allowed for the synthesis of oligosaccharide derivatives using both solid phase and solution phase strategies using TBAI as a promoter system.[59] Other promoter systems used for the synthesis of oligosaccharides include AgOTf,[60] tetrabutylammonium bromide/$Na_2CO_3$,[61] $AgNO_3$,[62] ZnI,[63] and TBAI/DIPEA.[64]

**Scheme 1.9. Synthesis of O-glycosides using glycosyl iodides**

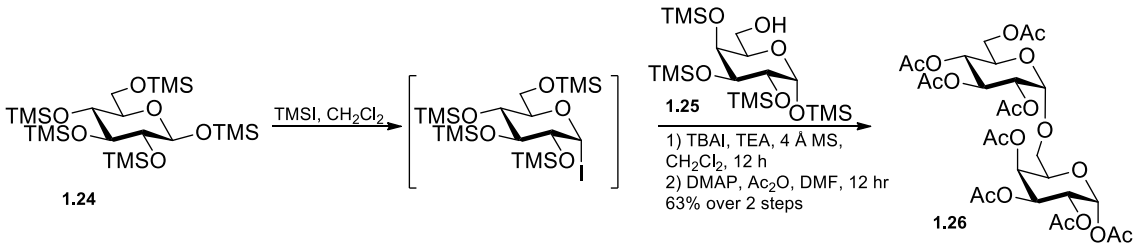



Another method to help combat the interglycosidic bond cleavage employs fully trimethylsilyl protected substrates. Introduced by Gervay and co-workers,[65] this approach allowed to achieve high yields in glycosidations of per-O-silylated galactosyl iodide. This approach was successfully applied to α-stereoselective synthesis of glycolipids, however some decline in yields was seen due to the formation of silylated acceptors as side products. The reaction wasn't perfected until later when Gervay[66] found that the formation of silylated side products can be suppressed by reducing the amount of TBAI to 1.5 equiv as opposed to 3.0 equiv used previously. Since this discovery, many research groups have used per-O-silylated sugars to synthesize a variety of natural products.[67-69] Glycosyl iodides have been used in a variety of ways that were comprehensively

discussed in previous reviews by Kulkarni,[10] Lowary,[70] and Gervay.[71]

More recently, in 2016 Zhang[72] expanded the scope of per-O-TMS glycosyl donors such as **1.24** and improved the outcome of the reaction by supplementing TBAI-promoted glycosylations with triethylamine (Scheme 1.10). Under these conditions, glycosyl donor **1.24** was reacted with acceptor **1.25** to form disaccharide **1.26** in 63% yield over two steps after successive acetylation. These reactions worked well with a variety of sugar series such as glucosyl, galactosyl, and fucosyl donors.

**Scheme 1.10. O-glycosylation using per-O-silylated donors.**

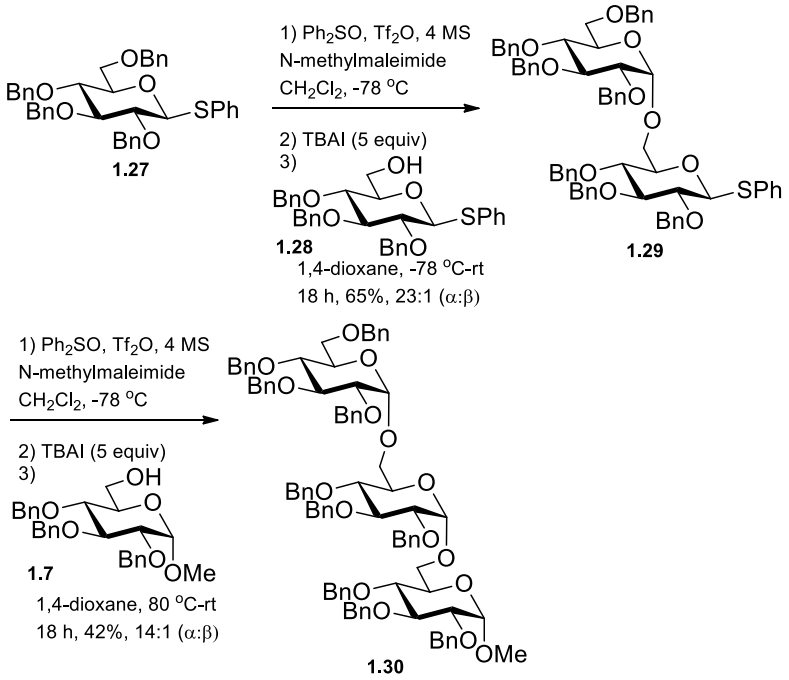



Bennett[73] used a glycosyl iodide generated in situ for the synthesis of α-glycosides without directing groups in 2013. Starting from stable thioglycoside **1.27**, the corresponding anomeric triflate was generated in the presence of $Ph_2SO$, $Tf_2O$, and 4Å molecular sieves in dichloromethane at -78 °C (Scheme 1.11). Following the generation of the triflate, 5 equiv of TBAI was added to produce the glycosyl iodide *in situ*. 1,4-Dioxane was then added along with glycosyl acceptor **1.28** to improve α-stereoselectivity. As a result, disaccharide **1.29** was generated in 65% yield in high α-stereoselectivity (α/β = 23/1). This reaction sequence was reiterated with glycosyl acceptor **1.7** allowing for the synthesis of trisaccharide **1.30**. However, a modest yield of 42% was observed due to the fact that a sterically bulky glycosyl donor was used at this stage.

Glycosyl iodides were also used in α-stereoselective ribofuranosylation of alcohols.[74] Ribofuranosyl iodide could be generated using TMSI from **1.31** (Scheme

1.12). Following the addition of *i*-Pr$_2$NEt and triphenylphosphine oxide, which acts as an additive to improve α-stereoselectivity, and acceptor **1.7**, ribofuranosylation would occur. Complete α-stereoselective reaction occurred with glycosyl acceptor **1.7** providing compound **1.32** in 77% yield. These conditions worked well for a variety of glycosyl acceptors ranging from primary aliphatic alcohols to hindered sugar alcohols with yields of 75% or higher. Ribosylation was also studied by Houston and Koreeda[75] using *i*PrOH as the acceptor and $I_2$ as a promoter in THF. This reaction gave the corresponding β-riboside in high yields. The authors also found that ribosylations performed in the presence of acetone led to the formation of a 1,2-O-isopropylidene derivative instead.

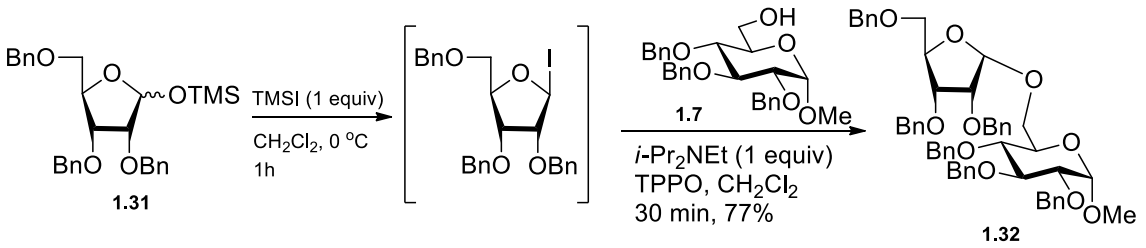
**Scheme 1.11. Iterative synthesis of trisaccharide 1.30 using glycosyl iodides**




The most recent advancement in the application of glycosyl iodides was reported by Park and Gervay.[76] The authors achieved the first, promoter-free sialylations with sialyl iodides, which was applied to the synthesis of steryl β-sialosides. These glycosylations only worked with C-5 modified sialic acid donors, whereas traditional N-

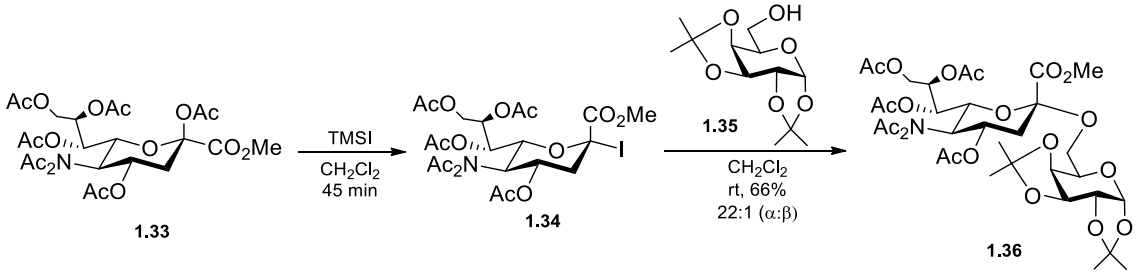
acetamido sialic acids underwent 2,3-elimination upon the attempt to obtain a sialyl iodide donor. 2,3-Dehydro derivatives along with other decomposition products were obtained instead.

**Scheme 1.12. Ribofuranosylation using glycosyl iodides**




However, when 5-N-acetylacetamido precursor **1.33** was used instead of the previously investigate 5-acetamido derivative the corresponding α-iodide donor **1.34** was smoothly produced (Scheme 1.13). Sialylation could then be performed in a one-pot manner at room temperature. Sialylation of the primary glycosyl acceptor **1.35** gave disaccharide **1.36** in 66% yield with excellent α-stereoselectivity of α:β = 22:1. Cholesterol-based acceptors provided respectable yields ranging from 52 to 85% giving sialosides with complete β-stereoselectivity.

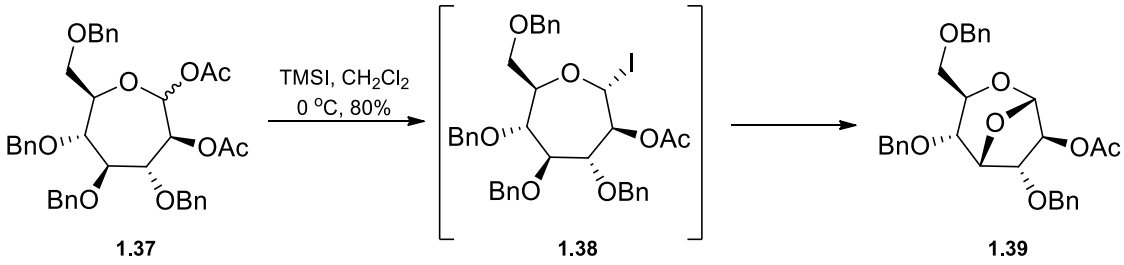
**Scheme 1.13. Sialylations using sialic acid iodide 1.34**




Applications of glycosyl iodides in synthesis span beyond their use as glycosyl donors. For instance, glycosyl iodides were used as precursors in the formation of 1,4-anhydroseptanoses.[77] Septanose **1.37** was reacted with TMSI to form septanosyl iodide

**1.38** that readily rearranged to form 1,4-anhydroseptanose **1.39** in 30 min in 80% yield (Scheme 1.14). This rapid cyclization was occurring in septanoses derived from glucose, mannose, xylose, and galactose.

**Scheme 1.14. Using glycosyl iodides to form 1,4-anhydroseptanose 1.39**




1.37 1.38 1.39

## 1.5. Conclusions and Outlook

Glycosyl halides are one of the most established and widely used building blocks in carbohydrate chemistry. In this section we focused mainly on glycosyl chlorides and iodides. First reported in 1870, glycosyl chlorides are traditionally synthesized from glycosyl esters or hemiacetals. Traditional methods for the synthesis of glycosyl chlorides often involved harsh reaction conditions and required excess of toxic reagents such as oxalyl chloride, thionyl chloride, or acetyl chloride. However, newer methods are slowly incorporating greener reagents such as triphenyl phosphine and hexachloroacetone or trichlorotriazine as well as using only stoichiometric amounts of chlorine.

The requirement of using only glycosyl ester or hemiacetals has also proven to be a deterrent in the use of glycosyl chlorides. Most carbohydrate synthesis routes involve thioglycosides due to their ability to withstand most protecting group manipulations. Recent discoveries introduced new methods for the direct conversion of thioglycosides to glycosyl chlorides, although their scope at this stage is limited to only few examples. New general methods which would work with all mainstream thioglycosides and/or those

that use greener and milder reaction conditions are still needed.

The activation of glycosyl chlorides has traditionally been performed using stoichiometric amounts of silver or mercury salts. Recent advances in the activation of glycosyl chlorides has dealt with moving away from these heavy metal salts to urea-based catalysts. The Ye and the Jacobsen groups used different catalysts to perform high yielding glycosylations. Further improvements to glycosyl chloride activation are shown in the subsequent Chapters of this dissertation.

Few major advances in the synthesis and application of glycosyl iodides have occurred over the last decade. Improvements in iterative synthesis using glycosyl iodides using *in situ* generation of glycosyl iodides has been shown to give respectable yields with high α-stereoselectivity. Glycosyl iodides have also been used in ribofuranosylation and sialylations in recent years. Lastly, septanosyl iodides have been shown to rapidly rearrange to form 1,4-anhydroseptanoses.

## 1.6. References

(1) *Handbook of chemical glycosylation: advances in stereoselectivity and therapeutic relevance*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

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

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

(4) Nukada, T.; Berces, A.; Whitfield, D. M. Can the stereochemical outcome of glycosylation reactions be controlled by the conformational preferences of the glycosyl donor? *Carbohydr. Res.* **2002**, *337*, 765-774.

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

(6) Toshima, K.; Tatsuta, K. Recent progress in O-glycosylation methods and its application to natural-products synthesis. *Chem. Rev.* **1993**, *93*, 1503-1531.

(7) Davis, B. G. Recent developments in oligosaccharide synthesis. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137-2160.

(8) Koenigs, W.; Knorr, E. Über einige derivate des traubenzuckers und der galactose. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 957-981.

(9) Igarashi, K. The Koenigs-Knorr reaction. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243-283.

(10) Kulkarni, S. S.; Gervay-Hague, J.: Glycosyl chlorides, bromides and iodides. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 59-93.

(11) Helferich, B.; Wedemeyer, K. F. Preparation of glucosides from acetobromoglucose. *Ann.* **1949**, *563*, 139-145.

(12) Chauvin, A. L.; Nepogodiev, S. A.; Field, R. A. Synthesis of an apiose-containing disaccharide fragment of rhamnogalacturonan-II and some analogues. *Carbohydr. Res.* **2004**, *339*, 21-27.

(13) Kondo, T.; Tomoo, T.; Abe, H.; Isobe, M.; Goto, T. Simple construction of Neu5Ac(α2-8)Neu5Ac and total synthesis of ganglioside $GD_3$. *J. Carbohydr. Chem.* **1996**, *15*, 857-878.

(14) Chernyak, A.; Oscarson, S.; Turek, D. Synthesis of the Lewis b hexasaccharide and squarate acid-HSA conjugates thereof with various saccharide loadings. *Carbohydr. Res.* **2000**, *329*, 309-316.

(15) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. Halide ion catalyzed glycosylation reactions. Syntheses of α-linked disaccharides. *J. Am. Chem. Soc.* **1975**, *97*, 4056-4062 and references therein.

(16) Kaeothip, S.; Yasomanee, J. P.; Demchenko, A. V. Glycosidation of thioglycosides in the presence of bromine: mechanism, reactivity, and stereoselectivity. *J. Org. Chem.* **2012**, *77*, 291-299.

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

(18) Nicolaou, K. C.; Ueno, H.: Oligosaccharide synthesis from glycosyl fluorides and sulfides. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, Inc.: New York, 1997; pp 313-338.

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

(20) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. Practical synthesis of oligosaccharides. Partial synthesis of avermectin B1a. *J. Am. Chem. Soc.* **1984**, *106*, 4189-4192.

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

(22) Mukaiyama, T. Explorations into new reaction chemistry. *Angew. Chem. Int. Ed.* **2004**, *43*, 5590-5614.

(23) Jona, H.; Mandai, H.; Chavasiri, W.; Takeuchi, K.; Mukaiyama, T. Protic acid catalyzed stereoselective glycosylation using glycosyl fluorides. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291-309 and references therein.

(24) Colley, A. *Ann. Chem. J.* **1870**, *4*, 367.

(25) Colley, A. *Compt. Rend.* **1870**, *70*, 401.

(26) Kononov, L. O.; Magnusson, G. Synthesis of methyl and allyl α-glycosides of N-acetylneuraminic acid in the absence of added promoter. *Acta Chem. Scand.* **1998**, *52*, 141-144.

(27) Shpirt, A. M.; Kononov, L. O.; Torgov, V. I.; Shibaev, V. N. Conversion of N-acetylneuraminic acid glycosyl chloride into dibenzyl glycosyl phosphate: O-glycosylation in the absence of a promoter. *Russ. Chem. Bull.* **2004**, *53*, 717-719.

(28) Bonomi, P.; Attieh, M. D.; Gonzato, C.; Haupt, K. A New Versatile Water-Soluble Iniferter Platform for the Preparation of Molecularly Imprinted Nanoparticles by Photopolymerisation in Aqueous Media. *Chem. Eur. J.* **2016**, *22*, 10150-10154.

(29) Singhamahapatra, A.; Sahoo, L.; Paul, K. J. V.; Varghese, B.; Loganathan, D. Improved synthesis of per-O-acetylated C1 hydroxyglycopyranose and structural study as non-covalent organic framework. *Tetrahedron Lett.* **2013**, *54*, 6121-6124.

(30) Ibatullin, F. M.; Selivanov, S. I. Reaction of 1,2-trans-glycosyl acetates with phosphorus pentachloride: new efficient approach to 1,2-trans-glycosyl chlorides. *Tetrahedron Lett.* **2002**, *43*, 9577-9580.

(31) Bednarczyk, D.; Walczewska, A.; Grzywacz, D.; Sikorski, A.; Liberek, B.; Myszka, H. Differently N-protected 3,4,6-tri-O-acetyl-2-amino-2-deoxy-d-glucopyranosyl chlorides and their application in the synthesis of diosgenyl 2-amino-2-deoxy-β-d-glucopyranoside. *Carbohydr. Res.* **2013**, *367*, 10-17.

(32) Ziegler, T.; Seidl, U. Preparation of some Amygdalin-Derived Gentiobiosyl Donors and Acceptors for Oligosaccharide Syntheses. *J. Carbohydr. Chem.* **1991**, *10*, 813-831.

(33) Watt, G. M.; Boons, G.-J. A convergent strategy for the preparation of N-glycan core di-, tri-, and pentasaccharide thioaldoses for the site-specific glycosylation of peptides and proteins bearing free cysteines. *Carbohydr. Res.* **2004**, *339*, 181-193.

(34) Iversen, T.; Bundle, D. R. Antigenic determinants of *Salmonella* serogroups A and $D_1$. Synthesis of trisaccharide glycosides for use as artificial antigens. *Carbohydr. Res.* **1982**, *103*, 29-40.

(35) Encinas, L.; Chiara, J. L. Polymer-Assisted Solution-Phase Synthesis of Glycosyl Chlorides and Bromides Using a Supported Dialkylformamide as Catalyst. *J. Comb. Chem.* **2008**, *10*, 361-363.

(36) Gómez, A. M.; Pedregosa, A.; Casillas, M.; Uriel, C.; López, J. C. Synthesis of C-1 Alkyl and Aryl Glycals from Pyranosyl or Furanosyl Chlorides by Treatment with Organolithium Reagents. *Eur. J. Org. Chem.* **2009**, *2009*, 3579-3588.

(37) Hung, S. C.; Wong, C. H. Synthesis of glycosyl chlorides with acid-labile protecting groups. *Tetrahedron Lett.* **1996**, *37*, 4903-4906.

(38) Ernst, B.; Winkler, T. Preparation of glycosyl halides under neutral conditions. *Tetrahedron Lett.* **1989**, *30*, 3081-3084.

(39) Cicchillo, R. M.; Norris, P. A convenient synthesis of glycosyl chlorides from sugar hemiacetals using triphosgene as the chlorine source. *Carbohydr. Res.* **2000**, *328*, 431-434.

(40) Traboni, S.; Liccardo, F.; Bedini, E.; Giordano, M.; Iadonisi, A. Solvent-free synthesis of glycosyl chlorides based on the triphenyl phosphine/hexachloroacetone system. *Tetrahedron Lett.* **2017**, *58*, 1762-1764.

(41) Huy, P. H.; Filbrich, I. A General Catalytic Method for Highly Cost- and Atom-Efficient Nucleophilic Substitutions. *Chem. Eur. J.* **2018**, *24*, 7410-7416.

(42) Tatina, M. B.; Khong, D. T.; Judeh, Z. M. A. Efficient Synthesis of α-Glycosyl Chlorides Using 2-Chloro-1,3-dimethylimidazolinium Chloride: A Convenient Protocol for Quick One-Pot Glycosylation. *Eur. J. Org. Chem.* **2018**, *2018*, 2208-2213.

(43) Pongener, I.; Nikitin, K.; McGarrigle, E. M. Synthesis of glycosyl chlorides using catalytic Appel conditions. *Org. Biomol. Chem.* **2019**, *17*, 7531-7535.

(44) Sugiyama, S.; Diakur, J. M. A convenient preparation of glycosyl chlorides from aryl/alkyl thioglycosides. *Org. Lett.* **2000**, *2*, 2713-2715.

(45) Verma, V. P.; Wang, C.-C. Highly Stereoselective Glycosyl-Chloride-Mediated Synthesis of 2-Deoxyglucosides. *Chem. Eur. J.* **2013**, *19*, 846-851.

(46) Michael, A. On the synthesis of helicin and phenolglucoside. *Am. Chem. J.* **1879**, *1*, 305-312.

(47) Ito, Y.; Ogawa, T. Highly stereoselective glycosylation of sialic acid aided by stereocontrolling auxiliaries. *Tetrahedron* **1990**, *46*, 89-102.

(48) Sun, L.; Wu, X.; Xiong, D. C.; Ye, X. S. Stereoselective Koenigs-Knorr glycosylation catalyzed by urea. *Angew. Chem. Int. Ed.* **2016**, *55*, 8041-8044.

(49) Park, Y.; Harper, K. C.; Kuhl, N.; Kwan, E. E.; Liu, R. Y.; Jacobsen, E. N. Macrocyclic bis-thioureas catalyze stereospecific glycosylation reactions. *Science* **2017**, *355*, 162-166.

(50) Fischer, E.; Fischer, H. Über einige Derivate des Milchzuckers und der Maltose und über zwei neue Glucoside. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2521-2536.

(51) Kronzer, F. J.; Schuerch, C. The use of 2,3,4,6-tetra-O-benzyl-α-D-glycopyranosyl iodides in α-glycoside synthesis. *Carbohydr. Res.* **1974**, *34*, 71-78 and references therein.

(52) Thiem, J.; Meyer, B. Synthesen mit Iod- und Bromtrimethylsilan in der Saccharidchemie. *Chem. Ber.* **1980**, *113*, 3075-3085.

(53) Gervay, J.; Nguyen, T. N.; Hadd, M. J. Mechanistic studies on the stereoselective formation of glycosyl iodides: first characterization of glycosyl iodides. *Carbohydr. Res.* **1997**, *300*, 119-125.

(54) Bhat, A. S.; Gervay-Hague, J. Efficient Syntheses of β-Cyanosugars Using Glycosyl Iodides Derived from Per-O-silylated Mono- and Disaccharides. *Org. Lett.* **2001**, *3*, 2081-2084.

(55) Kulkarni, S. S.; Gervay-Hague, J. Efficient Synthesis of a C-Analogue of the Immunogenic Bacterial Glycolipid BbGL2. *Org. Lett.* **2006**, *8*, 5765-5768.

(56) Gervay, J.; Hadd, M. J. Anionic additions to glycosyl iodides: highly stereoselective syntheses of β-C-, N-, and O-glycosides. *J. Org. Chem.* **1997**, *62*, 6961-6967.

(57) Lam, S. N.; Gervay-Hague, J. Efficient Route to 2-Deoxy β-O-Aryl-d-Glycosides via Direct Displacement of Glycosyl Iodides. *Org. Lett.* **2003**, *5*, 4219-4222.

(58) Lam, S. N.; Gervay-Hague, J. Solution-phase hexasaccharide synthesis using glucosyl iodides. *Org. Lett.* **2002**, *4*, 2039-2042.

(59) Lam, S. N.; Gervay-Hague, J. Solution- and solid-phase oligosaccharide synthesis using glucosyliodides: a comparative study. *Carbohydr. Res.* **2002**, *337*, 1953-1965.

(60) Lam, S. N.; Gervay-Hague, J. Efficient Synthesis of Man2, Man3, and Man5 Oligosaccharides, Using Mannosyl Iodide Donors1. *J. Org. Chem.* **2005**, *70*, 8772-8779.

(61) Salvadó, M.; Amgarten, B.; Castillón, S.; Bernardes, G. J. L.; Boutureira, O. Synthesis of Fluorosugar Reagents for the Construction of Well-Defined Fluoroglycoproteins. *Org. Lett.* **2015**, *17*, 2836-2839.

(62) Zhang, W.; Luo, X.; Wang, Z.; Zhang, J. One-pot synthesis of β-2,6-dideoxyglycosides via glycosyl iodide intermediates. *J. Carbohydr. Chem.* **2016**, *35*, 315-325.

(63) Baldoni, L.; Marino, C. Synthetic tools for the characterization of galactofuranosyl transferases: glycosylations via acylated glycosyl iodides. *Carbohydr. Res.* **2013**, *374*, 75-81.

(64) Wałejko, P.; Baj, A. The synthesis of vitamin E sugar 1,2-orthoesters. *Monatsh. Chem.* **2019**, *150*, 275-282.

(65) Du, W.; Kulkarni, S. S.; Gervay-Hague, J. Efficient, one-pot syntheses of biologically active α-linked glycolipids. *Chem. Commun.* **2007**, 2336-2338.

(66) Schombs, M.; Park, F. E.; Du, W.; Kulkarni, S. S.; Gervay-Hague, J. One-Pot Syntheses of Immunostimulatory Glycolipids. *J. Org. Chem.* **2010**, *75*, 4891-4898.

(67) Jervis, P. J.; Veerapen, N.; Bricard, G.; Cox, L. R.; Porcelli, S. A.; Besra, G. S. Synthesis and biological activity of alpha-glucosyl C24:0 and C20:2 ceramides. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3475-3478.

(68) Veerapen, N.; Reddington, F.; Bricard, G.; Porcelli, S. A.; Besra, G. S. Synthesis and biological activity of α-l-fucosyl ceramides, analogues of the potent agonist, α-d-galactosyl ceramide KRN7000. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3223-3226.

(69) Gu, X.; Chen, L.; Wang, X.; Liu, X.; You, Q.; Xi, W.; Gao, L.; Chen, G.; Chen, Y.-L.; Xiong, B.; Shen, J. Direct Glycosylation of Bioactive Small Molecules with Glycosyl Iodide and Strained Olefin as Acid Scavenger. *J. Org. Chem.* **2014**, *79*, 1100-1110.

(70) Meloncelli, P. J.; Lowary, T. L. Glycosyl iodides. History and recent advances. *Carbohydr. Res.* **2009**, *344*, 1110-1122.

(71) Gervay-Hague, J. Taming the Reactivity of Glycosyl Iodides To Achieve Stereoselective Glycosidation. *Acc Chem Res* **2016**, *49*, 35-47.

(72) Wang, H.; Cui, Y.; Zou, R.; Cheng, Z.; Yao, W.; Mao, Y.; Zhang, Y. Synthesis of oligosaccharides using per-O-trimethylsilyl-glycosyl iodides as glycosyl donor. *Carbohydr. Res.* **2016**, *427*, 1-5.

(73) Chu, A.-H. A.; Nguyen, S. H.; Sisel, J. A.; Minciunescu, A.; Bennett, C. S. Selective Synthesis of 1,2-cis-α-Glycosides without Directing Groups. Application to Iterative Oligosaccharide Synthesis. *Org. Lett.* **2013**, *15*, 2566–2569.

(74) Oka, N.; Kajino, R.; Takeuchi, K.; Nagakawa, H.; Ando, K. α-Selective Ribofuranosylation of Alcohols with Ribofuranosyl Iodides and Triphenylphosphine Oxide. *J. Org. Chem.* **2014**, *79*, 7656-7664.

(75) Houston, T. A.; Koreeda, M. Iodine-promoted ribosylation leads to a facile acetonide-forming reaction. *Carbohydr. Res.* **2009**, *344*, 2240-2244.

(76) Park, S. S.; Gervay-Hague, J. Step-economy synthesis of β-steryl sialosides using a sialyl iodide donor. *J. Antibiotics* **2019**, *72*, 449-460.

(77) Vannam, R.; Pote, A. R.; Peczuh, M. W. Formation and selective rupture of 1,4-anhydroseptanoses. *Tetrahedron* **2017**, *73*, 418-425.

# CHAPTER 2

## Picoloyl Protecting Group in Synthesis: Focus of a Highly Chemoselective Catalytic Removal

- S. A. Geringer, M. P. Mannino, Mithila. D. Bandara, A. V. Demchenko. Picoloyl Protecting Group in Synthesis: Focus of a Highly Chemoselective Catalytic Removal. **2020**, Submitted.

## 2.1 Introduction

The chemical synthesis of glycans is a difficult task that typically involves manipulation of a variety of protecting groups to obtain selectively protected building blocks.[1-4] However, protecting groups do more than protect: they are also known to control all types of selectivity: regio-, stereo-, and chemo-.[5] Protecting groups may also have a powerful effect on the building block reactivity.[6] During the synthesis of carbohydrates, protecting groups often need to be chemoselectively removed over other protecting and functional groups present in the molecule. Some reaction conditions used for chemoselective protecting group removal are harsh or rely on using toxic reagents. Others lead to only marginal chemoselectivity and hence require careful refinement of reaction conditions to avoid undesired removal of other protecting groups. Dedicated studies in this area led to the discovery of a few sets of orthogonal protecting group. Orthogonal combinations developed by Boons: levulinoyl (Lev), acetyl, fluorenylmethoxycarbonyl (Fmoc), tert-butyldiphenylsilyl (TBDPS);[7] and Fmoc, naphthyl, Lev, and allyloxycarbonyl (Alloc);[8] Schmidt: Fmoc, phenoxyacetyl, Lev, Alloc;[9] Seeberger: naphthyl, Lev, Fmoc, 2-(azidomethyl)benzoyl;[10-13] and others[13-14] offer excellent flexibility for selective liberation of particular hydroxyl groups. These strategies are commonly employed in glycan assembly using reactions in solution and on solid supports.[15] Nevertheless, identifying other stable and selectively removable protecting groups that can be selectively removed under mild and/or unique reaction conditions is always a desirable direction of research in the field of polyfunctional compound synthesis and modification. In particular, new orthogonal protecting groups

that would easily fit into existing schemes and orthogonal combinations are of particular interest.

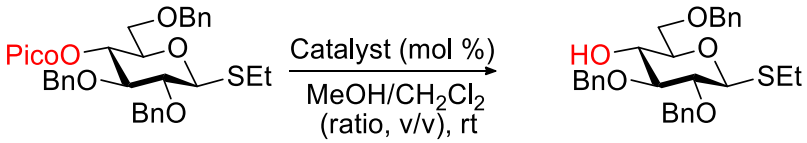
Recently, our group[16-25] and others[26-36] have done extensive studies on the use of the picoloyl (Pico) protecting group. In particular, Pico group assisted H-bond-mediated aglycone delivery (HAD) glycosylation reaction provided high facial α- or β-stereoselectivity that was always *syn* in respect to the Pico group. The stereoselectivity was only one advantage of using the Pico protecting group. The Pico group can be cleaved in traditional Zemplén conditions[37] using sodium methoxide in methanol.[23] It was also found that Pico could be selectively cleaved off in the presence of practically all other known protecting groups using zinc(II) acetate[27] or copper(II) acetate.[17-18, 20, 23] This reaction, however, is slow with reported times of 16 h, and typically requires stoichiometric amount of $Cu(OAc)_2$ (1-1.3 equiv). Reported herein are new reaction conditions that allow for entirely chemoselective removal of Pico using catalytic (30 mol %) ferric chloride or $Cu(OAc)_2$. The developed conditions are directly compatible with all other protecting groups used in all orthogonal combinations used for glycan synthesis.

**2.2 Results and discussion**

After preliminary screening of potential reagents, we discovered that iron(III) chloride provides a much faster removal of Pico under the same reaction conditions to those previously reported for $Cu(OAc)_2$. We have purposefully chosen compounds equipped with Pico at the C-4 position that was particularly resistant towards removal in our previous study. Thus, deprotection of 4-Pico in a series of linear and branched glycans required excess $Cu(OAc)_2$ and prolonged reaction time (16 h). Deprotection of thioglycoside **2.1**[16] equipped with 4-Pico group with $Cu(OAc)_2$ (1.3 equiv) in MeOH-

$CH_2Cl_2$ (1/9, v/v) was more rapid, but still required 3 h to complete (Table 2.1, entry 1). As a result, the deprotected derivative **2.2** was obtained in 99% yield. Performing the reaction with $FeCl_3$ (1.3 equiv) under similar reaction conditions afforded compound **2.2** in 99% yield in 3.5 h (entry 2).

**Table 2.1. Optimization of the Pico group removal under catalytic conditions**




**2.1** **2.2**

| Entry | Catalyst, solvent, time | Yield |
|---|---|---|
| 1 | $Cu(OAc)_2$ (130), MeOH/DCM (1/9), 3 h | 99% |
| 2 | $FeCl_3$ (130), MeOH/DCM (1/9), 3.5 h | 98% |
| 3 | $FeCl_3$ (30), MeOH/DCM (1/9), 48 h | 75% |
| 4 | $FeCl_3$ (30), MeOH/DCM (1/1), 18 h | 87% |
| 5 | $FeCl_3$ (30), MeOH/DCM (9/1), 5 h | 91% |
| 6 | $FeCl_3$ (30), MeOH (neat), 5 h | 89% |
| 7 | $FeCl_3$ (15), MeOH/DCM (9/1), 10 h | 99% |
| 8 | $FeCl_3$ (5), MeOH/DCM (9/1), 28 h | 92% |
| 9 | $Cu(OAc)_2$ (30), MeOH/DCM (9/1), 1.5 h | 99% |

After recording these promising results, we endeavored to optimizing the reaction condition to determine whether substoichimetric amounts of metal salts would be sufficient for driving the Pico deprotection to completion. We first found that upon reducing the amount of $FeCl_3$ to 30 mol %, the reaction still occurred. However, this reaction was significantly slower, and required 48 h to obtain compound **2.2** in 75% yield (entry 3). In the further attempt to refine the reaction conditions, we investigated the effect of the solvent. Increasing the amount of MeOH in respect to DCM gave us the desired outcome. Thus, deprotection in MeOH-$CH_2Cl_2$ (1/1) produced compound **2.2** in 87% in 18 h (entry 4). Furthermore, deprotection in MeOH-$CH_2Cl_2$ (9/1) afforded

compound **2.2** in 91% yield in 5 h (entry 5). Using neat methanol showed no further improvement (entry 6). Reactions using even lower amounts of $FeCl_3$, 15 and even 5 mol %, could still be driven to completion, but required longer reaction time, 10 and 28 h, respectively (entries 7 and 8). Nevertheless, compound **2.2** was obtained in excellent yields of 99% and 92%, respectively. We also wanted to see how well $Cu(OAc)_2$ worked under these new reaction conditions. As depicted in entry 9, this reaction was even faster, and compound **2.2** was produced in 99% yield in only 1.5 h.

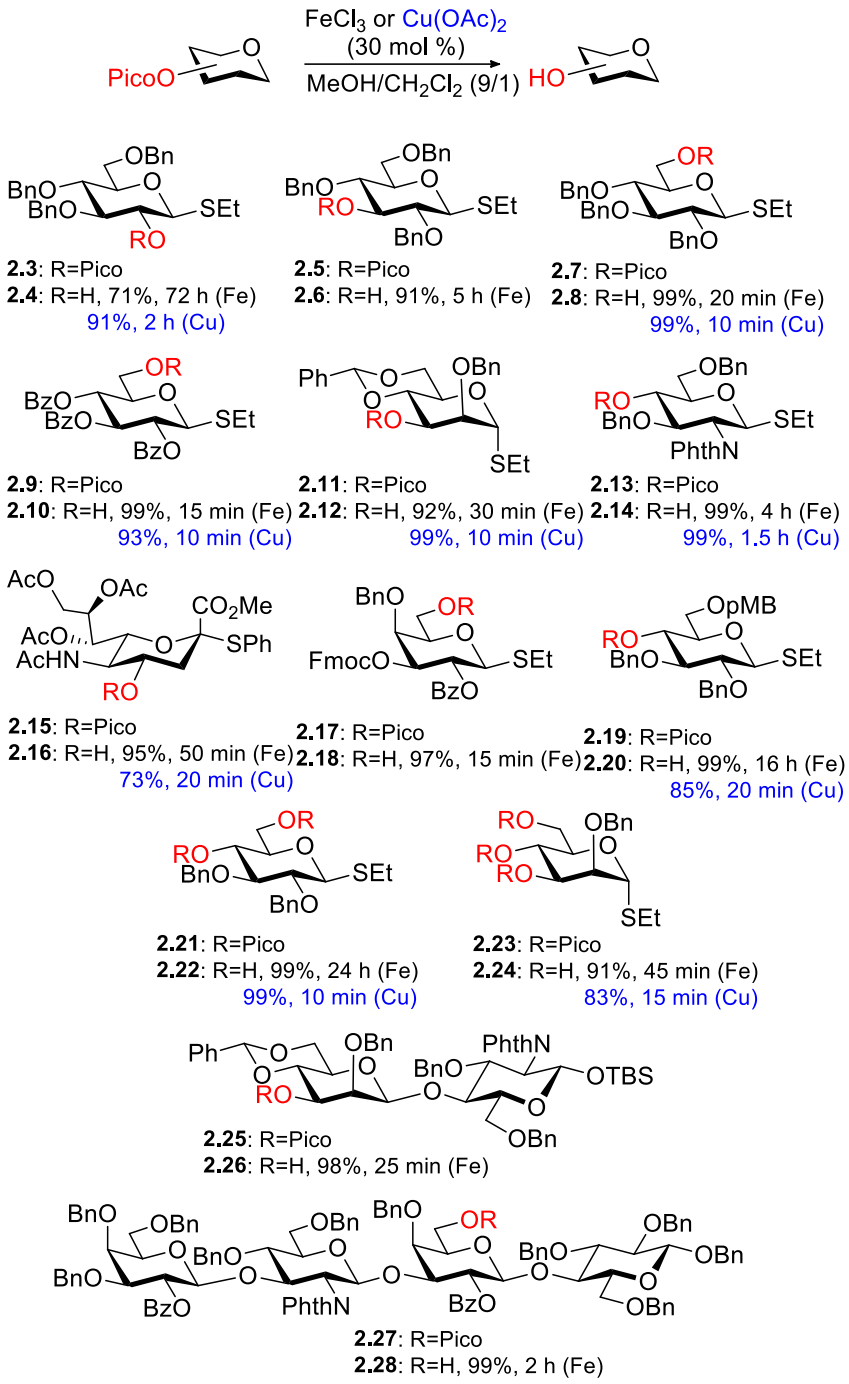
From these optimizations, we carried out subsequent deprotection reactions using 30 mol % of the catalyst in MeOH- $CH_2Cl_2$ (9/1). First, we wanted to investigate other regioisomers of **2.1** wherein Pico was present at C-2, C-3, and C-6 positions, compounds **2.3**, **2.5**,[24-25] and **2.7**,[16] respectively (Scheme 2.1). Interestingly, removing Pico from the C-2 position in **2.3** with $FeCl_3$ was very sluggish, which resulted in a much longer and incomplete reaction giving compound **2.4** in only 71% yield after 3 days. In contrast, a similar reaction in the presence $Cu(OAc)_2$ rapidly produced 2-OH derivative **2.4** in 91% yield in 2 h. Deprotection of 3-Pico in **2.5** with $FeCl_3$ afforded 3-OH derivative **2.6** in 91% yield with a similar reaction speed of 5 h when compared to **2.1**. The removal of 6-Pico in **2.7** was very rapid and efficient in the presence of either catalyst, and 6-OH derivative **2.8** was obtained in 99% in 10-20 min.

Following the success of our preliminary trials, we moved on to investigating the compatibility of the developed reaction conditions with other temporary protecting groups. Removing the 6-Pico group in benzoylated thioglycoside **2.9** was rapid and chemoselective with either catalyst. The desired 6-OH derivative **2.10** was obtained in 93-99% yield in 10-15 min (Scheme 2.1). This result demonstrates that Pico can be

chemoselectively removed in the presence of benzoyl groups. Deprotection of the 3-Pico group in benzylidene-protected thiomannoside **2.11**[18] was also swift and efficient. 3-OH derivative **2.12** was rapidly produced (10-30 min) in the presence of either catalyst. The yields for the formation of **2.12** were also excellent (92-99%), which confirms compatibility of the acid-labile benzylidene acetal group with the developed reaction conditions. The removal of 4-Pico in glucosamine derivative **2.13** was also very efficient, and the resulting 4-OH derivative **2.14** was obtained in 99% yield in 1.5-4 h. This result indicates the efficiency of the developed method in application to aminosugars and compatibility of the phthlalimido group with these reaction conditions.

The method also proved successful in chemoselective removal of the 4-Pico group in acetylated sialic acid derivative **2.15**.[32] 4-OH sialoside **2.16** was rapidly produced in the presence of $FeCl_3$ in 95% yield in 50 min. A similar reaction in the presence of copper(II) acetate was even faster (20 min), but this translated in a somewhat lower yield of compound **2.16** (73%). Deprotection of 6-Pico with $FeCl_3$ in the differentially protected thioglycoside **2.17**[38] was very rapid (15 min) affording 6-OH derivative **2.18** in 97% yield. This result indicated excellent compatibility with the Fmoc group that is commonly used as a selectively removable protecting group in iterative oligosaccharide synthesis. The removal of 4-Pico in compound **2.19** was somewhat slow with $FeCl_3$, but the desired 4-OH derivative **2.20** was smoothly produced in an excellent yield (99%). This result ultimately confirms the compatibility of p-methoxybenzyl group with the developed reaction conditions. The 4-Pico group removal in **2.19** in the presence of copper(II) acetate was significantly faster (20 min), but the yield of product **2.20** was somewhat lower (85%).

**Scheme 2.1. Broadening the scope of the chemoselective Pico cleavage using Fe(III) or Cu(II) catalysts**




We also wanted to evaluate whether these reaction conditions are capable of concomitant removal of multiple Pico groups. When 4,6-di-O-Pico derivative **2.21** was

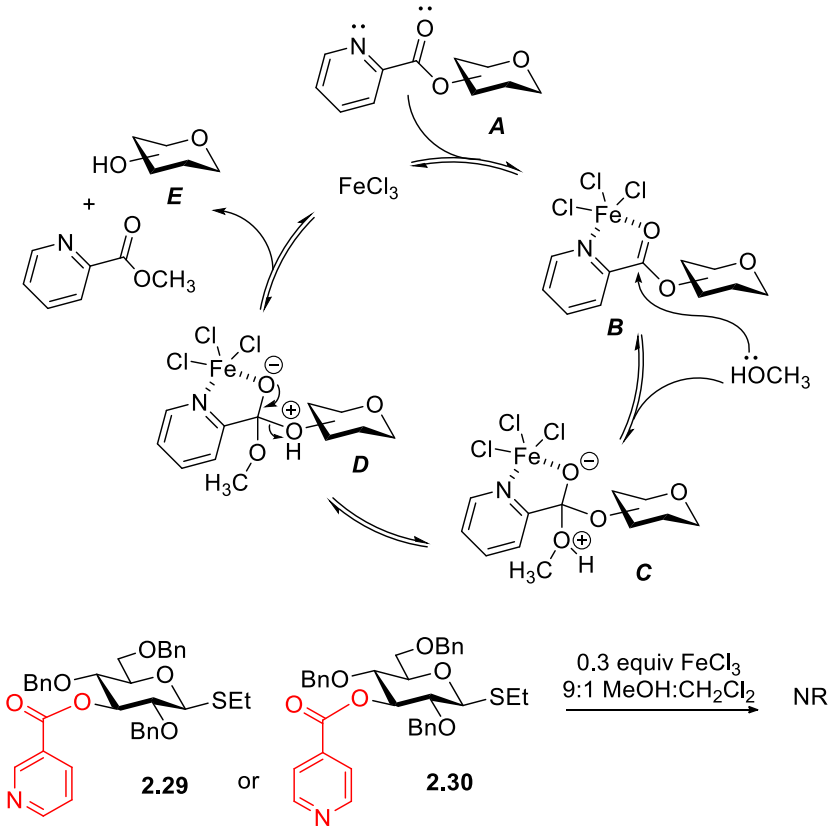
treated with 30 mol % of iron(III) chloride the desired diol **2.22** was produced in 99% yield. This reaction required 24 h to complete. As in a number of previous cases, deprotection in the presence of copper acetate was much faster (10 min) without affecting the efficiency: diol **2.22** was produced in 99% yield. Even tri-Pico compound **2.23**[23] could be efficiently deprotected using only 30 mol % of either catalyst. As a result, triol **2.24** was isolated in 83-91% yield in 15-45 min.

Finally, we also investigated the removal of the Pico group from oligosaccharides. When 3'-Pico protected disaccharide **2.25** was treated with $FeCl_3$ compound **2.26** was efficiently produced in 98% yield in 25 min. This result signified compatibility of the developed conditions with *tert*-butyldimethylsilyl (TBS), benzylidene, and phthalimido groups, all in one platform. Lacto-*N*-tetraose **2.27**,[39-40] a common core human milk tetrasaccharide, equipped with the 6'-Pico group could also be efficiently deprotected with $FeCl_3$ to afford compound **2.28** in 99% in 2 h.

Mechanistically, we hypothesize that when a picoloylated derivative **A** is used, iron(III) chloride (or copper acetate) coordinates between both the carbonyl oxygen and the nitrogen atoms of the Pico group as shown in Scheme 2.2 for intermediate **B**. This pulls electron density away from the carbonyl carbon allowing for a nucleophile to attack, in our case methanol, via tetrahedral intermediate **C**. The subsequent proton exchange leads to intermediate **D**, and the tetrahedral intermediate collapses to form the transesterification products, unprotected alcohol **E** and methyl picolinate. Iron(III) chloride is released and is available for the next catalytic cycle. To reinforce the viability of this reaction mechanism, we also investigated whether other positional isomers of the Pico group could be removed accordingly. For this purpose we obtained 3-niconoyl and

3-*O*-*iso*-niconoyl protected compounds **2.29** and **2.30**, respectively (Scheme 2.2).[24-25] No reprotection took place under the established reaction conditions even after 24 h. This outcome ultimately proves the complexation mode of metal salts that leads to swift deprotection of Pico groups.

**Scheme 2.2. Proposed mechanism of picoloyl cleavage**




## 2.3 Conclusions

We showed that the Pico group can be used as an effective temporary protecting group. In contrast to previous reports that employed stoichiometric reagents, this study demonstrated that the Pico group can be removed in a catalytic manner using 30 mol % of iron(III) chloride or copper(II) acetate. These conditions are also capable of chemoselective removal of even multiple Pico groups. Reactions performed with $Cu(OAc)_2$ were generally faster, but on a number of occasions $FeCl_3$-catalyzed reactions

provided better yields. The developed reaction conditions are directly compatible with all other protecting groups used in other orthogonal protection schemes. Hence, it is to be expected that the Pico group can enhance the arsenal of existing orthogonal group combinations used for glycan synthesis.

## 2.4 Experimental

### 2.4.1 General methods

Column chromatography was performed on silica gel 60 (70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. Optical rotations were measured at 'Jasco P-2000' polarimeter. Unless noted otherwise, $^{1}H$ NMR spectra were recorded in $CDCl_3$ at 300, $^{13}C$ NMR spectra were recorded in $CDCl_3$ at 75 MHz. Accurate mass spectrometry determinations were performed using Agilent 6230 ESI TOF LCMS.

### 2.4.2 Synthesis of picoloyl containing compounds

**General procedure for the Pico group introduction.**

Picolinic acid (2-3 equiv per OH), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 2-3 equiv per OH), and 4-dimethylaminopyridine (DMAP, 0.2-0.5 equiv per OH) were added to a solution of a starting material containing at least one OH group in $CH_2Cl_2$, and the resulting mixture was stirred under argon for 16 h at rt. After that, the reaction mixture was diluted with $CH_2Cl_2$ and washed with water (twice). The organic phase was separated, dried with magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate

- hexane gradient elution) to give the corresponding compound containing one or more Pico groups

**Ethyl 3,4,6-tri-*O*-benzyl-2-*O*-picoloyl-1-thio-β-D-glucopyranoside (2.3).**

The title compound was prepared from ethyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[41] (**2.4**, 34.6 mg, 0.07 mmol) in $CH_2Cl_2$ (2.0 mL), picolinic acid (26.0 mg, 0.21 mmol), EDC (40.3 mg, 0.21 mmol), and DMAP (4.3 mg, 0.03 mmol) in accordance with the general procedure as a white amorphous solid in 87% yield (36.3 mg, 0.60 mmol). Analytical data for **2.3**: $R_f$ = 0.50 (ethyl acetate/toluene, 1/1, v/v); $[\alpha]_D^{23}$ +22.3 (*c* = 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.77 (d, 1H, aromatic), 8.12 (d, 1H, aromatic), 7.83 (m, 1H, aromatic), 7.48 (m, 1H, aromatic), 7.40–7.24 (m, 8H, aromatic), 7.24–7.15 (m, 2H, aromatic), 7.15–7.05 (m, 5H, aromatic), 5.38 (dd, $J_{2,3}$ = 9.6 Hz, 1H, H-2), 4.82 (d, $^2J$ = 10.6, 1H, C*H*Ph), 4.75 (m, $^2J$ = 11.0 Hz, 2H, 2 x C*H*Ph) 4.67 (d, $J_{1,2}$ = 9.6 Hz, 1H, H-1) 4.68–4.51 (m, 3H, 3 x C*H*Ph), 3.97 (dd, $J_{3,4}$ = 9.1 Hz, 1H, H-3), 3.77 (dd, $J_{4,5}$ = 9.6 Hz, 1H, H-4), 3.76 (m, 1H, H-6a), 3.75 (m, $J_{6a,6b}$ = 4.6 Hz, 1H, H-6b), 3.57 (dd, $J_{5,6a} = J_{5,6b}$ = 9.1 Hz, 1H, H-5), 2.85–2.62 (m, 2H, SC$H_2$CH$_3$), 1.24 (t, *J* = 7.4 Hz, 3H, SCH$_2$C$H_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 164.3, 150.0, 147.8, 138.3, 138.1, 138.0, 137.2, 128.6 (x 2), 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.2, 126.0, 84.4, 83.4, 79.6 (x2), 78.1 (x2), 75.6 (x2), 75.3 (x2), 73.6 (x2), 73.4 (x2), 69.0 (x2), 24.1, 15.1 ppm; HRMS $[M+Na]^+$ calcd for $C_{35}H_{37}NO_6SNa$ 622.2236 found 622.2244.

**Ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-picoloyl-1-thio-β-D-glucopyranoside (2.9).**

The title compound was prepared from ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside[42] (**2.10**, 4.65 g, 8.66 mmol) in $CH_2Cl_2$ (100 mL), picolinic acid (2.15 g, 17.32 mmol), EDC (3.32 g, 17.32 mmol), and DMAP (0.21 g, 1.73 mmol) in accordance

with the general procedure as a white amorphous solid in 99% yield (5.56 g, 8.65 mmol). Analytical data for **2.9**: $R_f$ = 0.30 (ethyl acetate/ hexane, 1/1, v/v); $[\alpha]_D^{24}$ +16.2 (*c* = 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.71 (m, 1H, aromatic), 8.10 (m, 1H, aromatic), 8.00–7.92 (m, 2H, aromatic), 7.92–7.85 (m, 2H, aromatic), 7.85–7.76 (m, 3H, aromatic), 7.55–7.23 (m, 10H, aromatic), 5.93 (dd, $J_{3,4}$ = 9.5 Hz, 1H, H-3), 5.66 (dd, $J_{4,5}$ = 9.8 Hz, 1H, H-4), 5.58 (dd, $J_{2,3}$ = 9.7 Hz, 1H, H-2), 4.87 (dd, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 4.68 (dd, 1H, H-6a), 4.62 (dd, $J_{6a,6b}$ = 12.2 Hz, 1H, H-6b), 4.27 (dd, $J_{5,6a}$ = 3.4 Hz, $J_{5,6b}$ = 5.5 Hz, 1H, H-5), 2.86–2.65 (m, 2H, S$CH_2$$CH_3$), 1.23 (t, *J* = 7.4 Hz, 3H, $SCH_2CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 165.9, 165.4 (x2), 164.7, 150.2, 147.6, 137.2, 133.7, 133.5 (x2), 130.1 (x2), 130.0 (x2), 129.9 (x2), 129.2, 128.9, 128.8, 128.6 (x4), 128.5 (x2), 127.2, 125.5, 84.1, 76.2, 74.2, 70.7, 69.9, 64.4, 24.6, 15.1 ppm; HRMS $[M+Na]^+$ calcd for $C_{35}H_{31}NO_9SNa$ 664.1617 found 664.1626.

**Ethyl 3,6-di-*O*-benzyl-2-deoxy-4-*O*-picoloyl-2-phthalimido-1-thio-β-D-glucopyranoside (2.13)**

The title compound was prepared from ethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside[43] (**2.14**, 1.20 g, 1.88 mmol) in $CH_2Cl_2$ (50 mL), picolinic acid (0.46 g, 3.76 mmol), EDC (0.58 g, 3.76 mmol), and DMAP (0.045 g, 0.37 mmol) in accordance with the general procedure as a white amorphous solid in 85% yield (0.86 g, 1.62 mmol). Analytical data for **2.13**: $R_f$ = 0.2 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{24}$ +59.4 (*c* = 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.77 (d, 1H, aromatic), 8.08 (d, 1H, aromatic), 7.88–7.76 (m, 2H, aromatic), 7.74–7.62 (m, 3H, aromatic), 7.53–7.45 (m, 1H, aromatic), 7.29–7.12 (m, 6H, aromatic), 6.93 (m, 2H, aromatic), 6.85–6.74 (m, 3H, aromatic), 5.52 (dd, 1H, H-4), 5.35 (d, $J_{1,2}$ = 10.6 Hz, 1H, H-1), 4.74 (dd, 1H, H-3), 4.57

(d, $^{2}J$ = 12.1 Hz, 1H, C*H*Ph), 4.51 (s, 2H, C$H_2$Ph), 4.45–4.33 (m, 2H, H-2, C*H*Ph), 4.06 (m, $J_{5,6a} = J_{5,6b}$ = 4.4 Hz, 1H, H-5), 3.71 (dd, 2H, H-6a, 6b), 2.68 (m, 2H, SC$H_2$CH$_3$), 1.19 (t, $J$ = 7.4 Hz, 3H, SCH$_2$C$H_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 168.1, 167.5, 164.3, 150.1, 147.6, 138.0, 137.7, 137.2, 134.1, 134.0, 131.7, 128.3 (x2), 128.1 (x4), 127.8 (x2), 127.6, 127.5, 127.3, 125.8, 123.7, 123.5, 81.3, 77.9, 77.6, 74.4, 74.1, 73.6, 69.8, 54.9, 24.2, 15.1 ppm; HRMS $[M+Na]^+$ calcd for $C_{36}H_{34}N_2O_7SNa$ 661.1984 found 661.1993

**Ethyl 2,3-di-*O*-benzyl-4-*O*-p-methoxybenzyl-6-*O*-picoloyl-1-thio-β-D-glucopyranoside (2.19).**

NaH (60% in mineral oil, 703.4 mg 17.60 mmol) was added portionwise to a solution of ethyl 4,6-O-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside[44] (**2.31**, 3.0 g, 8.79 mmol) in dimethylformamide (25 mL), and the resulting mixture was cooled to 0 °C. Benzyl bromide (4.5 g, 26.37 mmol) was added dropwise, a second batch of NaH (60% in mineral oil, 703.4 mg, 17.60 mmol) was then added portionwise, and the resulting mixture was stirred under argon for 5 h. After that, the reaction mixture was poured into ice water (50 mL) and stirred for 30 min. The equeoud phase was extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 x 75 mL). The combined organic extract (~225 mL) was washed with cold water (3 x 30 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane gradient elution) to give ethyl 2,3-di-O-benzyl-4,6-O-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside **2.32** in 96% yield (4.42 g, 8.46 mmol). Selected analytical data for **2.32**: $R_f$ = 0.65 (ethyl acetate/hexane, 2/3, v/v); $^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.18 (m, 12H, aromatic), 6.95 – 6.85 (m, 2H, aromatic), 5.54 (s, 1H, C*H*Ph), 4.85 (dd, $^{2}J$ = 11.3 Hz, 2H, C$H_2$Ph),

4.84 (dd, $^{2}J$ = 10.2 Hz, 2H, C$H_2$Ph), 4.56 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.33 (dd, $J_{3,4}$ = 10.4, 1H, H-3), 3.81 (s, 3H, $OCH_3$), 3.80 – 3.64 (m, 3H, H-4, 6a, 6b), 3.50-3.39 (m, 2H, H-2, 5), 2.76 (m, 2H, SC$H_2$$CH_3$), 1.32 (t, $J$ = 7.4 Hz, 3H, $SCH_2CH_3$) ppm.

A mixture containing compound **2.32** (4.42 g, 8.46 mmol), molecular sieves (4Å, 3.0 g) in dimethylformamide (20 mL) was stirred under argon for 1 h at rt. The resulting mixture was cooled to 0 °C, sodium cyanoborohydride (2.66 g, 42.3 mmol) was added followed by slow dropwise addition of trifluoroacetic acid (9.65 g, 84.6 mmol), the reaction mixture was allowed to warm to ambient temperature and stirred for 16 h at rt. After that, the solids were filtered off through a pad of Celite and rinsed successively with DCM. The combined filtrate (~150 mL) was washed with sat. aq. $NaHCO_3$ (3 x 40 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 x 150 mL). The combined organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give ethyl 2,3-di-*O*-benzyl-4-*O*-p-methoxybenzyl-1-thio-β-D-glucopyranoside **2.20** in 79% yield (3.51 g, 6.68 mmol). Analytical data for **2.20**: $R_f$ = 0.45 (ethyl acetate/hexane, 3/2, v/v); $[\alpha]_D^{25}$ -32.5 ($c$ = 1.86, $CHCl_3$); $^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.50 – 7.19 (m, 12H, aromatic), 6.87 (d, 2H, aromatic), 4.85 (dd, $^{2}J$ = 9.4 Hz, 2H, C$H_2$Ph), 4.83 (dd, $^{2}J$ = 10.2 Hz, 2H, C$H_2$Ph), 4.50 (s, 2H, C$H_2$Ph), 4.48 (d, $J_{1,2}$ = 9.7 Hz, 1H, H-1), 3.80 (s, 3H, $OCH_3$), 3.71 (d, 1H, H-6a), 3.70 (d, 1H, H-6b), 3.62 (dd, $J_{4,5}$ = 9.1 Hz, 1H, H-4), 3.51 (dd, $J_{3,4}$ = 8.6 Hz, 1H, H-3), 3.44 (dd, $J_{5,6a}$ = $J_{5,6b}$ = 4.8 Hz, 1H, H-5), 3.40 (dd, $J_{2,3}$ = 9.0 Hz, 1H, H-2), 2.87 – 2.62 (m, 2H, SC$H_2$$CH_3$), 1.32 (t, $J$ = 7.4 Hz, 3H, $SCH_2CH_3$) ppm; $^{13}$C NMR (75

MHz, $CDCl_3$): δ 159.5, 138.7, 138.1, 130.0, 129.6, 128.8, 128.6 (x2), 128.2, 128.1 (x2), 114.0, 86.2, 85.3, 81.4, 77.9, 75.7, 75.6, 73.5, 72.5, 70.6, 55.5, 25.3, 15.4 ppm; HRMS $[M+Na]^+$ calcd for $C_{30}H_{36}O_6SNa$ 547.2125 found 547.2131

Compound **2.19** was prepared from **2.20** (1.48 g, 2.83 mmol) in $CH_2Cl_2$ (50 mL), picolinic acid (0.701 g, 5.65 mmol), EDC (1.08 g, 5.65 mmol), and DMAP (0.069 g, 0.57 mmol) in accordance with the general procedure as a white amorphous solid in 97% yield (1.72 g, 2.74 mmol). Analytical data for **2.19**: $R_f$ = 0.55 (acetone/ hexane, 1/1, v/v); $[\alpha]_D^{24}$ -27.6 (*c* = 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.78 – 8.69 (m, 1H, aromatic), 7.98 (m, 1H, aromatic), 7.78 (m, 1H, aromatic), 7.46 (m, 1H, aromatic), 7.41 – 7.24 (m, 5H, aromatic), 7.18 – 7.02 (m, 7H, aromatic), 6.77 – 6.66 (m, 2H, aromatic), 5.37 (dd, $J_{4,5}$ = 9.7 Hz, 1H, H-4), 4.84 (dd, $^2J$ = 10.2 Hz, 2H, C$H_2$Ph), 4.73 (dd, $^2J$ = 11.2 Hz, 2H, C$H_2$Ph), 4.55 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.39 (dd, 2H, H-6a, 6b), 3.90 (dd, $J_{3,4}$ = 9.1 Hz, 1H, H-3), 3.82 (dd, 1H, H-5), 3.73 (s, 3H, $OCH_3$), 3.60 (dd, $^2J$ = 4.4 Hz, 2H, C$H_2$Ph), 3.56 (dd, $J_{2,3}$ = 8.9 Hz, 1H, H-2), 2.89 – 2.69 (m, 2H, SC$H_2$C$H_3$), 1.34 (t, *J* = 7.4 Hz, 3H, $SCH_2CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 164.3, 159.1, 145.0, 147.7, 138.1, 138.0, 137.1, 130.1, 129.5 (x2), 128.6 (x4), 128.3 (x2), 128.1 (x3), 127.7, 127.1, 125.7, 113.7, 85.3, 83.8, 81.8, 77.4, 75.8, 75.6, 73.3, 72.5, 69.5, 55.3 (x2), 25.2, 15.4 ppm; HRMS $[M+Na]^+$ calcd for $C_{36}H_{39}NO_7SNa$ 652.2345 found 652.2347

**Ethyl 2,3-di-*O*-benzyl-4,6-di-*O*-picoloyl-1-thio-β-D-glucopyranoside (2.21).**

The title compound was prepared from ethyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside[45] (**2.22**, 237.3 mg, 0.59 mmol) in $CH_2Cl_2$ (10 mL), picolinic acid (364.0 mg, 2.90 mmol), EDC (555.93 mg, 2.90 mmol), and DMAP (36.07 mg, 0.30 mmol) in

accordance with the general procedure as a white amorphous solid in 86% yield (311.1 mg, 0.51 mmol). Analytical data for **2.21**: $R_f$ = 0.30 (acetone/hexane, 1/3, v/v); $[\alpha]_D^{24}$ -6.40 (*c* = 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.77 – 8.64 (m, 2H, aromatic), 8.15 – 8.06 (m, 1H, aromatic), 8.06 – 7.98 (m, 1H, aromatic), 7.86 – 7.74 (m, 2H, aromatic), 7.52 – 7.29 (m, 7H, aromatic), 7.08 (s, 5H, aromatic), 5.52 (dd, $J_{4,5}$ = 9.8 Hz, 1H, H-4), 4.85 (dd, $^2J$ = 10.2 Hz, 2H, C*H*$_2$Ph), 4.76 (dd, $^2J$ = 11.2 Hz, 2H, C*H*$_2$Ph),4.61 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 4.56 (d, 2H, H-6a, 6b), 4.06 (dd, $J_{5,6a}$ = 4.3 Hz, $J_{5,6b}$ = 4.4 Hz, 1H, H-5), 3.97 (dd, $J_{3,4}$ = 9.1 Hz, 1H, H-3), 3.61 (dd, $J_{2,3}$ = 8.9 Hz, 1H, H-2), 2.89 – 2.65 (m, 2H, SC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 164.6, 164.3, 150.1, 150.0, 147.7, 147.4, 137.9, 137.8, 137.2, 137.1, 128.6 (x3), 128.4 (x2), 128.2 (x2), 128.1 (x2), 127.8, 127.3, 127.1, 125.9, 125.6, 85.4, 83.7, 81.7, 75.9, 75.8, 75.5, 71.9, 64.3, 25.2, 15.3 ppm; HRMS $[M+Na]^+$ calcd for $C_{34}H_{34}N_2O_7SNa$ 637.1984 found 637.1988

**Ethyl 2-*O*-benzyl-3,4,6-tri-*O*-picoloyl-1-thio-α-D-mannopyranoside (2.23).**

*p*-Toluenesulfonic acid (3.1 mg, 0.016 mmol) and ethanethiol (12.3 mg, 0.198 mmol) were added to a solution of ethyl 2-O-benzyl-4,6-O-benzylidene-3-picoloyl-1-thio-α-D-mannopyranoside[18] (**2.31**, 16.6 mg, 0.033 mmol) in DCM (0.5 mL), and the resulting solution was stirred under argon for 2 h at rt. The reaction mixture was then neutralized with triethylamine, the volatiles were removed under reduced pressure, and the residue containing ethyl 2-O-benzyl-1-thio-α-D-mannopyranoside(**2.33**) was dried in *vacuo* for 2 h. The title compound was then obtained from crude **2.33** (0.033 mmol) in dichloromethane (0.5 mL), picolinic acid (24.6 mg, 0.198 mmol), EDC (38.0 mg, 0.198 mmol), and DMAP (0.81 mg, 0.007 mmol) in accordance with the general procedure as a

white amorphous solid in 86% yield (17.7 mg, 0.028 mmol). Analytical data for **2.23**: $R_f$ = 0.4 (acetone/toluene, 1/1, v/v); $[\alpha]_D^{21}$ +52.5 (*c* = 2.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.70 (d, 3H, aromatic), 8.17 – 7.95 (m, 3H, aromatic), 7.84 – 7.66 (m, 3H, aromatic), 7.51 – 7.38 (m, 3H, aromatic), 7.38 – 7.25 (m, 2H, aromatic), 7.25 – 7.10 (m, 3H, aromatic), 6.17 (dd, $J_{4,5}$ = 10.0 Hz, 1H, H-4), 5.70 (dd, $J_{3,4}$ = 10.0 Hz, 1H, H-3), 5.51 (dd, 1H, H-1), 4.87 (dd, 1H, H-5), 4.68 (dd, $^2J$ = 12.0 Hz, 2H, C*H*$_2$Ph), 4.67-4.64 (m, 2H, H-6a, 6b), 4.27 (dd, $J_{2,3}$ = 1.5 Hz, 1H, H-2), 2.84 – 2.47 (m, 2H, SC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 164.5, 164.0, 163.7, 150.2, 150.1 (x2), 147.6, 147.1, 147.0, 137.5, 137.2 (x2), 137.1, 128.4 (x2), 127.9 (x3), 127.3, 127.1, 126.9, 125.7, 125.6, 125.4, 82.0, 77.1, 73.1, 72.8, 68.8, 68.3, 64.0, 25.4, 14.9 ppm; HRMS $[M+Na]^+$ calcd for $C_{33}H_{31}N_3O_8SNa$ 652.1724 found 652.1738

### 2.4.3 Selective deprotection of the Pico group

**General procedure for Pico removal.**

Iron(III) chloride (0.017 mmol) or copper(II) acetate (0.017 mmol) was added to a solution of a Pico derivative (0.051 mmol) in MeOH-DCM (1.0 mL, 1.0/1, v/v), and the resulting mixture was stirred under argon at rt. Upon completion (see the reaction time listed in Scheme 2.1), the volatiles were removed under reduced pressure. The residue was diluted with DCM (~5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL) and water (2 x 5 mL). The organic phase was separated, dried using magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane gradient elution) to give the corresponding deprotected derivative in yields listed in Scheme 2.1.

**Ethyl 2,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2.2).**

The title compound was obtained from ethyl 2,3,6-tri-O-benzyl-4-O-picoloyl-1-thio-β-D-glucopyranoside[16] (**2.1**, 29.1 mg, 0.052 mmol) and iron(III) chloride (2.5 mg, 0.016 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 5 h in 91% yield (23.3 mg, 0.047 mmol). Alternatively, the title compound was obtained from thioglycoside **2.1** (29.6 mg, 0.049 mmol) and copper(II) acetate (3.0 mg, 0.015 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 1.5 h in 99% yield (24.8 mg, 0.048 mmol). Analytical data for **2.2** was in accordance with that reported previously.[46]

**Ethyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2.4).**

The title compound was obtained from **2.3** (29.0 mg, 0.048 mmol) and iron(III) chloride (2.4 mg, 0.015 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 48 h in 71% yield (17.0 mg, 0.034 mmol). Alternatively, the title compound was obtained from thioglycoside **2.3** (33.1 mg, 0.055 mmol) and copper(II) acetate (3.3 mg, 0.017 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 2 h in 91% yield (15.2 mg, 0.03 mmol). Analytical data for **2.4** was in accordance with that reported previously.[41]

**Ethyl 2,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2.6).**

The title compound was obtained from ethyl 2,4,6-tri-O-benzyl-3-O-picoloyl-1-thio-β-D-glucopyranoside[24-25] (**2.5**, 9.5 mg, 0.017 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup

in 91% yield (8.1 mg, 0.016 mmol). Analytical data for **2.6** was in accordance with that reported previously.[47]

**Ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2.8).**

The title compound was obtained from 2,3,4-tri-O-benzyl-6-O-picoloyl-1-thio-β-D-glucopyranoside[16] (**2.7**, 35.4 mg, 0.055 mmol) and iron(III) chloride (2.7 mg, 0.016 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 20 min in 98% yield (28.8 mg, 0.054 mmol). Alternatively, the title compound was obtained from thioglycoside **2.7** (18.1 mg, 0.03 mmol) and copper(II) acetate (1.8 mg, 0.009 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 10 min in 99% yield (15.2 mg, 0.03 mmol). Analytical data for **2.8** was in accordance with that reported previously.[48]

**Ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (2.10).**

The title compound was obtained from **2.9** (31.9 mg, 0.050 mmol) and iron(III) chloride (2.4 mg, 0.015 mmol) in methanol (0.9 mL) and dichloromethane (0.10 mL) in accordance with the general procedure as a colorless syrup in 15 min in 96% yield (25.7 mg, 0.0048 mmol). Alternatively, the title compound was obtained from thioglycoside **2.9** (32.3 mg, 0.050 mmol) and copper(II) acetate (3.0 mg, 0.015 mmol) in methanol (0.9 mL) and dichloromethane (0.10 mL) in accordance with the general procedure as a colorless syrup in 10 min in 93% yield (25.1 mg, 0.047 mmol). Analytical data for **2.10** was essentially the same as reported previously.[42]

**Ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (2.12).**

The title compound was obtained from ethyl 2-O-benzyl-4,6-O-benzylidene-3-O-picoloyl-1-thio-α-D-mannopyranoside[18] (**2.11**, 31.7 mg, 0.062 mmol) and iron(III) chloride (3.0 mg, 0.019 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 30 min in 88% yield (22.2 mg, 0.055 mmol). Alternatively, the title compound was obtained from **2.11** (14.6 mg, 0.029 mmol) and copper(II) acetate (1.8 mg, 0.0087 mmol) in methanol (0.45 mL) and dichloromethane (0.05 mL) in accordance with the general procedure as a colorless syrup in 10 min in 93% yield (25.1 mg, 0.047 mmol). Analytical data for **2.12** was essentially the same as reported previously.[49]

**Ethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (2.14).**

The title compound was obtained from **2.13** (29.9 mg, 0.047 mmol) and iron(III) chloride (2.3 mg, 0.014 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 5 h in 99% yield (25.2 mg, 0.047 mmol). Alternatively, the title compound was obtained from thioglycoside **2.13** (36.4 mg, 0.057 mmol) and Copper(II) acetate (1.8 mg, 0.017 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 1.5 h in 99% yield (30.0 mg, 0.056 mmol). Analytical data for **2.14** was essentially the same as reported previously.[43]

**Methyl (phenyl 5-acetamido-7,8,9-tri-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-non-2-ulopyranosid)onate (2.16).**

The title compound was obtained from methyl (phenyl 5-acetamido-7,8,9-tri-*O*-acetyl-3,5-dideoxy-4-O-picoloyl-2-thio-D-glycero-α-D-galacto-non-2-ulopyranosid)onate[32]

(**2.15**, 22.9 mg, 0.035 mmol) and iron(III) chloride (1.7 mg, 0.01 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 50 min in 95% yield (17.9 mg, 0.033 mmol). Alternatively, the title compound was obtained from thioglycoside **2.15** (26.8 mg, 0.041 mmol) and copper(II) acetate (2.5 mg, 0.012 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 20 min in 73% yield (16.2 mg, 0.030 mmol). Analytical data for **2.16**: $R_f$ = 0.40 (methanol/ dichloromethane, 1/9, v/v); $[\alpha]_D^{25}$ +25.3 (*c* = 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.53 – 7.46 (m, 2H, aromatic), 7.43 – 7.29 (m, 3H, aromatic), 5.99 (d, *J* = 8.4 Hz, 1H, NH), 5.32 (dd, $J_{7,8}$ = 7.3 Hz, 1H, H-7), 5.27 (dt, $J_{8,9a}$ = 5.0 Hz, $J_{8,9b}$ = 2.4 Hz 1H, H-8), 4.39 (dd, $J_{9a,9b}$ = 12.6 Hz, 1H, H-9a), 4.26 (dd, 1H, H-9b), 3.90 (dd, $J_{6,7}$ = 10.4 Hz, 1H, H-6), 3.86 (s, 1H, 4-OH), 3.64 (dd, $J_{4,5}$ = 10.6, 1H, H-4), 3.57 (s, 3H, $OCH_3$), 3.50 (dd, $J_{5,6}$ = 8.5 Hz, 1H, H-5), 2.89 (dd, $J_{3eq,3ax}$ = 13.0, $J_{3eq,4}$ = 4.4 Hz, 1H, H-$3_{eq}$), 2.15, 2.06, 2.03, 1.96 (4 s, 12H, $NCOCH_3$, 3 x $OCOCH_3$), 1.86 (dd, $J_{3ax,4}$ =11.4 Hz, 1H, H-$3_{ax}$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 172.4 (x2), 170.9 (x2), 170.5 (x2), 170.3 (x2), 168.3 (x2), 136.5 (x3), 130.0, 129.0 (x4), 88.0, 74.1, 70.1, 69.2, 68.1, 62.1, 52.8 (x3), 41.4, 29.5, 23.7, 21.2 (x2), 21.0 (x3) ppm; HRMS $[M+Na]^+$ calcd for $C_{24}H_{31}NO_{11}SNa$ 564.1510 found 564.1521.

**Ethyl 2-*O*-benzoyl-4-*O*-benzyl-3-*O*-(9-fluorenylmethoxycarbonyl)-1-thio-β-D-galactopyranoside (2.18).**

The title compound was obtained from ethyl 2-O-benzoyl-4-O-benzyl-3-O-(9-fluorenylmethoxycarbonyl)-6-O-picoloyl-1-thio-β-D-galactopyranoside[38] (**2.17**, 31.2 mg, 0.042 mmol) and iron(III) chloride (2.0 mg, 0.013 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup

in 15 min in 91% yield (25.2 mg, 0.047 mmol). Analytical data for **2.18**: $R_f$ = 0.45 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ +25.7 (*c* = 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, 2H, aromatic), 7.69 (dd, 2H, aromatic), 7.59 – 7.22 (m, 12H, aromatic), 7.19 – 7.04 (m, 2H, aromatic), 5.76 (dd, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 5.07 (dd, $J_{3,4}$ = 2.8 Hz, 1H, H-3), 4.68 (dd, $^2J$ = 11.6 Hz, 2H, C$H_2$Ph), 4.60 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.34 (dd, 1H, H-6a), 4.24 (dd, $J_{6a,6b}$ = 10.3 Hz, 1H, H-6b),4.08 (dd, $J_{5,6a}$ = 7.9 Hz, $J_{5,6b}$ = 7.1 Hz, 1H, H-5), 4.04 (dd, $J_{4,5}$ = 5 Hz, 1H, H-4), 3.86 (dd, *J* = 11.1, 6.8 Hz, 1H, Fmoc), 3.67 (m, 1H, Fmoc), 3.56 (m, 1H, Fmoc), 2.88 – 2.60 (m, 2H, SC$H_2$CH$_3$), 1.23 (t, *J* = 7.3 Hz, 3H, SCH$_2$C$H_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 165.5, 154.7, 143.4, 142.9, 141.4, 141.3, 137.6, 133.5, 130.1 (x2), 129.6, 128.8 (x3), 128.7 (x3), 128.6 (x2), 128.4, 128.1 (x2), 127.3 (x2), 125.4, 125.1, 120.2, 84.0, 79.3, 79.1, 75.0, 73.5, 70.4, 62.0, 46.6, 24.1, 15.0 ppm; HRMS $[M+Na]^+$ calcd for $C_{37}H_{36}O_8SNa$ 663.2029 found 663.2027

**Ethyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenyl-1-thio-β-D-glucopyranoside (2.20).**

The title compound was obtained from **2.19** (32.8 mg, 0.052 mmol) and iron(III) chloride (2.5 mg, 0.015 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 16 h in 99% yield (28.5 mg, 0.054 mmol). Alternatively, the title compound was obtained from **2.19** (29.4 mg, 0.047 mmol) and copper(II) acetate (2.8 mg, 0.014 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 15 min in 85% yield (20.8 mg, 0.040 mmol).

**Ethyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (2.22).**

The title compound was obtained from **2.21** (57.0 mg, 0.093 mmol) and iron(III) chloride (4.5 mg, 0.028 mmol) in methanol (1.8 mL) and dichloromethane (0.2 mL) in accordance

with the general procedure as a colorless syrup in 24 h in 99% yield (37.2 mg, 0.092 mmol). Alternatively, the title compound was obtained from thioglycoside **2.21** (30.4 mg, 0.049 mmol) and copper(II) acetate (3.0 mg, 0.015 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 10 min in 99% yield (20.3 mg, 0.048 mmol). Analytical data for **2.20** was essentially the same as reported previously.[45]

**Ethyl 2-*O*-benzyl-1-thio-α-D-mannopyranoside (2.24).**

The title compound was obtained from **2.23** (36.5 mg, 0.058 mmol) and iron(III) chloride (2.8 mg, 0.017 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 45 min in 91% yield (16.6 mg, 0.052 mmol). Alternatively, the title compound was obtained from **2.23** (37.3 mg, 0.059 mmol) and copper(II) acetate (3.6 mg, 0.018 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 15 min in 83% yield (15.5 mg, 0.049 mmol). Analytical data for **2.24**: $R_f$ = 0.50 (acetone/toluene, 1/1, v/v); $[\alpha]_D^{21}$ +103.1 (*c* = 1.0, $CHCl_3$); $^1$H NMR (300 MHz, MeOD): δ 7.49 – 7.22 (m, 5H, aromatic), 5.32 (s, 1H, H-1), 4.68 (dd, $^2J$ = 11.9, 2H, C$H_2$Ph), 3.97 – 3.60 (m, 6H, H-2, 3, 4, 5, 6a, 6b), 2.76 – 2.48 (m, 2H, SC$H_2$CH$_3$), 1.23 (t, *J* = 7.4 Hz, 3H, SCH$_2$C$H_3$) ppm; $^{13}$C NMR (75 MHz, MeOD): δ 139.7 (x2), 129.5 (x2), 129.3, 128.9, 83.1, 81.5, 75.1, 73.8, 73.3, 69.4, 62.9, 26.0, 15.4 ppm; HRMS $[M+Na]^+$ calcd for $C_{15}H_{22}O_5SNa$ 337.1080 found 337.1120.

***tert*-Butyldimethylsilyl *O*-(2-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (2.26).**

The title compound was obtained from *tert*-butyldimethylsilyl O-(2-O-benzyl-4,6-O-benzylidene-3-O-picoloyl-β-D-mannopyranosyl)-(1→4)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside[23] (**2.25**, 29.0 mg, 0.028 mmol) and iron(III) chloride (1.3 mg, 0.083 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 25 min in 91% yield (25.5 mg, 0.027 mmol). Analytical data for **2.26** was essentially the same as reported previously.[23]

**Benzyl *O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-*O*-(4,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-*O*-(2-*O*-benzoyl-4-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (2.28).**

The title compound was obtained from benzyl O-(2-O-benzoyl-3,4,6-tri-O-benzyl-β-D-galactopyranosyl)-(1→3)-O-(4,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-O-(2-O-benzoyl-4-O-benzyl-6-O-picoloyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside[39] (**2.27**, 9.9 mg, 0.0049 mmol) and iron(III) chloride (2.3 mg, 0.0015 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL) in accordance with the general procedure as a colorless syrup in 45 min in 99% yield (9.3 mg, 0.0049 mmol). Analytical data for **2.28** was essentially the same as reported previously.[39]

### 2.4.4 Attempted deprotection of Pico regioisomers

Iron(III) chloride (1.3 mg, 0.0008 mmol) was added to a solution of ethyl 2,4,6-tri-O-benzyl-3-O-nicotinoyl-1-thio-β-D-glucopyranoside[24-25] (**2.29**, 14.8 mg, 0.026 mmol) in

methanol (0.9 mL) and dichloromethane (0.1 mL), and the resulting mixture was stirred under argon at rt. No reaction took place after 24 h.

Iron(III) chloride (1.5 mg, 0.0009 mmol) was added to a solution of ethyl 2,4,6-tri-O-benzyl-3-O-*iso*-nicotinoyl-1-thio-β-D-glucopyranoside[24-25] (**2.30**, 17.3 mg, 0.031 mmol) in methanol (0.9 mL) and dichloromethane (0.1 mL), and the resulting mixture was stirred under argon at rt. No reaction took place after 24 h.

**2.5 References**

1. Jager, M.; Minnaard, A. J., Regioselective modification of unprotected glycosides. *Chem. Commun.* **2016,** *52* (4), 656-664.

2. Kulkarni, S. S.; Wang, C. C.; Sabbavarapu, N. M.; Podilapu, A. R.; Liao, P. H.; Hung, S. C., "One-Pot" Protection, Glycosylation, and Protection-Glycosylation Strategies of Carbohydrates. *Chem. Rev.* **2018,** *118* (17), 8025-8104.

3. Volbeda, A. G.; van der Marel, G. A.; Codée, J. D. C., Protecting Group Strategies in Carbohydrate Chemistry. In *Protecting Groups – Strategies and Applications in Carbohydrate Chemistry*, Vidal, S., Ed. Wiley-VCH: Weinheim, 2019; pp 1-28.

4. Wang, T.; Demchenko, A. V., Synthesis of carbohydrate building blocks via regioselective uniform protection/deprotection strategies. *Org. Biomol. Chem.* **2019,** *17*, 4934-4950.

5. Fraser-Reid, B.; Jayaprakash, K. N.; López, J. C.; Gómez, A. M.; Uriel, C., Protecting groups in carbohydrate chemistry profoundly influence all selectivities in glycosyl couplings. In *ACS Symp. Ser. (Frontiers in Modern Carbohydrate Chemistry)* Demchenko, A. V., Ed. Oxford Univ. Press: 2007; Vol. 960, pp 91-117.

6. Bandara, M. D.; Yasomanee, J. P.; Demchenko, A. V., Application of armed, disarmed, superarmed and superdisarmed building blocks in stereocontrolled glycosylation and expeditious oligosaccharide synthesis. In *Selective Glycosylations: Synthetic Methods and Catalysts*, Bennett, C. S., Ed. Wiley: 2017; pp 29-58.

7. Prabhu, A.; Venot, A.; Boons, G. J., New set of orthogonal protecting groups for the modular synthesis of heparan sulfate fragments. *Org. Lett.* **2003,** *5*, 4975-4978.

8. Wang, Z.; Chinoy, Z. S.; Ambre, S. G.; Peng, W.; McBride, R.; de Vries, R. P.; Glushka, J.; Paulson, J. C.; Boons, G. J., A general strategy for the chemoenzymatic synthesis of asymmetrically branched N-glycans. *Science* **2013,** *341* (6144), 379-383.

9. Markad, S. D.; Schmidt, R. R., Temporary Carbohydrate Diol Protection with Ester Groups - Orthogonality under Solid-Phase Oligosaccharide Synthesis Conditions. *Eur. J. Org. Chem.* **2009**, 5002-5011.

10. Seeberger, P. H., The logic of automated glycan assembly. *Acc. Chem. Res.* **2015,** *48* (5), 1450-1463.

11. Senf, D.; Ruprecht, C.; de Kruijff, G. H. M.; Simonetti, S. O.; Schuhmacher, F.; Seeberger, P. H.; Pfrengle, F., Active site mapping of xylan-deconstructing enzymes with arabinoxylan oligosaccharides produced by automated glycan assembly. *Chem. Eur. J.* **2017,** *23* (13), 3197-3205.

12. Guberman, M.; Seeberger, P. H., Automated Glycan Assembly: A Perspective. *J. Am. Chem. Soc.* **2019,** *141* (14), 5581-5592.

13. Pfrengle, F.; Seeberger, P. H., Orthogonally Protected Building Blocks for Automated Glycan Assembly. In *Protecting Groups – Strategies and Applications in Carbohydrate Chemistry*, Vidal, S., Ed. Wiley-VCH: Weinheim, 2019; pp 451-472.

14. Ágoston, K.; Streicher, H.; Fügedi, P., Orthogonal protecting group strategies in carbohydrate chemistry. *Tetrahedron: Asymmetry* **2016,** *27* (16), 707-728.

15. Panza, M.; Pistorio, S. G.; Stine, K. J.; Demchenko, A. V., Automated Chemical Oligosaccharide Synthesis: Novel Approach to Traditional Challenges. *Chem. Rev.* **2018,** *118*, 8105−8150.

16. Yasomanee, J. P.; Demchenko, A. V., The effect of remote picolinyl and picoloyl substituents on the stereoselectivity of chemical glycosylation. *J. Am. Chem. Soc.* **2012,** *134*, 20097-20102.

17. Yasomanee, J. P.; Demchenko, A. V., Hydrogen bond-mediated aglycone delivery: the synthesis of linear and branched α-glucans. *Angew. Chem. Int. Ed.* **2014,** *53*, 10453–10456.

18. Pistorio, S. G.; Yasomanee, J. P.; Demchenko, A. V., Hydrogen bond-mediated aglycone delivery: focus on β-mannosylation. *Org. Lett.* **2014,** *16*, 716-719.

19. Yasomanee, J. P.; Demchenko, A. V., Hydrogen bond-mediated aglycone delivery (HAD): a highly stereoselective synthesis of 1,2-cis α-D-glucosides from common glycosyl donors in the presence of bromine. *Chem. Eur. J.* **2015,** *21*, 6572-6581.

20. Kayastha, A. K.; Jia, X. G.; Yasomanee, J. P.; Demchenko, A. V., 6-O-Picolinyl and 6-O-picoloyl building blocks as glycosyl donors with switchable stereoselectivity. *Org. Lett.* **2015,** *17*, 4448-4451.

21. Mannino, M. P.; Yasomanee, J. P.; Demchenko, A. V.; Patteti, V., Picoloyl group in oligosaccharide synthesis: installation, H-bond-mediated aglycone delivery (HAD), and selective removal. In *Carbohydrate Chemistry: Proven Synthetic Methods*, Murphy, P.; Vogel, P., Eds. CRC Press: Boca Raton - London - New York, 2017; Vol. 4, pp 3-10.

22. Mannino, M. P.; Yasomanee, J. P.; Demchenko, A. V., Investigation of the H-bond-mediated aglycone delivery reaction in application to the synthesis of β-glucosides. *Carbohydr. Res.* **2018,** *470*, 1-7.

23. Pistorio, S. G.; Geringer, S. A.; Stine, K. J.; Demchenko, A. V., Manual and automated syntheses of the N-linked glycoprotein core glycans. *J. Org. Chem.* **2019,** *84*, 6576-6588.

24. Mannino, M. P.; Demchenko, A. V., Synthesis of β-glucosides with 3-O-picoloyl-protected glycosyl donors in the presence of excess triflic acid: a mechanistic study. *Chem. Eur. J.* **2019,** 26, 2927-2937.

25. Mannino, M. P.; Demchenko, A. V., Synthesis of β-glucosides with 3-O-picoloyl-protected glycosyl donors in the presence of excess triflic acid: Defining the scope. *Chem. Eur. J.* **2019**, 26, 2938-2946.

26. Prasad, V.; Birzin, E. T.; McVaugh, C. T.; van Rijn, R. D.; Rohrer, S. P.; Chicchi, G.; Underwood, D. J.; Thornton, E. R.; Smith III, A. B.; Hirschmann, R., Effects of Heterocyclic Aromatic Substituents on Binding Affinities at Two Distinct Sites of Somatostatin Receptors. Correlation with the Electrostatic Potential of the Substituents *J. Med. Chem.* **2003,** *46*, 1858-1869.

27. Baek, J. Y.; Shin, Y.-J.; Jeon, H. B.; Kim, K. S., Picolinyl group as an efficient alcohol protecting group: cleavage with $Zn(OAc)_2 \cdot 2H_2O$ under a neutral condition *Tetrahedron Lett.* **2005,** *46*, 5143-5147.

28. Ruei, J.-H.; Venukumar, P.; Ingle, A. B.; Mong, K.-K. T., C6 Picoloyl protection: a remote stereodirecting group for 2-deoxy-β-glycoside formation. *Chem. Commun.* **2015,** *51*, 5394-5397.

29. Xiang, S.; Hoang Kle, M.; He, J.; Tan, Y. J.; Liu, X. W., Reversing the stereoselectivity of a palladium-catalyzed O-glycosylation through an inner-sphere or outer-sphere pathway. *Angew. Chem. Int. Ed.* **2015,** *54* (2), 604-607.

30. Lu, Y. L.; Ghosh, B.; Mong, K. T., Unusually Stable Picoloyl-Protected Trimethylsilyl Glycosides for Nonsymmetrical 1,1'-Glycosylation and Synthesis of 1,1'-Disaccharides with Diverse Configurations. *Chem. Eur. J.* **2017,** *23* (28), 6905-6918.

31. Wu, Y. F.; Tsai, Y. F., Assistance of the C-7,8-picoloyl moiety for directing the glycosyl acceptors into the alpha-orientation for the glycosylation of sialyl donors. *Org. Lett.* **2017,** *19* (16), 4171-4174.

32. Escopy, S.; Geringer, S. A.; De Meo, C., Combined effect of the picoloyl protecting group and triflic acid in sialylation. *Org. Lett.* **2017,** *19* (10), 2638-2641.

33. Shadrick, M.; Yu, C.; Geringer, S.; Ritter, S.; Behm, A.; Cox, A.; Lohman, M.; De Meo, C., Facile and robust methods for the regioselective acylation of N-acetylneuraminic acid. *New J. Chem.* **2018,** *42* (17), 14138-14141.

34. Jones, B.; Behm, A.; Shadrick, M.; Geringer, S. A.; Escopy, S.; Lohman, M.; De Meo, C., Comparative Study on the Effects of Picoloyl Groups in Sialylations Based on Their Substitution Pattern. *J. Org. Chem.* **2019,** *84* (23), 15052-15062.

35. Dubey, A.; Tiwari, A.; Mandal, P. K., An eco-friendly N-benzoylglycine/thiourea cooperative catalyzed stereoselective synthesis of beta-L-rhamnopyranosides. *Carbohydr. Res.* **2019,** *487*, 107887.

36. Shit, P.; Gucchait, A.; Misra, A. K., Straightforward sequential and one-pot synthesis of a pentasaccharide repeating unit corresponding to the cell wall O-antigen of Shigella boydii type 18. *Tetrahedron* **2019,** *75* (49), 130697.

37. Zemplén, G.; Pacsu, E., Über die Verseifung acetylierter Zucker und verwandter Substanzen. *Ber. Dtsch. Chem. Ges.* **1929,** *62*, 1613-1614.

38. Bandara, M. D.; Stine, K. J.; Demchenko, A. V., The chemical synthesis of human milk oligosaccharides: lacto-N-neotetraose (Galβ1-4GlcNAcβ1-3Galβ1-4Glc). *Carbohydr. Res.* **2019,** *483*, 107743.

39. Bandara, M. D.; Stine, K. J.; Demchenko, A. V., Chemical synthesis of human milk oligosaccharides: lacto-N-hexaose Galβ1-3GlcNAcβ1-3[Galβ1-4GlcNAcβ1-6]Galβ1-4Glc. *J. Org. Chem.* **2019**, 84, 16192-16198.

40. Bandara, M. D.; Stine, K. J.; Demchenko, A. V., The chemical synthesis of human milk oligosaccharides: lacto-N-tetraose (Galβ1-3GlcNAcβ1-3Galβ1-4Glc). *Carbohydr. Res.* **2019,** *486*, 107824.

41. Thijssen, M. J. L.; Halkes, K. M.; Kamerling, J. P.; Vliegenthart, J. F. G., Synthesis of a spacer-containing tetrasaccharide representing a repeating unit of the capsular polysaccharide of *Streptococcus pneumoniae* type 6B. *Bioorg. Med. Chem.* **1994,** *2* (11), 1309-1317.

42. Veeneman, G. H.; van Boom, J. H., An efficient thioglycoside-mediated formation of alpha-glycosidic linkages promoted by iodonium dicollidine perchlorate. *Tetrahedron Lett.* **1990,** *31* (2), 275-278.

43. Nagorny, P.; Fasching, B.; Li, X.; Chen, G.; Aussedat, B.; Danishefsky, S. J., Toward Fully Synthetic Homogeneous β-Human Follicle-Stimulating Hormone (β-hFSH) with a Biantennary N-Linked Dodecasaccharide. Synthesis of β-hFSH with Chitobiose Units at the Natural Linkage Sites. *J. Am. Chem. Soc.* **2009,** *131*, 5792-5799.

44. Mende, M.; Nieger, M.; Brase, S., Chemical Synthesis of Modified Hyaluronic Acid Disaccharides. *Chemistry (Weinheim an der Bergstrasse, Germany)* **2017,** *23* (50), 12283-12296.

45. Garegg, P. J.; Kvarnstrom, I.; Niklasson, A.; Niklasson, G.; Svensson, S. C. T., Partial substitution of thioglycosides by phase transfer catalyzed benzoylation and benzylation. *J. Carbohydr. Chem.* **1993,** *12* (7), 933-953.

46. Koto, S.; Uchida, T.; Zen, S., Syntheses of isomaltose, isomaltotetraose, and isomaltooctaose. *Bull. Chem. Soc. Jpn.* **1973,** *46*, 2520-2523.

47. Thijssen, M. J. L.; Bijkerk, M. H. G.; Kamerling, J. P.; Vliegenthart, J. F. G., Synthesis of four spacer-containing 'tetrasaccharides' that represent four possible repeating units of the capsular polysaccharide of *Streptococcus pneumoniae* type 6B. *Carbohydr. Res.* **1998,** *306*, 111-125.

48. Ray, A. K.; Roy, N., Synthesis of the tetrasaccharide repeating-unit of the polysaccharide from Klebsiella type 23. *Carbohydr. Res.* **1990,** *196*, 95-100.

49. Cherif, S.; Clavel, J.-M.; Monneret, C., Synthesis of the tetrasaccharide Glc α (1→3) Man α (1→2) Man α (1→2) Man α (OMe) as inhibitor of calnexin binding to GlcMan 9GlcNAc2. *J. Carbohydr. Chem.* **2002,** *21* (1-2), 123-130.

# CHAPTER 3

## Iron(III) Chloride-Catalyzed Activation of Glycosyl Chlorides


- S. A. Geringer, A. V. Demchenko. Iron(III) Chloride-Catalyzed Activation of Glycosyl Chlorides. *Org. Biomol. Chem.*, **2018**, 16(47), 9133-9137

## 3.1 Introduction

Introduced by Michael in 1879[1] and subsequently studied by many, glycosyl chlorides have been very influential building blocks that helped to establish basic principles of carbohydrate chemistry.[2-3] Once prominent glycosyl donors, in recent years glycosyl chlorides have been outshadowed by other, more powerful glycosyl donors,[4-11] and for a reason. Traditionally, the activation of glycosyl chlorides demanded stoichiometric and often toxic reagents, such as silver(I)[2, 12-13] or mercury(II) salts.[14] This, along with a fairly high propensity to hydrolysis, hampered the application of glycosyl chloride in recent years. Glycosyl chlorides, however, have many positive traits. They can be obtained using a variety of substrates and methods,[15-25] many chlorides are stable, and recent studies by Ye et al.[26] and Jacobsen et al.[27] have demonstrated that these compounds can be activated without toxic promoters under organocatalytic conditions using urea- or thiourea-based catalysts. Good stereoselectivity was obtained using various additives[26] or with complex chiral catalytic constructs,[27] but these reactions are slow (24-48 h), require high temperatures and provide practical yields only with highly reactive (alkylated) chlorides. In an active pursuit of catalytic activation methods for glycosylation,[28-29] we observed that glycosidation of chlorides can be achieved in the presence of catalytic amounts of iron(III) chloride ($FeCl_3$ aka ferric chloride). This discovery is at the basis of this communication.

$FeCl_3$ is naturally abundant, inexpensive and relatively benign.[30] Ferric chloride has been employed in the introduction of protecting groups in carbohydrates.[31-32] The application of $FeCl_3$ in *O*-glycosylation has also emerged, most prominently for the activation of glycosyl donors bearing the anomeric acetate.[33-42] Other applications for the

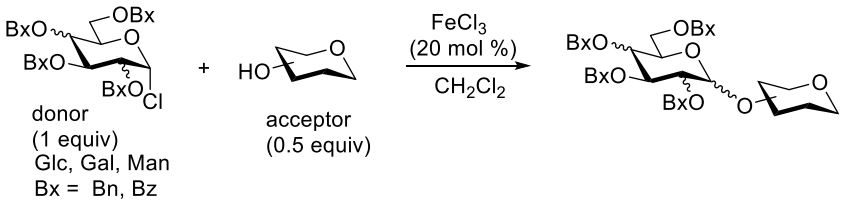
activation of aryl glycoside,[43] pivaloate,[44] bromide,[45] imidate,[46] or hemiacetal donors (as a co-catalyst)[47] have also been explored. Using this prior knowledge, we theorized that glycosyl chlorides may also offer a promising new substrate for the catalytic activation with $FeCl_3$.

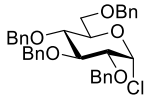
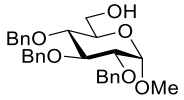
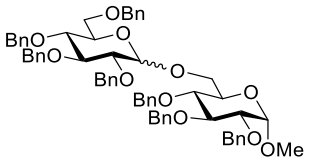
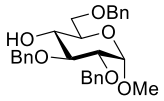
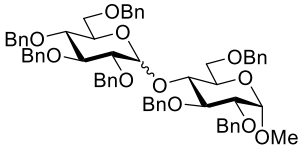
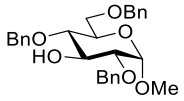
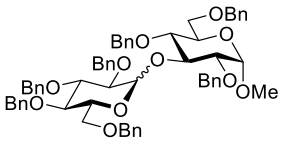
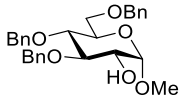
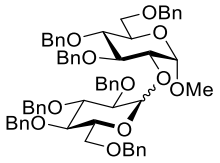
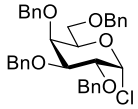
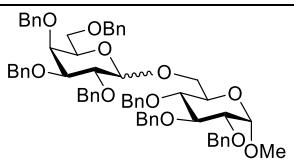
**3.2 Results and discussion**

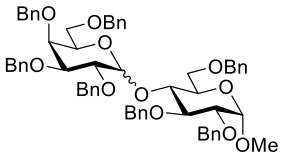
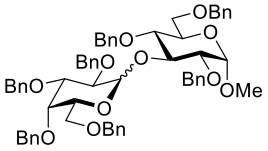
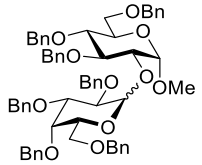
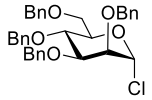
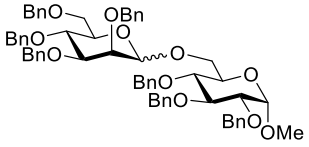
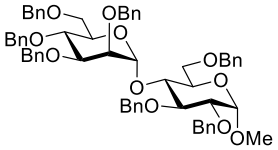
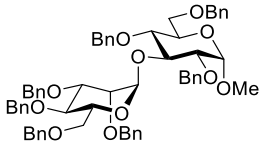
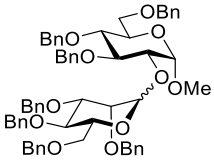
To test this hypothesis, we chose known per-benzylated glucosyl chloride donor **3.1**[23] to couple with the standard glycosyl acceptor **3.2**.[48] The glycosylation was set-up in the presence of molecular sieves (4 Å) in dichloromethane. For this preliminary study we chose access of donor **3.1** (2.0 equiv) similarly to that used by Ye et al.[26] and Jacobsen et al.[27] After a brief preliminary experimentation, we established that 20 mol % of $FeCl_3$ provides the most favorable balance between yields and the reaction time. Thus, the coupling of donor **3.1** with acceptor **3.2**[48] provided disaccharide **3.3** in 67% yield in only 2 h (Table 3.1, entry 1). Also, glycosidations of chloride **3.1** with secondary acceptors **3.4**, **3.6**, and **3.8**[48] were conducted under essentially the same reaction conditions. These reactions were slower (3-16 h), but the respective disaccharides **3.5**, **3.7** and **3.9** have successfully been obtained in 47-80% yields (entries 2-4). This preliminary set of experiments has demonstrated both the advantages and limitations of this approach. The main advantage of this approach is the availability and low cost of the catalytic activator. Also the reaction times are notably shorter than those reported for the organocatalytic reactions and even for the traditional heavy metal-based stoichiometric activators. Somewhat average yields for the formation of all products, perhaps except **3.9**, still on a par with traditional approaches and the results reported by Ye et al.[26] and Jacobsen et al.,[27] are mainly attributed to a substantial formation of a side product of 1,6-anhydro-

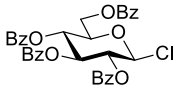
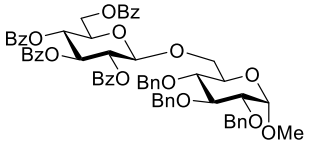
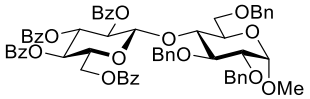
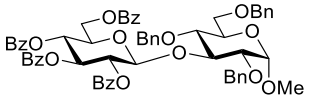
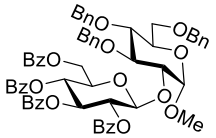
2,3,4-tri-*O*-benzyl-β-D-glucopyranose. While somewhat unexpected in this particular setting, the formation of 1,6-anhydro sugars in the presence of $FeCl_3$ has been reported.[49]

**Table 3.1. Iron(III) chloride-catalyzed glycosylations**




| entry | donor | acceptor | time | product | yield | α/β ratio |
|---|---|---|---|---|---|---|
| 1 |  **3.1** |  **3.2** | 2 h |  **3** | 67% | 1.1/1 |
| 2 | **3.1** |  **3.4** | 16 h |  **5** | 47% | 1.2/1 |
| 3 | **3.1** |  **3.6** | 3 h |  **7** | 60% | 1.5/1 |
| 4 | **3.1** |  **3.8** | 16 h |  **3.9** | 80% | 1.0/1 |
| 5 |  **3.10** | **3.2** | 0.5 h |  **3.11** | 88% | 1/1.4.0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 6 | **3.10** | **3.4** | 0.5 h |  **3.12** | 57% | 1.6/1 |
| 7 | **3.10** | **3.6** | 0.5 h |  **3.13** | 80% | 1.3/1 |
| 8 | **3.10** | **3.8** | 16 h |  **3.14** | 90% | 1/2.7 |
| 9 |  **3.15** | **3.2** | 2 h |  **3.16** | 80% | 4.5/1 |
| 10 | **3.15** | **3.4** | 16 h |  **3.17** | 66% | α-only |
| 11 | **3.15** | **3.6** | 16 h |  **3.18** | 56% | α-only |
| 12 | **3.15** | **3.8** | 16 h |  **3.19** | 95% | 2.6/1 |

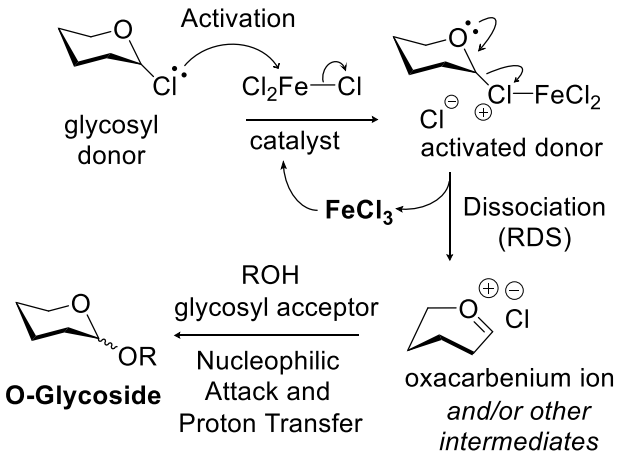
| | | | | | | |
|---|---|---|---|---|---|---|
| 13 |  **3.20** | **3.2** | 16 h |  **3.21** | 98% | β-only |
| 14 | **3.20** | **3.4** | 16 h |  **3.22** | 80% | β-only |
| 15 | **3.20** | **3.6** | 16 h |  **3.23** | 52% | β-only |
| 16 | **3.20** | **3.8** | 16 h |  **3.24** | 73% | β-only |

As evident from Table 3.1, all four disaccharides have been produced with poor selectivity (α/β = 1-1.5/1); our method, however, does not employ stereodirecting functionalities, additives,[26] or complex chiral catalytic constructs[27] at this stage. Following the general success of glucosyl chloride donor **3.1** we investigated galactosyl chloride **3.10**[23] that provided even faster reaction times (entry 5-8), probably due to the generally higher reactivity of the galactosyl donors versus similarly equipped glucose counterparts, and a noticeable increase in yields. The latter could be attributed to the entire absence of the 1,6-anhydro side-product that hampered the yields with donor **3.1**.

Thus, primary acceptor **3.2** led to the formation of disaccharide **3.11** in a respectable yield of 88% (entry 5). For comparison, glucosyl chloride donor **3.1** produced the 1→6 linked disaccharide **3.3** in 67% (see entry 1). A similar enhancement in yields

(up to 90%) and decrease in the reaction time have been observed for the secondary acceptors to produce the respective disaccharides **3.12-3.14** (entries 6-8). Expectedly, mannosyl donor **3.15**[13] showed lower reactivity than its glucosyl and galactosyl counterparts. This was reflected by the increase in reaction times; nevertheless, we obtained respectable yields (up to 95%) for the synthesis of disaccharides **3.16-3.19** (entries 9-12). No formation of the 1,6-anhydro side product was detected in this case either. We believe this reaction follows a traditional Lewis acid-catalyzed mechanistic pathway depicted in Scheme 3.1. Presumably, this reaction follows the traditional unimolecular $S_N1$ mechanism according to which the catalyst-mediated leaving group departure results in the formation of the oxacarbenium ion. The latter exists in a flattened half-chair conformation that explains poor stereoselectivity observed.

**Scheme 3.1. Proposed mechanism of the activation of glycosyl chlorides with ferric chloride**




Having demonstrated that $FeCl_3$-catalyzed reactions work reasonably well with per-benzylated sugars, we wanted to investigate whether electronically deactivated benzoylated chloride **3.20** could be activated using our method. As expected, when donor **3.20** was glycosidated with acceptor **3.2** a slower reaction time 16 h (entry 13, Table 3.1)

was recorded in comparison to that with the benzylated glucosyl donor **3.1** (2 h, see entry 1). Nevertheless, the reaction still proceeded to completion and provided disaccharide **3.21** in an impeccable yield of 98% and no indication for the side product formation. The glycosidation of donor **3.20** also proceeded well with the secondary acceptors **3.4**, **3.6**, and **3.8** providing the corresponding disaccharides **3.22-3.24** in respectable yields of 52-80% and complete β-selectivity due to the neighboring group participation. It is noteworthy that neither Ye's nor Jacobsen's conditions were able to activate these deactivated benzoylated chlorides.

### 3.3 Conclusions

We have shown that a variety of glycosyl chlorides can be activated with catalytic iron(III) chloride. This method allows for a cheap and relatively benign activation of glycosyl chlorides compared to previous methods using harsher and less environmentally friendly conditions. While the yield of glycosylation reactions are still far from being ideal, a majority of results obtained herein are on a par with recently developed organocatalytic reactions reported by Ye et al.[26] and Jacobsen et al.[27] The stereoselectivity obtained in reactions with benzylated chlorides is unimpressive, which is not a surprise because we do not currently employ any directing auxiliaries, catalysts, or additives as in other similar studies. However, our study employs a very inexpensive activator, and this method can serve as a basis for refining stereoselectivity in the future. One of the possible directions for this to explore the known effect of stoichiometric $FeCl_3$ that is capable of producing the α-product preferentially, presumably due to post-glycosylational anomerization reaction.[40]

Of particular significance is that electronically deactivated, benzoylated chlorides can also be activated using our reaction conditions, whereas other catalytic systems fail to activate those unreactive substrates. The investigation of the scope and limitations of this method, including screening other Lewis acids, are currently underway in our laboratory and will be reported in due course. Our preliminary attempt to broaden the scope of this reaction by investigating $SnCl_4$, $BF_3$-$OEt_2$, and $Fe(OTf)_3$ indicated similar reaction yields and reaction times to those reported herein.

### 3.4 Experimental

#### 3.4.1 General methods

Column chromatography was performed on silica gel 60 (70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. $CH_2Cl_2$ and $ClCH_2CH_2Cl$ (1,2-DCE) were distilled from $CaH_2$ directly prior to application. Anhydrous DMF was used as it is. Molecular sieves (4 Å), used for reactions, were crushed and activated *in vacuo* at 390 °C during 8 h in the first instance and then for 2-3 h at 390 °C directly prior to application. Optical rotations were measured at 'Jasco P-2000' polarimeter. $^1$H NMR spectra were recorded in $CDCl_3$ at 300 or 600 MHz.

#### 3.4.2 Synthesis of glycosyl chloride donors

**2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride (3.1).**

A solution of oxalyl chroride (621 mg, 4.89 mmol) in dichloromethane (2.0 mL) was added dropwise to a stirring solution of 2,3,4,5-tetra-*O*-benzyl-D-glucopyranose (881.8 mg, 1.63 mmol) in dichloromethane (6.0 mL) and DMF (2.0 mL) and the resulting

mixture was stirred under argon for 30 min at 0 °C. The external cooling was then removed and the reaction mixture was allowed to slowly warm to rt and stirred for additional 1 h at rt. After that, the resulting mixture was concentrated *in vacuo.* The residue was dissolved in a mixture of ethyl acetate and hexane (10 mL, 1/1, v/v) and passed through a pad of silica gel (10 g). The pad of silica gel was washed with a mixture of ethyl acetate and hexane (100 mL, 1/1, v/v) and the combined eluate was concentrated *in vacuo* to afford the title compound as a clear oil in 98% yield (899.1 mg, 1.59 mmol). Analytical data for **3.1** was essentially the same as reported previously.[23]

**2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl chloride (3.10).**

Thionyl chloride (302.8 mg, 2.54 mmol) was added dropwise to a stirring solution of 2,3,4,5-tetra-*O*-benzyl-D-galactopyranose (458.7 mg, 0.848 mmol) in 1,2-dichloroethane (5.0 mL) and DMF (0.1 mL) and the resulting mixture was stirred under argon for 1 h at 0 °C. The reaction mixture was concentrated *in vacuo*, the residue was dissolved in a mixture of ethyl acetate and hexane (5 mL, 1/1, v/v) and passed through a pad of silica gel (5 g). The pad of silica gel was washed with a mixture of ethyl acetate and hexane (75 mL, 1/1, v/v) and the combined eluate was concentrated *in vacuo* to afford the title compound as a clear oil in 95% yield (451.0 mg, 0.81 mmol). Analytical data for **3.10** was essentially the same as reported previously.[23]

**2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl chloride (3.15).**

A solution of oxalyl chroride (322.6 mg, 2.54 mmol) in dichloromethane (6.5 mL) was added dropwise to a stirring solution of 2,3,4,5-tetra-*O*-benzyl-D-mannopyranose (458.1 mg, 0.847 mmol) in 1,2-dichloroethane (5.0 mL) and DMF (0.1 mL) and the resulting mixture was stirred under argon for 30 min at 0 °C. The external cooling was then

removed and the reaction mixture was allowed to slowly warm to rt and stirred for additional 1 h at rt. After that, the resulting mixture was concentrated *in vacuo*. The residue was dissolved in a mixture of ethyl acetate and hexane (5 mL, 1/1, v/v) and passed through a pad of silica gel (5 g). The pad of silica gel was washed with a mixture of ethyl acetate and hexane (100 mL, 1/1, v/v) and the combined eluate was concentrated *in vacuo* to afford the title compound as a clear oil in 95% yield (452mg, 0.81 mmol). Analytical data for **3.15** was essentially the same as reported previously.[13]

**2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl chloride (3.20).**

Thionyl chloride (106.85 mg, 0.898 mmol) was added dropwise to a stirring solution of 2,3,4,5-tetra-*O*-benzoyl-D-glucopyranose (242.8 mg, 0.45 mmol) in 1,2-dichloroethane (5.0 mL) and DMF (0.1 mL) and the resulting mixture was stirred under argon for 1 h at 0 °C. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in a mixture of ethyl acetate and hexane (5 mL, 1/1, v/v) and passed through a pad of silica gel (3.5 g). The pad of silica gel was washed with a mixture of ethyl acetate and hexane (50 mL, 1/1, v/v) and the combined eluate was concentrated *in vacuo* to afford the title compound as a white foam in 98% yield (276.8 mg, 0.44 mmol). Analytical data for **3.20** was essentially the same as reported previously.[22]

### 3.4.3 Synthesis of disaccharides

**General procedure for glycosidation of glycosyl chlorides in the presence of $FeCl_3$.**

A mixture of glycosyl chloride donor (0.05 mmol), glycosyl acceptor (0.025 mmol) and molecular sieves (4 Å, 60 mg) in dichloromethane (1.0 mL) was stirred under argon for 1 h at rt. The mixture was then cooled to 0 °C, $FeCl_3$ (0.01 mmol) was added, and the reaction mixture was stirred for the time specified in Table 1 of the article. If the reaction

was incomplete after 3 h at 0 °C, the external cooling was removed, the reaction mixture was allowed to slowly warm to rt, and stirred for additional 13 h at rt. After that, the solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~30 mL) was washed with sat. aq. $NaHCO_3$ (10 mL) and water (2 x 10 mL). The organic phase was separated, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution). If necessary, further purification was accomplished by size-exclusion column chromatography on Sephadex LH20 (methanol/ dichloromethane, 1/1, v/v, isocratic elution). Anomeric ratios were determined by comparison of integral intensities of their respective signals in the $^1$H NMR spectra of anomeric mixtures.

**Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (3.3).**

The title compound was obtained from donor **3.1** and acceptor **3.2**[48] under the general glycosylation method as a colorless foam in 67% yield (α/β = 1.1/1). Analytical data for **3.3** was in accordance with that previously reported.[50]

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

The title compound was obtained from donor **3.1** and acceptor **3.4**[48] under the general glycosylation method as an oil in 47% yield of **3.5** (α/β = 1.2/1). Analytical data for **3.5** was in accordance with previously reported values.[51]

**Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (3.7).**

The title compound was obtained from donor **3.1** and acceptor **3.6**[48] under the general glycosylation method as an oil in 60% yield of **3.7**(α/β = 1.5/1). Analytical data for **3.7** was in accordance with previously reported values.[52]

**Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (3.9).**

The title compound was obtained from donor **3.1** and acceptor **3.8**[48] under the general glycosylation method as a colorless foam in 80% yield of **3.9** (α/β = 1.0/1). Analytical data for **9** was in accordance with previously reported values.[53]

**Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (3.11).**

The title compound was obtained from donor **3.10** and acceptor **3.2** under the general glycosylation method as an oil in 88% yield of **11** (α/β = 1/1.4). Analytical data for **11** was in accordance with previously reported values.[54]

**Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (3.12).**

The title compound was obtained from donor **3.10** and acceptor **3.4** under the general glycosylation method as an oil in 57% yield of **3.12** (α/β = 1.6/1). Analytical data for **3.12** was in accordance with previously reported values.[55]

**Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (3.13).**

The title compound was obtained from donor **3.10** and acceptor **3.6** under the general glycosylation method as an oil in 80% yield of **3.13** (α/β = 1.3/1). Analytical data for **3.13** was in accordance with previously reported values.[56]

**Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (3.14).**

The title compound was obtained from donor **3.10** and acceptor **3.8** under the general glycosylation method as an oil in 90% yield of **3.14** (α/β =1/2.7). Analytical data for **3.14** was in accordance with previously reported values.[57]

**Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside(3.16).**

The title compound was obtained from donor **3.15** and acceptor **3.5** under the general glycosylation method as an oil in 80% yield of **3.16** (α/β = 4.5/1). Analytical data for **3.16** was in accordance with previously reported values.[58]

**Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside (3.17).**

The title compound was obtained from donor **3.15** and acceptor **3.6** under the general glycosylation method as an oil in 66% yield of **3.17**. Analytical data for **3.17** was in accordance with previously reported values.[59]

**Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside (3.18).**

The title compound was obtained from donor **3.15** and acceptor under the general glycosylation method as an oil in 56% yield of **3.18**. Analytical data for **3.18** was in accordance with previously reported values.[60]

**Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside (3.19).**

The title compound was obtained from donor **3.15** and acceptor **3.8** under the general glycosylation method as an oil in 95% yield of **3.19** (α/β = 2.6/1). Analytical data for **3.19** was in accordance with previously reported values.[53]

**Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (3.21).**

The title compound was obtained from donor **3.20** and acceptor **3.5** under the general glycosylation method as an oil in 98% yield of **3.21**. Analytical data for **3.21** was in accordance with previously reported values.[61]

**Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (3.22).**

The title compound was obtained from donor **3.20** and acceptor **3.6** under the general glycosylation method as an oil in 80% yield of **3.22**. Analytical data for **3.22** was in accordance with previously reported values.[61]

**Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (3.23).**

The title compound was obtained from donor **3.20** and acceptor **3.7** under the general glycosylation method as an oil in 52% yield of **3.23**. Analytical data for **3.23** was in accordance with previously reported values.[48]

**Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (3.24).**

The title compound was obtained from donor **3.20** and acceptor **3.8** under the general glycosylation method as an oil in 73% yield of **3.24**. Analytical data for **3.24** was in accordance with previously reported values.[62]

**3.5 References**

1. Michael, A., On the synthesis of helicin and phenolglucoside. *Am. Chem. J.* **1879,** *1*, 305-312.

2. Koenigs, W.; Knorr, E., Über einige derivate des traubenzuckers und der galactose. *Ber. Dtsch. Chem. Ges.* **1901,** *34*, 957-981.

3. Kulkarni, S. S.; Gervay-Hague, J., Glycosyl chlorides, bromides and iodides. In *Handbook of Chemical Glycosylation*, Demchenko, A. V., Ed. Wiley-VCH: Weinheim, Germany, 2008; pp 59-93.

4. Toshima, K.; Tatsuta, K., Recent progress in O-glycosylation methods and its application to natural-products synthesis. *Chem. Rev.* **1993,** *93* (4), 1503-1531.

5. Schmidt, R. R.; Kinzy, W., Anomeric-oxygen activation for glycoside synthesis: the trichloroacetimidate method. *Adv. Carbohydr. Chem. Biochem.* **1994,** *50*, 21-123.

6. Whitfield, D. M.; Douglas, S. P., Glycosylation reactions - present status future directions. *Glycoconjugate J.* **1996,** *13* (1), 5-17.

7. Gyorgydeak, Z.; Pelyvas, I. E., General synthetic methods: Reactions at the anomeric center: C-glycosylation. In *Glycoscience: Chemistry and Chemical Biology*, Fraser-Reid, B.; Tatsuta, K.; Thiem, J., Eds. Springer: Berlin - Heidelberg - New York, 2001; Vol. 1, pp 691-747.

8. Demchenko, A. V., *Handbook of chemical glycosylation: advances in stereoselectivity and therapeutic relevance*. Wiley-VCH: Weinheim, Germany, 2008.

9. Nigudkar, S. S.; Demchenko, A. V., Stereocontrolled 1,2-cis glycosylation as the driving force of progress in synthetic carbohydrate chemistry. *Chem. Sci.* **2015,** *6*, 2687–2704.

10. Das, R.; Mukhopadhyay, B., Chemical O-Glycosylations: An Overview. *ChemOpen* **2016,** *5* (5), 401-433.

11. Bennett, C. S., *Selective Glycosylations: Synthetic Methods and Catalysts*. Wiley-VCH: Weinheim, 2017.

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

13. Matsuoka, K.; Terabatake, M.; Umino, A.; Esumi, Y.; Hatano, K.; Terunuma, D.; Kuzuhara, H., Carbosilane Dendrimers Bearing Globotriaoses: Syntheses of Globotrioasyl Derivative and Introduction into Carbosilane Dendrimers. *Biomacromol.* **2006,** *7* (8), 2274-2283.

14. Helferich, B.; Wedemeyer, K. F., Preparation of glucosides from acetobromoglucose. *Ann.* **1949,** *563*, 139-145.

15. Grob, V. D.; Squires, T. G.; Vercellotti, J. R., Glycosyl chlorides through reaction with zinc chloride-thionyl chloride *Carbohydr. Res.* **1969,** *10*, 595-597.

16. Jansson, K.; Noori, G.; Magnusson, G., 2-(Trimethylsiliyl)ethyl glycosides. Transformation into glycopyranosyl chlorides. *J. Org. Chem.* **1990,** *55*, 3181-3185.

17. Chittenden, G. J. F., Reaction of some 1,2-trans-aldose peracetates with thionyl chloride - acetic acid -- a convenient synthesis of some 1,2-trans-per-O-acetyl-D-glycosyl chlorides. *Carbohydr. Res.* **1992,** *242*, 297-301.

18. Hung, S. C.; Wong, C. H., Synthesis of glycosyl chlorides with acid-labile protecting groups. *Tetrahedron Lett.* **1996,** *37* (28), 4903-4906.

19. Zhang, Z.; Magnusson, G., Conversion of p-Methoxyphenyl Glycosides into the Corresponding Glycosyl Chlorides and Bromides, and into Thiophenyl Glycosides. *Carbohydr. Res.* **1996,** *925*, 41-55.

20. Sugiyama, S.; Diakur, J. M., A convenient preparation of glycosyl chlorides from aryl/alkyl thioglycosides. *Org. Lett.* **2000,** *2* (17), 2713-2715.

21. Ibatulin, F. M.; Selivanov, S. I., Reaction of 1,2-trans-glycosyl acetates with phosphorus pentachloride: new efficient approach to 1,2-trans-glycosyl chlorides. *Tetrahedron Lett.* **2002,** *43* (52), 9577-9580.

22. Encinas, L.; Chiara, J. L., Polymer-Assisted Solution-Phase Synthesis of Glycosyl Chlorides and Bromides Using a Supported Dialkylformamide as Catalyst. *J. Comb. Chem.* **2008,** *10* (3), 361-363.

23. Gómez, A. M.; Pedregosa, A.; Casillas, M.; Uriel, C.; López, J. C., Synthesis of C-1 Alkyl and Aryl Glycals from Pyranosyl or Furanosyl Chlorides by Treatment with Organolithium Reagents. *Eur. J. Org. Chem.* **2009,** *2009* (21), 3579-3588.

24. Beale, T. M.; Moon, P. J.; Taylor, M. S., Organoboron-catalyzed regio- and stereoselective formation of beta-2-deoxyglycosidic linkages. *Org. Lett.* **2014,** *16* (13), 3604-7.

25. Tatina, M. B.; Khong, D. T.; Judeh, Z. M. A., Efficient Synthesis of α-Glycosyl Chlorides Using 2-Chloro-1,3-dimethylimidazolinium Chloride: A Convenient Protocol for Quick One-Pot Glycosylation. *Eur. J. Org. Chem.* **2018,** *2018* (19), 2208-2213.

26. Sun, L.; Wu, X.; Xiong, D. C.; Ye, X. S., Stereoselective Koenigs-Knorr glycosylation catalyzed by urea. *Angew. Chem. Int. Ed.* **2016,** *55* (28), 8041-8044.

27. Park, Y.; Harper, K. C.; Kuhl, N.; Kwan, E. E.; Liu, R. Y.; Jacobsen, E. N., Macrocyclic bis-thioureas catalyze stereospecific glycosylation reactions. *Science* **2017,** *355*, 162-166.

28. Singh, Y.; Wang, T.; Geringer, S. A.; Stine, K. J.; Demchenko, A. V., Regenerative Glycosylation. *J. Org. Chem.* **2018,** *83* (1), 374-381.

29. Nigudkar, S. S.; Stine, K. J.; Demchenko, A. V., Regenerative glycosylation under nucleophilic catalysis. *J. Am. Chem. Soc.* **2014,** *136*, 921-923.

30. Bauer, I.; Knolker, H. J., Iron catalysis in organic synthesis. *Chem. Rev.* **2015,** *115* (9), 3170-387.

31. Huang, T. Y.; Zulueta, M. M.; Hung, S. C., Regioselective one-pot protection, protection-glycosylation and protection-glycosylation-glycosylation of carbohydrates: a case study with D-glucose. *Org. Biomol. Chem.* **2014,** *12* (2), 376-382.

32. Gouasmat, A.; Lemétais, A.; Solles, J.; Bourdreux, Y.; Beau, J.-M., Catalytic Iron(III) Chloride Mediated Site-Selective Protection of Mono- and Disaccharides and One Trisaccharide. *Eur. J. Org. Chem.* **2017,** *2017* (23), 3355-3361.

33. Kiso, M.; Anderson, L., The ferric chloride-catalyzed glycosylation of alcohols by 2-acylamido-2-deoxy-β-D-glucopyranose 1-acetates. *Carbohydr. Res.* **1979,** *72*, C12-C14.

34. Kiso, M.; Anderson, L., The synthesis of disaccharides by the ferric chloride-catalyzed coupling of 2-acylamido-2-deoxy-b-D-glucopyranose 1-acetates to protected sugar acceptors. *Carbohydr. Res.* **1979,** *72*, C15-C17.

35. Kiso, M.; Nishiguchi, H.; Hasegawa, A., Application of ferric chloride-catalyzed glycosylation to a synthesis of glycolipids. *Carbohydr. Res.* **1980,** *81*, C13-C15.

36. Dasgupta, F.; Garegg, P. J., Synthesis of ethyl and phenyl 1-thio-1,2-trans-D-glycopyranosides from the corresponding per-O-acetylated glycopyranoses having a 1,2-trans-configuration using anhydrous ferric chloride as a promoter. *Acta Chem. Scand.* **1989,** *43*, 471-475.

37. Lerner, L. M., Ferric chloride-molecular sieve-catalyzed formation of a nonreducing disaccharide derivative. *Carbohydr. Res.* **1990,** *207*, 138-141.

38. Chatterjee, S. K.; Nuhn, P., Stereoselective α-glycosidation using $FeCl_3$ as a Lewis acid catalyst. *Chem. Commun.* **1998,** (16), 1729-1730.

39. Seibel, J.; Hillringhaus, L.; Moraru, R., Microwave-assisted glycosylation for the synthesis of glycopeptides. *Carbohydr. Res.* **2005,** *340* (3), 507-11.

40. Wei, G.; Lv, X.; Du, Y., FeCl3-catalyzed alpha-glycosidation of glycosamine pentaacetates. *Carbohydr. Res.* **2008,** *343* (18), 3096-3099.

41. Narayanaperumal, S.; César da Silva, R.; Monteiro, J. L.; Corrêa, A. G.; Paixão, M. W., Iron(III) Chloride Catalyzed Glycosylation of Peracylated Sugars with Allyl/Alkynyl Alcohols

*J. Braz. Chem. Soc.* **2012,** *23*, 1982-1988.

42. Marzag, H.; Robert, G.; Dufies, M.; Bougrin, K.; Auberger, P.; Benhida, R., FeCl3-promoted and ultrasound-assisted synthesis of resveratrol O-derived glycoside analogs. *Ultrason. Sonochem.* **2015,** *22*, 15-21.

43. Laursen, J. B.; Petersen, L.; Jensen, K. J., Intramolecular glycosylation under neutral conditions for synthesis of 1,4-linked disaccharides. *Org. Lett.* **2001,** *3*, 687-690.

44. Rasmussen, M. R.; Marqvorsen, M. H.; Kristensen, S. K.; Jensen, H. H., A protocol for metal triflate catalyzed direct glycosylations with GalNAc 1-OPiv donors. *J. Org. Chem.* **2014,** *79* (22), 11011-11019.

45. Shetye, G. S.; Singh, N.; Jia, C.; Nguyen, C. D.; Wang, G.; Luk, Y. Y., Specific maltose derivatives modulate the swarming motility of nonswarming mutant and inhibit bacterial adhesion and biofilm formation by Pseudomonas aeruginosa. *Chembiochem : a European journal of chemical biology* **2014,** *15* (10), 1514-23.

46. Mukherjee, M. M.; Basu, N.; Ghosh, R., Iron(III) chloride modulated selective 1,2-trans glycosylation based on glycosyl trichloroacetimidate donors and its application in orthogonal glycosylation. *RSC Adv.* **2016,** *6* (107), 105589-105606.

47. Mukaiyama, T.; Matsubara, K.; Hora, M., An efficient glycosylation reaction of 1-hydroxy sugars with various nucleophiles using a catalytic amount of activator and haxamethyldisiloxane. *Synthesis* **1994**, 1368-1373.

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

49. Miranda, P. O.; Brouard, I.; Padrón, J. I.; Bermejo, J., Ferric chloride: a mild and versatile reagent for the formation of 1,6-anhydro glucopyranoses. *Tetrahedron Lett.* **2003,** *44* (20), 3931-3934.

50. Eby, R.; Schuerch, C., Use of positively charged leaving-groups in the synthesis of α-D-linked glucosides. Synthesis of methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside. *Carbohydr. Res.* **1975,** *39*, 33-38.

51. Pougny, J. R.; Nassr, M. A. M.; Naulet, N.; Sinay, P., A novel glucosidation reaction. Application to the synthesis of α-linked disaccharides. *Nouveau J. Chem.* **1978,** *2* (4), 389-395.

52. Chiba, H.; Funasaka, S.; Mukaiyama, T., Catalytic and stereoselective glycosylation with glucosyl thioformimidates. *Bull. Chem. Soc. Jpn.* **2003,** *76*, 1629-1644.

53. Ito, Y.; Ogawa, T.; Numata, M.; Sugimoto, M., Benzeneselenenyl triflate as an activator of thioglycosides for glycosylation reactions. *Carbohydr. Res.* **1990,** *202*, 165-175.

54. Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R., *Tetrahedron* **1991,** *47*, 9985-9992.

55. Wegmann, B.; Schmidt, R. R., Glycosylimidates. 27. The application of the trichloroacetimidate method to the synthesis of α-D-glucopyranosides and α-D-galactopyranosides. *J. Carbohydr. Chem.* **1987,** *6* (3), 357-375.

56. Kobashi, Y.; Mukaiyama, T., Glycosyl phosphonium halide as a reactive intermediate in highly α−selective glycosylation. *Bull. Chem. Soc. Jpn.* **2005,** *78*, 910-916.

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

58. Hotha, S.; Kashyap, S., Propargyl glycosides as stable glycosyl donors: anomeric activation and glycosyl syntheses. *J. Am. Chem. Soc.* **2006,** *128*, 9620-9621.

59. Nguyen, H. M.; Chen, Y. N.; Duron, S. G.; Gin, D. Y., Sulfide-mediated dehydrative glycosylation. *J. Am. Chem. Soc.* **2001,** *123*, 8766-8772.

60. Jayakanthan, K.; Vankar, Y. D., Glycosyl trichloroacetylcarbamate: a new glycosyl donor for O-glycosylation. *Carbohydr. Res.* **2005,** *340*, 2688-2692.

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

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

# CHAPTER 4

## A Highly Efficient Glycosidation of Glycosyl Chlorides using Cooperative Silver(I) Oxide – Triflic Acid Catalysis


- S. A. Geringer, Y. Singh, D. J. Hoard, A. V. Demchenko. A Highly Efficient Glycosidation of Glycosyl Chlorides using Cooperative Silver(I) Oxide – Triflic Acid Catalysis. *Chem. Eur. J.*, **2020**, in press

## 4.1 Introduction

Glycosyl chlorides, once prominent glycosyl donors, have helped shape the modern synthetic glycochemistry.[1-2] The story of chemical glycosylation started with exploration of glycosyl chlorides way back in the late 19th century by Michael.[3] Those first glycosylations employed per-acetylated glycosyl chloride as the glycosyl donor for reaction with phenoxide. A notable advancement of glycosylations with chlorides was made by Koenigs and Knorr who utilized simple alcohols as glycosyl acceptors instead of charged nucleophiles.[1] Those reactions were conducted in the presence of silver salts as acid scavengers because the active role of silver salts as promoters of glycosylation was yet unknown. Only after extensive studies over the following decades, scientists began appreciating that silver salts are able to mediate glycosylation by helping dissociate the anomeric carbon-halogen bonds.[4] However, activation of glycosyl halides commonly requires stoichiometric amounts of expensive or toxic reagents such as silver(I)[1, 5] or mercury(II) salts.[6] Some halides are cumbersome to synthesize, store, and apply due to their proclivity to hydrolyze. As a result, modern glycosyl donors, thioglycosides, trichloroacetimidates, and others, outshadowed the application of glycosyl halides in glycan synthesis.

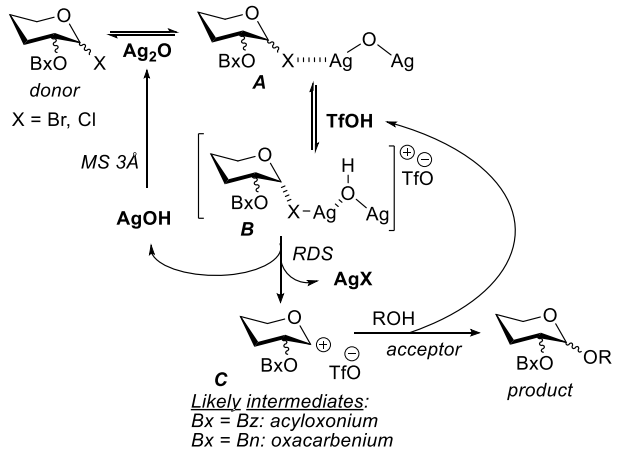
Recently, Ye *et al.*[7] and Jacobsen *et al.*[8] largely resurrected glycosyl chlorides as glycosyl donors by demonstrating that these compounds can be activated under organocatalytic conditions with urea or thiourea-based catalysts, used along with stoichiometric additives. We have recently reported that glycosyl chlorides can be activated with catalytic ferric chloride.[9] Glycosylation with benzylated donors under these benign reaction conditions was typically completed in a couple of hours. The

activation of electronically deactivated, benzoylated glycosyl chlorides could also be achieved with catalytic ferric chloride. However, these glycosylations were rather slow (16 h), and the yields remained moderate, typically within a 60-80% range. Nevertheless, these results were a significant improvement over other promoters and catalysts that previously failed to activate those unreactive substrates.

Over the course of our recent study with glycosyl bromides, we discovered that slow silver-promoted glycosylations can be dramatically accelerated in the presence of acid additives. Thus, glycosylation in the presence of 2.0 equiv of silver(I) oxide that typically requires many hours or even days to complete, became very swift (5-15 min) upon addition of 0.20 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf).[10] An effort dedicated to studying the reaction mechanism, made it possible to reduce the amount of $Ag_2O$ to only 0.50 equiv and replace TMSOTf with TfOH.[4] Although we achieved a significantly improved outcome of the Koenigs-Knorr-like glycosylation reactions, a few limitations and uncertainties remained. First, glycosidation of bromide donors containing the nitrogen atom such as derivatives of glucosamine were very slow and provided poor yields. This limitation was presumably due to the competing protonation of the nitrogen atom with TfOH that led to partial deactivation of the donor. Second, lower reaction rates and fair product yields were also seen with thioglycoside acceptors. This phenomenon was presumably due to the competing interaction of silver oxide with the sulfur atom that led to partial deactivation of the promoter system. Additionally, while glycosidation of supposedly deactivated, benzoylated glycosyl bromides was swift and high-yielding, glycosidation of benzylated glycosyl bromides was much slower and hence much less efficient.

To improve the outcome of this new reaction, we turned our attention to investigating glycosyl chlorides as donors. Mechanistically, the activation of bromides and chlorides would be similar. As proposed in our previous study, after initial interaction of the donor with $Ag_2O$, the resulting species **A** produce a strongly ionized species **B** due to interaction of TfOH (Scheme 4.1). This intermediate will rapidly dissociate producing AgX that precipitates out of the solution. Also produced at this stage is AgOH that loses water regenerating $Ag_2O$. Water is then scavenged by molecular sieves present in all of our reaction. Depending on the protecting group at C-2, glycosyl cation **C** will be stabilized either via an acyloxonium (2-*O*-benzoyl) or oxacarbenium (2-*O*-benzyl) ion. The subsequent nucleophilic attack of the glycosyl acceptor (ROH) occurs with regeneration of TfOH that is available for the next catalytic cycle. Since this reaction is driven by the irreversible formation of the AgX bond, we reasoned that glycosyl chloride activation would be favored by silver chloride formation.[4] This could also minimize propensity of silver interact with other heteroatoms in the system. Reported herein is our study of glycosyl chlorides using the new acid-catalyzed Koenigs-Knorr promoter system.

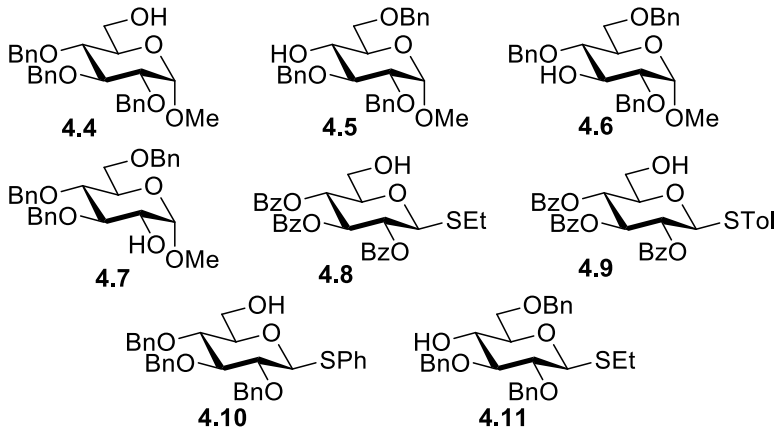
**Scheme 4.1. Activation of glycosyl halides in the presence of $Ag_2O$/TfOH**



**4.2 Results and discussion**

We first investigated glycosidation of benzoylated glycosyl chlorides **4.1-4.3** (Table 4.1)[11-14] with a series of standard glycosyl acceptors **4.4-4.7** (Figure 4.1).[15-16] After preliminary screening of the reaction conditions we determined that the activation of glucosyl chloride **4.1** with 0.50 equiv of silver(I) oxide and 0.25 equiv of TfOH offers the best combination of rates and yields. As listed in Table 4.1, glycosylation of primary acceptor **4.4** gave disaccharide **4.12** in 98% yield in 30 min (entry 1). These optimized conditions compare very favorably with those used for the glycosyl bromide activations, 0.50 equiv of silver(I) oxide and 0.35-0.40 equiv of TfOH.[4] Glycosylation of secondary acceptors **4.5-4.7** gave similar results. Thus, glycosylation of a relatively unreactive 4OH acceptor **4.5** afforded disaccharide **4.13** in 90% yield in 30 min (entry 2). Glycosylations of acceptors **4.6** and **4.7** were equally impressive. Disaccharides **4.14** and **4.15** were obtained in 98% and 91% yield, respectively, in 30 min (entries 3 and 4). As clearly evident from our results, we have not seen any noticeable decline in reaction rates with sterically hindered glycosyl acceptors. While 0.25 equiv TfOH worked universally for all acceptors investigated, some reactions could be smoothly driven to completion using as little as 0.15 equiv of TfOH (data is not shown). All glycosidations of chloride **4.1** were completely 1,2-*trans* diastereoselective due to the assistance of the neighboring participating group. As expected, glycosidations of benzoylated glycosyl chloride **4.1** in the presence of $Ag_2O$ only, standard Koenigs-Knorr reaction conditions, were very sluggish, and only trace amounts of disaccharides were observed after 48 h. The reaction did not proceed at all in the presence of TfOH-only proving the cooperative catalysis nature of the activation pathway.

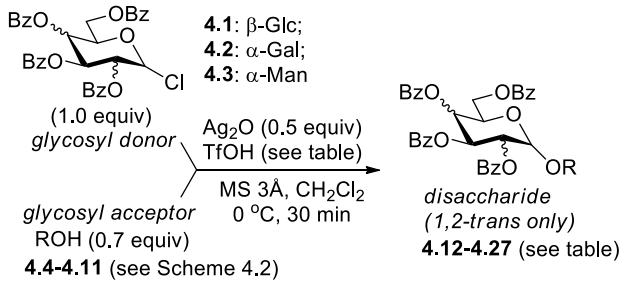
**Scheme 4.2. Standard glycosyl acceptors 4.4-4.7 and thioglycoside acceptors 4.8-4.11 used in this study**

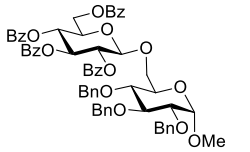
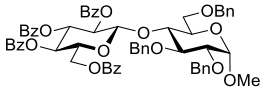
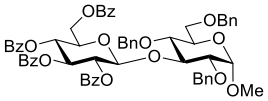
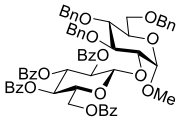
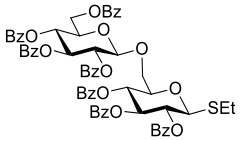
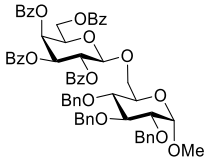
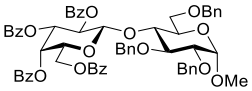


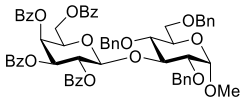
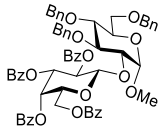
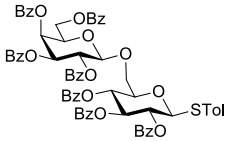
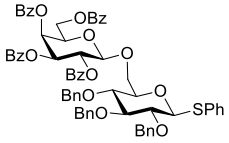
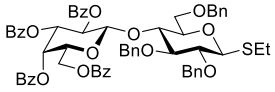
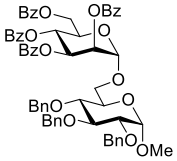
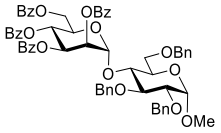
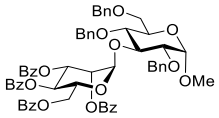
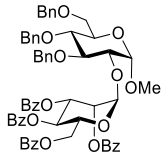

Glycosylation of thioglycoside acceptor **4.8** also proceeded very smoothly affording disaccharide **4.16** in 98% yield in 30 min (entry 5). This glycosylation reaction represents an important strategic step because it encompasses selective activation of one leaving group over another.[17] This approach is commonly used in expeditious oligosaccharide synthesis[18] because disaccharide **4.16** can be used as the glycosyl donor for subsequent chain elongation directly. However, glycosylation of thioglycoside acceptors was somewhat inefficient in our previous studies with ferric chloride promoter[9] or with glycosyl bromides as donors.[4, 10] In addition, these glycosylations could be prone to competing aglycone transfer reactions,[19] which was not observed in this case.

With notable success with glucosyl donor **4.1**, we turned our attention to investigating benzoylated chlorides of the D-galacto and D-manno series, **4.2** and **4.3**, respectively. Glycosidations of both mannosyl and galactosyl chlorides were somewhat less efficient under the established reaction conditions for glucosyl chloride **4.1**, 0.50 equiv of silver(I) oxide and 0.25 equiv of TfOH. The reactions were slower, and

**Table 4.1. Glycosidation of benzoylated glycosyl chlorides 4.1-4.3 in the presence of $Ag_2O$ and TfOH**




| Entry | Donor + Acceptor (TfOH equiv) | Product, Yield[a] |
|---|---|---|
| 1 | **4.1** + **4.4** (0.25) |  **4.12**, 98% |
| 2 | **4.1** + **4.5** (0.25) |  **4.13**, 90% |
| 3 | **4.1** + **4.6** (0.25) |  **4.14**, 98% |
| 4 | **4.1** + **4.7** (0.25) |  **4.15**, 91% |
| 5 | **4.1** + **4.8** (0.25) |  **4.16**, 98% |
| 6 | **4.2** + **4.4** (0.50) |  **4.17**, 99% |
| 7 | **4.2** + **4.5** (0.50) |  **4.18**, 99% |

| | | |
|---|---|---|
| 8 | **4.2** + **4.6** (0.50) |  **4.19**, 99% |
| 12 | **4.2** + **4.7** (0.50) |  **4.20**, 99% |
| 9 | **4.2** + **4.9** (0.50) |  **4.21**, 73% |
| 10 | **4.2** + **4.10** (0.50) |  **4.22**, 75% |
| 11 | **4.2** + **4.11** (0.50) |  **4.23**, 60% |
| 13 | **4.3** + **4.4** (0.50) |  **4.24**, 98% |
| 14 | **4.3** + **4.5** (0.50) |  **4.25**, 98% |
| 15 | **4.3** + **4.6** (0.50) |  **4.26**, 98% |
| 16 | **4.3** + **4.7** (0.50) |  **4.27**, 99% |

[a] – all yields are isolated yields after column chromatography

remained incomplete, even in prolonged experiments (16 h). After a brief screening of the reaction conditions, we found that increasing the amount of TfOH to 0.50 equiv is optimal for driving these reactions to completion. As in case of glucosyl chloride **4.1**, we have achieved very effective, rapid, and high-yielding reactions with both primary and secondary glycosyl acceptors. As listed in Table 1, glycosylation of acceptors **4.4-4.7** with galactosyl chloride **4.2**, produced the respective disaccharides **4.17-4.20** in 30 min nearly quantitatively (99% yield in all experiments, entries 6-9). A large-scale glycosylation using 1.0 g of donor **4.2** and acceptor **4.5** was also performed. During this experiment glycosyl acceptor **4.5** was completely consumed and disaccharide **4.18** was obtained in 83% yield.

To elaborate on our previous success with glycosylating thioglycoside acceptor **4.8** (see entry 5) we investigated other thioglycoside acceptors **4.9-4.11**.[20-22] Glycosylations of primary thioglycoside acceptors **4.9** and **4.10** with galactosyl chloride **4.2** gave promising results producing the respective disaccharides **4.21** and **4.22** in 73-75% yields in 30 min. Glycosylation of a less reactive secondary acceptor **4.11** led to disaccharide **4.23** in a moderate yield of 60% in 1 h. The lower yield, in part, can be attributed to small amounts of a by-product resulting from a competing aglycone transfer reaction.[19] Nevertheless, this result favorably compares to inefficient glycosylations of thioglycoside acceptors in our previous studies with glycosyl bromides as donors.[4, 10]

A very similar outcome was achieved with mannosyl donor **4.3**. Thus, glycosylation of acceptors **4.4-4.7** afforded the corresponding disaccharides **4.24-4.27** in 30 min in 98-99% yield (entries 10-13). These glycosylations were also 1,2-trans selective, and β-galactosides and α-mannosides were all obtained with complete

diastereoselectivity. As evident from the product yields, these glycosylations are spot-to-spot, and are practically free of by-products beyond trace amounts of hemiacetal resulting from hydrolysis of the donor and 1→1-linked disaccharide resulting from glycosylation of the hemiacetal. While 0.50 equiv TfOH worked universally for all acceptors investigated, some reactions with galactosyl and mannosyl chlorides could be smoothly driven to completion using as little as 0.25 equiv of TfOH.

Having obtained excellent results with all per-benzoylated chlorides, we turned our attention to investigating per-benzylated chlorides **4.28-4.30** (Table 4.2).[9, 11-13, 23-24] It is well established that the building block reactivity and stereoselectivity can be modulated through the choice of protecting groups.[25] According to Fraser-Reid's seminal work on the armed-disarmed strategy, benzylated (electronically activated, armed) building blocks are more reactive than their acylated (Bz, disarmed) counterparts.[26-27] Our recent discovery that benzylated glycosyl bromide does not follow this trend when activated in the presence of $Ag^+$/TMSOTf or TfOH was striking.[4, 10] The observed lower reactivity of benzylated glycosyl bromides resulted in reduced yields and their glycosidations required longer reaction times to complete.

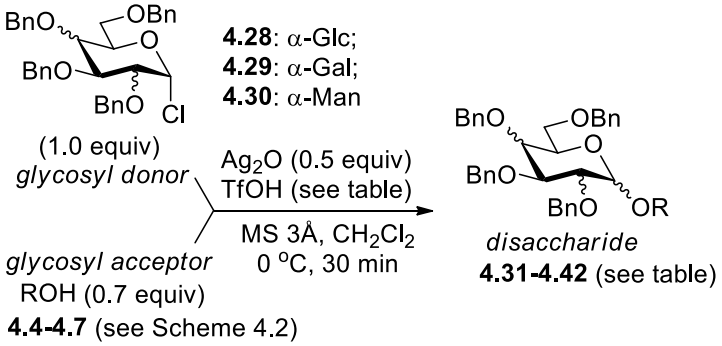
Therefore, investigation of benzylated glycosyl chlorides under these reaction conditions appealed to us more than just broadening the scope of the methodology. A reaction between glycosyl donor **4.28** and primary glycosyl acceptor **4.4** in the presence of 0.50 equiv of silver(I) oxide and 0.25 equiv of TfOH afforded disaccharide **4.31** in 97% yield is only 30 min (α/β = 1.1/1, entry 1, Table 4.2). This result was quite pleasing, particularly in the light of results previously achieved with the respective glucosyl bromide under similar reaction conditions (18 h, 46%).[10] The outcome of this reaction

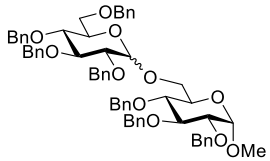
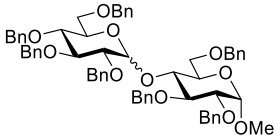
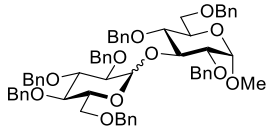
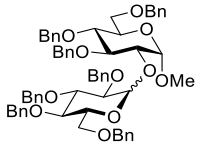
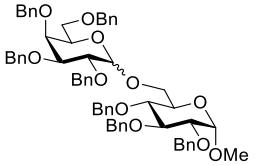
also indicates no particular reactivity difference between benzoylated and benzylated chlorides under these reaction conditions. No reactivity difference was verified by a direct competition experiment between donors **4.1** and **4.28**. However, it is possible that reducing the equivalence of TfOH or modulating other factors could lead to reaction conditions under which the reactivity difference could be observed. Glycosylation of secondary glycosyl acceptors **4.5-4.7** with donor **4.28** was equally impressive. The corresponding disaccharides **4.32-4.34** were obtained in 95-99% yield in 30 min (α/β = 1.3-1.5/1, entries 2-4).

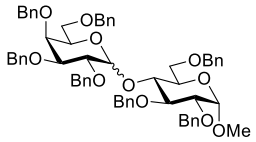
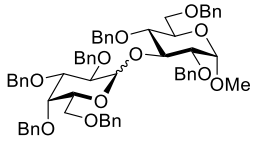
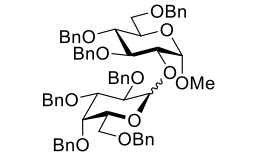
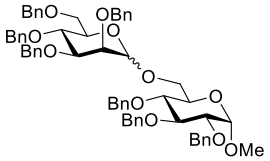
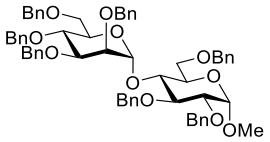
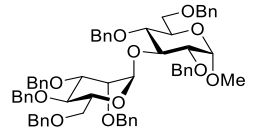
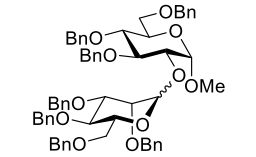
With a notable success with glucosyl donor **4.28**, we turned our attention to investigating benzylated chlorides of the D-galacto and D-manno series, **4.29** and **4.30**, respectively. Again, a majority of glycosidations of galactosyl and mannosyl chlorides in the presence of 0.25 equiv of TfOH were somewhat slower, practically stalled after 30 min, and remained incomplete even after 16 h. Like in the case of benzoylated chlorides of these series, increasing the amount of TfOH to 0.50 equiv was found to be optimal for driving all of these reactions to completion. Very effective, rapid, and high-yielding reactions we achieved with both primary and secondary glycosyl acceptors. As listed in Table 4.2, glycosylation of acceptors **4.4-4.7** with galactosyl chloride **4.29** afforded the respective disaccharides **4.35-4.38** in 30 min nearly quantitatively (99% yield in all experiments, α/β = 1.2-4.9/1, entries 5-8). Similarly, glycosylation of acceptors **4.4-4.7** with mannosyl chloride **4.29** produced the corresponding disaccharides **4.39-4.42** in 98% yield in all experiments in 30 min (from α/β = 1.3/1 to α-only, entries 9-12). We note that some reactions between galactosyl and mannosyl chlorides and reactive acceptors could be smoothly driven to completion using as little as 0.25 equiv of TfOH.

Having obtained excellent results with all per-benzoylated and per-benzylated chlorides of neutral sugars, we turned our attention to investigating *N*-phthaloyl protected

**Table 4.2. Glycosidation of benzylated glycosyl chlorides 4.28-4.30 in the presence of $Ag_2O$ and TfOH**




| Entry | Donor + Acceptor (TfOH equiv) | Product, yield,[a] ratio α/β |
|---|---|---|
| 1 | **4.28** + **4.4** (0.25) |  **4.31**, 97%, α/β = 1.1/1 |
| 2 | **4.28** + **4.5** (0.25) |  **4.32**, 99%, α/β = 1.5/1 |
| 3 | **4.28** + **4.6** (0.25) |  **4.33**, 99%, α/β = 1.3/1 |
| 4 | **4.28** + **4.7** (0.25) |  **4.34**, 95%, α/β = 1.5/1 |
| 5 | **4.29** + **4.4** (0.50) |  **4.35**, 99%, α/β = 1.2/1 |

| | | |
|---|---|---|
| 6 | **4.29** + **4.5** (0.50) |  **4.36,** 99%, α/β = 2.4/1 |
| 7 | **29** + **4.6** (0.50) |  **4.37**, 99%, α/β = 2.4/1 |
| 8 | **4.29** + **4.7** (0.50) |  **4.38**, 99%, α/β = 4.9/1 |
| 9 | **4.30** + **4.4** (0.50) |  **4.39**, 98%, α/β = 1.3/1 |
| 10 | **4.30** + **4.5** (0.50) |  **4.40**, 98%, α only |
| 11 | **4.30** + **4.6** (0.50) |  **4.41**, 98%, α only |
| 12 | **4.30** + **4.7** (0.50) |  **4.42**, 98%, α/β =3.6/1 |

[a] – all yields are isolated yields after column chromatography

glucosamine chloride **4.43** (Table 4.3). This was of particular interest because previous attempts to glycosidate glucosamine bromides resulted in poor yields and long reaction times. As aforementioned, this was attributed to the competing protonation of the nitrogen atom that led to partial deactivation of the donor, and further attempts to glycosidate glucosamine bromide were ceased. It has become a common knowledge that

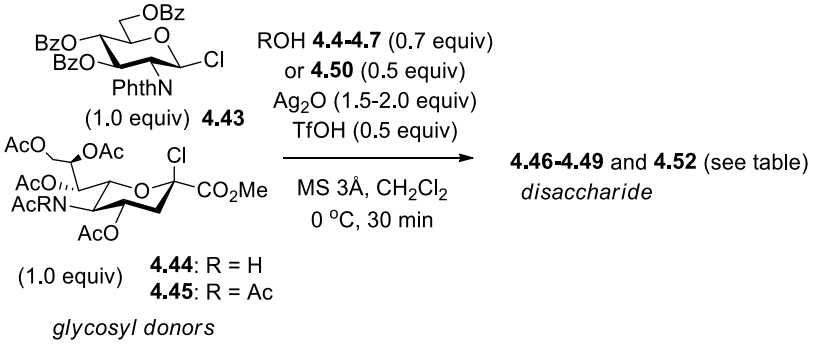
2-aminosugars may have a very different reactivity profile in comparison to their neutral sugar counterparts.[28] Glycosidation of aminosugars often requires different methods specifically designed for these substrates. We also included sialyl chlorides **4.44** and **4.45** (Table 4.3).[29-31] Being a common aminosugar in mammalian and microbial glycans, sialic acids represent a special case of glycosylation that spans beyond effects of the amino group functionality.[4, 32] The chemical synthesis of α-sialosides is considered challenging, and mild methods enhancing the product yields and suppressing common side reactions (elimination and hydrolysis) are needed.

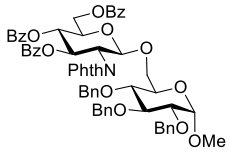
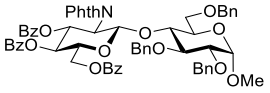
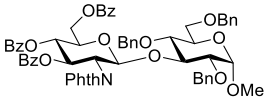
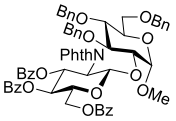
First test reaction with 2-phthalimido chloride donor **4.43** showed that the promoter deactivation could also be the case with glycosyl chlorides. Reactions with 0.50 or even 1.0 equiv of $Ag_2O$ were incomplete and led to lower product yields. Further optimization of our reaction conditions in application to glycosidation of *N*-phthaloyl protected glucosamine chloride **4.43** showed the necessity to increase the amount of $Ag_2O$ to 1.50 equiv, whereas 0.50 equiv of TfOH was sufficient. Under these modified reaction conditions, glycosidation of glycosyl donor **4.43** with primary acceptor **4.4** gave disaccharide **4.46** in 97% yield in 30 min (entry 1, Table 4.3). Glycosylations of secondary glycosyl acceptors **4.5-4.7** with donor **4.43** were somewhat less efficient. The corresponding disaccharides **4.47-4.49** were obtained in commendable yields of 68-76% in 30 min (entries 2-4). These glycosylations were all completely 1,2-trans stereoselective due to the participation of the 2-phthalimido group. Prolonged experiments (beyond standard 30 min) did not help to achieve higher yields.

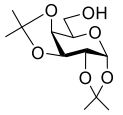
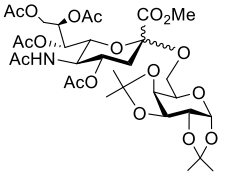
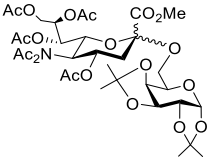
Lastly, we investigated glycosidation of sialyl chlorides. Unfortunately, reaction between sialyl donor **4.44** and galactosyl acceptor **4.50** only produced disaccharide **4.51** of $Ag_2O$

(to donor, entry 5, Table 4.3) in trace amounts, even in the presence of 2.0 equiv sialyl donor **4.44** and up to 2 equiv Having attributed this result to the deactivating nature of the acetamido moiety[33] we turned to investigating the *N*-acetylacetamido donor **4.45** because this type of protection is known to enhance the reactivity of sialyl donors.[34]

**Table 4.3. Glycosidation of 2-phthalimido chloride 4.43 and sialyl chlorides 4.44 and 4.45 with glycosyl acceptors 4.4-4.7 or 4.50 in the presence of $Ag_2O$ and TfOH**




| Entry | Donor + Acceptor ($Ag_2O$ equiv) | Product, yield,[a] ratio α/β |
|---|---|---|
| 1 | **4.43** + **4.4** (1.5) |  **4.46**, 97% |
| 2 | **4.43** + **4.5** (1.5) |  **4.47**, 76% |
| 3 | **4.43** + **4.6** (1.5) |  **4.48**, 72% |
| 4 | **4.43** + **4.7** (1.5) |  |

| | | |
|---|---|---|
| | | **4.49**, 68% |
| 5[b] |  **4.44** + **4.50** (2.0) |  **4.51**, traces |
| 6[b] | **4.45** + **4.49** (2.0) |  **4.52**, 97%, α/β = 1/1.7 |

[a] – all yields are isolated yields after column chromatography
[b] performed at –72 °C (2 h), then rt for 22 h

Glycosylation between **4.45** (2.0 equiv) and **4.50** was conducted in the presence of 2.0 equiv $Ag_2O$ and 0.50 equiv TfOH (to donor **4.45**). To prevent competing eliminations that hamper many types of sialylation reactions, the reaction was started at -78 °C and after 2 h the reaction was allowed to slowly warm to rt. As a result, we obtained disaccharide **4.52** in 97% yield in 24 h (α/β = 1/1.7, entry 6). This result is on a par or even surpasses those obtained with modern sialyl donors.[4]

**4.3 Conclusions**

This study showed how glycosyl chlorides can be activated in a similar manner to that of glycosyl bromides using 0.50 equiv of $Ag_2O$ and 0.25-0.50 equiv of TfOH. Efficient glycosylations of benzoylated glucosyl, galactosyl, and mannosyl chlorides have all been performed with a variety of differently protected primary and secondary glycosyl acceptors providing high yields and fast reaction times. Furthermore, glycosidations of benzylated glucosyl, galactosyl, and mannosyl chlorides have been performed with a similar efficiency. Lastly, nitrogen-containing glucosamine and sialic

acid chlorides were also successfully glycosidated, but these reactions required excess silver oxide. Another convenient feature of this glycosylation is that the progress of this reaction can be monitored by eye, and the completion of the reaction can be judged by the disappearance of characteristic dark color of $Ag_2O$. This is because since only the minimal amount of $Ag_2O$ is used to catalyze this reaction, it gets entirely converted in AgCl, which is a white crystalline solid.

## 4.4 Experimental

### 4.4.1 General methods

*General.* Column chromatography was performed on silica gel 60 (70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. $CH_2Cl_2$ and $ClCH_2CH_2Cl$ (1,2-DCE) were distilled from $CaH_2$ directly prior to application. Pyridine was dried by refluxing with $CaH_2$ and then distilled and stored over molecular sieves (3 Å). Anhydrous DMF was used as it is. Molecular sieves (3 Å or 4 Å), used for reactions, were crushed and activated *in vacuo* at 390 °C during 8 h in the first instance and then for 2-3 h at 390 °C directly prior to application. Optical rotations were measured using a Jasco polarimeter. $^{1}$H-NMR spectra were recorded in $CDCl_3$ at 300 or 600 MHz, $^{13}$C-NMR spectra were recorded in $CDCl_3$ at 75 or 151 MHz. Accurate mass spectrometry determinations were preformed using Agilent 6230 ESI TOF LCMS mass spectrometer

### 4.4.2 Synthesis of glycosyl donors

**2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl chloride (4.1)**

Was obtained from 2,3,4,6-tetra-O-benzoyl-D-glucopyranose[35] as described previously,[9] and its analytical data for were the same as those reported previously.[11-12]

**2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl chloride (4.2).**

Thionyl chloride (294 mg, 2.47 mmol) was added dropwise to a solution of 2,3,4,6-tetra-O-benzoyl-D-galactopyranose[36] (705 mg, 1.24 mmol) in 1,2-dichloroethane (10 mL) containing N,N-dimethylformamide (0.5 mL) and the resulting mixture was stirred under argon for 20 min at 0 °C. After that, the volatiles were removed under reduced pressure. The residue was dissolved in a mixture of ethyl acetate/hexane (25 mL, 1/1, v/v) and filtered through a pad of silica gel (10 g). The pad of silica gel was additionally eluted with a mixture of ethyl acetate and hexane (75 mL, 1/1, v/v) and the combined eluate was concentrated in *vacuo* to afford the title compound as colorless foam in 94% yield (681 mg, 1.11 mmol). Analytical data for **4.2** were essentially the same as reported previously.[13]

**2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl chloride (4.3).**

A mixture of oxalyl chloride (820 mg, 1.48 mmol) in dichloromethane (6.0 mL) and added dropwise to a solution of 2,3,4,6-tetra-O-benzoyl-D-mannopyranose[37] (1.28 g, 2.15 mmol) in dichloromethane (20 mL) containing N,N-dimethylformamide (0.7 mL) and the resulting mixture was stirred under argon for 1.5 h at 0 °C. After that, the volatiles were removed under reduced pressure. The residue was dissolved in a mixture of ethyl acetate/ hexane (30 mL, 1/1, v/v) and filtered through a pad of silica gel (15 g). The pad of silica gel was additionally eluted with a mixture of ethyl acetate and hexane (90 mL, 1/1, v/v)

and the combined eluate was concentrated in *vacuo* to afford the title compound as colorless foam in 94% yield (1.19 g, 1.77 mmol). Analytical data for **4.3** were essentially the same as that reported previously.[38]

**2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride (4.28)**

Was obtained from 2,3,4,6-tetra-O-benzyl-D-glucopyranose[39] as described previously,[9] and its analytical data for were the same as those reported previously.[12]

**2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl chloride (4.29)**

Was obtained from 2,3,4,6-tetra-O-benzyl-D-galactopyranose[40] as described previously,[9] and its analytical data were the same as those reported previously.[13]

**2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl chloride (4.30)**

Was obtained from 2,3,4,6-tetra-O-benzyl-D-mannopyranose[41] as described previously,[9] and its analytical data were the same as those reported previously.[24]

**3,4,6-Tri-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride (4.43).** Thionyl chloride (0.45 g, 3.76 mmol) was added dropwise to a solution of 3,4,5-tri-*O*-benzoyl-2-deoxy-2-phthalimido-D-glucopyranose[42] (1.17 g, 1.88 mmol) in dichloroethane (70 mL) containing DMF (5.0 mL) and the resulting mixture was stirred under argon for 1 h at 0 °C. The volatiles were then removed under reduced pressure. The residue was dissolved in a mixture of ethyl acetate/ hexane (50 mL, 1/1, v/v) and passed through a pad of silica gel (25 g). The pad of silica gel was additionally eluted with a mixture of ethyl acetate/ hexane (75 mL, 1/1, v/v) and the combined eluate was concentrated under reduced pressure to afford the title compound as a white foam in 87% yield (1.05 g, 1.64 mmol). Analytical data for **4.43**: $R_f$ = 0.70 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{21}$ 61.3 (*c* 3.2, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ, 8.07 (d, *J* = 7.6 Hz, 2H,

aromatic), 7.95 – 7.65 (m, 8H, aromatic), 7.62 – 7.39 (m, 5H, aromatic), 7.38 – 7.19 (m, 4H, aromatic), 6.41 (d, $J_{1,2}$ = 9.3 Hz, 1H, H-1), 6.29 (dd, $J_{3,4}$ = 9.7 Hz, 1H, H-3), 5.81 (dd, $J_{4,5}$ =10.1 Hz, 1H, H-4), 4.80 (dd, $J_{2,3}$ = 9.9 Hz, 1H, H-2), 4.68 (dd, $J_{6a,6b}$ = 12.4, 1H, H-6a), 4.53 (dd, 1H, H-6b), 4.38 (m, $J_{5,6a}$ = 2.5 Hz, $J_{5,6b}$ = 4.8 Hz, 1H, H-5) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 166.2, 165.6, 165.1, 134.5, 133.6, 133.5, 133.3, 131.2, 129.9 (x4), 129.8 (x3), 129.5, 128.5 (x7), 128.4 (x3), 128.3, 123.9 (x2), 85.8, 76.0, 71.0, 69.3, 62.8, 57.8 ppm; HRMS $[M+Na]^+$ calcd for $C_{35}H_{26}ClNO_9Na$ 662.1188, found 662.1201.

**Methyl (4,7,8,9-tetra-*O*-acetyl-5-acetamido-3,5-dideoxy-β-D-glycero-D-galacto-non-2-ulopyranosyl chloride)onate (4.44)**

Was obtained from methyl (2,4,7,8,9-penta-O-acetyl-5-acetamido-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranos)onate[43] as described previously,[29] and its analytical data was in accordance with that previously reported.[30]

**Methyl (4,7,8,9-tetra-*O*-acetyl-5-(N-acetyl)acetamido-3,5-dideoxy-β-D-glycero-D-galacto-non-2-ulopyranosyl chloride)onate (4.45)**

Was obtained from methyl (2,4,7,8,9-penta-O-acetyl-5-(N-acetyl)acetamido-3,5-dideoxy-D-glycero-D-galacto-non-2-ulopyranos)onate[44] as described previously, and its analytical data was in accordance with that previously reported.[31]

**4.4.3 Synthesis of disaccharides**

**General procedure for glycosylations in the presence of $Ag_2O$ and TfOH.**

A mixture of a glycosyl donor (0.05 mmol), glycosyl acceptor (0.035 mmol), and freshly activated molecular sieves (3 Å, 150 mg) in $CH_2Cl_2$ (1.0 mL) was stirred under argon for 1 h at rt. The mixture was cooled to 0 °C, $Ag_2O$ (0.025 mmol) was added and the resulting mixture was stirred under argon for 10 min at 0 °C. TfOH (0.25 or 0.50, see

Tables) was added and the reaction mixture was stirred under argon for 30 min at 0 °C. After that, the solid was filtered off and washed sucessively with $CH_2Cl_2$. The combined filtrate (~40 mL) was washed with saturated aq. $NaHCO_3$. (10 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – toluene gradient elution) to afford the respective disaccharides in yields and stereoselectivites listed in Tables and below. Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in $^1$H NMR spectra.

**Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (4.12)**

Was obtained from donor **4.1** and acceptor **4.4**[15] under the general glycosylation method as a colorless foam in 98% yield. Analytical data for **4.12** was in accordance with that previously reported.[45]

**Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (4.13)**

Was obtained from donor **4.1** and acceptor **4.5**[15] under the general glycosylation method as a colorless foam in 90% yield. Analytical data for **4.13** was in accordance with that previously reported.[45]

**Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4.14)**

Was obtained from donor **4.1** and acceptor **4.6**[15] under the general glycosylation method as a colorless foam in 98% yield. Analytical data for **4.14** was in accordance with that previously reported.[15]

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

Was obtained from donor **4.1** and acceptor **4.7**[15] under the general glycosylation method as a colorless foam in 91% yield. Analytical data for **4.15** was in accordance with that previously reported.[46]

**Ethyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (4.16)**

Was obtained from donor **4.1** and acceptor **4.8**[16] under the general glycosylation method as a colorless foam in 98% yield. Analytical data for **4.16** was in accordance with that previously reported.[47]

**Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (4.17)**

Was obtained from donor **4.2** and acceptor **4.4** under the general glycosylation method as a colorless foam in 99% yield. Analytical data for **4.17** was in accordance with that previously reported.[48]

**Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (4.18)**

Was obtained from donor **4.2** and acceptor **4.5** under the general glycosylation method as a colorless foam in 99% yield. Analytical data for **4.18** was in accordance with that previously reported.[46]

**Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4.19)**

Was obtained from donor **4.2** and acceptor **4.6** under the general glycosylation method as a colorless foam in 99% yield. Analytical data for **4.19** was in accordance with that previously reported.[49]

**Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4.20**)

Was obtained from donor **4.2** and acceptor **4.7** under the general glycosylation method as a colorless foam in 99% yield. Analytical data for **4.20** was in accordance with that previously reported.[49]

**Tolyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (4.21**)

Was obtained from donor **4.2** and acceptor **4.9**[20] under the general glycosylation method as a colorless foam in 73% yield. Analytical data for **4.21**: $R_f$ = 0.72 (ethyl acetate/toluene, 1/4, v/v); $[\alpha]_D^{23}$ 63.6 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.06 (m, 4H, aromatic), 7.94 (m, 4H, aromatic), 7.87 – 7.69 (m, 6H, aromatic), 7.67 – 7.04 (m, 26H, aromatic), 6.00 (dd, $J_{4',5'}$ = 3.1 Hz, 1H, H-4'), 5.81 (dd, $J_{2',3'}$ = 8.0 Hz, 1H, H-2'), 5.74 (dd, $J_{4,5}$ = 9.5 Hz, 1H, H-4), 5.58 (dd, $J_{3',4'}$ = 10.4 Hz, 1H, H-3'), 5.30 (dd, $J_{2,3}$ = 9.7 Hz, 1H, H-2), 5.26 (dd, $J_{3,4}$ = 9.4 Hz, 1H, H-3), 5.03 (d, $J_{1',2'}$ = 8.0 Hz, 1H, H-1'), 4.80 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.60 (dd, 1H, H-6b'), 4.39 (dd, $J_{6a',6b'}$ = 11.2 Hz, 1H, H-6a'), 4.28 (dd, $J_{5',6a'}$ = 6.6, $J_{5',6b'}$ = 6.4Hz, 1H, H-5'), 4.12 – 3.91 (m, 3H, H-5, 6a, 6b), 2.30 (s, 3H, $CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 166.1, 165.7, 165.6, 165.4 (x2), 165.0, 138.9, 134.0, 133.6 (x2), 133.4, 133.3 (x2), 130.1, 129.9, 129.8, 129.4 (x2), 129.3, 129.0,

128.8 (x2), 128.7, 128.6, 128.5, 128.4 (x2), 128.3, 127.5, 101.6, 85.9, 78.7, 74.1, 71.8, 71.4, 70.4, 69.7, 69.4, 68.3, 68.1, 61.9, 21.2 ppm; HRMS $[M+Na]^+$ calcd for $C_{68}H_{56}O_{17}SNa$ 1199.3130, found 1199.3150.

**Phenyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (4.22**)

Was obtained from donor **4.2** and acceptor **4.10**[21] under the general glycosylation method as a colorless foam in 75% yield. Analytical data for **4.22**: $R_f$ = 0.73 (ethyl acetate/toluene, 1/4, v/v); $[\alpha]_D^{23}$ 55.6 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.07 (m, 4H, aromatic), 7.82 (m, 4H, aromatic), 7.69 – 7.02 (m, 32H, aromatic), 5.97 (dd, $J_{4',5'}$ = 3.0 Hz, 1H, H-4'), 5.85 (dd, $J_{2',3'}$ = 10.3 Hz, 1H, H-2'), 5.53 (dd, $J_{3',4'}$ = 3.3 Hz, 1H, H-3'), 4.88 (d, $J_{1',2'}$ = 7.8 Hz, 1H, H-1'), 4.78 (dd, $^2J$ = 10.6 Hz, 2H, C$H_2$Ph), 4.71 (dd, $^2J$ = 10.6 Hz, 2H, C$H_2$Ph) 4.65 (dd, 1H, H-6b') 4.63 (dd, $^2J$ = 11.0 Hz, 2H, C$H_2$Ph) 4.62 (dd, $J_{2,3}$ = 9.6 Hz, 1H, H-2), 4.44 (d, $J_{1,2}$ = 10.1 Hz, 1H, H-1), 4.41 (dd, $J_{6a',6b'}$ = 7.0 Hz, 1H, H-6a'), 4.22 (dd, 1H, H-6b), 4.20 (dd, 1H, H-5'), 3.89 (dd, $J_{6a,6b}$ = 11.4, 1H, H-6a), 3.61 (dd, $J_{3,4}$ = 8.7 Hz, 1H, H-3), 3.49 (m, $J_{5,6a}$ = $J_{5,6b}$ = 4.6 Hz, 1H, H-5), 3.43 (dd, $J_{4,5}$ = 8.2 Hz, 1H, H-4), 3.40 (dd, $J_{2,3}$ = 9.1 Hz, 1H, H-2) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 166.1, 165.6, 165.2, 138.3, 138.0, 137.8, 133.6, 133.4 (x2), 133.2 (x2), 130.1, 129.9 (x2), 129.8, 129.5, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5 (x2), 128.4 (x2), 128.3 (x2), 128.0, 127.9 (x2), 127.8 (x2), 125.4, 101.3, 87.2, 86.6, 80.4, 78.9 (x2), 77.4, 75.8, 75.5, 75.0, 71.8, 71.3, 69.7, 68.1, 67.5, 61.9, 21.5 ppm; HRMS $[M+Na]^+$ calcd for $C_{67}H_{60}O_{14}SNa$ 1143.3596, found 1043.3608.

**Ethyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (4.23)**

Was obtained from donor **4.2** and acceptor **4.11**[22] under the general glycosylation method as a colorless foam in 60% yield. Analytical data for **4.23**: $R_f$ = 0.70 (ethyl acetate/toluene, 1/4, v/v); $[\alpha]_D^{23}$ 3.2 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.10-7.7o (m, 8H, aromatic), 7.65 – 7.04 (m, 27H, aromatic), 5.86 (br. d, 1H, H-4'), 5.72 (dd, $J_{2',3'}$ = 8.5 Hz, 1H, H-2'), 5.39 (dd, $J_{3',4'}$ = 3.2 Hz, 1H, H3'), 5.07 (dd, $^2J$ = 11.1 Hz, 2H, C$H_2$Ph), 4.97 (d, $J_{1',2'}$ = 7.9 Hz, 1H, H-1'), 4.77 (dd, $^2J$ = 10.3 Hz, 2H, C$H_2$Ph), 4.55 (dd, $^2J$ = 10.0 Hz, 2H, C$H_2$Ph), 4.40 (dd, 1H, H-6b'), 4.38 (d, $J_{1,2}$ = 11.6 Hz, 1H, H-1), 4.19 (dd, $J_{6a,6b}$ = 9.4 Hz, 1H, H-6a') 4.14 (dd, $J_{4,5}$ = 9.4 Hz, H-4), 3.94 (m, $J_{5',6a}$ = $J_{5',6b}$ = 6.6 Hz, 1H, H-5'), 3.75-3.54 (m, 3H, H-3, 6a, 6b), 3.41 (dd, $J_{2,3}$ = 9.2 Hz, 1H, H-2), 3.24 (dd, 1H, H-5), 2.78 – 2.56 (m, 2H, SC$H_2$CH$_3$), 1.28 (t, *J* = 7.0 Hz, 3H, SCH$_2$C$H_3$) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): δ 165.8, 165.4 (x2), 164.9, 139.0, 138.1, 138.0, 133.4, 133.3, 133.2, 129.8 (x2), 129.7, 129.6, 129.5, 129.1, 129.0, 128.8, 128.6, 128.5 (x2), 128.4, 128.3, 128.2 (x2), 128.1 (x2), 128.0, 127.7, 127.3 (x2), 100.3, 85.1, 84.4, 81.0, 78.6, 76.5, 75.5, 75.3, 73.5, 71.8, 71.1, 70.4, 67.9 (x2), 61.4, 24.8, 15.1 ppm; HRMS $[M+Na]^+$ calcd for $C_{63}H_{60}O_{14}SNa$ 1095.3596, found 1095.3609.

**Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (4.24)**

Was obtained from donor **4.3** and acceptor **4.4** under the general glycosylation method as a colorless foam in 98% yield. Analytical data for **4.24** was in accordance with that previously reported.[46]

**Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (4.25)**

Was obtained from donor **4.3** and acceptor **4.5** under the general glycosylation method as a colorless foam in 98% yield. Analytical data for **4.25** was in accordance with that previously reported.[45]

**Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4.26)**

Was obtained from donor **4.3** and acceptor **4.6** under the general glycosylation method as a colorless foam in 98% yield. Analytical data for **4.26** was in accordance with that previously reported.[50]

**Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4.27)**

Was obtained from donor **4.3** and acceptor **4.7** under the general glycosylation method as a colorless foam in 98% yield. Analytical data for **4.27** was in accordance with that previously reported.[50]

**Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (4.31)**

Was obtained from donor **4.28** and acceptor **4.4** under the general glycosylation method as a colorless foam in 97% yield (α/β = 1.1/1). Analytical data for **4.31** was in accordance with that previously reported.[51]

**Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (4.32)**

Was obtained from donor **4.28** and acceptor **4.5** under the general glycosylation method as a colorless foam in 99% yield (α/β = 1.5/1). Analytical data for **4.32** was in accordance with that previously reported.[52]

**Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (4.33)**

Was obtained from donor **4.28** and acceptor **4.6** under the general glycosylation method as a colorless foam in 99% yield (α/β = 1.3/1). Analytical data for **4.33** was in accordance with that previously reported.[53]

**Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (4.34)**

Was obtained from donor **4.28** and acceptor **4.7** under the general glycosylation method as a colorless foam in 95% yield (α/β = 1.5/1). Analytical data for **4.34** was in accordance with that previously reported.[54]

**Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (4.35)**

Was obtained from donor **4.29** and acceptor **4.4** under the general glycosylation method as a colorless foam in 99% yield (α/β = 1.2/1). Analytical data for **4.35** was in accordance with that previously reported.[55]

**Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (4.36)**

Was obtained from donor **4.29** and acceptor **4.5** under the general glycosylation method as a colorless foam in 99% yield (α/β = 2.4/1). Analytical data for **4.36** was in accordance with that previously reported.[56]

**Methyl 2,4,6-tri-*O*-benzyl-3-O-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (4.37)**

Was obtained from donor **4.29** and acceptor **4.6** under the general glycosylation method as a colorless foam in 99% yield (α/β = 2.4/1). Analytical data for **4.37** was in accordance with that previously reported.[57]

**Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (4.38)**

Was obtained from donor **4.29** and acceptor **4.7** under the general glycosylation method as a colorless foam in 99% yield (α/β = 4.9/1). Analytical data for **4.38** was in accordance with that previously reported.[58]

**Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside (4.39)**

Was obtained from donor **4.30** and acceptor **4.4** under the general glycosylation method as a colorless foam in 98% yield (α/β = 1.3/1). Analytical data for **4.39** was in accordance with that previously reported.[59]

**Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside (4.40)**

Was obtained from donor **4.30** and acceptor **4.5** under the general glycosylation method as a colorless foam in 98% yield. Analytical data for **4.40** was in accordance with that previously reported.[60]

**Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside (4.41)**

Was obtained from donor **4.30** and acceptor **4.6** under the general glycosylation method as a colorless foam in 98% yield. Analytical data for **4.41** was in accordance with that previously reported.[61]

**Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside (4.42)**

Was obtained from donor **4.30** and acceptor **4.7** under the general glycosylation method as a colorless foam in 98% yield (α/β = 3.6/1). Analytical data for **4.42** was in accordance with that previously reported.[54]

**Methyl 6-*O*-(3,4,6-tri-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (4.46)**

Was obtained from donor **4.42** and acceptor **4.4** under the general glycosylation method using 1.0 equiv of $Ag_2O$ and 0.5 equiv of TfOH as a colorless foam in 97% yield. Analytical data for **4.46** was in accordance with that previously reported.[62]

**Methyl 4-*O*-(3,4,6-tri-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (4.47)**

Was obtained from donor **4.42** and acceptor **4.5** under the general glycosylation method using $Ag_2O$ (1.50 equiv) and TfOH (0.50 equiv) as a colorless foam in 76% yield. Analytical data for **4.47**: $R_f$ = 0.60 (ethyl acetate/toluene, 1/4, v/v); $[\alpha]_D^{21}$ 31.1 (*c* 2.05, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.04 – 7.93 (m, 2H, aromatic), 7.88 – 7.78 (m, 2H, aromatic), 7.75 – 7.69 (m, 2H, aromatic), 7.69 – 7.59 (m, 2H, aromatic), 7.55 – 7.12 (m, 26H, aromatic), 6.16 (dd, $J_{3',4'}$ = 9.3 Hz, 1H, H-3'), 5.77 (d, $J_{1',2'}$ = 8.4 Hz, 1H, H-1'), 5.60 (dd, $J_{4',5'}$ = 9.7 Hz, 1H, H-4'), 4.98 (dd, $^2J$ = 11.8 Hz, 2H, C$H_2$Ph), 4.60 (dd, $^2J$ = 12.2 Hz, 2H, C$H_2$Ph), 4.51 (dd, $J_{2',3'}$ = 10.7 Hz, 1H, H-2') 4.50 (d, $J_{1,2}$ = 3.0 Hz, 1H, H-1), 4.44 (dd, $^2J$ = 2.7 Hz, 2H, C$H_2$Ph), 4.34 (dd, $J_{6a',6b'}$ = 12.2, 1H, H-6a'), 4.14 (dd, 1H, H-6b'), 4.08 (dd, $J_{4,5}$ = 9.2 Hz, 1H, H-4), 3.90 (dd, $J_{3,4}$ = 9.2 Hz, 1H, H-3), 3.70 – 3.53 (m, $J_{5',6b'}$ = 3.3 Hz, 2H, H-5, 5'), 3.53 – 3.47 (m, 2H, H-6a, 6b), 3.43 (dd, $J_{2,3}$ = 9.5 Hz, 1H, H-2), 3.26 (s, 3H, $OCH_3$) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): δ 166.2, 165.9, 165.2, 139.6, 138.5, 138.4, 133.5, 133.5, 133.1, 130.0 (x6), 129.9 (x4), 129.1, 128.7, 128.5 (x12), 128.4 (x3), 128.2 (x3), 127.9, 127.6 (x3), 127.3, 127.2 (x3), 98.4, 97.6, 80.3, 79.5, 75.7, 75.0, 73.7, 73.0, 71.9, 71.4, 70.4, 69.5, 68.5, 63.2, 55.8, 55.5 ppm; HRMS $[M+Na]^+$ calcd for $C_{63}H_{57}NO_{15}Na$ 1090.3620, found 1090.3627.

**Methyl 3-*O*-(3,4,6-tri-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4.48)**

Was obtained from donor **4.43** and acceptor **4.6** under the general glycosylation method using $Ag_2O$ (1.50 equiv) and TfOH (0.50 equiv) as a colorless foam in 72% yield. Analytical data for **4.48**: $R_f$ = 0.60 (ethyl acetate/toluene, 1/4, v/v); $[\alpha]_D^{21}$ 6.4 (*c* 2.34,

$CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.97 (m, 2H, aromatic), 7.91-7.76 (m, 6H, aromatic), 7.75 – 7.64 (m, 2H, aromatic), 7.53 – 7.37 (m, 3H, aromatic,), 7.37 – 7.20 (m, 15H, aromatic), 7.20 – 7.10 (m, 6H, aromatic), 6.43 (dd, $J_{3',4'}$ = 9.6 Hz, 1H, H-3'), 6.01 (d, $J_{1',2'}$ = 8.3 Hz, 1H, H-1'), 5.70 (dd, 1H, H-4'), 5.06 (d, $^2J$ = 11.2 Hz, 1H, C*H*Ph), 4.86 (dd, $^2J$ = 12.6 Hz, 2H, C$H_2$Ph), 4.61 (dd, $J_{2',3'}$ = 10.7 Hz, 1H, H-2'), 4.51 (dd, $J_{6a',6b'}$ = 12.0 Hz, 1H, H-6a'), 4.44 (dd, $^2J$ = 9.0 Hz, 2H, C$H_2$Ph), 4.40 (dd, 1H, H-6b'), 4.38 (dd, $J_{3',4'}$ = 12.2 Hz, 1H, H-3), 4.37 (d, 1H, C*H*Ph), 4.17 (dd, $J_{5',6a'}$ = 3.1 Hz, 1H, H-5'), 4.13 (d, $J_{1,2}$ = 6.0 Hz, 1H, H-1), 3.84 (d, $^2J$ = 12.6 Hz, 1H, C*H*Ph), 3.67-3.43 (m, 4H, H-4, 5, 6a, 6b), 3.23 (dd, $J_{2,3}$ = 9.6 Hz, 1H, H-2), 3.08 (s, 3H, $OCH_3$) ppm; $^{13}C$ NMR (151 MHz, $CDCl_3$): δ 166.3, 165.8, 165.4, 138.8, 138.5, 138.1, 133.5, 133.4, 133.0 (x8), 129.9, 129.1, 128.9, 128.6 (x3), 128.52 (x10), 128.4 (x3), 128.4 (x3), 128.3 (x2), 128.2, 128.1 (x4), 127.8, 127.6, 98.5, 97.7, 81.0, 78.7, 76.0, 74.9, 74.0, 73.6, 71.7, 71.1, 70.8, 69.6, 68.7, 63.5, 56.0, 55.0 ppm; HRMS $[M+Na]^+$ calcd for $C_{63}H_{57}NO_{15}Na$ 1090.3620 found 1090.3617.

**Methyl 2-*O*-(3,4,6-tri-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4.49)**

Was obtained from donor **4.43** and acceptor **4.7** under the general glycosylation method using $Ag_2O$ (1.50 equiv) and TfOH (0.50 equiv) as a colorless foam in 68% yield. Analytical data for **4.49**: $R_f$ = 0.65 (ethyl acetate/toluene, 1/4, v/v); $[\alpha]_D^{21}$ 72.1 (*c* 2.35, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.12 – 8.02 (m, 2H, aromatic), 7.94 – 7.88 (m, 2H, aromatic), 7.76 – 7.65 (m, 2H, aromatic), 7.60 – 7.08 (m, 21H, aromatic), 7.08 – 6.95 (m, 3H, aromatic), 6.84 (m, 4H, aromatic), 6.23 (dd, $J_{3',4'}$ = 9.7 Hz, 1H, H-3'), 5.84 (d, $J_{1',2'}$ = 8.4 Hz, 1H, H-1'), 5.72 (dd, $J_{4',5'}$ = 9.7 Hz, 1H, H-4'), 5.10 (d, $J_{1,2}$ = 3.3 Hz, 1H,

H-1), 4.77 (dd, $J_{2',3'}$ = 10.6 Hz, 1H, H-2'), 4.72 (dd, $J_{6a',6b'}$ = 11.6 Hz, 1H, H-6a'), 4.53 (dd, $^2J$ = 12.1 Hz, 2H, C$H_2$Ph), 4.44 (dd, 1H, H-6b'), 4.40 (dd, $^2J$ = 12.1 Hz, 2H, C$H_2$Ph), 4.39 (s, 2H, C$H_2$Ph), 4.28 (ddd, $J_{5',6a'}$ = 2.7 Hz, $J_{5',6b'}$ = 5.0 Hz, 1H, H-5'), 3.85 (dd, $J_{3,4}$ = 8.7 Hz, 1H, H-3), 3.73 (dd, $J_{2,3}$ = 9.8 Hz, 1H, H-3), 3.72 - 3.54 (m, 3H, H-5, 6a, 6b), 3.57 (dd, $J_{4,5}$ = 10.7 Hz, 1H, H-4), 3.32 (s, 3H, $OCH_3$) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): δ 166.0, 165.6, 165.1, 138.5, 138.0 (x2), 133.8, 133.4, 133.2 (x2), 129.8 (x5), 129.7 (x3), 129.4, 128.8, 128.5, 128.4 (x4), 128.3 (x3), 128.2 (x2), 128.12 (x3), 127.9 (x5), 127.8 (x4), 127.6, 127.5, 126.5, 126.0 (x2), 100.1, 99.2, 82.9, 80.3, 77.7, 74.9, 74.6, 73.5, 72.2, 71.2, 69.9, 69.8, 68.5, 63.0, 55.2, 54.8; HRMS $[M+Na]^+$ calcd for $C_{63}H_{57}NO_{15}Na$ 1090.3620 found 1090.3615.

**1,2:3,4-Di-*O*-isopropylidene-6-*O*-[methyl (4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetyl)acetamido-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulo-pyranosyl)onate]-α-D-galactopyranose (4.52).**

A mixture of a glycosyl donor **4.45**[31] (29.5 mg, 0.053 mmol), glycosyl acceptor **4.50** (6.8 mg, 0.026 mmol), and freshly activated molecular sieves (3 Å, 150 mg) in $CH_2Cl_2$ (1.0 mL) was stirred under argon for 1 h. The mixture was cooled to -78 °C, $Ag_2O$ (24.8 mg, 0.11 mmol) was added, and the resulting mixture was stirred for 10 min. TfOH (4.0 mg, 0.027 mmol) was then added, and the resulting mixture was stirred under argon for 2 h at -78 °C. After that, the reaction mixture was allowed to warm to rt over the course of 6 h and left stirring for additional 16 h at rt. The solid was filtered off and washed sucessively with $CH_2Cl_2$. The combined filtrate (~40 mL) was washed with saturated $NaHCO_3$ (10 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel

(acetone – hexane gradient elution) to give the title compound as a clear syrup in 97% yield (19.6 mg, 0.025 mmol). Analytical data for **4.52** was in accordance with that previously reported.[63]

*Large-scale glycosylation.* A mixture of donor **2** (1049 mg, 1.72 mmol)**,** acceptor **4.5** (533.0 mg, 1.15 mmol), and freshly activated molecular sieves (3.0 g) in $CH_2Cl_2$ (50 mL) was stirred under argon for 2 h at rt. The mixture was cooled to 0 °C, $Ag_2O$ (199 mg, 0.86 mmol) was added, and the resulting mixture was stirred under argon for 10 min. TfOH (129 mg, 0.086 mmol) was then added, and the resulting mixture was stirred under argon for 30 min at o °C. After that, the solid was filtered off and washed sucessively with $CH_2Cl_2$. The combined filtrate (~150 mL) was washed with saturated aq. $NaHCO_3$ (30 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – toluene gradient elution) to afford **4.18** (996 mg, 0.95 mmol) in 83% yield.

*A competition experiment.* A mixture of benzoylated donor **4.1** (30.8 mg, 0.050 mmol), benzylated donor **4.28** (33.0 mg, 0.050 mmol), glycosyl acceptor **4.4** (16.3 mg, 0.035 mmol), and freshly activated molecular sieves (3 Å, 150 mg) in $CH_2Cl_2$ (1.5 mL) was stirred under argon for 1 h at rt. The mixture was cooled to 0 °C, $Ag_2O$ (5.8 mg, 0.025 mmol) was added, and the resulting mixture was stirred under argon for 10 min. TfOH (1.9 mg, 0.013 mmol) was then added and the resulting mixture was stirred under argon for 30 min at 0 °C. After that, the solid was filtered off and washed sucessively with $CH_2Cl_2$. The combined filtrate (~40 mL) was washed with saturated aq. $NaHCO_3$ (10 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated

in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate – hexane gradient elution) to afford a mixture of disaccharides **4.12** and **4.31** in approximately equal amounts, judged by NMR.

**4.5 References**

1. Koenigs, W.; Knorr, E., Über einige derivate des traubenzuckers und der galactose. *Ber. Deutsch. Chem. Ges.* **1901,** *34*, 957-981.

2. Kulkarni, S. S.; Gervay-Hague, J., Glycosyl chlorides, bromides and iodides. In *Handbook of Chemical Glycosylation*, Demchenko, A. V., Ed. Wiley-VCH: Weinheim, Germany, 2008; pp 59-93.

3. Michael, A., On the synthesis of helicin and phenolglucoside. *Am. Chem. J.* **1879,** *1*, 305-312.

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

6. Helferich, B.; Wedemeyer, K. F., Preparation of glucosides from acetobromoglucose. *Ann.* **1949,** *563*, 139-145.

7. Sun, L.; Wu, X.; Xiong, D. C.; Ye, X. S., Stereoselective Koenigs-Knorr glycosylation catalyzed by urea. *Angew. Chem. Int. Ed.* **2016,** *55* (28), 8041-8044.

8. Park, Y.; Harper, K. C.; Kuhl, N.; Kwan, E. E.; Liu, R. Y.; Jacobsen, E. N., Macrocyclic bis-thioureas catalyze stereospecific glycosylation reactions. *Science* **2017,** *355*, 162-166.

9. Geringer, S. A.; Demchenko, A. V., Iron(III) Chloride-Catalyzed Activation of Glycosyl Chlorides. *Org. Biomol. Chem.* **2018,** *16*, 9133-9137.

10. Singh, Y.; Demchenko, A. V. Koenigs-Knorr Glycosylation Reaction Catalyzed by Trimethylsilyl Trifluoromethanesulfonate. *Chem. Eur. J.* **2019**, *25*, 1461-1465.

11. Tatina, M. B.; Khong, D. T.; Judeh, Z. M. A., Efficient Synthesis of α-Glycosyl Chlorides Using 2-Chloro-1,3-dimethylimidazolinium Chloride: A Convenient Protocol for Quick One-Pot Glycosylation. *Eur. J. Org. Chem.* **2018,** *2018* (19), 2208-2213.

12. Encinas, L.; Chiara, J. L., Polymer-Assisted Solution-Phase Synthesis of Glycosyl Chlorides and Bromides Using a Supported Dialkylformamide as Catalyst. *J. Comb. Chem.* **2008,** *10* (3), 361-363.

13. Chang, C.-W.; Chang, S.-S.; Chao, C.-S.; Mong, K.-K. T., A mild and general method for preparation of α-glycosyl chlorides. *Tetrahedron Lett.* **2009,** *50* (31), 4536-4540.

14. Pozsgay, V., A synthesis of 2-(trimethylsilyl)ethyl α-D-mannopyranoside. *Tetrahedron Lett.* **1993,** *34* (45), 7175-7178.

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

16. Pornsuriyasak, P.; Jia, X. G.; Kaeothip, S.; Demchenko, A. V., Templated oligosaccharide synthesis: the linker effect on the stereoselectivity of glycosylation. *Org. Lett.* **2016,** *18*, 2316-2319.

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

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

19. Li, Z.; Gildersleeve, J., Mechanistic studies and methods to prevent aglycon transfer of thioglycosides. *J. Am. Chem. Soc.* **2006,** *128*, 11612-11619.

20. Huang, X.; Huang, L.; Wang, H.; Ye, X. S., Iterative one-pot synthesis of oligosaccharides. *Angew. Chem. Int. Ed.* **2004,** *43*, 5221-5224.

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

22. Van Steijn, A. M. P.; Kamerling, J. P.; Vliegenthart, J. F. G., Synthesis of trisaccharide methyl glycosides related to fragments of the capsular polysaccharide of Streptococcus pneumoniae type 18C. *Carbohydr. Res.* **1992,** *225* (2), 229-245.

23. Grob, V. D.; Squires, T. G.; Vercellotti, J. R., Glycosyl chlorides through reaction with zinc chloride-thionyl chloride *Carbohydr. Res.* **1969,** *10*, 595-597.

24. Gómez, A. M.; Pedregosa, A.; Casillas, M.; Uriel, C.; López, J. C., Synthesis of C-1 Alkyl and Aryl Glycals from Pyranosyl or Furanosyl Chlorides by Treatment with Organolithium Reagents. *Eur. J. Org. Chem.* **2009,** *2009* (21), 3579-3588.

25. Bandara, M. D.; Yasomanee, J. P.; Demchenko, A. V., Application of armed, disarmed, superarmed and superdisarmed building blocks in stereocontrolled glycosylation and expeditious oligosaccharide synthesis. In *Selective Glycosylations: Synthetic Methods and Catalysts*, Bennett, C. S., Ed. Wiley: 2017; pp 29-58.

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

27. Fraser-Reid, B.; Udodong, U. E.; Wu, Z. F.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R., n-Pentenyl glycosides in organic chemistry: a contemporary example of serendipity. *Synlett* **1992,** (12), 927-942 and references therein.

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

29. Shpirt, A. M.; Kononov, L. O.; Torgov, V. I.; Shibaev, V. N., Conversion of N-acetylneuraminic acid glycosyl chloride into dibenzyl glycosyl phosphate: O-glycosylation in the absence of a promoter. *Russ. Chem. Bull.* **2004,** *53* (3), 717-719.

30. Kononov, L. O.; Magnusson, G., Synthesis of methyl and allyl α-glycosides of N-acetylneuraminic acid in the absence of added promoter. *Acta Chem. Scand.* **1998,** *52*, 141-144.

31. Orlova, A. V.; Shpirt, A. M.; Kulikova, N. Y.; Kononov, L. O., N,N-Diacetylsialyl chloride—a novel readily accessible sialyl donor in reactions with neutral and charged nucleophiles in the absence of a promoter. *Carbohydr. Res.* **2010,** *345* (6), 721-730.

32. Boons, G. J.; Demchenko, A. V., Recent advances in O-sialylation. *Chem. Rev.* **2000,** *100* (12), 4539-4565.

33. De Meo, C.; Priyadarshani, U., C-5 Modifications in N-acetyl-neuraminic acid: scope and limitations. *Carbohydr. Res.* **2008,** *343*, 1540-1552.

34. Demchenko, A. V.; Boons, G. J., A novel and versatile glycosyl donor for the preparation of glycosides of N-Acetylneuraminic acid. *Tetrahedron Lett.* **1998,** *39* (19), 3065-3068.

35. Pilgrim, W.; Murphy, P. V., SnCl4- and TiCl4-Catalyzed Anomerization of Acylated O- and S-Glycosides: Analysis of Factors That Lead to Higher α:β Anomer Ratios and Reaction Rates. *J. Org. Chem.* **2010,** *75* (20), 6747-6755.

36. Mikamo, M., Facile 1-O-deacetylation of per-O-acylaldoses. *Carbohydr. Res.* **1989,** *191*, 150-153.

37. Saksena, R.; Zhang, J.; Kovac, P., Synthesis of 2-(trimethylsilyl)ethyl-α-D-mannopyranosides revisited. *J. Carbohydr. Chem.* **2002,** *21*, 453-470.

38. Pozsgay, V.; Coxon, B.; Yeh, H., Synthesis of di- to penta-saccharides related to the O-specific polysaccharide of Shigella dysenteriae type 1, and their nuclear magnetic resonance study. *Bioorg. Med. Chem.* **1993,** *1* (4), 237-257.

39. Damager, I.; Erik Olsen, C.; Lindberg Møller, B.; Saddik Motawia, M., Chemical synthesis of 6‴-α-maltotriosyl-maltohexaose as substrate for enzymes in starch biosynthesis and degradation. *Carbohydr. Res.* **1999,** *320* (1), 19-30.

40. Barua, P. M. B.; Sahu, P. R.; Mondal, E.; Bose, G.; Khan, A. T., A Mild and Environmentally Benign Synthetic Protocol for Catalytic Hydrolysis of Thioglycosides. *Synlett* **2002,** *2002* (01), 0081-0084.

41. Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W., Direct C-Glycosylation of Organotrifluoroborates with Glycosyl Fluorides and Its Application to the Total Synthesis of (+)-Varitriol. *Org. Lett.* **2011,** *13* (1), 42-45.

42. Auzanneau, F.-I.; Forooghian, F.; Pinto, B. M., Efficient, convergent syntheses of oligosaccharide allyl glycosides corresponding to the Streptococcus Group A cell-wall polysaccharide. *Carbohydr. Res.* **1996,** *291*, 21-41.

43. Byramova, N. E.; Tuzikov, A. B.; Bovin, N. V., A simple procedure for the synthesis of the methyl and benzyl glycosides of Neu5Ac and 4-*epi*-Neu5Ac. Conversion of the benzyl and methyl glycosides of Neu5Ac into N-trifluoroacetylneuraminic acid benzyl glycosides. *Carbohydr. Res.* **1992,** *237*, 161-175.

44. Demchenko, A. V.; Boons, G. J., A novel direct glycosylation approach for the synthesis of dimers of N-acetylneuraminic acid. *Chem. Eur. J.* **1999,** *5* (4), 1278-1283.

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

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

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

48. Codee, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boeckel, C. A. A.; Van Boom, J. H.; Van der Marel, G. A., Chemoselective glycosylations using sulfonium triflate activator systems. *Tetrahedron* **2004,** *60*, 1057-1064.

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

50. Singh, Y.; Wang, T.; Geringer, S. A.; Stine, K. J.; Demchenko, A. V., Regenerative Glycosylation. *J. Org. Chem.* **2018,** *83* (1), 374-381.

51. Nigudkar, S. S.; Parameswar, A. R.; Pornsuriyasak, P.; Stine, K. J.; Demchenko, A. V., O-Benzoxazolyl imidates as versatile glycosyl donors for chemical glycosylation. *Org. Biomol. Chem.* **2013,** *11* (24), 4068-4076.

52. Pougny, J. R.; Nassr, M. A. M.; Naulet, N.; Sinay, P., A novel glucosidation reaction. Application to the synthesis of α-linked disaccharides. *Nouveau J. Chem.* **1978,** *2* (4), 389-395.

53. Chiba, H.; Funasaka, S.; Mukaiyama, T., Catalytic and stereoselective glycosylation with glucosyl thioformimidates. *Bull. Chem. Soc. Jpn.* **2003,** *76*, 1629-1644.

54. Ito, Y.; Ogawa, T.; Numata, M.; Sugimoto, M., Benzeneselenenyl triflate as an activator of thioglycosides for glycosylation reactions. *Carbohydr. Res.* **1990,** *202*, 165-175.

55. Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R., *Tetrahedron* **1991,** *47*, 9985-9992.

56. Wegmann, B.; Schmidt, R. R., Glycosylimidates. 27. The application of the trichloroacetimidate method to the synthesis of α-D-glucopyranosides and α-D-galactopyranosides. *J. Carbohydr. Chem.* **1987,** *6* (3), 357-375.

57. Kobashi, Y.; Mukaiyama, T., Glycosyl phosphonium halide as a reactive intermediate in highly α–selective glycosylation. *Bull. Chem. Soc. Jpn.* **2005,** *78*, 910-916.

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

59. Hotha, S.; Kashyap, S., Propargyl glycosides as stable glycosyl donors: anomeric activation and glycosyl syntheses. *J. Am. Chem. Soc.* **2006,** *128*, 9620-9621.

60. Nguyen, H. M.; Chen, Y. N.; Duron, S. G.; Gin, D. Y., Sulfide-mediated dehydrative glycosylation. *J. Am. Chem. Soc.* **2001,** *123*, 8766-8772.

61. Jayakanthan, K.; Vankar, Y. D., Glycosyl trichloroacetylcarbamate: a new glycosyl donor for O-glycosylation. *Carbohydr. Res.* **2005,** *340*, 2688-2692.

62. Kamkhachorn, T.; Parameswar, A. R.; Demchenko, A. V., Comparison of the armed/disarmed building blocks of the D-gluco and D-glucosamino series in the context of chemoselective oligosaccharide synthesis. *Org. Lett.* **2010,** *12* 3078-3081.

63. Crich, D.; Li, W., Efficient Glycosidation of a Phenyl Thiosialoside Donor with Diphenyl Sulfoxide and Triflic Anhydride in Dichloromethane. *Org. Lett.* **2006,** *8* (5), 959-962.

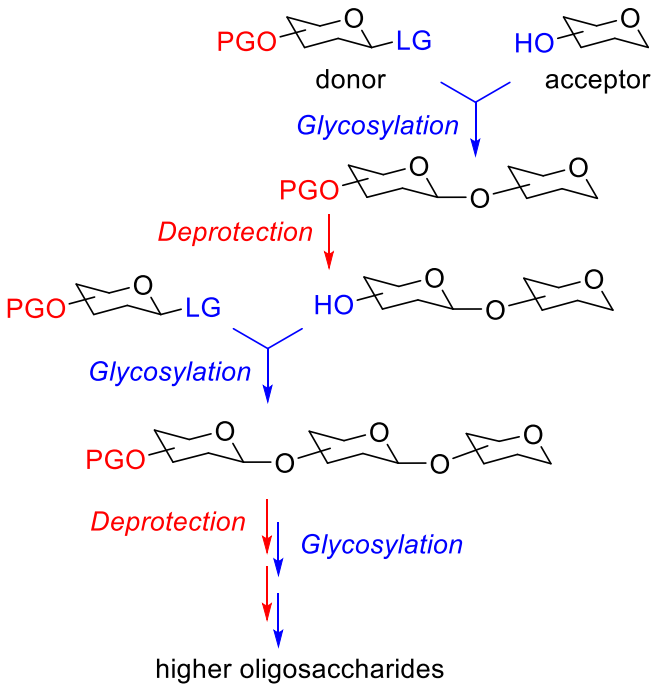
# CHAPTER 5

## Broadening the Scope of the Reverse Orthogonal Strategy for Oligosaccharide Synthesis

## 5.1 Introduction

Chemical synthesis provides a very powerful means to obtain natural or unnatural oligosaccharides for study of their properties and roles. However, even with significant progress in the recent years, chemical synthesis of oligosaccharides remains challenging.[1] Traditional oligosaccharide synthesis comprises a stepwise linear approach according to which first glycosylation takes place between two monosaccharide building blocks, glycosyl donor equipped with a suitable leaving group (LG) and glycosyl acceptor carrying a free hydroxyl group. Upon glycosylation, a disaccharide derivative is obtained (Scheme 5.1). The latter is then converted into a glycosyl acceptor of the second generation via liberation of a specific hydroxyl group. This is typically performed as a separate synthetic step involving chemoselective removal of a strategically placed temporary protecting group (PG) and may also include additional chromatographic purification.

**Scheme 5.1. Traditional oligosaccharide synthesis**

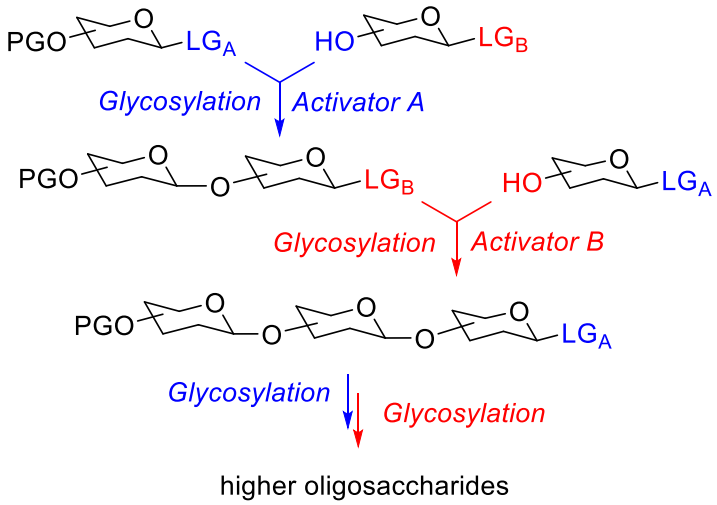


The disaccharide acceptor is then reacted with a new glycosyl donor, resulting in the formation of a trisaccharide. The deprotection–glycosylation sequence is then reiterated to yield a tetrasaccharide, etc. The requirement to perform an additional deprotection step or even multiple steps between each glycosylation is the major disadvantage of the conventional linear approach. However, since the monosaccharide donor is used at every step, the rates of glycosylations are easy to maintain, and the yields typically remain high, even with longer oligosaccharide acceptors.[2] Essentially the same strategic blueprint was used for the automated polymer-supported synthesis of 30-mer[3] and 50-mer[4] mannans by Seeberger *et al*.

Chemoselective or selective activation of leaving groups form the basis for many modern expeditious strategies for oligosaccharide synthesis.[5] Regardless of the underpinning principles for differentiating or tuning the reactivity of building blocks, all of these strategies help to eliminate protecting group manipulations between coupling steps. This, in turn, leads to streamlined glycan assembly. Amongst these strategies is the orthogonal concept invented by Kanie, Ito, and Ogawa.[6,7] This method relies on the differential reactivity (orthogonality) of two leaving groups ($LG_A$ and $LG_B$, Scheme 5.2, SPh and F in the original study). Availability of two complementary sets of reaction conditions that would independently activate one LG, but not the other, is the key for success of the orthogonal method. For example, Activator A will selectively activate $LG_A$ of the glycosyl donor, and $LG_B$ installed at the anomeric center of the glycosyl acceptor will stay intact under these reaction conditions. Conversely, Activator B will selectively activate $LG_B$, whereas $LG_A$ stays intact. This set of two orthogonal reaction conditions is the key feature of the orthogonal approach that hypothetically allows for unlimited

number of reiterations of LGs. This sets the orthogonal approach apart from other approaches based on selective activation of different LGs whereat a more reactive LG is activated over a less reactive one, and does not permit the come-back available only in the orthogonal approach. While the orthogonal approach aims to become an ideal way to make oligosaccharides, in practice however, it has been unable to reach this efficiency. The yields of glycosylation decline rapidly with the increase of the bulk of glycosyl donor: di(85%) →tri(72%) →tetra(66%).[6] In our related study, wherein S-thiazolinyl versus SEt orthogonal activation was achieved, a similar observation was made, and the following decline in yields was noted di(98%) →tri(93%) →tetra(77%) →penta(59%).[8]

**Scheme 5.2. Orthogonal oligosaccharide synthesis**




Aiming at improving the state-of-the-art of oligosaccharide synthesis, previously we communicated a new concept for oligosaccharide synthesis that we named the reverse orthogonal strategy.[9] This strategy looked to employ the advantages of both traditional synthesis (high and consistent yields) and orthogonal strategy (less steps) into one superior platform. Differently from Ogawa's orthogonal approach that relies on the orthogonality of LGs, we based our approach on orthogonal PGs. This resulted in the

change of the direction of the oligosaccharide chain assembly, the reverse approach. Thus, while the glycan chain elongation during orthogonal activation takes at the reducing end (left to right), the elongation during the reverse approach proceeds at the non-reducing end, from right to left, just like in the linear assembly.

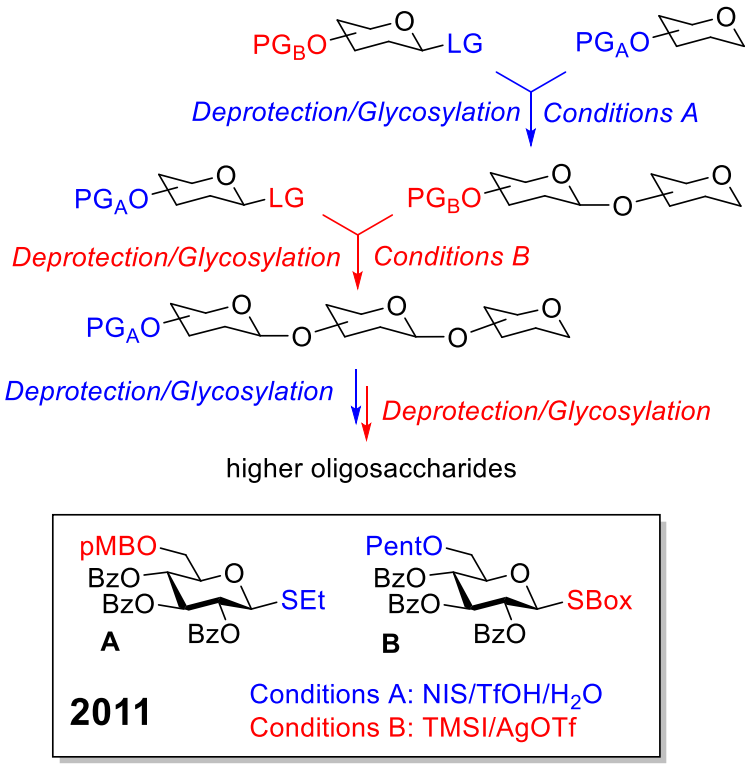
This reverse strategy requires two orthogonal protecting groups ($PG_A$ and $PG_A$) that can be removed during the glycosylation and in principle the couplings can be executed with only one type of leaving group (Scheme 5.3). Thus, in the first step glycosyl donor bearing $PG_B$ with be reacted with glycosyl acceptor bearing $PG_A$ under Conditions A. During this step $PG_A$ is removed and the liberated hydroxyl is glycosylated to form a respective disaccharide derivative bearing $PG_B$ that remains intact during this step. In the second step a new glycosyl donor bearing $PG_A$ with be set to react with disaccharide acceptor bearing $PG_B$ under Conditions B. During this step $PG_B$ is removed and the liberated hydroxyl is glycosylated to form a respective trisaccharide derivative bearing $PG_A$ that remains intact during this step.

To execute this concept, we identified an orthogonal PG combination that comprised pentenoyl (Pent, $PG_A$) that could be deprotected/glycosylated in the presence of NIS/TfOH/$H_2O$ and *p*-methoxybenzyl (pMB) that could be deprotected/glycosylated in the presence of TMSI/AgOTf. We have also matched two different LGs, S-ethyl and S-benzoxazolyl (SBox), respectively. Building blocks **A** and **B** shown in Scheme 5.3 allowed us to synthesize a 1→6-linked pentasaccharide with good efficiency and consistent yields: di(81%) →tri(82%) →tetra(71%) →penta(75%).

One remaining downside to the reverse orthogonal approach is a limited scope because it remained applicable to only this particular combination of protecting (and

leaving) groups. With a goal of extending this reverse approach to other orthogonal combinations, and hence expanding the scope of the reverse orthogonal strategy, reported herein is a new promising orthogonal combination.

**Scheme 5.3. Reverse orthogonal strategy**

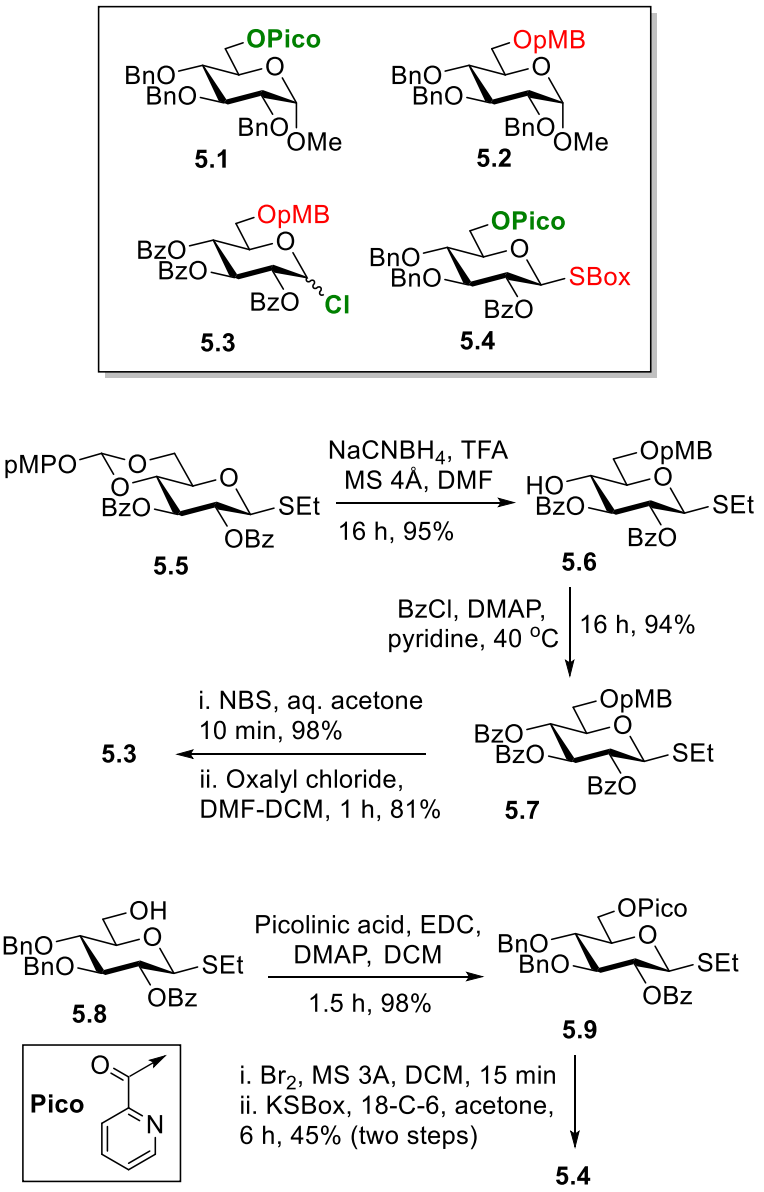



## 5.2 Results and Discussion

The development of this new promising orthogonal PG-LG combination of was made possible thanks to our recent studies dedicated to green catalysis in carbohydrate synthesis. On one hand, we showed that iron(III) chloride ($FeCl_3$) could be used for the activation of glycosyl chlorides.[10] On the other hand, we discovered that $FeCl_3$ could be used to selectively cleave the picoloyl (Pico) protecting group.[11] Because both of these methods, chloride LG activation and Pico PG removal, needed the same reagent $FeCl_3$ we

hypothesized that this offers a possibility for establishing another leaving-protecting group combination that would fit into the reverse orthogonal concept.

**Scheme 5.4. New building blocks 5.1-5.4 for the reverse orthogonal activation**



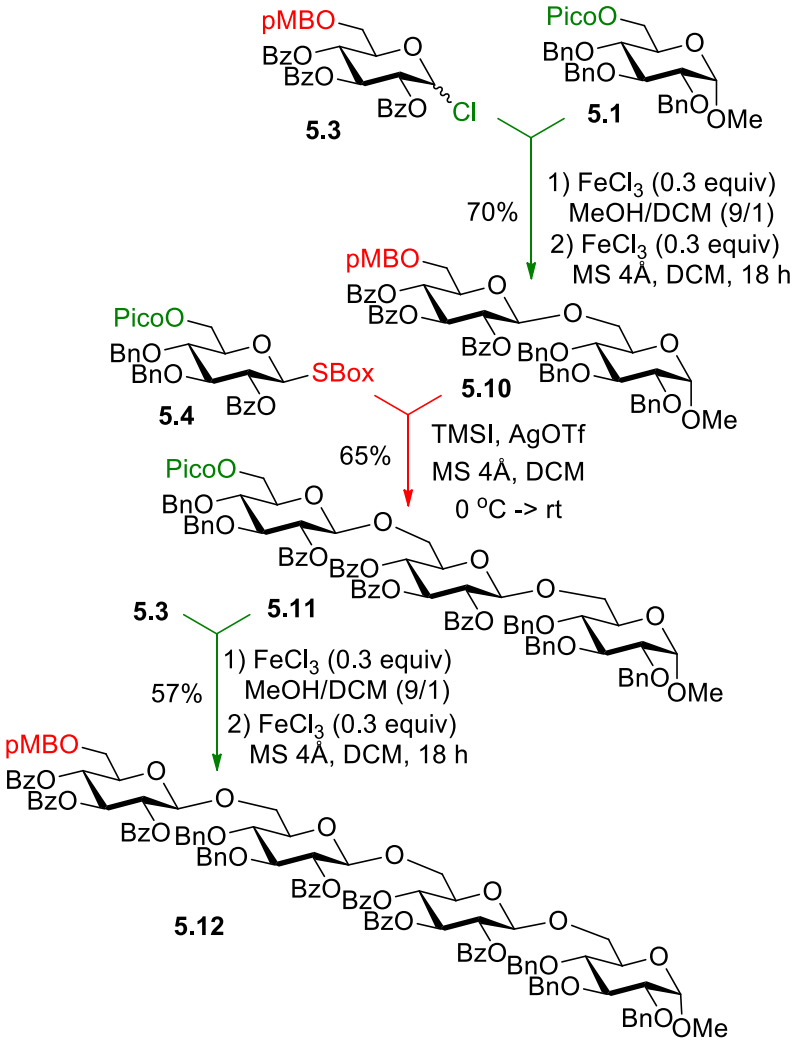

To test our theory, we synthesized two glycosyl acceptors: **5.1** was obtained via a one-step protection of a common 6-OH precursor[12] using the standard picoloylation protocol[13,14] and **5.2** was obtained as previously reported.[9] We have also obtained two glycosyl donors **5.3** and **5.4** as shown in Scheme 5.4.

The synthesis of 6-pMB protected donor **5.3** originated from known p-methoxybenzylidene-protected compound **5.5**,[15] which was subjected to the reductive acetal opening to afford 6-pMB derivative **5.6** with high regioselectivity in 95% yield. Subsequent benzoylation of the liberated 4-OH group afforded compound **5.7**. The latter was converted into the desired glycosyl chloride donor **5.3** in a high yield via a conventional two-step thioglycoside hydrolysis with NBS in wet acetone followed by chlorination of the intermediate hemiacetal with oxalyl chloride. The synthesis of 6-Pico substituted SBox donor **5.3** originated from known thioglycoside precursor **5.8**,[16] which was protected with picolinic acid in the presence of EDC and DMAP to afford compound **5.9** in 98% yield. The latter was the converted into the desired SBox glycosyl donor **5.4** in 45% yield over two steps involving bromination with bromine followed by the SBox LG introduction using KSBox in the presence of 18-crown-6 in acetone.

With building blocks **5.1**-**5.4** in hand, we investigated the respective orthogonal coupling geactions. Acceptor **5.1** and SBox donor **5.4** are each equipped with the 6-Pico group, whereas acceptor **5.2** and chloride donor **5.3** are each equipped with 6-pMB protecting group. In accordance with our design, glycosyl chloride donor **5.3** will pair with 6-Pico building blocks **5.1** and **5.4** in the presence of $FeCl_3$ to deprotect the Pico group and activate the chloride LG thereby allowing for the intended deprotection/glycosylation in a single step. SBox donor **5.4** will then pair with pMB-protected building blocks **5.2** and **5.3**. In this case deprotection/glycosylation will be affected in the presence of TMSI (to remove pMB) and AgOTf (to activate SBox), as shown in our previous study.[9]

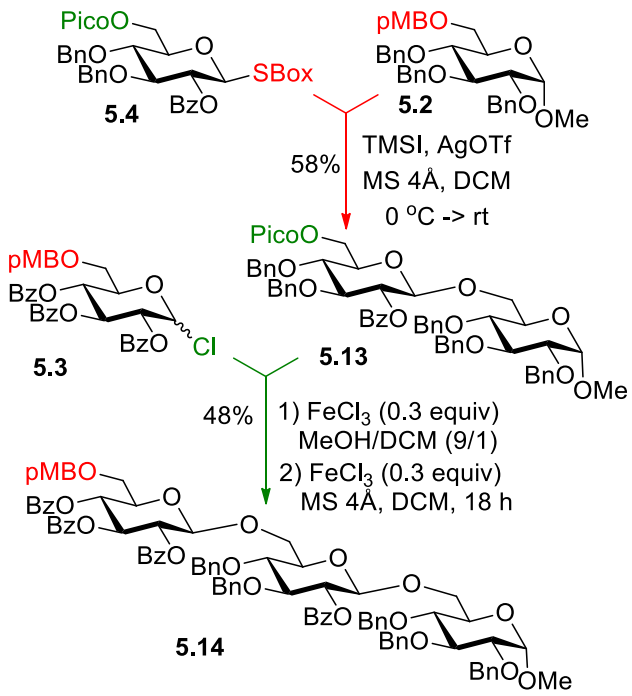
With these considerations, we first investigated the reaction of glycosyl acceptor **5.1** with glycosyl donor **5.3**. A thorough preliminary experimentation brought us to a realization that we could not perform these reactions in a one-pot manner. Due to the Pico group cleavage requiring the presence of a nucleophile, normally methanol, we would have to do the deprotection-glycosylation with the temporary removal of methanol. First, cleaving the Pico group off acceptor **5.1** using 30 mol % of $FeCl_3$ in 9:1 MeOH:$CH_2Cl_2$ occurs in 15 min (Scheme 5.5).

**Scheme 5.5. A three-step assembly of tetrasaccharide 5.12 using the reverse orthogonal strategy**



The reaction was then concentrated and dried in *vacuo* for 1 h. The residue was then redissolved in dichloromethane, molecular sieves (4Å) were added, and the resulting mixture was stirred for 1 h. Donor **5.3** was then added along with another 30 mol % portion of $FeCl_3$. The additional $FeCl_3$ was required to drive this reaction to completion. As a result, disaccharide **5.10** was obtained in 70% yield. Generally satisfied with the outcome of this preliminary experiment, we carried out the next glycosylation using glycosyl donor **5.4**. Applying similar reaction conditions to those previously developed, TMSI was used to selectively cleave off the *p*-methoxybenzyl group from disaccharide **5.10** followed by the activation of donor **5.4** using silver triflate. This resulted in the formation of trisaccharide **5.11** in 65% yield. The first step was then repeated with 6"-Pico protected trisaccharide acceptor **5.11** and glycosyl chloride donor **5.3** to obtain the desired tetrasaccharide **5.12** in 57% yield.

**Scheme 5.6. Synthesis of trisaccharide 5.14 using alternative sequence**



Following the general success of the original scheme, we sought to see whether reversing the synthetic steps would offer any benefit. Starting with acceptor **5.2** and donor **5.4** we first performed the deprotection/glycosylation using TMSI and AgOTf (Scheme 5.6). As a result, disaccharide **5.13** was obtained in 58% yield. Continuing the synthesis, trisaccharide **5.14** was produced from glycosyl chloride donor **5.3** and 6'-Pico protected disaccharide **5.13** in 48% yield using $FeCl_3$ mediated deprotection/glycosylation reactions, as detiled for the synthesis of **5.10** (*vide supra*).

**5.3 Conclusions**

The reverse orthogonal strategy is a useful strategy for synthetic carbohydrate chemists to help reduce the number of steps compared to traditional linear synthetic routes. It however was limited in scope due to the restriction to only two certain LG-PG combinations. We have successfully shown that the scope of the reverse orthogonal strategy can be expanded to a new LG-PG combination comprising glycosyl chloride donors and of picoloylated acceptors. Cleavage of the picoloyl group can be performed using 30 mol % of $FeCl_3$ and following liberation of the hydroxyl group the glycosyl chloride donor activated using another 30 mol % of $FeCl_3$ providing moderate yields. These new reaction conditions were shown to pair well with the existing LG-PG pair comprising the SBox glycosyl donor and f *p*-methoxylbenzene protected glycosyl acceptor, which can be coupled in the presence of TMSI and AgOTf. This new combination was tested in application to the synthesis of a tetrasaccharide and trisaccharide that were obtained in moderate-to-good yields using conventions of the reverse orthogonal strategy.

## 5.4 Experimental

### 5.4.1 General methods

Column chromatography was performed on silica gel 60 (70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. $CH_2Cl_2$ and $ClCH_2CH_2Cl$ (1,2-DCE) were distilled from $CaH_2$ directly prior to application. Pyridine was dried by refluxing with $CaH_2$ and then distilled and stored over molecular sieves (3 Å). Anhydrous DMF was used as it is. Molecular sieves (3 Å or 4 Å), used for reactions, were crushed and activated *in vacuo* at 390 °C during 8 h in the first instance and then for 2-3 h at 390 °C directly prior to application. Optical rotations were measured using a Jasco polarimeter. $^1H$ NMR spectra were recorded in $CDCl_3$ at 300 MHz or 600 MHz. $^{13}C$ NMR spectra were recorded in $CDCl_3$ at 75 or 151 MHz. Accurate mass spectrometry determinations were performed using Agilent 6230 ESI TOF LCMS mass spectrometer.

### 5.4.2 Synthesis of building blocks

**Methyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α-D-glucopyranoside (5.1).**

Picolinic acid (168.1 mg, 1.35 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 258.8 mg, 1.35 mmol), and 4-dimethylaminopyridine (DMAP, 16.6 mg, 0.14 mmol) were added to a solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[12] (314.6 mg, 0.68 mmol) in dichloromethane (10 mL), and the resulting mixture was stirred under argon for 1 h at rt. After that, the reaction mixture was diluted with $CH_2Cl_2$ (75 mL) and washed with water (2 x 15 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was

purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound in 95% yield (366.5 mg, 0.64 mmol). Analytical data for **5.1**: $R_f$ = 0.3 (ethyl ethyl acetate/hexane, 1/1, v/v); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.76 (m, 1H, aromatic), 8.02 (m,1H, aromatic), 7.81 (m, 1H, aromatic), 7.47 (m, 1H, aromatic), 7.42-7.17 (m, 15H, aromatic), 4.93 (dd, $^2J$ = 10.6 Hz, 2H, C$H_2$Ph), 4.86 (d, $^2J$ = 10.9 Hz, 1H, C*H*Ph), 4.82 (d, $^2J$ = 12.1 Hz, 1H, C*H*Ph), 4.72-4.49 (m, 5H, H-1, 3, 4, 2 x C*H*Ph), 4.05 (dd, $J_{6a,6b}$ = 10.0 Hz, 1H, H-6a), 3.98 (ddd, $J_{5,6a}$ = 4.6, $J_{5,6b}$ = 2.4 Hz, 1H, H-5), 3.62 (d, 1H, H-6b), 3.58 (dd, $J_{2,3}$ = 9.5 Hz, 1H, H-2), 3.38 (s, 3H) ppm;

**Methyl 2,3,4-tri-*O*-benzyl-6-*O*-*p*-methoxybenzyl-α-D-glucopyranoside (5.2)**

Was synthesized from methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[12,17] and its analytical data in accordance with that previosuly reported.[9]

**Ethyl 2,3-di-*O*-benzoyl-6-*O*-p-methoxybenzyl-1-thio-β-D-glucopyranoside (5.3).**

A mixture containing ethyl 2,3-di-*O*-benzoyl-4,6-*O*-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside[15] (**5.5**, 1.83 g, 3.34 mmol) and molecular sieves (4 Å, 1.2 g) in dimethylformamide (40 mL) was stirred under argon for 1.5 h at rt. $NaCNBH_3$ (1.05 g, 16.7 mmol) was added and the resulting mixture was cooled to 0 °C. Trifluoroacetic acid (TFA, 3.82 g, 33.5 mmol) was added dropwise over a period of 1 h, the resulting mixture was allowed to warm to rt, and stirred for 16 h at rt. After that, the solids were filtered off through a pad of Celite and rinsed successively with DCM. The combined filtrate (~200 mL) was washed with sat. aq. $NaHCO_3$ (3 x 40 mL) and the aqueous layer was additionally extracted with dichloromethane (2 x 150 mL). The combined organic phase was dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane

gradient elution) to afford the title compound (1.75 g, 3.17 mmol) in 89% yield. Analytical data for **5.6**: $R_f$ = 0.5 (ethyl acetate/hexane, 2/3, v/v); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.02-7.91 (m, 4H, aromatic), 7.58-7.45 (m, 2H, aromatic), 7.43-7.31 (m, 4H, aromatic), 7.31-7.23 (m, 3H, aromatic), 6.93-6.83 (m, 2H, aromatic), 5.49 (dd, $J_{3,4}$ = 9.3 Hz, 1H, H-3), 5.44 (dd, $J_{2,3}$ = 9.4 Hz, 1H, H-2), 4.69 (d, $J_{1,2}$ = 9.6 Hz, 1H, H-1), 4.54 (dd, $^2J$ = 15.1 Hz, 2H, C$H_2$Ph), 3.96 (m, $J_{4,5}$ = 9.2, $J_{4,OH}$ = 3.1 Hz, 1H, H-4), 3.90-3.76 (m, 5H, H-6a, 6b, $OCH_3$), 3.71 (dd, $J_{5,6a}$ = $J_{5,6b}$ = 9.5 Hz, 1H, H-5), 3.29 (d, 1H, OH), 2.75 (m, 2H, SC$H_2$$CH_3$), 1.27 (m, 3H, $SCH_2$C$H_3$) ppm;

**Ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (5.7).** DMAP (180.8 mg, 1.5 mmol) was added to a solution of compound **5.6** (1.64 g, 3.0 mmol) in pyridine (30 mL) followed by a dropwise addition of benzoyl chloride (1.25 g, 8.9 mmol), and the resulting mixture was stirred under argon for 16 h at 40 °C. The reaction mixture was cooled to rt, MeOH (20 mL) was added, and the resulting mixture was stirred for 30 min. After that, the volatiles were removed under reduced pressure, and the residue was co-evaporated with toluene. The residue was dissolved in dichloromethane (~200 mL) and washed with water (40 mL), 1 N aq. HCl (40 mL), sat. aq. $NaHCO_3$ (40 mL), and water (2 x 40 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to afford the title compound (1.85 g, 2.8 mmol) in 94% yield. Analytical data for **5.7** was in accordance with that previously reported.[9]

**2,3,4-Tri-*O*-benzoyl-6-*O*-*p*-methoxybenzyl-α/β-D-glucopyranosyl chloride (5.3).**

*N*-Bromosuccinimide (2.34 g, 13.1 mmol) was added to a solution of compound **5.7** (1.73 g, 2.6 mmol) in acetone-water (150 mL, 9/1, v/v), and the resulting mixture was stirred for 15 min at rt. After that, the volatiles were removed under reduced pressure. The residue was dissolved in dichloromethane (~200 mL) and washed with water (40 mL), sat. aq. $NaHCO_3$ (40 mL), and water (2 x 40 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give 2,3,4-tri-*O*-benzoyl-6-*O*-*p*-methoxybenzyl-D-glucopyranose (**5.15**, 1.55 g, 2.5 mmol) in 98% yield (α/β = 2.9/1). Selected analytical data for **α-5.15**: $R_f$ = 0.4 (ethyl acetate/hexane, 2/3, v/v); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.05-7.76 (m, 7H, aromatic), 7.59-7.09 (m, 14H, aromatic), 6.70 (m, 1H, aromatic), 6.20 (dd, $J_{3,4}$ = 10.0 Hz, 1H, H-3), 5.74 (d, $J_{1,2}$ = 3.4 Hz, 1H, H-1), 5.55 (dd, $J_{4,5}$ = 9.8 Hz, 1H, H-4), 5.29 (dd, $J_{2,3}$ = 10.2 Hz, 1H, H-2), 4.62-4.32 (m, 3H, H-5, C$H_2$Ar), 4.23 (d, $J_{1,OH}$ = 3.3 Hz, 1H, OH), 3.78 (s, 3H, $OCH_3$), 3.66-3.48 (m, 2H, H-6a, 6b) ppm.

A solution of oxalyl chroride (0.96 g, 7.6 mmol) in dichloromethane (15 mL) was added dropwise to a stirring solution of compound **5.15** (1.55 g, 2.5 mmol) in dichloromethane (50 mL) and DMF (5.0 mL), and the resulting mixture was stirred under argon for 30 min at 0 °C. The external cooling was then removed and the reaction mixture was allowed to slowly warm to rt and stirred for additional 1 h at rt. After that, the volatiles were removed under reduced pressure. The residue was dissolved in a mixture of ethyl acetate and hexane (40 mL, 1/1, v/v) and passed through a pad of silica gel (40 g) that was additionally eluted with a mixture of ethyl acetate and hexane (150 mL, 1/1, v/v). The

combined eluate was concentrated under reduced pressure and dried in *vacuo* to afford the title compound as a clear syrup in 81% yield (1.23 g, 2.0 mmol). Analytical data for **α-5.3**: $R_f$ = 0.8 (ethyl acetate/hexane, 2/3, v/v); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.10-7.73 (m, 6H, aromatic), 7.60-7.06 (m, 11H, aromatic), 6.73 (m, 2H, aromatic), 6.57 (d, $J_{1,2}$ = 3.9 Hz, 1H, H-1), 6.19 (dd, $J_{3,4}$ = 9.9 Hz, 1H, H-3), 5.80 (dd, $J_{4,5}$ = 9.6 Hz, 1H, H-4), 5.45 (dd, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 4.63-4.31 (m, 3H, H-5, C$H_2$Ph), 3.81 (s, 3H, $OCH_3$), 3.75-3.58 (m, 2H, H-6a, 6b) ppm. Analytical data for **β-5.3**: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.10-7.73 (m, 6H, aromatic), 7.60-7.06 (m, 11H, aromatic), 6.73 (m, 2H, aromatic), 5.73-5.51 (m, 4H, H-1, 2, 3, 4), 4.63-4.31 (m, 2H, C$H_2$Ph), 4.09 (m, 1H, H-5), 3.81 (s, 3H, $OCH_3$), 3.75-3.58 (m, 2H, H-6a, 6b) ppm.

**Ethyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-picoloyl-1-thio-β-D-glucopyranoside (5.9).** Picolinic acid (1.9 g, 15.2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 2.9 g, 15.2 mmol), and 4-dimethylaminopyridine (DMAP, 185.9 mg, 1.5 mmol) were added to a solution of ethyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-1-thio-β-D-glucopyranoside[16,18] (**5.8**, 3.90 g, 7.6 mmol) in dichloromethane (100 mL), and the resulting mixture was stirred under argon for 1 h at rt. After that, the reaction mixture was diluted with $CH_2Cl_2$ (~200 mL) and washed with water (2 x 75 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (acetone - hexane gradient elution) to give the title compound (4.6 g, 7.4 mmol) in 98% yield. Analytical data for **5.9**: $R_f$ = 0.45 (acetone/hexane, 2/3, v/v); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.78 (dd, 1H, aromatic), 8.08-8.00 (m, 3H, aromatic), 7.84 (m, 1H, aromatic), 7.63-7.54 (m, 1H, aromatic), 7.48 (ddd, 3H, aromatic), 7.34-7.06 (m, 10H, aromatic),

5.35 (dd, $J_{4,5}$ = 9.8 Hz, 1H, H-4), 4.89 (d, $^{2}J$ = 10.9 Hz, 1H, C*H*Ph), 4.82- 4.53 (m, 6H, H-1, 2, 3, 3 x C*H*Ph), 3.98-3.86 (dd, 1H, H-5), 3.85-3.74 (m, 2H, H-6a, 6b), 2.85-2.52 (m, 2H, SC$H_2$CH$_3$), 1.17 (t, $J$ = 7.4 Hz, 3H, SC$H_2$CH$_3$).

**Benzoxazolyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-picoloyl-1-thio-β-D-glucopyranoside (5.4).**

A mixture containing compound **5.9** (1.63 g, 2.7 mmol) and molecular sieves (3 Å, 2.44 g) in dichloromethane (40 mL) was stired under argon for 1.5 h at rt. The mixture was cooled to 0 °C, a 0.6 M solution of bromine in dichloromethane (25.5 mL) was added dropwise, and the resulting mixture was stirred for 15 min at 0 °C. The reaction mixture was then neutralized with triethylamine (15 mL). The solids were filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~100 mL) was washed with cold water (2 x 40 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in a mixture of acetone and hexane (40 mL 1/1, v/v) and filtered through a pad of silica gel (40 g). that was additionally eluted with a mixture of ethyl acetate and hexane (150 mL, 1/1, v/v).The combined eluate was concentrated under reduced pressure, and dried in *vacuo* for 2 h. The crude residue containing glycosyl bromide intermediate was dissolved in acetone (100 mL), 18-crown-6 (207.7 mg, 0.85 mmol) and KSbox (1.61 g, 8.5 mmol) were added, and the resulting mixture was stirred under argon for 6 h at rt. The volatiles were then removed under reduced pressure. The residue was dissolved in dichloromethane (200 mL) and washed with water (50 mL), 1% aq. NaOH (50 mL), and water (2 x 50 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by

column chromatography on silica gel (ethyl acetate - dichloromethane gradient elution) to give the title compound (890.1 mg, 1.27 mmol) in 45% yield. Analytical data for **5.4**: $R_f$ = 0.55 (ethyl acetate/dichloromethane, 1/4, v/v); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.71 (d, 1H, aromatic), 8.05-7.96 (m, 2H, aromatic), 7.90 (d, 1H, aromatic), 7.67-7.47 (m, 3H, aromatic), 7.47-7.05 (m, 16H, aromatic), 5.82 (d, $J_{1,2}$ = 10.3 Hz, 1H, H-1), 5.54 (dd, $J_{2,3}$ = 9.0 Hz, 1H, H-2), 4.80 (dd, $^2J$ = 11.0 Hz, 2H, C$H_2$Ph) 4.78 (dd, $^2J$ = 10.9 Hz, 2H, C$H_2$Ph), 4.63 (dd, 1H, H-6b), 4.55 (dd, $J_{6a,6b}$ = 12.1 Hz, 1H, H-6a), 4.07 (dd, $J_{3,4}$ = 8.9 Hz, 1H, H-3), 4.03 (ddd, $J_{5,6a}$ = $J_{5,6b}$ = 5.4 Hz, 1H, H-5), 3.86 (dd, $J_{4,5}$ = 9.0 Hz, 1H, H-4) ppm.

### 5.4.3 Synthesis of oligosaccharides by reverse orthogonal glycosylation

**Methyl 6-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (5.10).**

$FeCl_3$ (1.5 mg, 0.009 mmol) was added to a solution of compound **5.1** (17.8 mg, 0.031 mmol) in MeOH (0.9 mL) and dichloromethane (0.1 mL), and the resulting mixture was stirred for 30 min at rt. After that, the reaction mixture was concentrated under reduced pressure and the residue was dried in *vacuo* for 1.5 h. The resulting residue was dissolved in dichloromethane (1.0 mL), molecular sieves (4 Å, 150 mg) were added, and the resulting mixture was stirred under argon for 1 h at rt. Glycosyl chloride **5.3** (40.0 mg, 0.059 mmol) and $FeCl_3$ (2.9 mg, 0.018 mmol) were added, and the resulting mixture was stirred under argon for 16 h at rt. After that, the solids were filtered off through a pad of Celite, rinsed successively with dichloromethane, and the combined filtrate (~40 mL) was washed with sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was

purified by column chromatography on silica gel (ethyl acetate - toluene, gradient elution) to give the title compound (22.8 mg, 0.022 mmol) in 70% yield. Analytical data for **5.10** was essentially the same as previously reported.[9]

**Methyl *O*-(3,4-di-*O*-benzyl-2-*O*-benzoyl-6-*O*-picoloyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-glucopyranoside (5.11)**

Compounds **5.5** (40.1 mg, 0.038 mmol) and **5.4** (34.5 mg, 0.049 mmol) were dissolved in 1,2-dichloroethane (1 mL), molecular sieves (3 Å, 150 mg) were added and the resulting mixture was stirred for 1 h under argon at rt. The reaction was then cooled to 0 °C and TMSI (24.51 mg, 0.12 mmol) was added and stirred for 20 minutes. Silver triflate (AgOTf, 37.8 mg, 0.15 mmol) was added and the resulting mixture was stirred for 3 h at rt. After that, the solids were filtered off through a pad of Celite, rinsed successively with dichloromethane, and the combined filtrate (~40 mL) was washed with water (10 mL), sat. aq. $NaHCO_3$ (10 mL), and water (2 x 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - dichloromethane gradient elution) to give the title compound (36.8 mg, 0.025 mmol) in 65% yield. Analytical data for **5.11**: $R_f$ = 0.83 (ethyl acetate/dichloromethane, 1/4, v/v); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.78 (d, 1H, aromatic), 8.01 (m, 3H, aromatic), 7.91-7.65 (m, 7H, aromatic), 7.55-6.89 (m, 42H, aromatic), 5.70 (dd, $J_{3',4'}$ = 9.6 Hz, 1H, H-3'), 5.41 (dd, $J_{2',3'}$ = 8.3 Hz, 1H, H-2'), 5.29 (dd, $J_{2'',3''}$ = 8.4Hz, 1H, H-2''), 5.24 (dd, $J_{4',5'}$ = 9.4 Hz, 1H, H-4') 4.85 (m, 2H), 4.77-4.41 (m, 12H, H-1, 1', 1", C*H*Ph x9), 4.25 (dd, $^2J$ = 11.2 Hz, 1H, C$H_2$Ph), 3.98-3.65 (m, 8H, H-3, 3", 5', 5", 6a, 6a', 6b, 6b'), 3.49-3.29 (m, 4H,

H-2, 4, 4", 5), 3.24 (s, 3H, OC*H*$_3$) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$) δ 165.9, 165.5, 165.2, 165.0, 164.7, 150.3, 147.8, 139.0, 138.5, 138.3, 137.6, 137.6, 137.2, 133.6, 133.4, 133.3, 133.2, 130.0, 129.9 (x3), 129.8 (x7), 129.3, 128.9 (x2), 128.7 (x2), 128.6 (x5), 128.5 (x5), 128.4 (x5), 128.3 9 (x5), 128.2, 128.1 (x4), 128.0, 127.7, 127.6, 127.5, 127.1, 125.5, 101.3, 100.8, 98.3, 83.0, 82.0, 79.9, 77.7, 77.1, 75.6, 75.4, 75.3, 74.6, 74.4, 73.9, 73.6, 73.4, 73.0, 71.9, 69.8, 69.5, 68.3, 67.5, 64.2, 55.5.

**Methyl *O*-(2,3,4-tri-*O*-benzoyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranosyl)-(1→6)-*O*-(3,4-di-*O*-benzyl-2-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-glucopyranoside (5.12).**

$FeCl_3$ (1.7 mg, 0.008 mmol) was added to a solution of compound **5.11** (37.7 mg, 0.025 mmol) in MeOH (0.9 mL) and dichloromethane (0.1 mL), and the resulting mixture was stirred for 30 min at rt. After that, the reaction mixture was concentrated under reduced pressure and the residue was dried in *vacuo* for 1.5 h. The resulting residue was dissolved in dichloromethane (1.0 mL), molecular sieves (4 Å, 150 mg) were added, and the resulting mixture was stirred under argon for 1 h at rt. Glycosyl chloride **5.3** (47.6 mg, 0.075 mmol) and $FeCl_3$ (3.7 mg, 0.022 mmol) were added, and the resulting mixture was stirred under argon for 16 h at rt. After that, the solids were filtered off through a pad of Celite, rinsed successively with dichloromethane, and the combined filtrate (~40 mL) was washed with sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - toluene, gradient elution) to give the title compound (29.0 mg, 0.015 mmol) in 58% yield. Analytical data for **5.12**: $R_f$ = 0.7 (ethyl acetate/toluene, 3/7, v/v); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.02 –

7.80 (m, 11H, aromatic), 7.76 (d, 2H, aromatic), 7.58 – 7.04 (m, 42H, aromatic), 7.04 – 6.93 (m, 4H, aromatic), 6.70 (t, *J* = 9.4 Hz, 1H), 5.94 (t, *J* = 9.7 Hz, 1H), 5.74 (t, *J* = 9.6 Hz, 1H), 5.61 – 5.43 (m, 3H), 5.35 (dd, *J* = 18.1, 8.5 Hz, 1H), 5.24 – 5.11 (m, 1H), 4.94 – 4.81 (m, 2H), 4.76 – 4.62 (m, 2H), 4.62 – 4.29 (m, 10H), 4.17 (dd, 2H), 4.07 – 3.87 (m, 2H), 3.88 – 3.50 (m, 11H), 3.48 – 3.26 (m, 4H), 3.22 (s, 3H).

**Methyl 6-*O*-(3,4-di-*O*-benzyl-2-*O*-benzoyl-6-*O*-picoloyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (5.13)**

Compounds **5.2** (25.5 mg, 0.044 mmol) and **5.4** (40.0 mg, 0.057 mmol) were dissolved in 1,1-dichloroethane (1 mL), molecular sieves (3Å , 150 mg) were added and the resulting mixture was stirred for 1 h at rt. The reaction was cooled to 0 °C and TMSI (34.17 mg, 0.17 mmol) was added and stirred for 20 minutes. Silver triflate (AgOTf, 43.9 mg, 0.17 mmol) was added and the resulting mixture was stirred for 3 h at rt. The reaction was diluted with dichloromethane (40 mL) and washed with water (10 mL), sat. $NaHCO_3$ (10 mL), and water (2x 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was then purified by column chromatography on silica gel (ethyl acetate/toluene, gradient elution) to give the title compound in 58% yield (25.7 mg, 0.025 mmol). Analytical data for **5.13**: $R_f$ = 0.3 (ethyl acetate/toluene, 3/7, v/v); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.76 (d, 1H, aromatic), 8.05 (d, 1H, aromatic), 7.94 (d, 2H, aromatic), 7.79 (t, 1H, aromatic), 7.50 – 7.40 (m, 2H, aromatic), 7.36 – 7.17 (m, 21H, aromatic), 7.08 – 6.93 (m, 2H, aromatic), 5.39 (t, $J_{2',3'}$ = 8.5 Hz, 1H, H-2'), 4.96 – 4.80 (m, 2H, C*H*Ph x2), 4.80 – 4.52 (m, 9H, H-1', 4', 5', 6 x C*H*Ph), 4.45 (d, $J_{1,2}$ = 3.5 Hz, 1H, H-1), 4.30 (dd, $^2J$ = 11.0 Hz, 2H, C$H_2$Ph), 4.08 (d, $J_{6a,6b}$ = 9.1 Hz, 1H, H-6a), 3.93-3.72 (m, 4H, H-3, 3', 6a', 6b'), 3.70 –

3.58 (m, 2H, H-5, 6b), 3.40 (dd, $J_{2,3}$ = 9.7 Hz, 1H, H-2), 3.32 (dd, $J_{4,5}$ = 9.4 Hz, 1H, H-4), 3.16 (s, 3H, $OCH_3$) ppm; $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 165.1, 164.8, 150.2, 147.8, 139.0, 138.3 (x2), 137.7, 137.6, 137.1, 133.2, 129.9 (x2), 128.7 (x3), 128.6 (x3), 128.5 (x4), 128.4 (x4), 128.3 (x4), 128.2 (x3), 128.0 (x4), 127.7, 127.6 (x2), 127.1, 125.5, 101.4, 98.0, 83.1, 82.0, 79.8, 77.8, 77.6, 75.6, 75.5, 75.2, 74.8, 73.8, 73.5, 73.4, 69.5, 68.2, 64.3, 55.1.

**Methyl *O*-(2,3,4-tri-*O*-benzoyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranosyl)-(1→6)-*O*-(3,4-di-*O*-benzyl-2-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-glucopyranoside (5.14)**

$FeCl_3$ (1.2 mg, 0.008 mmol) was added to a solution of compound **5.13** (25.4 mg, 0.025 mmol) in MeOH (0.9 mL) and dichloromethane (0.1 mL), and the resulting mixture was stirred for 30 min at rt. After that, the reaction mixture was concentrated under reduced pressure and the residue was dried in *vacuo* for 1.5 h. The resulting residue was dissolved in dichloromethane (1.0 mL), molecular sieves (4 Å, 150 mg) were added, and the resulting mixture was stirred under argon for 1 h at rt. Glycosyl chloride **5.3** (39.9 mg, 0.063 mmol) and $FeCl_3$ (3.1 mg, 0.019 mmol) were added, and the resulting mixture was stirred under argon for 16 h at rt. After that, the solids were filtered off through a pad of Celite, rinsed successively with dichloromethane, and the combined filtrate (~40 mL) was washed with sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - toluene, gradient elution) to give the title compound (18.2 mg, 0.012 mmol) in 49% yield. Analytical data for **5.14**: $R_f$ = 0.45 (ethyl acetate/toluene, 1/4, v/v); $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.96 –

7.70 (m, 8H, aromatic), 7.58 – 6.99 (m, 41H, aromatic), 6.93 (d, *J* = 3.7 Hz, 2H, aromatic), 6.67 (d, *J* = 8.4 Hz, 1H, aromatic), 5.79 (t, *J* = 9.7 Hz, 1H), 5.62 – 5.42 (m, 2H), 5.29 (dd, *J* = 8.6 Hz, 1H), 4.94 (d, *J* = 7.8 Hz, 1H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.75 – 4.51 (m, 7H), 4.48 (dd, *J* = 10.2 Hz, 1H), 4.41 (dd, *J* = 10.2 Hz, 1H), 4.38 – 4.25 (m, 3H), 4.25 – 4.07 (m, 3H), 4.03 – 3.60 (m, 11H), 3.60 – 3.31 (m, 7H), 3.28 (s, 3H, OC$H_3$) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$) δ 165.9, 165.4, 165.1, 165.0, 155.5, 139.1, 138.5, 138.4, 137.9, 137.8, 133.5, 133.3 (x2), 133.1 (x2), 131.5, 129.9, 129.9 (x6), 129.8 (x5), 128.6 (x4), 128.5 (x5), 128.6, 128.4 (x5), 128.3 (x3), 128.1 (x3), 128.0 (x5), 127.9 (x3), 127.8, 127.6 (x5), 127.5, 111.8, 111.5, 101.5, 101.0, 98.3, 82.8, 82.0, 79.8, 77.9, 75.6, 75.1, 75.0, 74.7, 73.9, 73.7, 73.6, 73.2, 72.7, 72.2, 70.0, 69.6, 69.0, 68.4, 67.6, 56.3, 55.4.

**5.5 References**

(1) Panza, M.; Pistorio, S. G.; Stine, K. J.; Demchenko, A. V. Automated Chemical Oligosaccharide Synthesis: Novel Approach to Traditional Challenges. *Chem. Rev.* **2018**, *118*, 8105−8150.

(2) Love, K. R.; Andrade, R. B.; Seeberger, P. H. Linear synthesis of a protected h-type II pentasaccharide using glycosyl phosphate building blocks. *J. Org. Chem.* **2001**, *66*, 8165-8176.

(3) Calin, O.; Eller, S.; Seeberger, P. H. Automated polysaccharide synthesis: assembly of a 30mer mannoside. *Angew. Chem. Int. Ed.* **2013**, *52*, 5862-5865.

(4) Naresh, K.; Schumacher, F.; Hahm, H. S.; Seeberger, P. H. Pushing the limits of automated glycan assembly: synthesis of a 50mer polymannoside. *Chem. Commun.* **2017**, *53*, 9085-9088.

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

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

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

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

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

(10) Geringer, S. A.; Demchenko, A. V. Iron(III) Chloride-Catalyzed Activation of Glycosyl Chlorides. *Org. Biomol. Chem.* **2018**, *16*, 9133-9137.

(11) Geringer, S. A.; Demchenko, A. V. Iron(III) chloride-catalyzed removal of O-picoloyl protecting group. *submitted* **2020**.

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

(13) Mannino, M. P.; Demchenko, A. V. Synthesis of β-glucosides with 3-O-picoloyl-protected glycosyl donors in the presence of excess triflic acid: a mechanistic study. *Chem. Eur. J.* **2020**, *26*, *26*, 2927-2937.

(14) Mannino, M. P.; Demchenko, A. V. Synthesis of β-glucosides with 3-O-picoloyl-protected glycosyl donors in the presence of excess triflic acid: defining the scope. *Chem. Eur. J.* **2020**, *26*, 2938-2946.

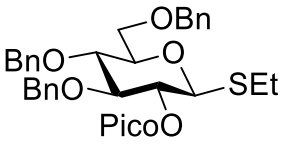
(15) Choudhury, A. K.; Ray, A. K.; Roy, N. Synthesis of Tetrasaccharide Repeating Unit of the K-Antigen from Klebsiella Type-16. *J. Carbohydr. Chem.* **1995**, *14*, 1153-1163.

(16) Daragics, K.; Fügedi, P. Synthesis of glycosaminoglycan oligosaccharides. Part 5: Synthesis of a putative heparan sulfate tetrasaccharide antigen involved in prion diseases. *Tetrahedron* **2010**, *66*, 8036-8046.

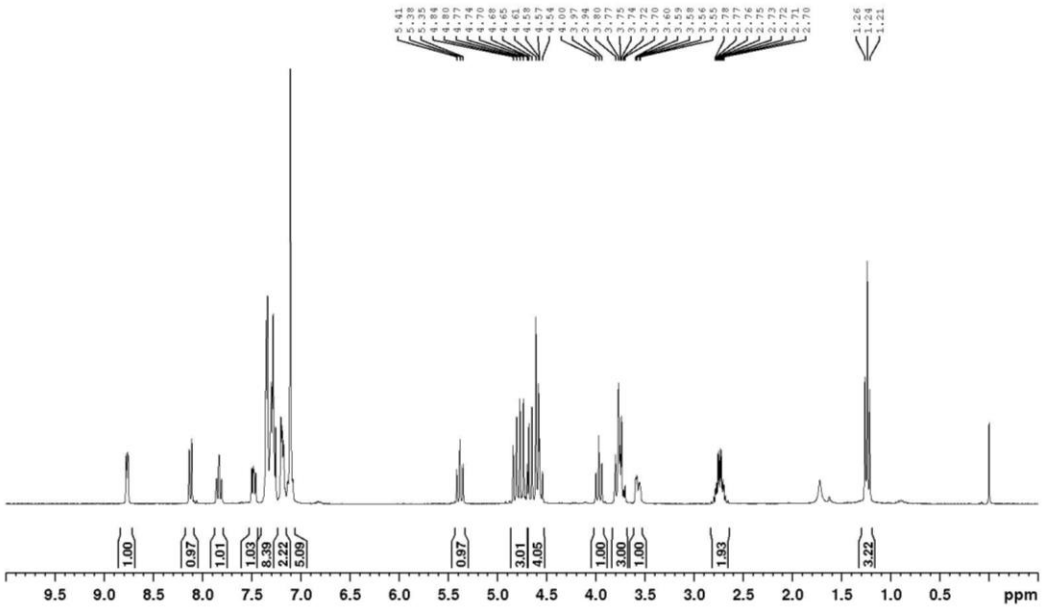
(17) Kuester, J. M.; Dyong, I. Partially benzylated carbohydrates, 2. Synthesis of all methyl mono-, di-, and tri-O-benzyl-α-D-glucopyranosides. *Justus Liebigs Ann. Chem.* **1975**, 2179-2189.

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

# APPENDIX

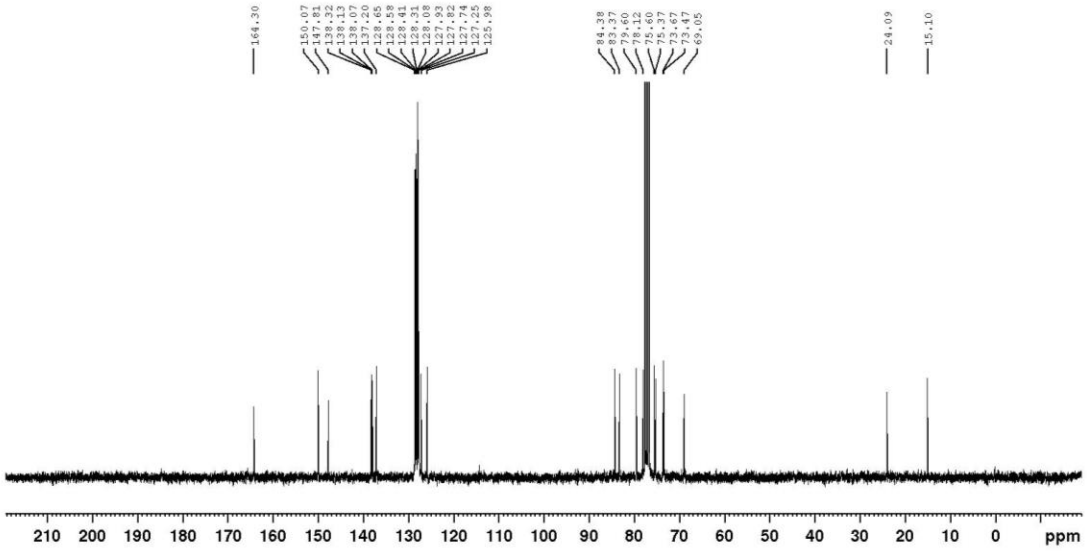



**2.3**




$CDCl_3$ 300 MHz

**Figure A-1:** $^{1}H$ NMR spectrum of Ethyl 3,4,6-tri-*O*-benzyl-2-*O*-picoloyl-1-thio-b-D-glucopyranoside **(2.3).**




$CDCl_3$ 75 MHz

**Figure A-2:** $^{13}C$ NMR spectrum of Ethyl 3,4,6-tri-*O*-benzyl-2-*O*-picoloyl-1-thio-b-D-glucopyranoside (**2.3**)

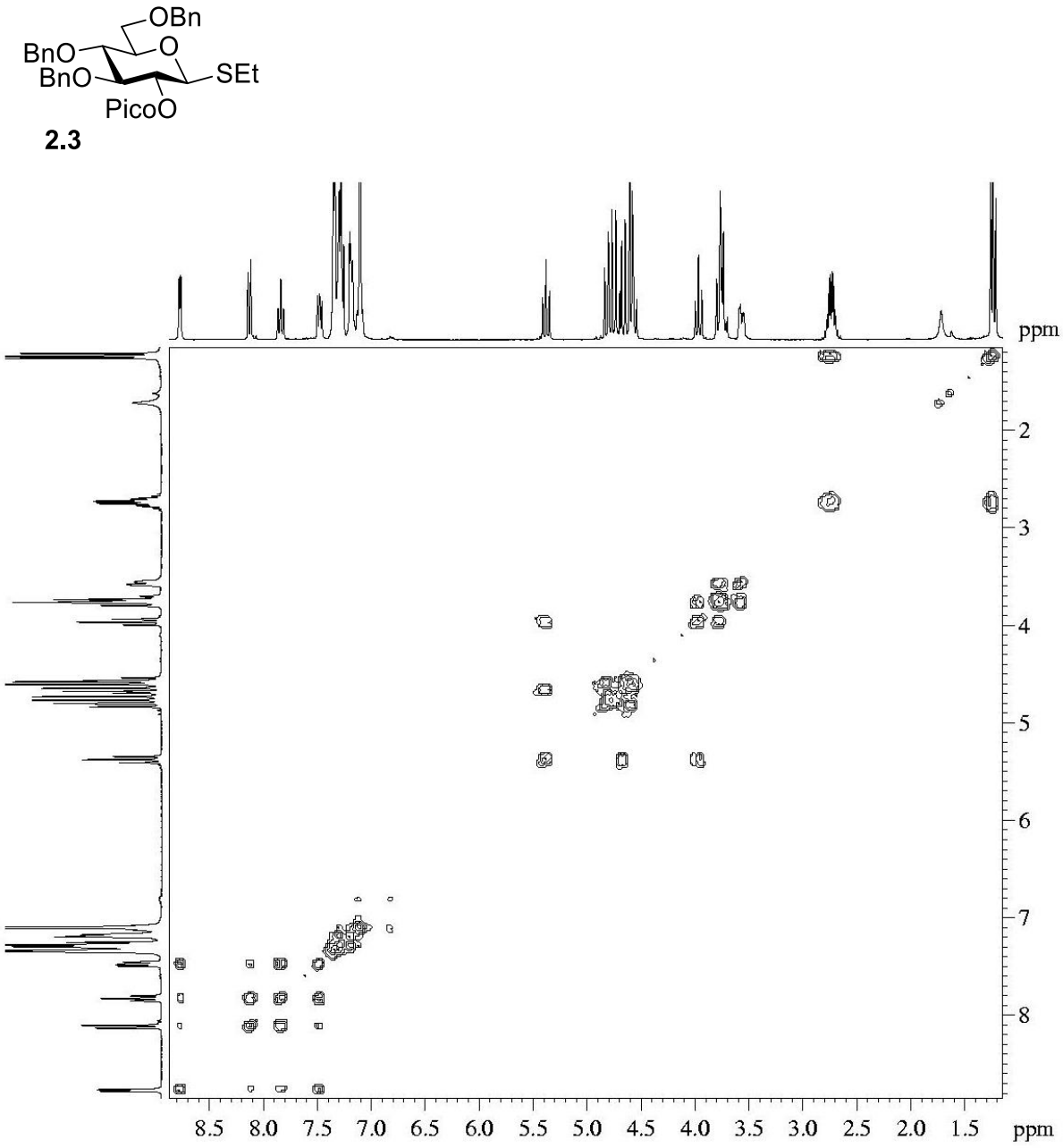
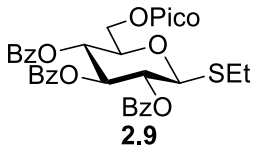
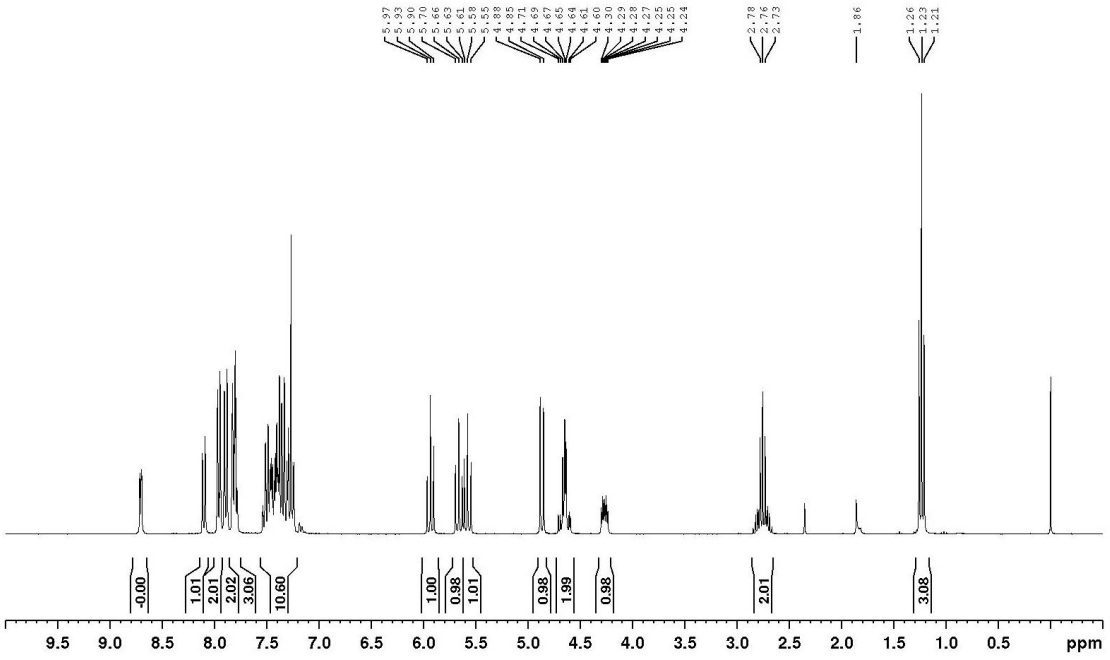



**Figure A-3:** 2-D NMR COSY spectrum of Ethyl 3,4,6-tri-*O*-benzyl-2-*O*-picoloyl-1-thio-b-D-glucopyranoside (**2.3**)

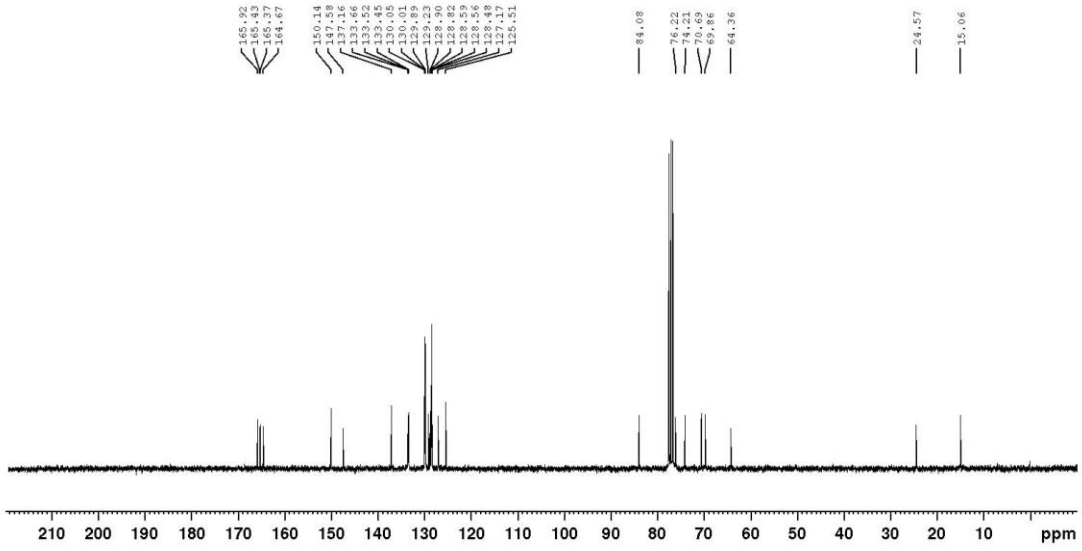



**2.9**




$CDCl_3$ 300 MHz

**Figure A-4:** $^{1}H$ NMR spectrum of Ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-picoloyl-1-thio-b-D-glucopyranoside **(2.9).**




$CDCl_3$ 75 MHz

**Figure A-5:** $^{13}C$ NMR spectrum of Ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-picoloyl-1-thio-b-D-glucopyranoside **(2.9).**

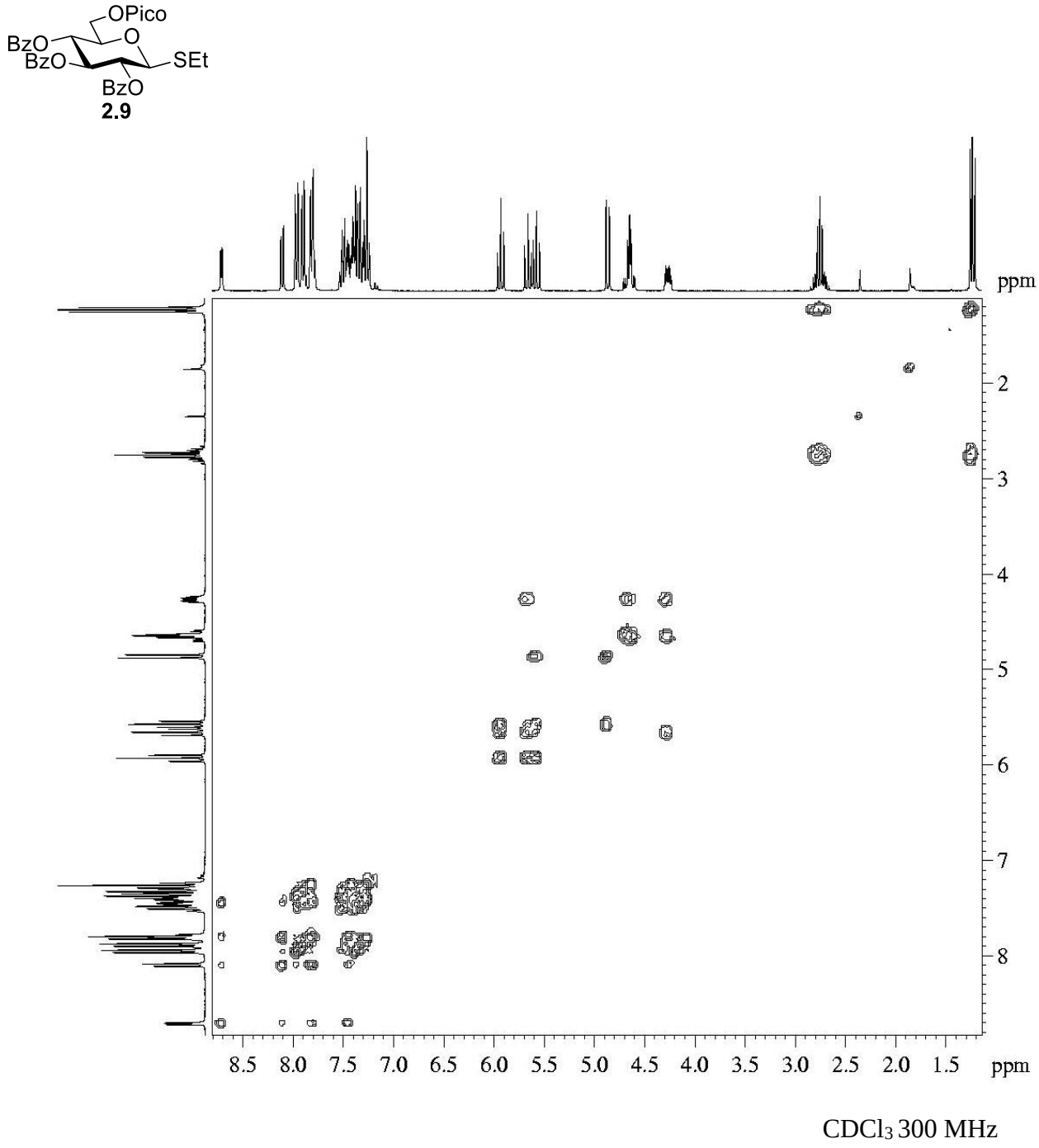
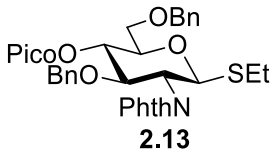
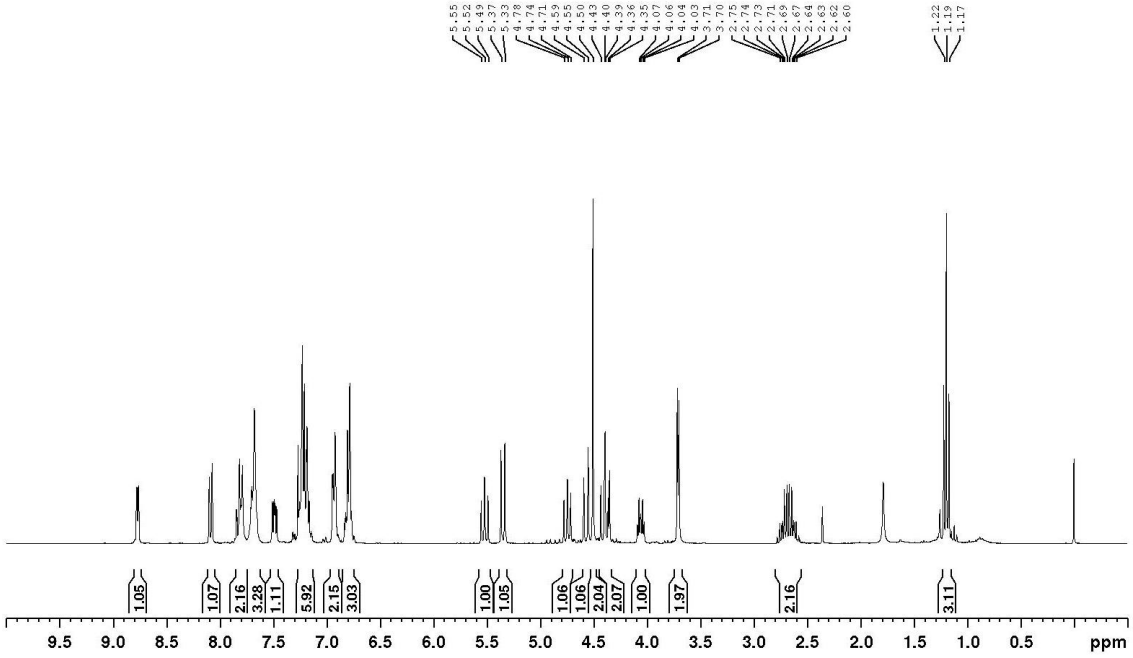



**Figure A-6:** 2-D NMR COSY spectrum of Ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-picoloyl-1-thio-b-D-glucopyranoside **(2.9).**

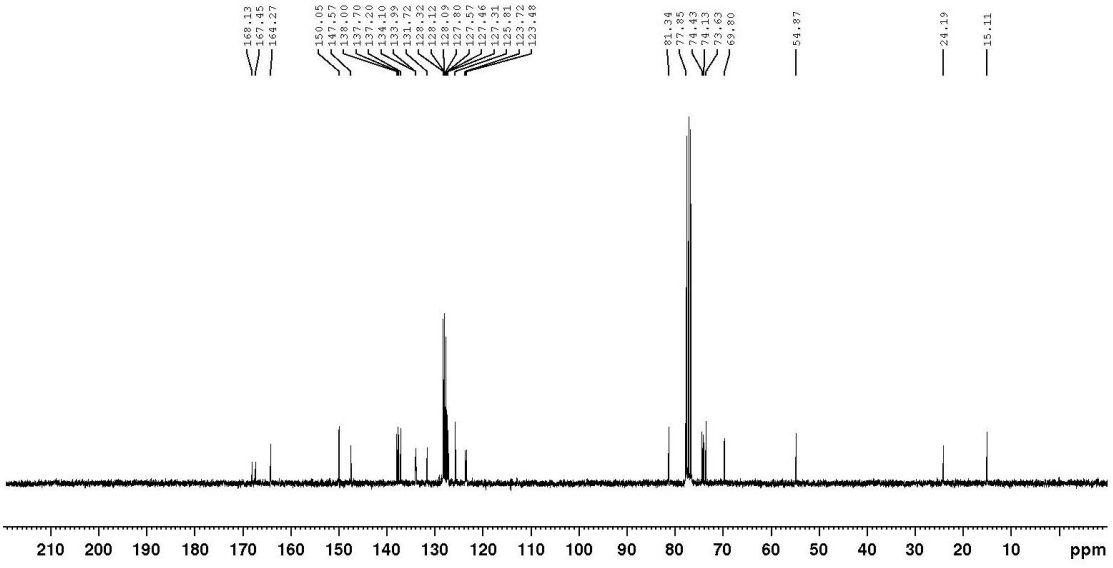



**2.13**




$CDCl_3$ 300 MHz

**Figure A-7:** $^{1}H$ NMR spectrum of Ethyl 3,6-di-*O*-benzyl-2-deoxy-4-*O*-picoloyl-2-phthalimido-1-thio-β-D-glucopyranoside **(2.13).**




$CDCl_3$ 75 MHz

**Figure A-8:** $^{13}C$ NMR spectrum of Ethyl 3,6-di-*O*-benzyl-2-deoxy-4-*O*-picoloyl-2-phthalimido-1-thio-β-D-glucopyranoside **(2.13).**

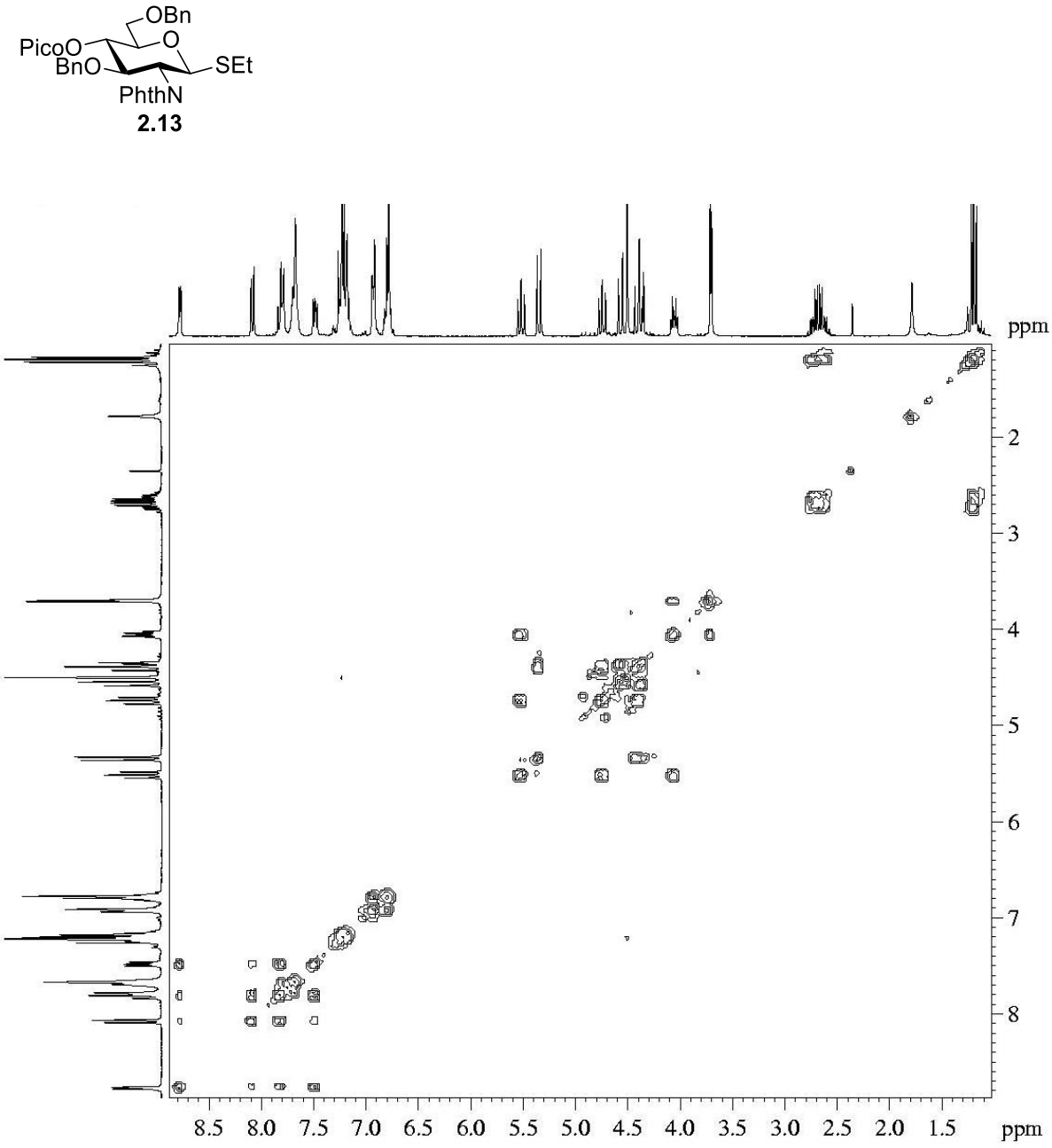



**Figure A-9:** 2-D NMR COSY spectrum of Ethyl 3,6-di-*O*-benzyl-2-deoxy-4-*O*-picoloyl-2-phthalimido-1-thio-β-D-glucopyranoside **(2.13).**

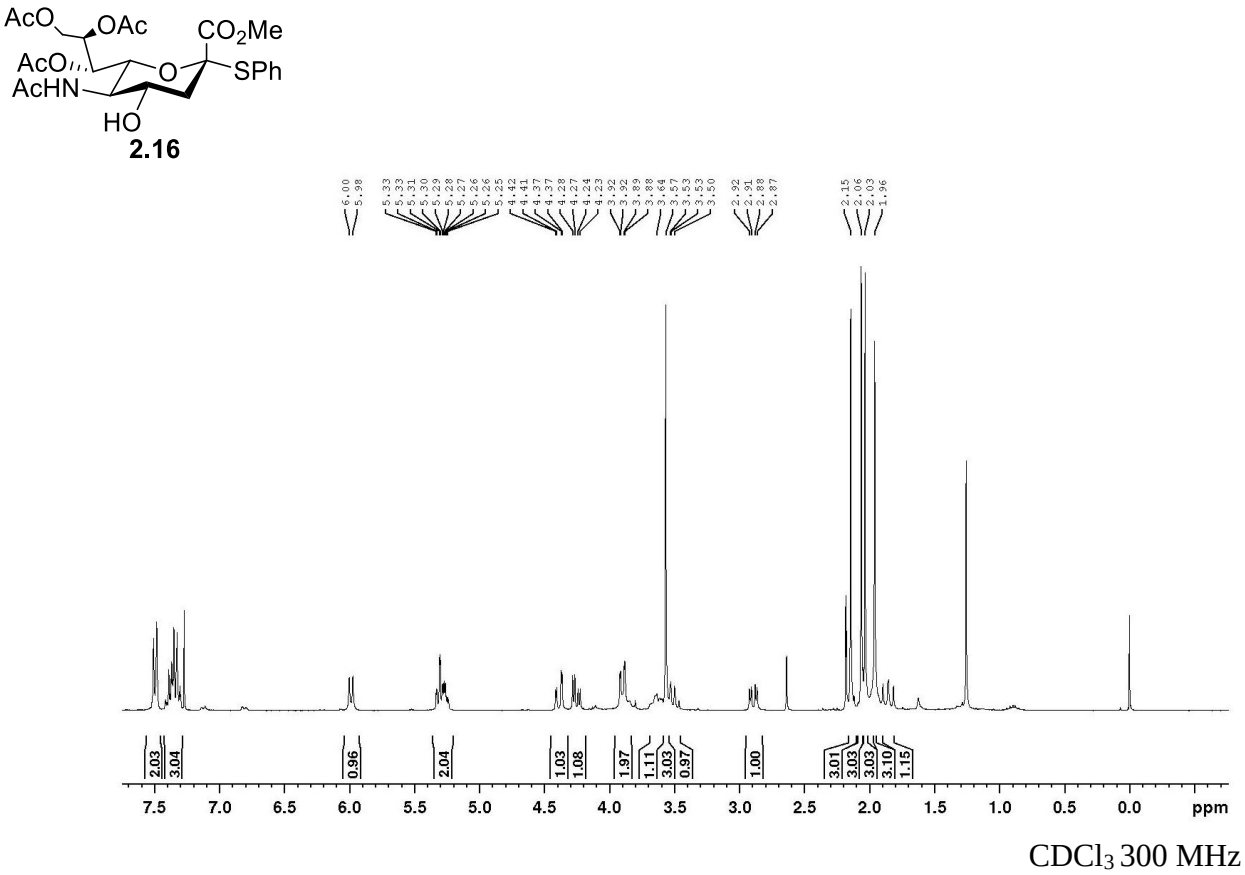



**Figure A-10:** $^{1}$H NMR spectrum of Methyl (phenyl 5-acetamido-7,8,9-tri-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-non-2-ulopyranosid)onate **(2.16).**

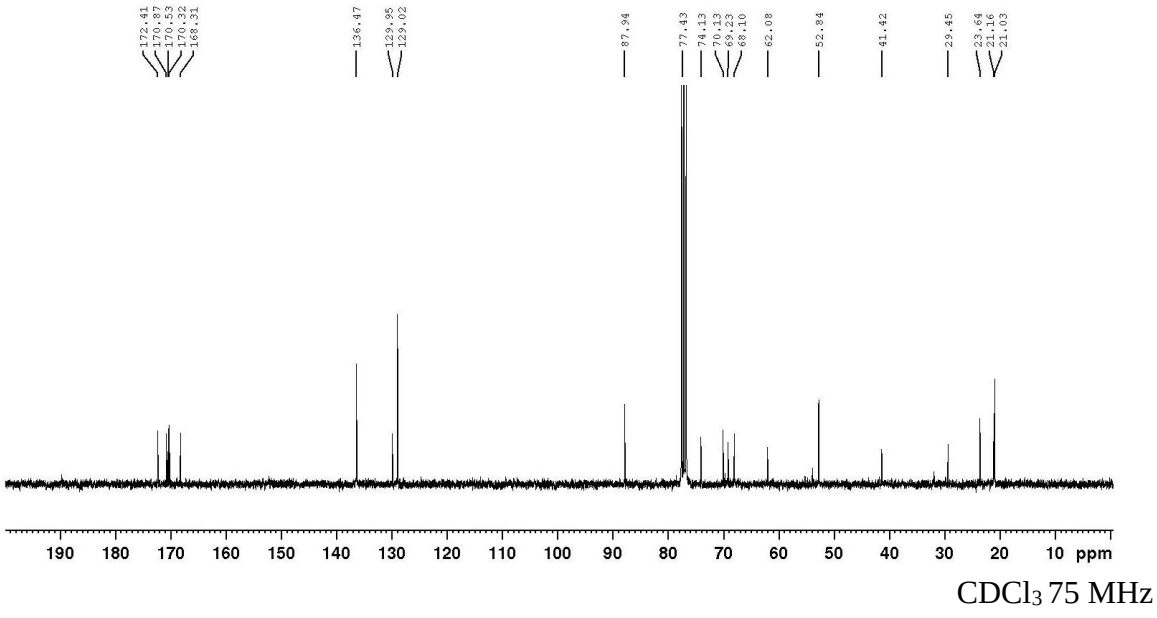



**Figure A-11:** $^{13}$C NMR spectrum of Methyl (phenyl 5-acetamido-7,8,9-tri-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-non-2-ulopyranosid)onate **(2.16).**

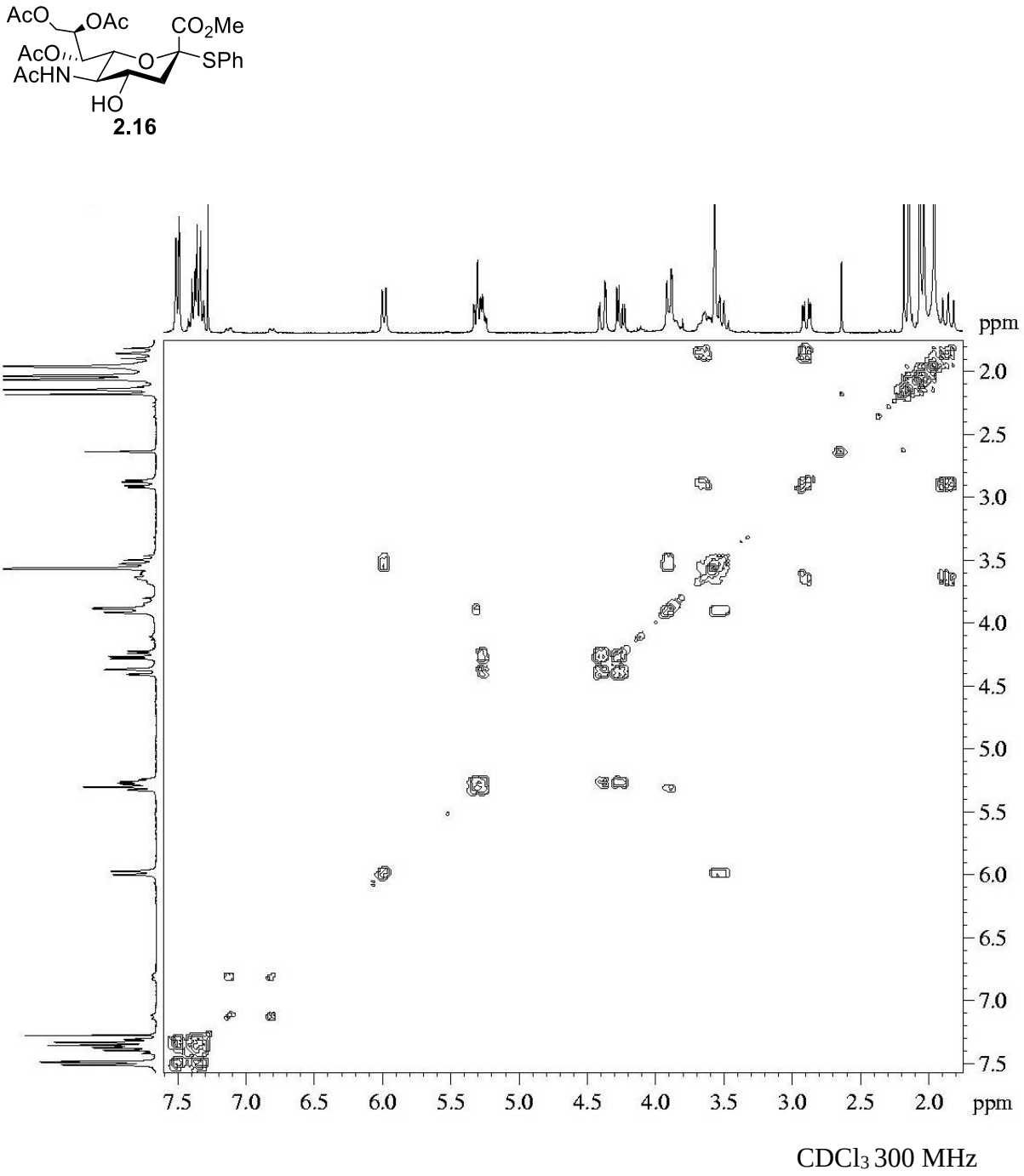
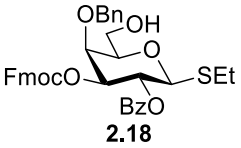
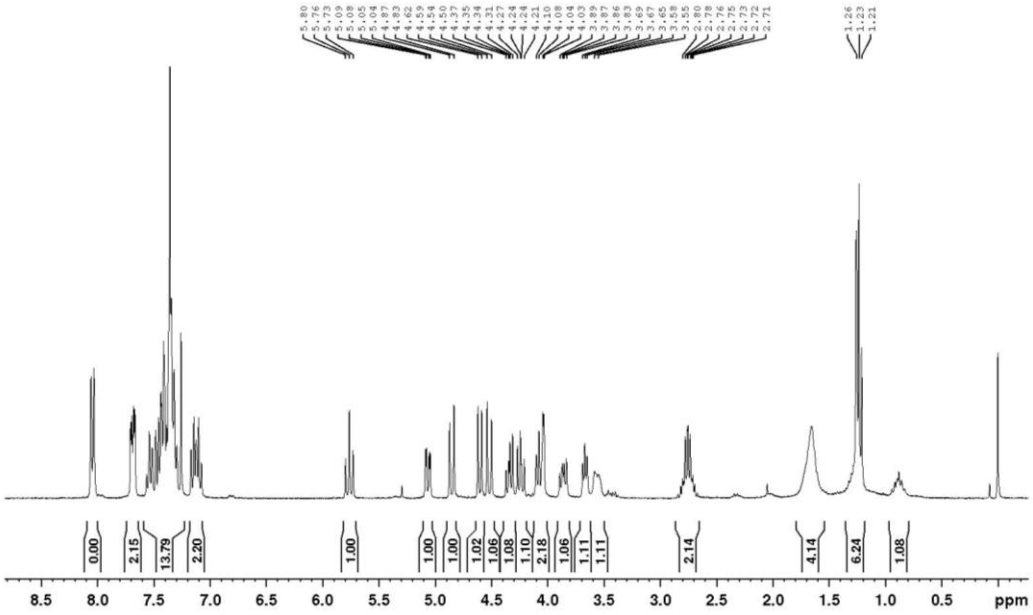



**Figure A-12:** 2-D NMR COSY spectrum of Methyl (phenyl 5-acetamido-7,8,9-tri-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-non-2-ulopyranosid)onate **(2.16).**

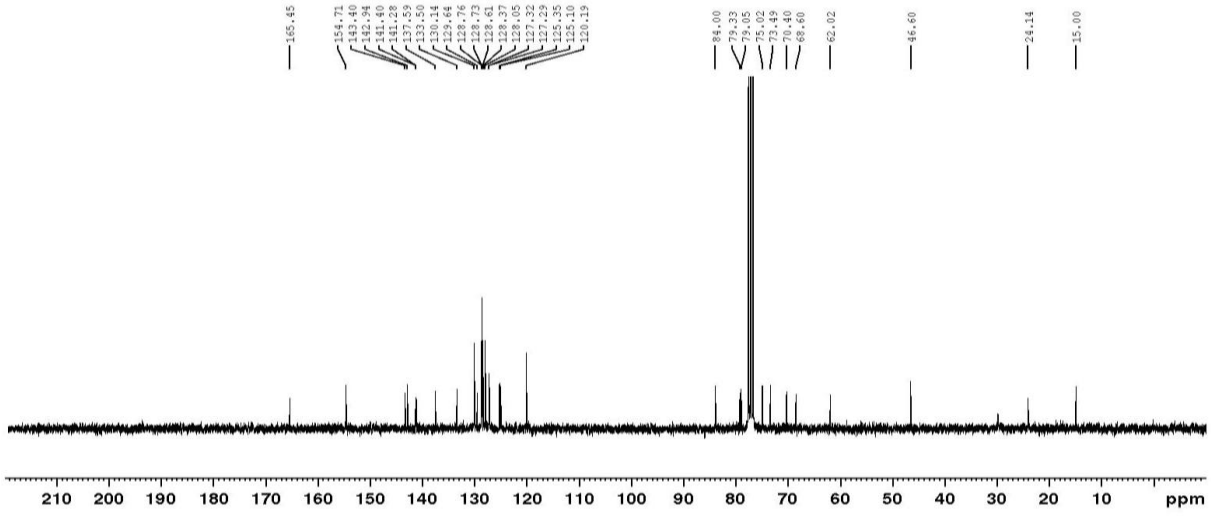



**2.18**




$CDCl_3$ 300 MHz

**Figure A-13:** $^{1}H$ NMR spectrum of Ethyl 2-O-benzoyl-4-O-benzyl-3-O-(9-fluorenylmethoxycarbonyl)-1-thio-β-D-galactopyranoside **(2.18).**




$CDCl_3$ 75 MHz

**Figure A-14:** $^{13}C$ NMR spectrum of Ethyl 2-O-benzoyl-4-O-benzyl-3-O-(9-fluorenylmethoxycarbonyl)-1-thio-β-D-galactopyranoside **(2.18).**

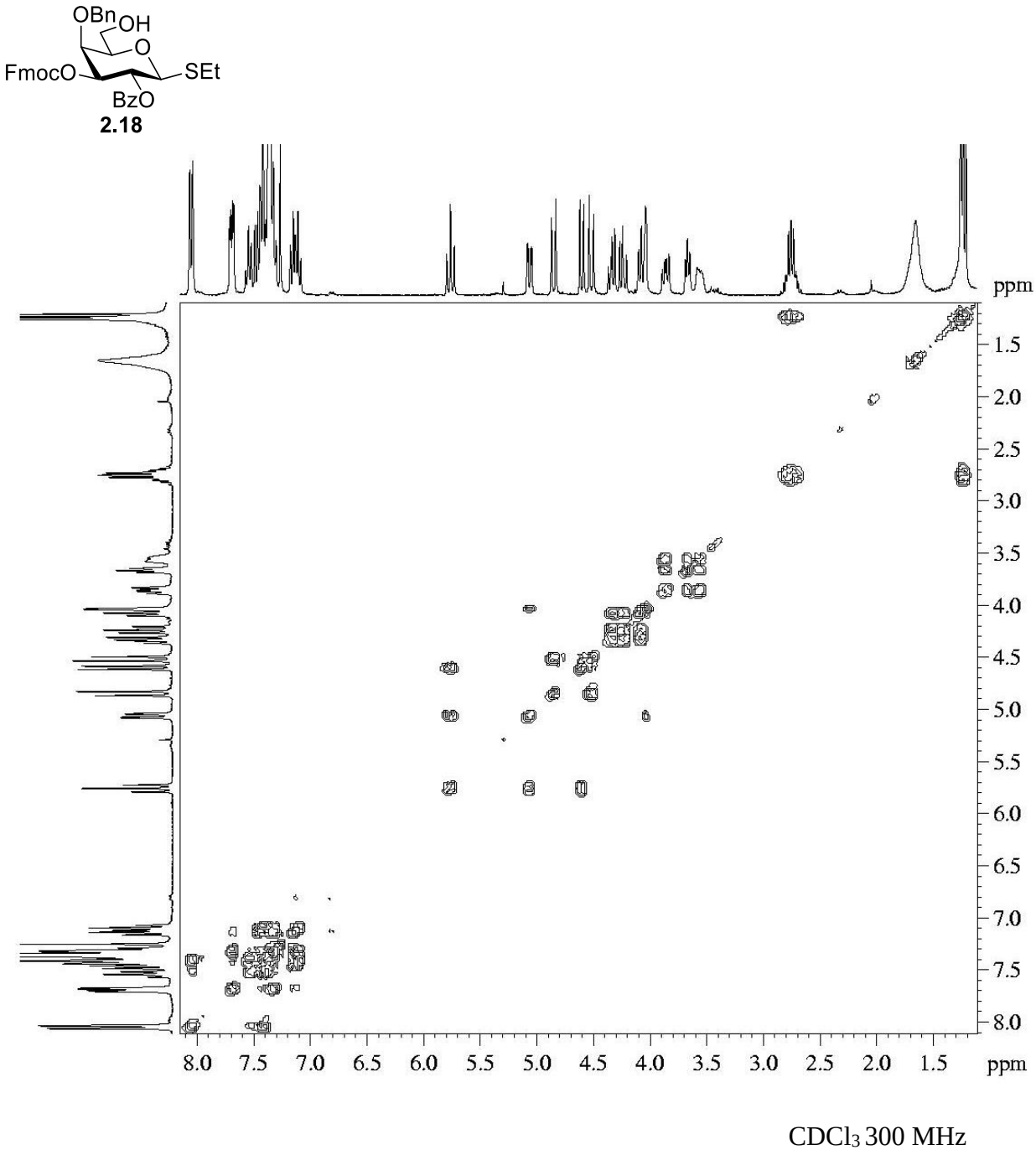
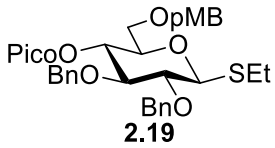
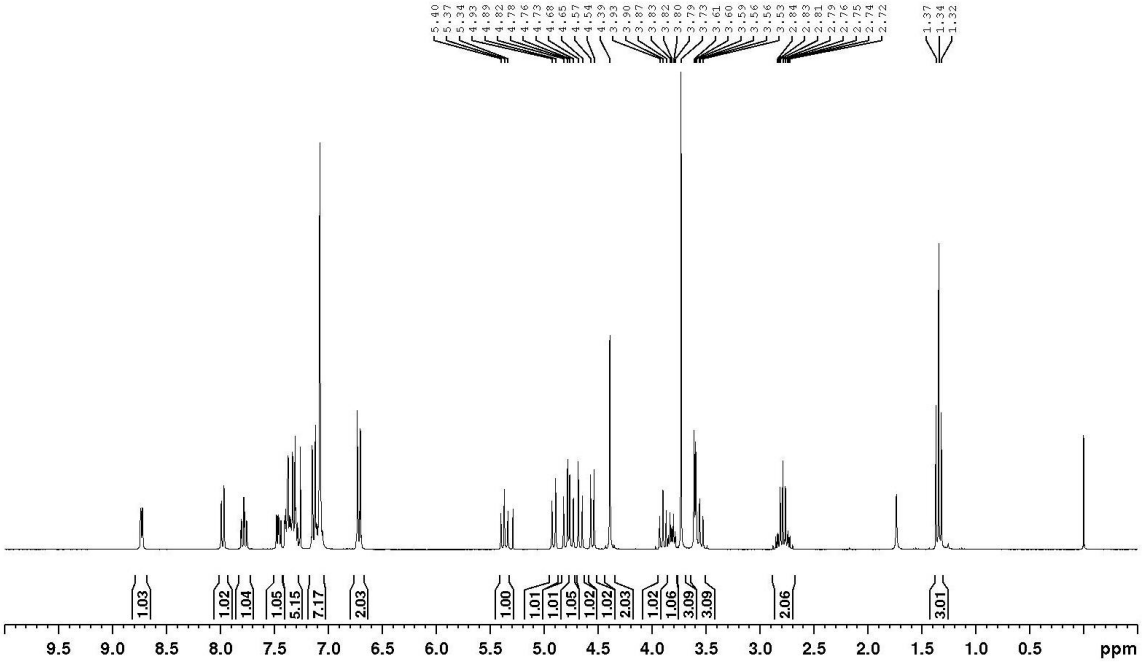



**Figure A-15:** 2-D NMR COSY spectrum of Ethyl 2-O-benzoyl-4-O-benzyl-3-O-(9-fluorenylmethoxycarbonyl)-1-thio-β-D-galactopyranoside **(2.18).**

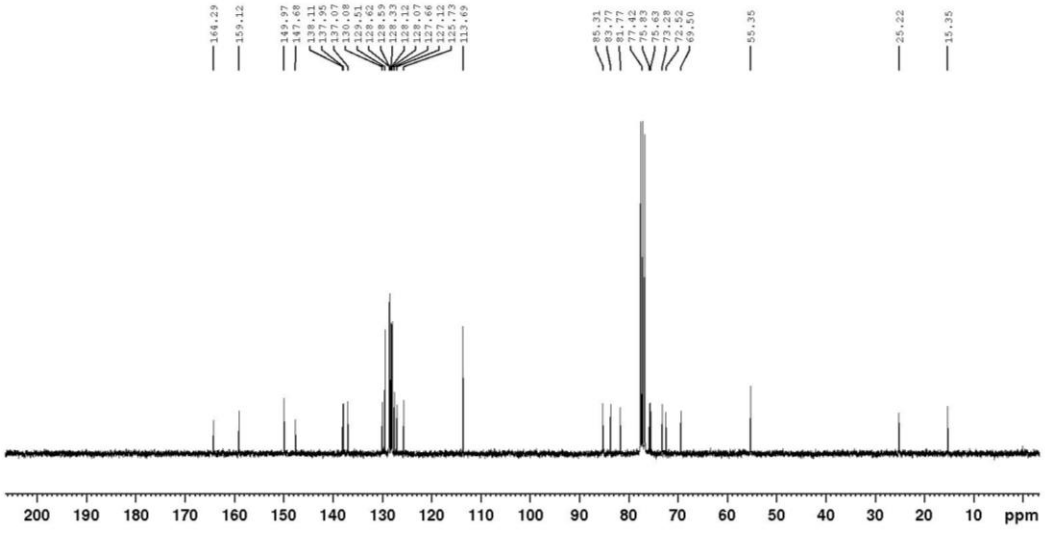



**2.19**



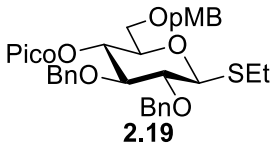

$CDCl_3$ 300 MHz

**Figure A-16:** $^{1}H$ NMR spectrum of Ethyl 2,3-di-O-benzyl-4-O-p-methoxybenzyl-6-O-picoloyl-1-thio-b-D-glucopyranoside **(2.19).**

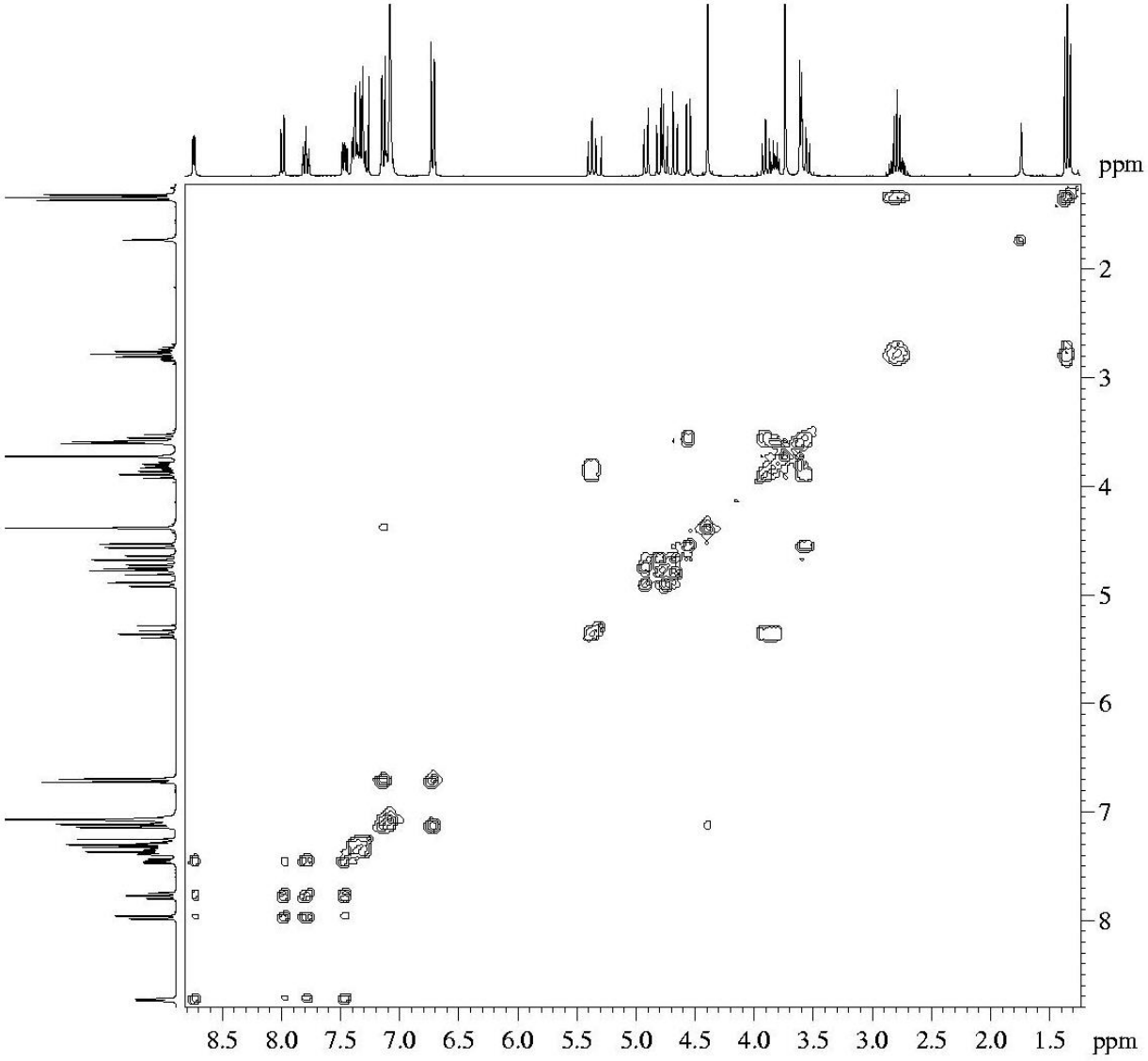



$CDCl_3$ 75 MHz

**Figure A-17:** $^{13}C$ NMR spectrum of Ethyl 2,3-di-O-benzyl-4-O-p-methoxybenzyl-6-O-picoloyl-1-thio-b-D-glucopyranoside **(2.19).**

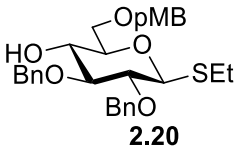



**2.19**

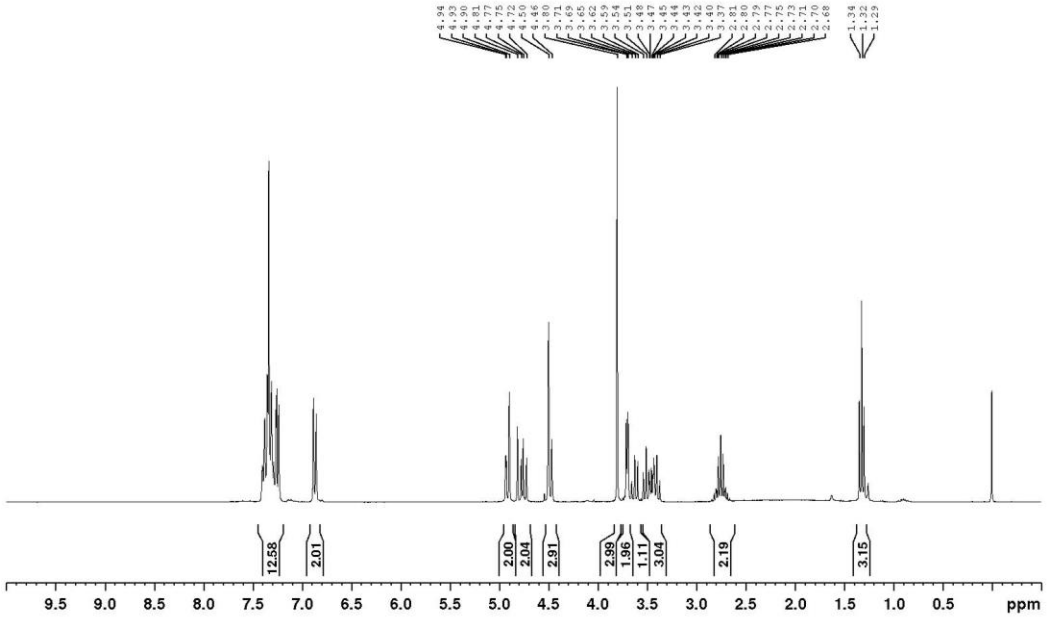



$CDCl_3$ 300 MHz

**Figure A-18:** 2-D NMR COSY spectrum of Ethyl 2,3-di-O-benzyl-4-O-p-methoxybenzyl-6-O-picoloyl-1-thio-b-D-glucopyranoside **(2.19).**

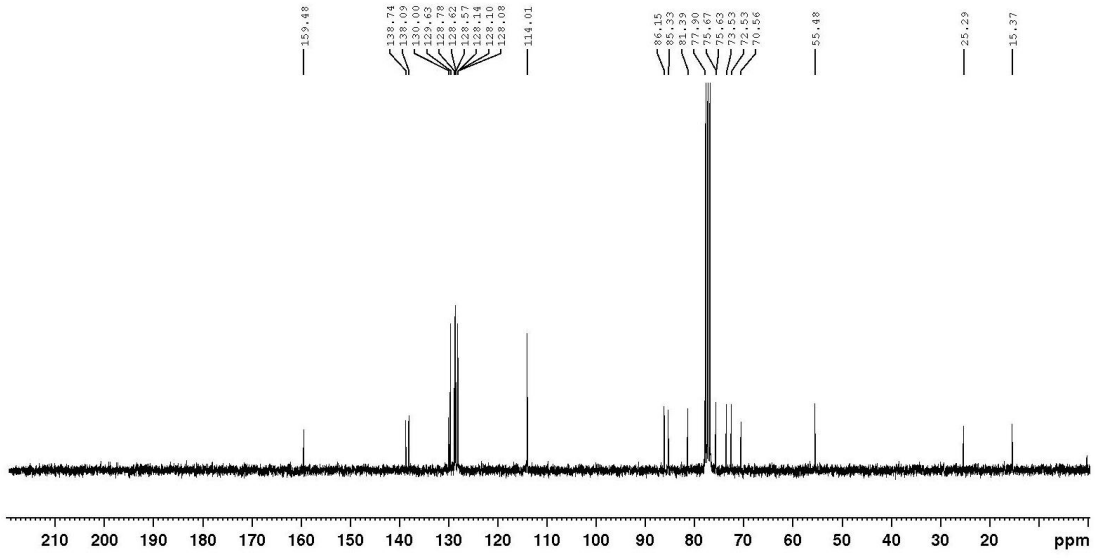



**2.20**



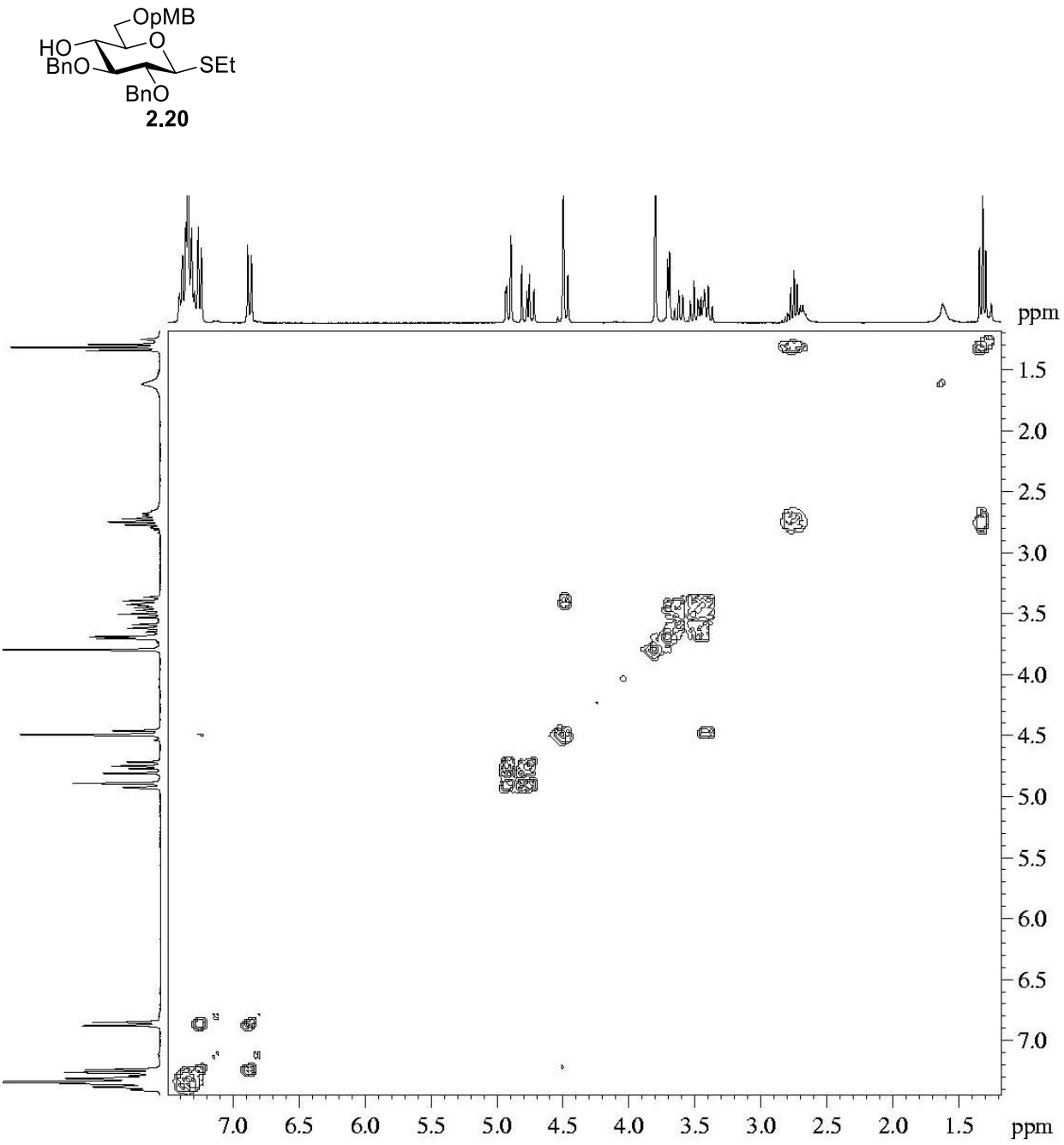

$CDCl_3$ 300 MHz

**Figure A-19:** $^{1}H$ NMR spectrum of Ethyl 2,3-di-O-benzyl-4-O-*p*-methoxybenyl-1-thio-β-D-glucopyranoside **(2.20).**



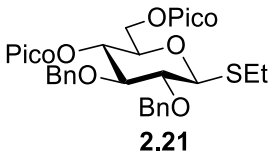

$CDCl_3$ 75 MHz

**Figure A-20:** $^{13}C$ NMR spectrum of Ethyl 2,3-di-O-benzyl-4-O-*p*-methoxybenyl-1-thio-β-D-glucopyranoside **(2.20).**

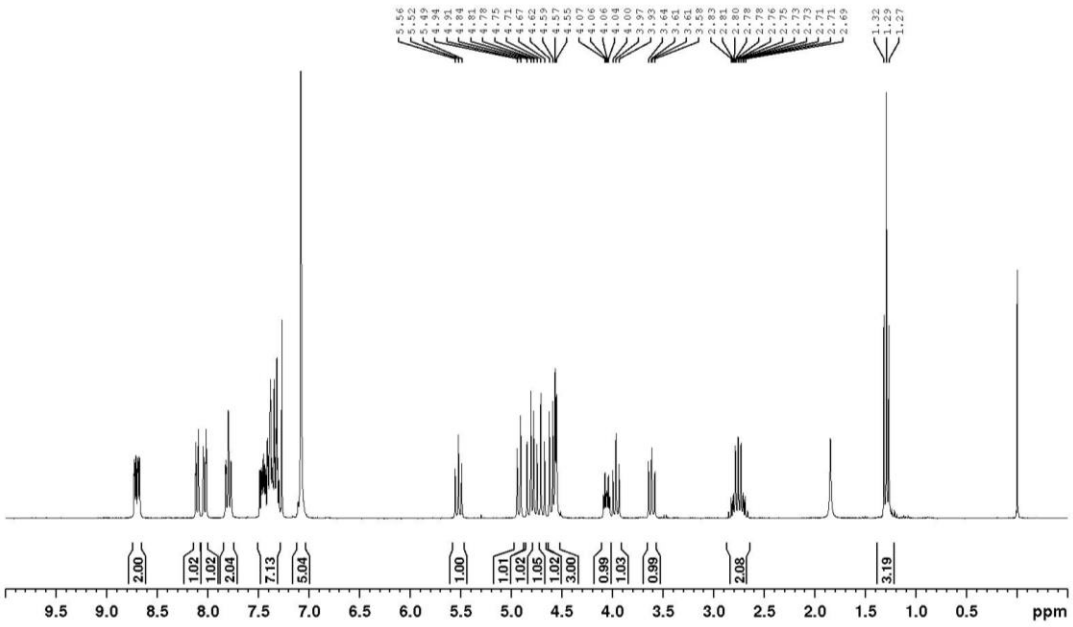



$CDCl_3$ 300 MHz

**Figure A-21:** 2-D NMR COSY spectrum of Ethyl 2,3-di-O-benzyl-4-O-*p*-methoxybenyl-1-thio-β-D-glucopyranoside **(2.20).**

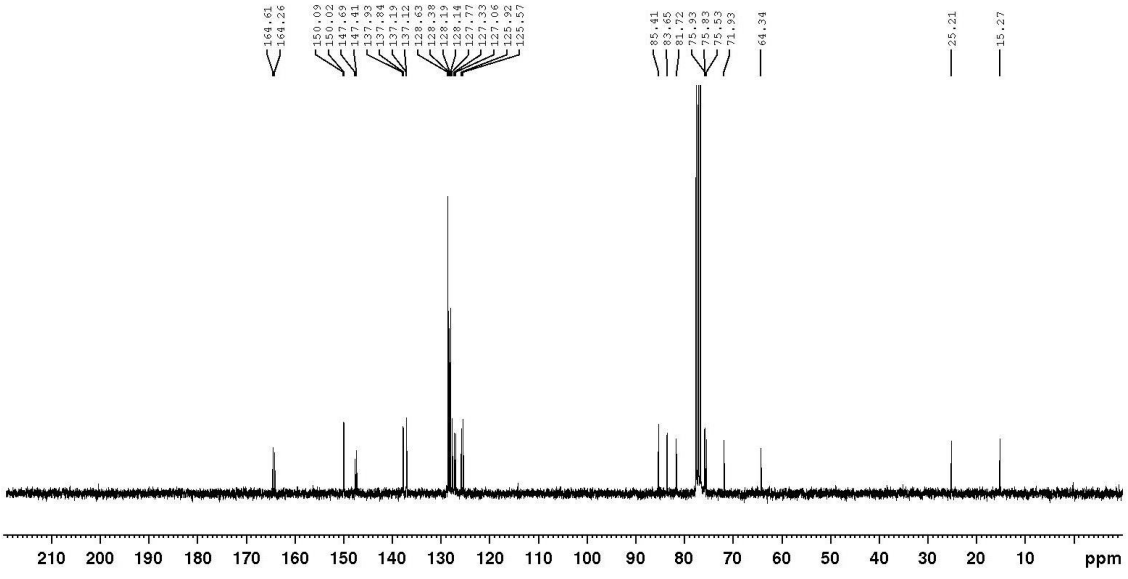



**2.21**



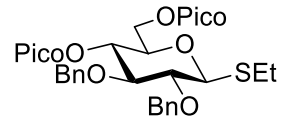

$CDCl_3$ 300 MHz

**Figure A-22:** $^{1}H$ NMR spectrum of Ethyl 2,3-di-*O*-benzyl-4,6-di-*O*-picoloyl-1-thio-b-D-glucopyranoside **(2.21).**

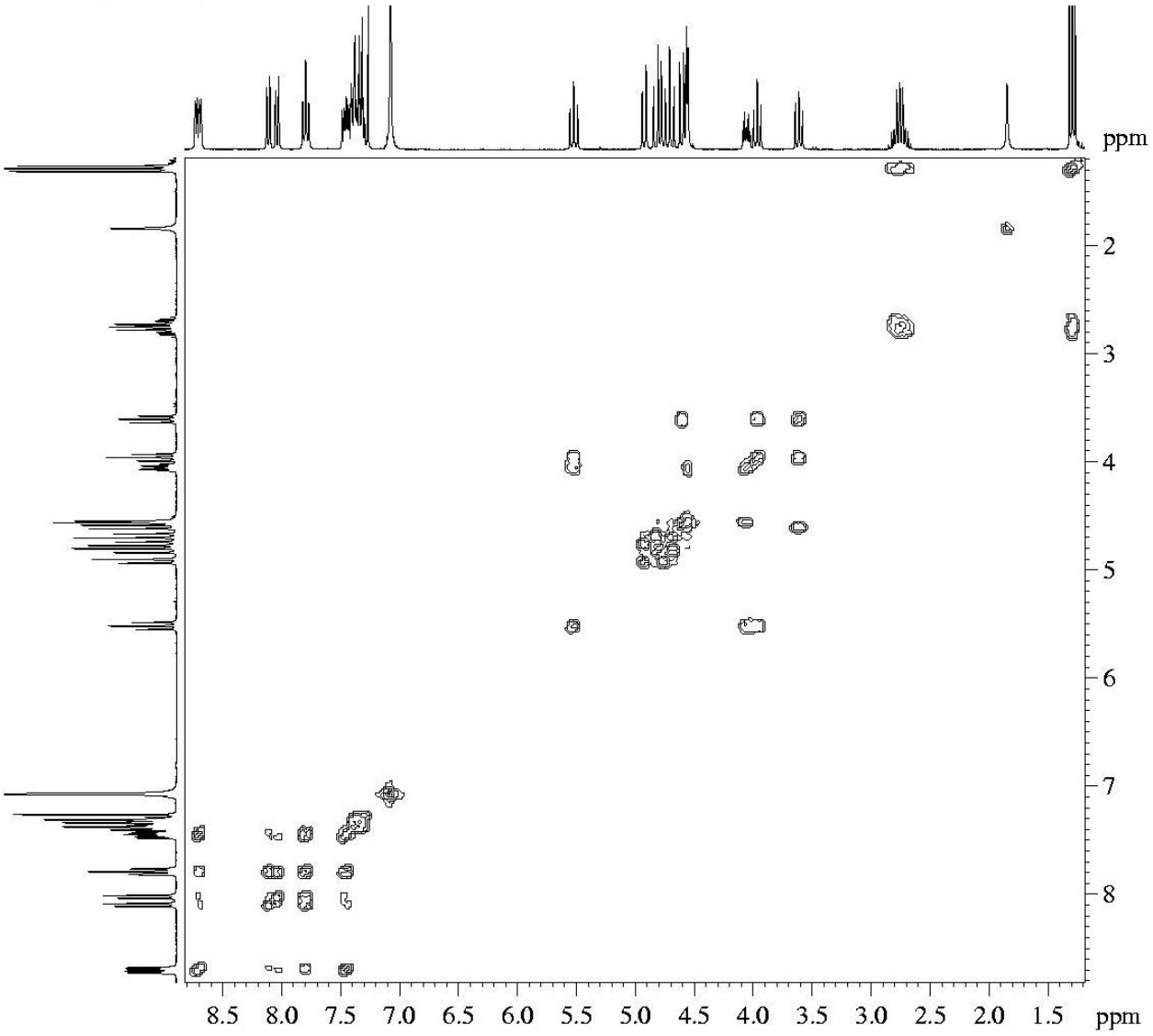



$CDCl_3$ 75 MHz

**Figure A-23:** $^{13}C$ NMR spectrum of Ethyl 2,3-di-*O*-benzyl-4,6-di-*O*-picoloyl-1-thio-b-D-glucopyranoside **(2.21).**

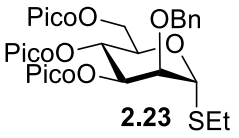



**2.21**

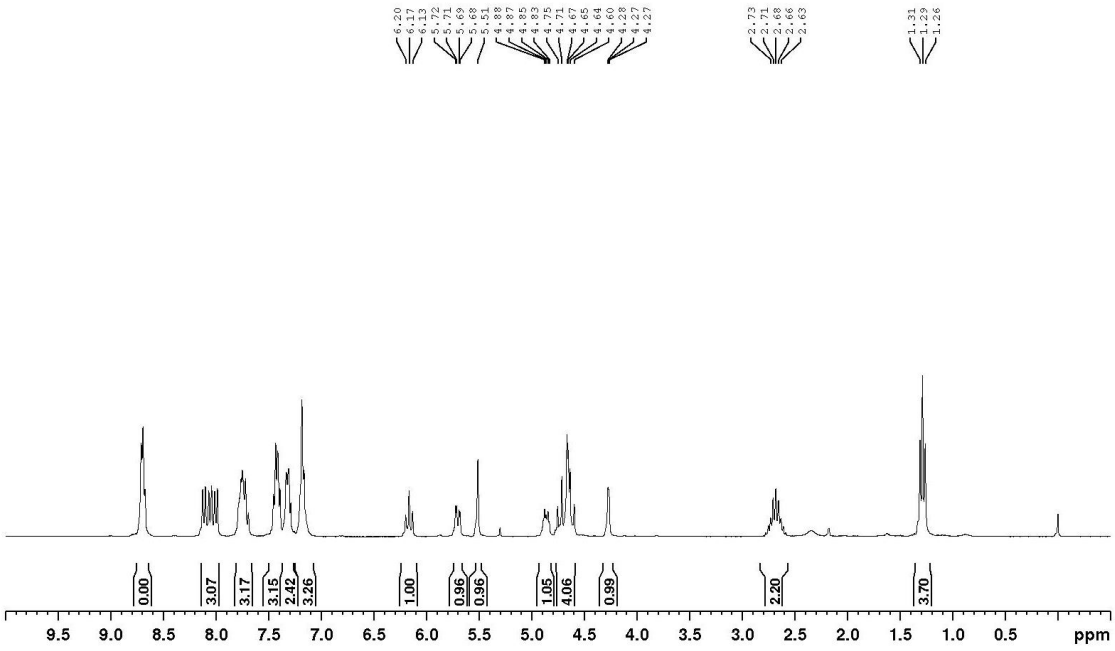



$CDCl_3$ 300 MHz

**Figure A-24:** 2-D NMR COSY spectrum of Ethyl 2,3-di-*O*-benzyl-4,6-di-*O*-picoloyl-1-thio-b-D-glucopyranoside **(2.21).**

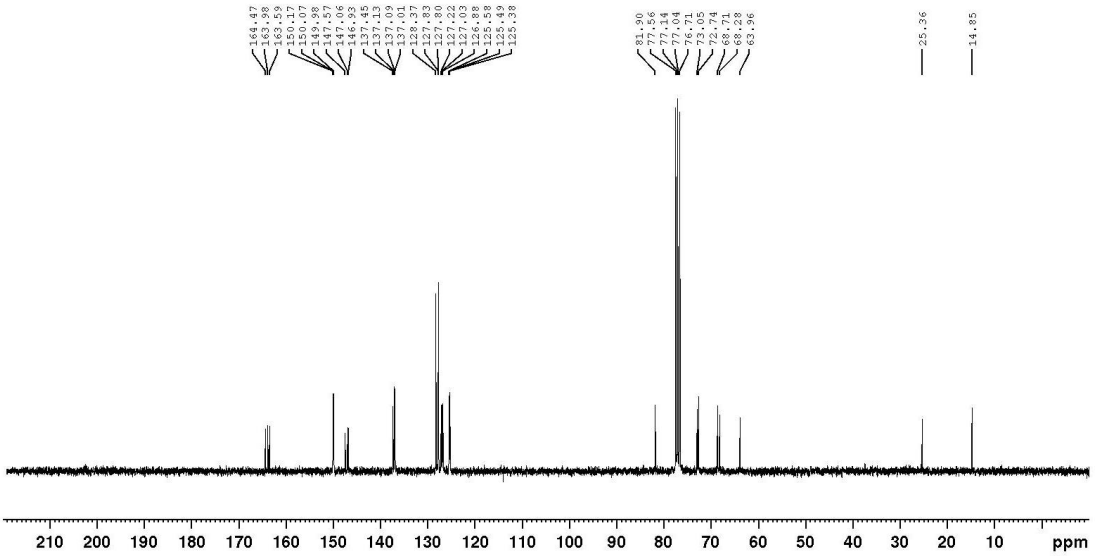



**2.23**



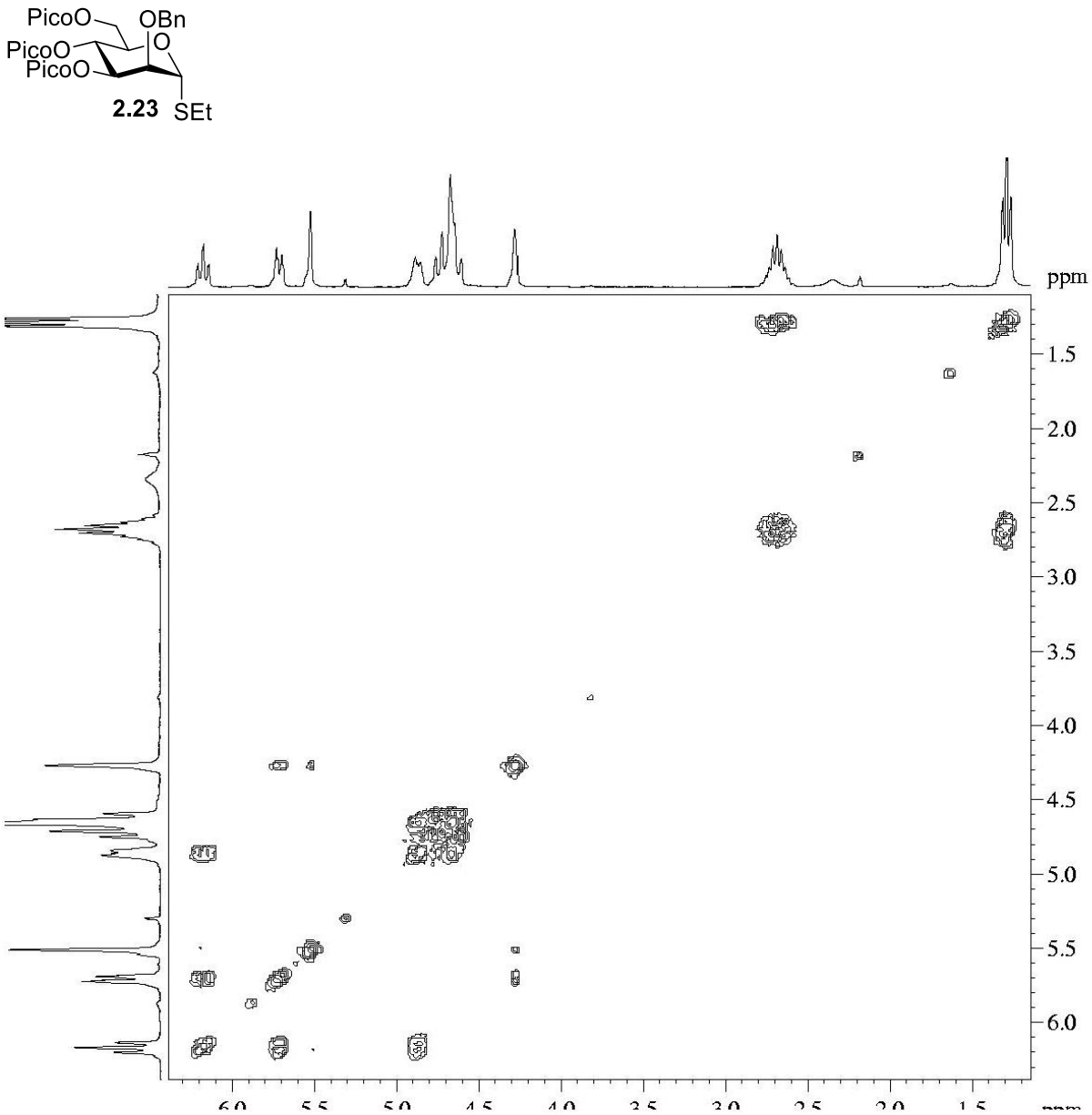

$CDCl_3$ 300 MHz

**Figure A-25:** $^{1}H$ NMR spectrum of Ethyl 2-O-benzyl-3,4,6-tri-O-picoloyl-1-thio-α-D-mannopyranoside **(2.23).**



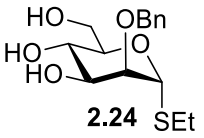

$CDCl_3$ 75 MHz

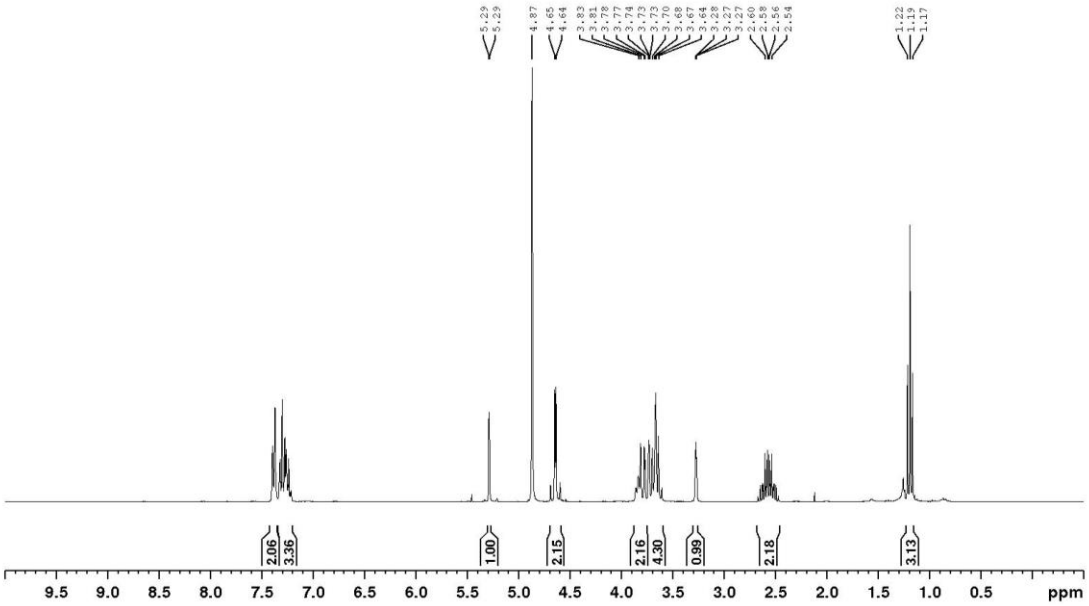
**Figure A-26:** $^{13}C$ NMR spectrum of Ethyl 2-O-benzyl-3,4,6-tri-O-picoloyl-1-thio-α-D-mannopyranoside **(2.23).**




$CDCl_3$ 300 MHz

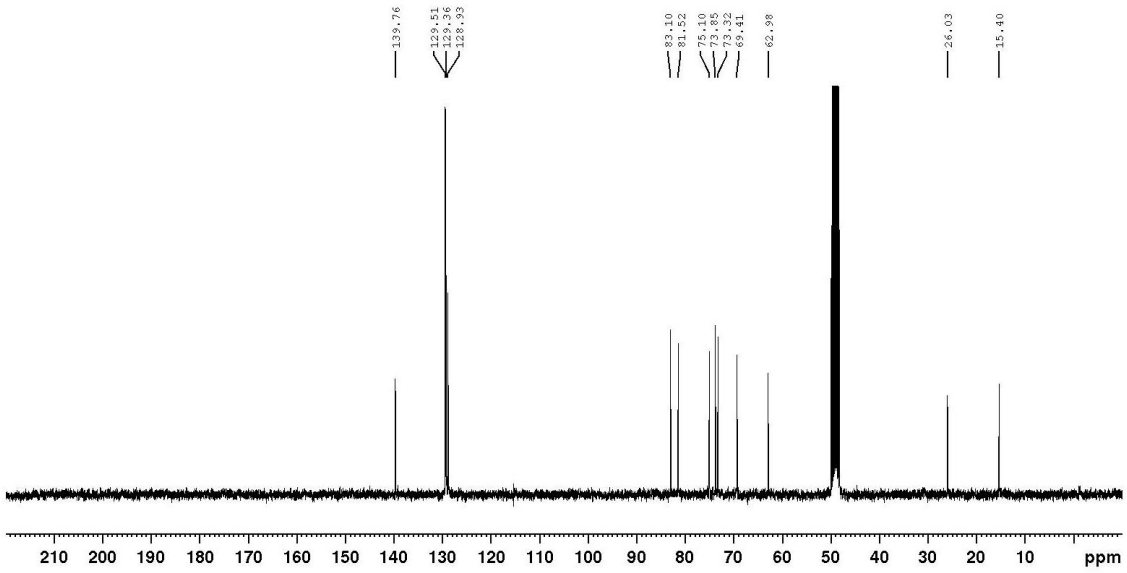
**Figure A-27:** 2-D NMR COSY spectrum of Ethyl 2-O-benzyl-3,4,6-tri-O-picoloyl-1-thio-α-D-mannopyranoside **(2.23).**



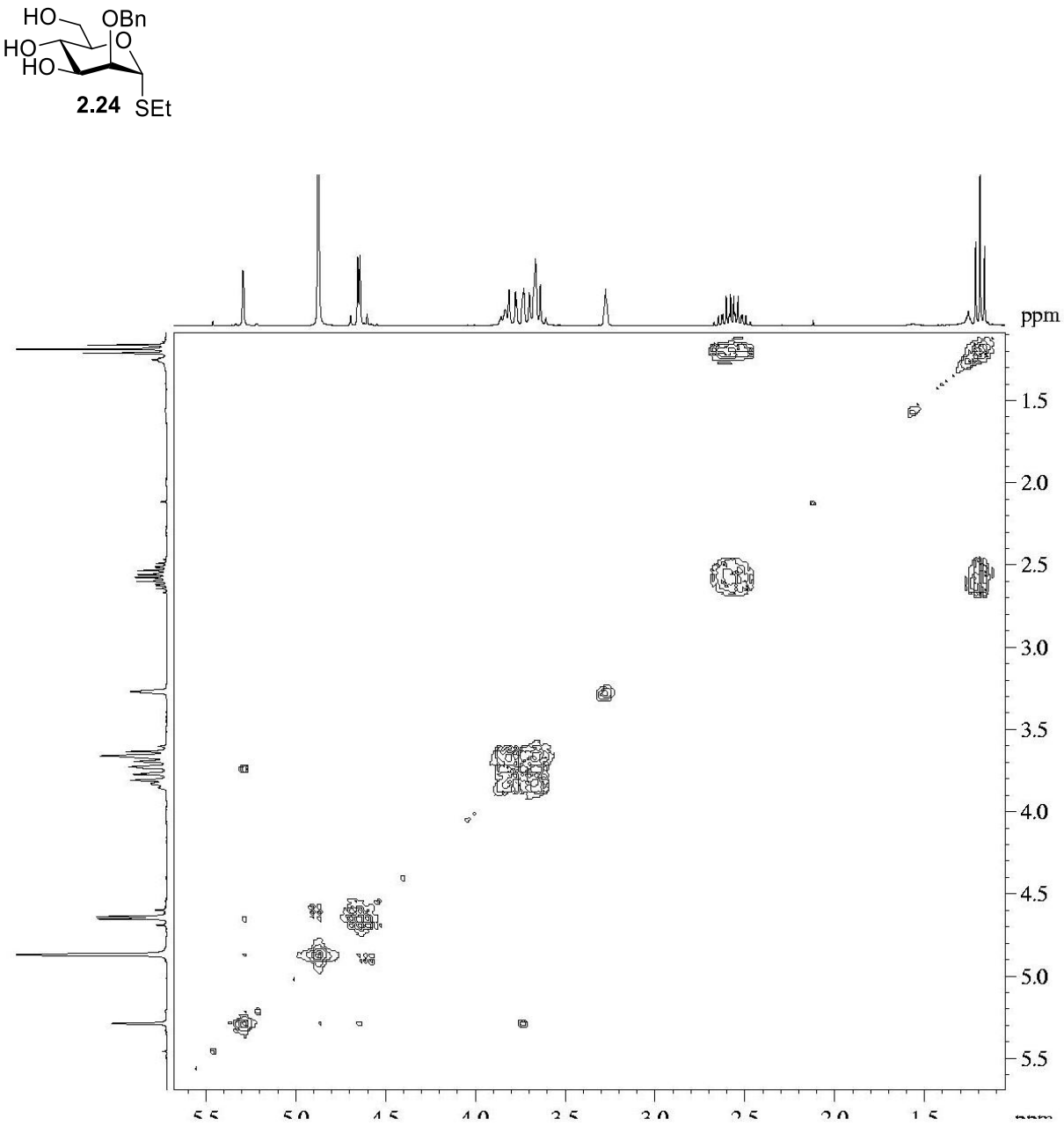

MeOD 300 MHz

**Figure A-28:** $^{1}$H NMR spectrum of Ethyl 2-O-benzyl-1-thio-α-D-mannopyranoside **(2.24).**



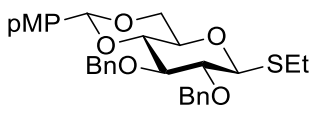

MeOD 75 MHz

**Figure A-29:** $^{13}$C NMR spectrum of Ethyl 2-O-benzyl-1-thio-α-D-mannopyranoside **(2.24).**

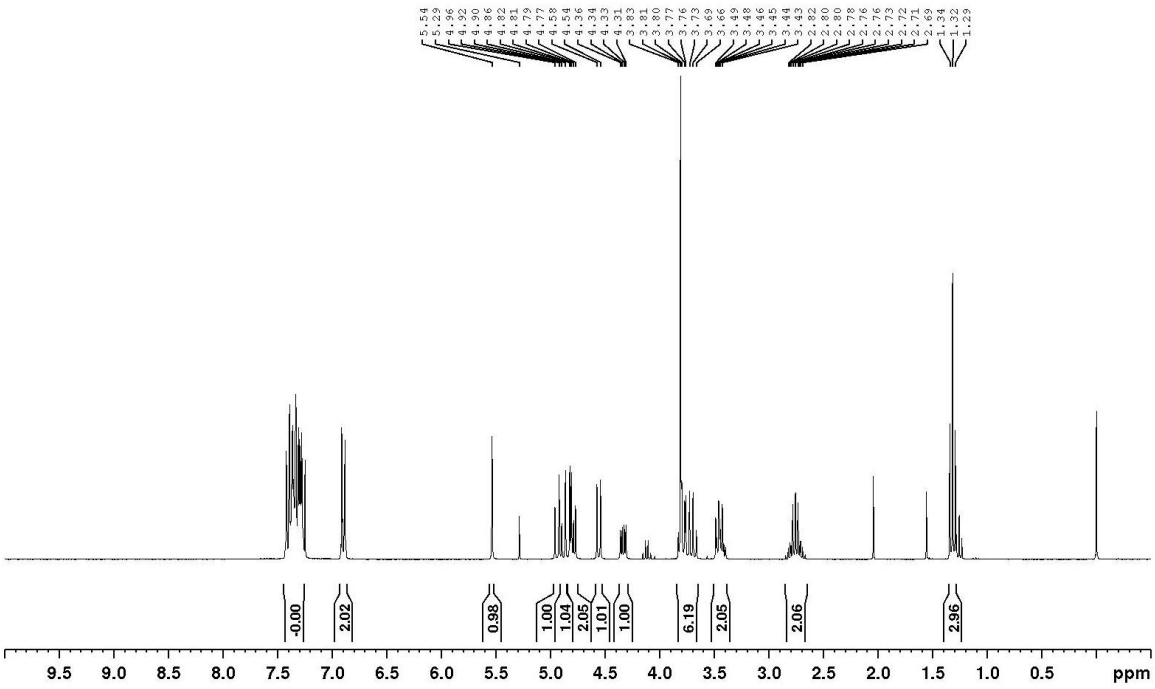



MeOD 300 MHz

**Figure A-30:** 2-D NMR COSY spectrum of Ethyl 2-O-benzyl-1-thio-α-D-mannopyranoside **(2.24).**




**2.31**




$CDCl_3$ 300 MHz

**Figure A-31:** $^1$H NMR spectrum of ethyl 2,3-di-O-benzyl-4,6-O-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside (**2.31)**

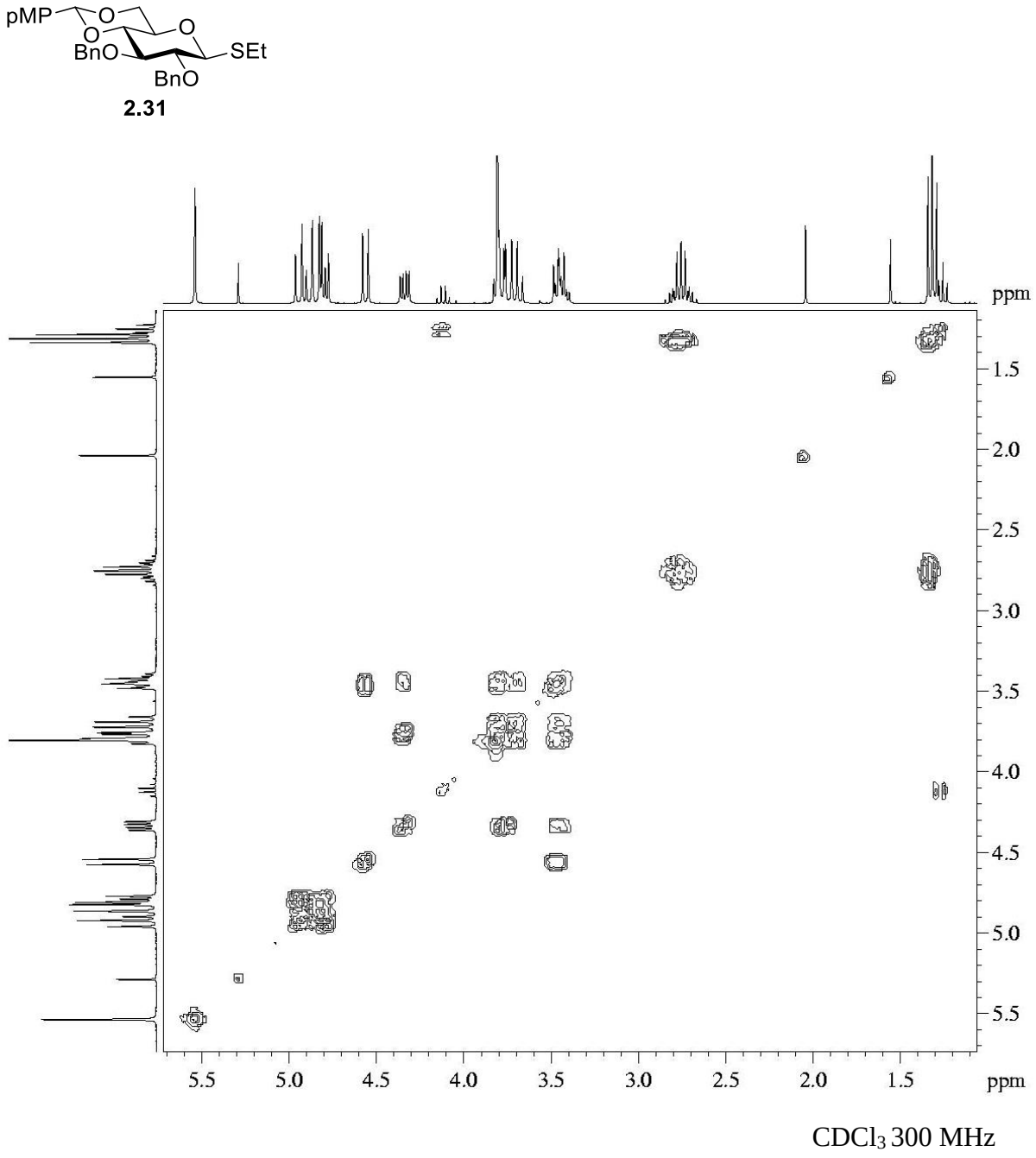
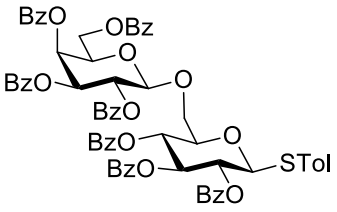
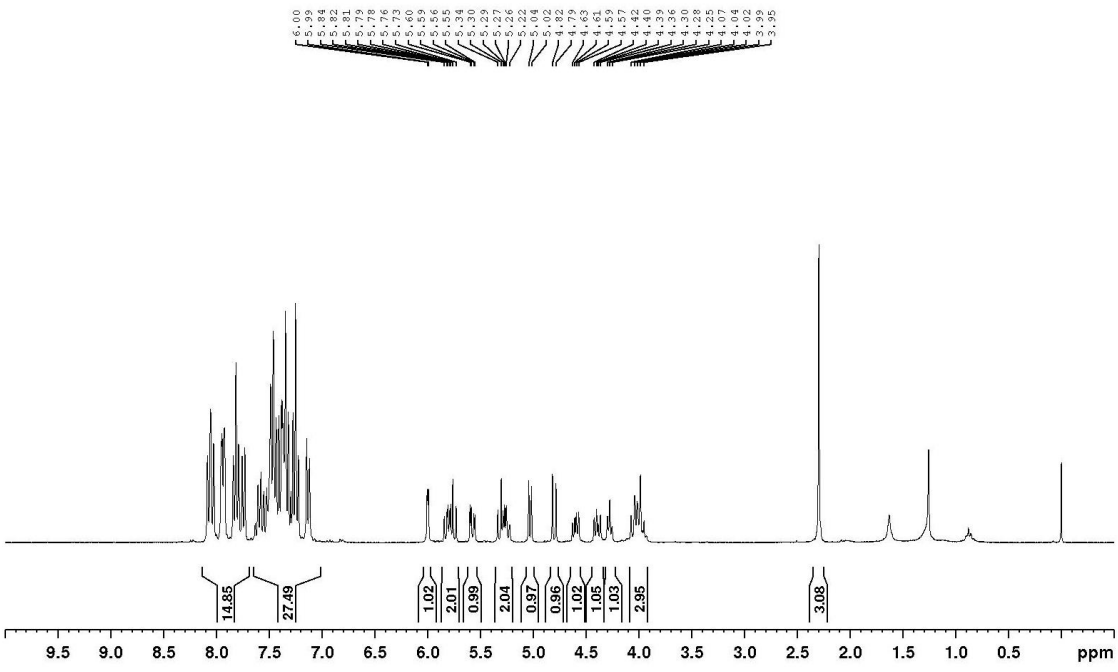



**Figure A-32:** 2-D NMR COSY spectrum of ethyl 2,3-di-O-benzyl-4,6-O-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside (**2.31)**

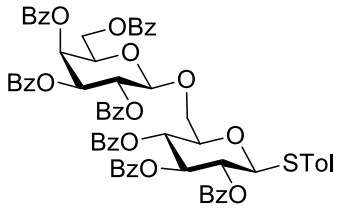



**4.21**

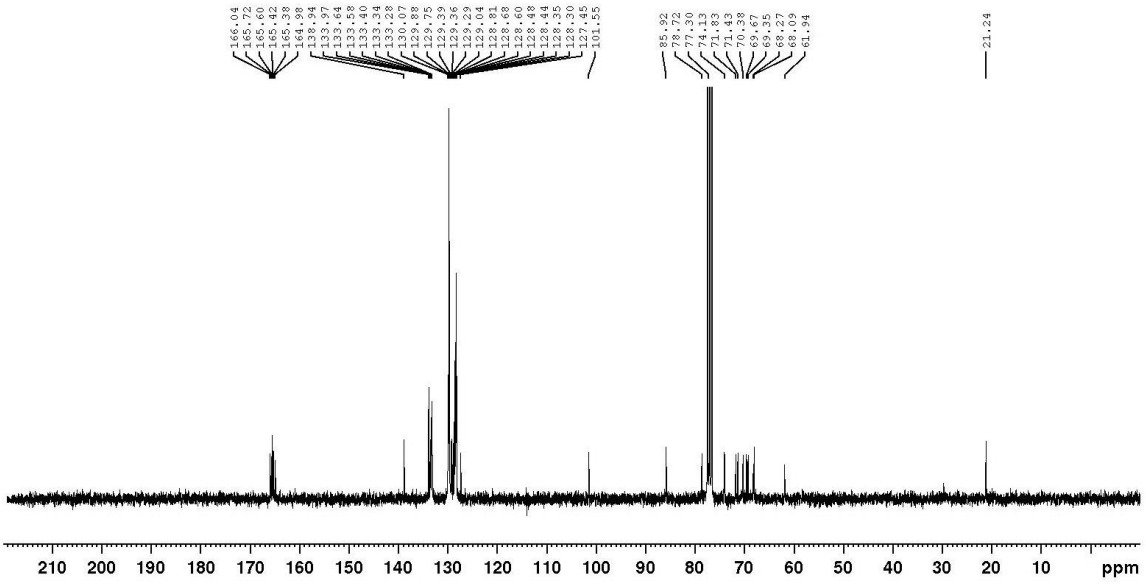



$CDCl_3$ 300 MHz

**Figure A-33:** $^1$H NMR spectrum of Tolyl 6-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-O-benzoyl-1-thio-β-D-glucopyranoside **(4.21**)

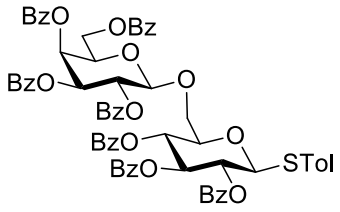



**4.21**

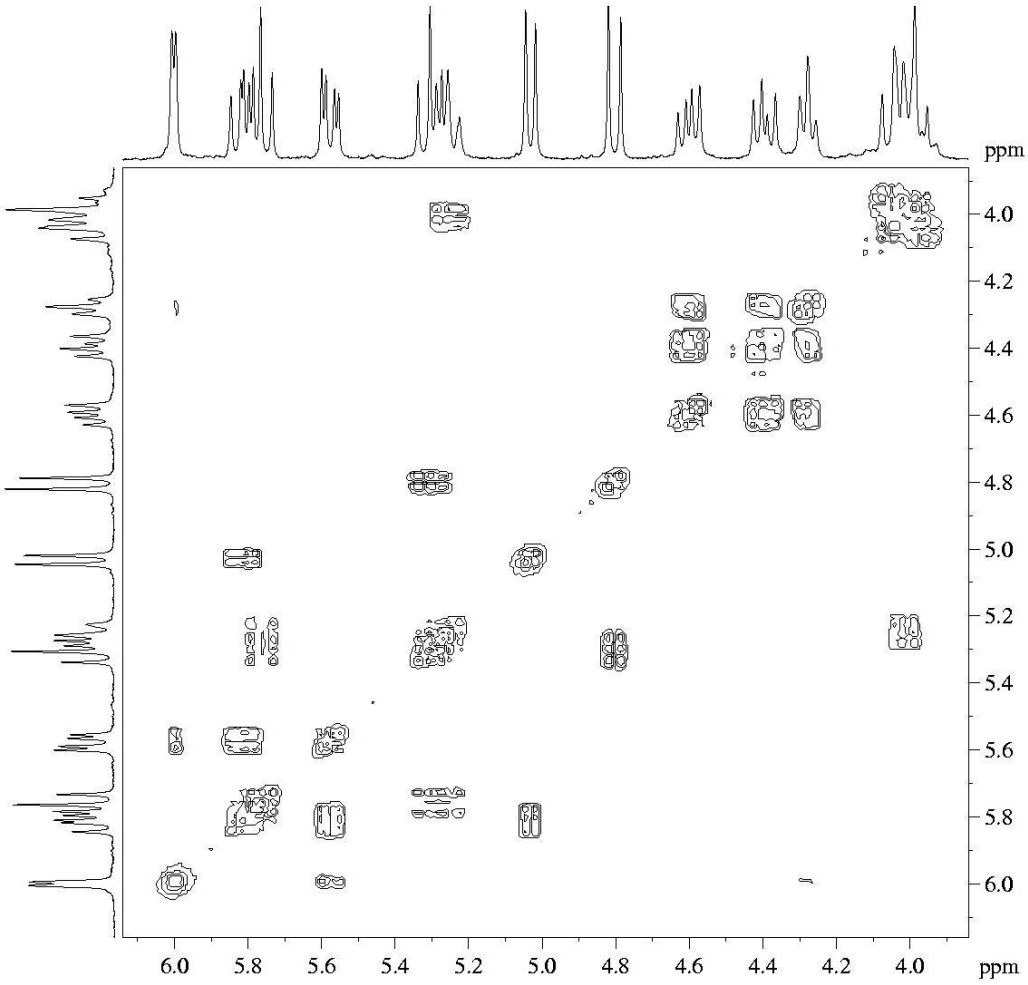



$CDCl_3$ 75 MHz

**Figure A-34:** $^{13}C$ NMR spectrum of Tolyl 6-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-O-benzoyl-1-thio-β-D-glucopyranoside **(4.21**)

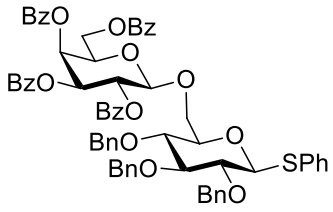



**4.21**

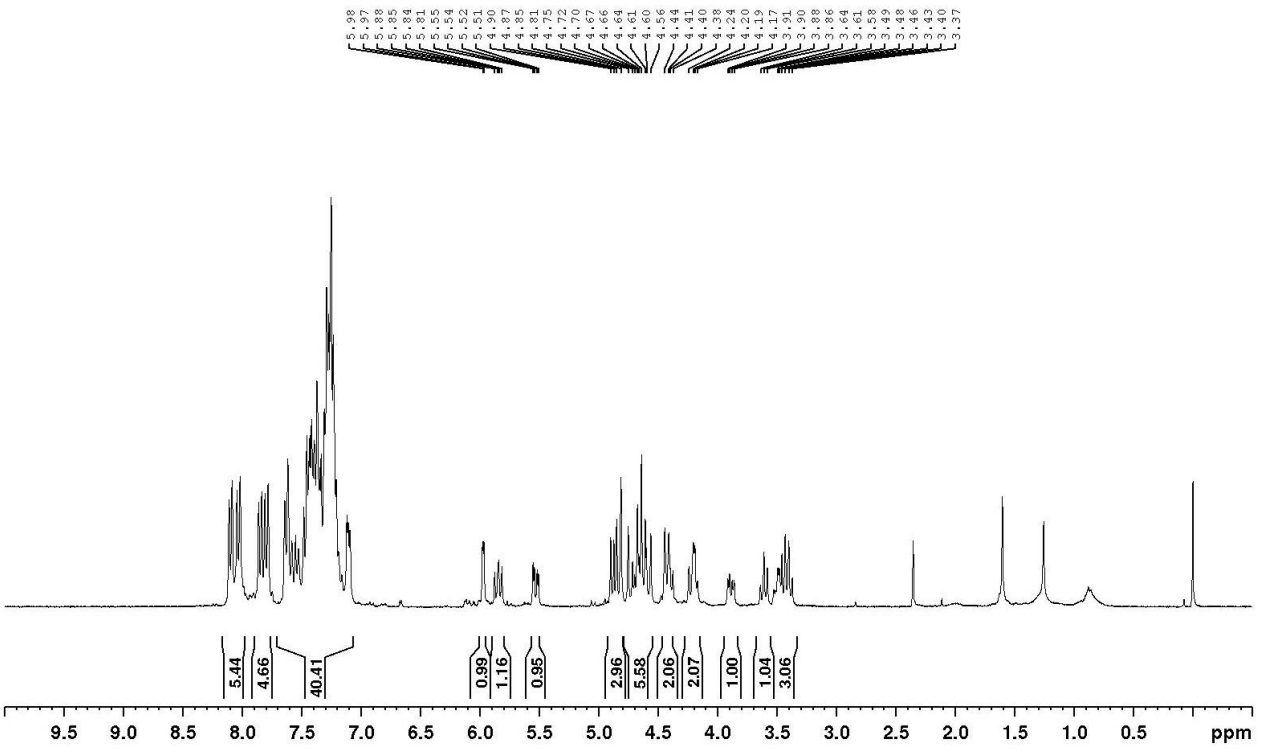



$CDCl_3$ 300 MHz

**Figure A-35:** 2-D NMR COSY spectrum of Tolyl 6-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-O-benzoyl-1-thio-β-D-glucopyranoside **(4.21**)

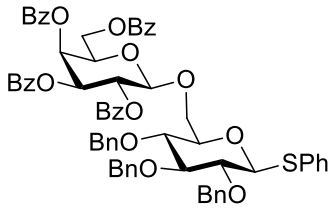



**4.22**

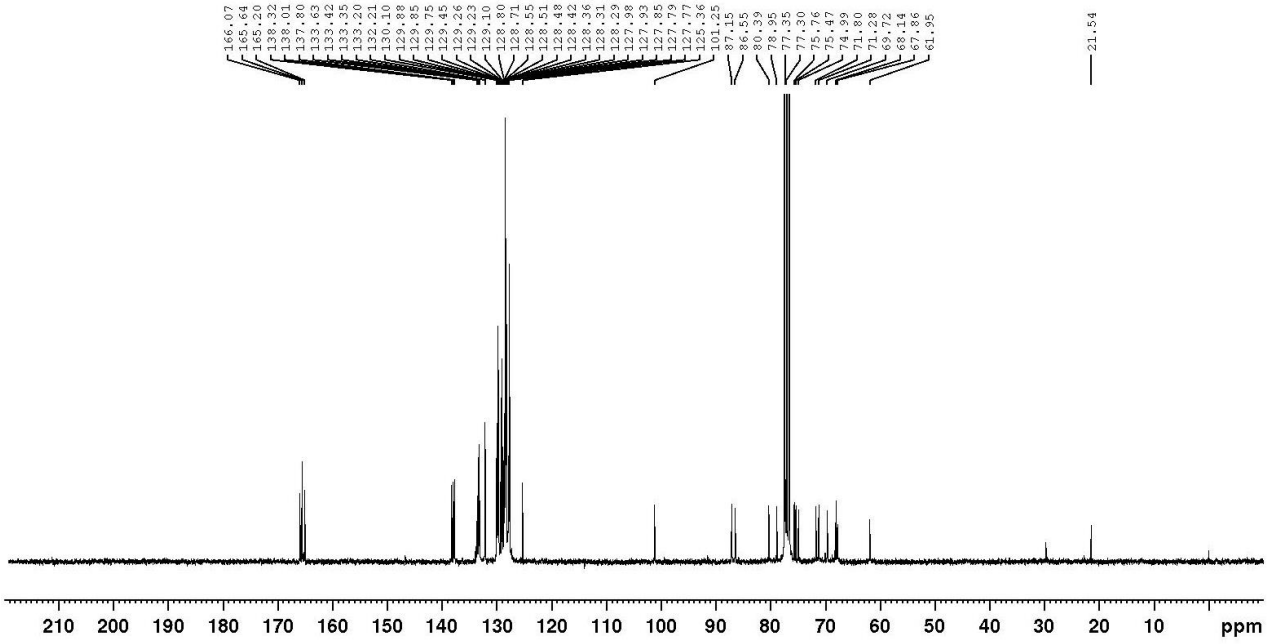



$CDCl_3$ 300 MHz

**Figure A-36:** $^1H$ NMR spectrum of Phenyl 6-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranoside **(4.22**)

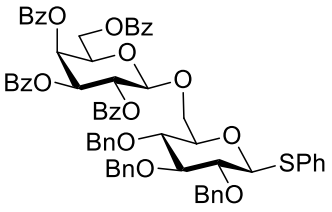



**4.22**

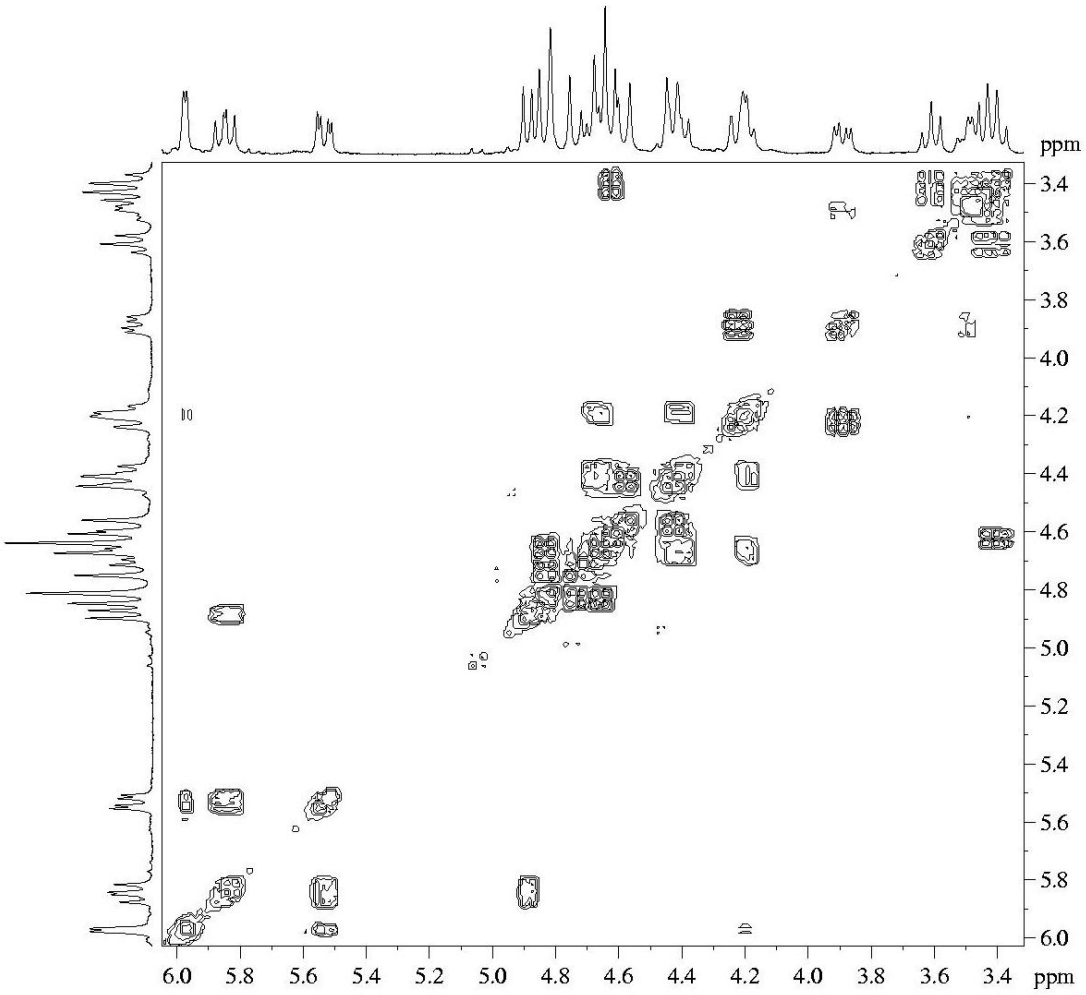



$CDCl_3$ 75 MHz

**Figure A-37:** $^{13}C$ NMR spectrum of Phenyl 6-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranoside **(4.22**)

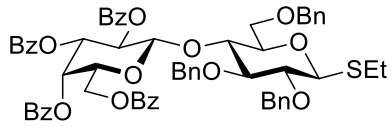



**4.22**

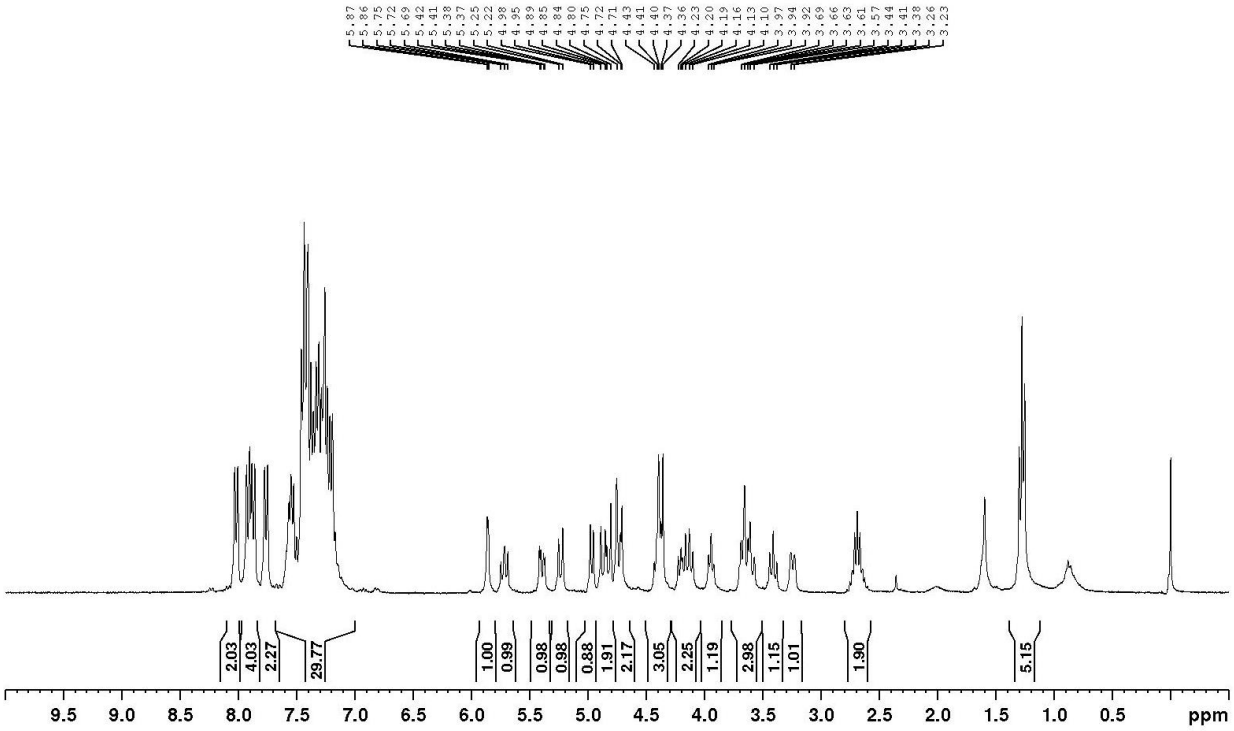



$CDCl_3$ 300 MHz

**Figure A-38:** 2-D NMR COSY spectrum of Phenyl 6-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranoside **(4.22**)

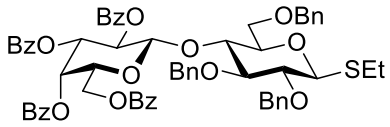



**4.23**

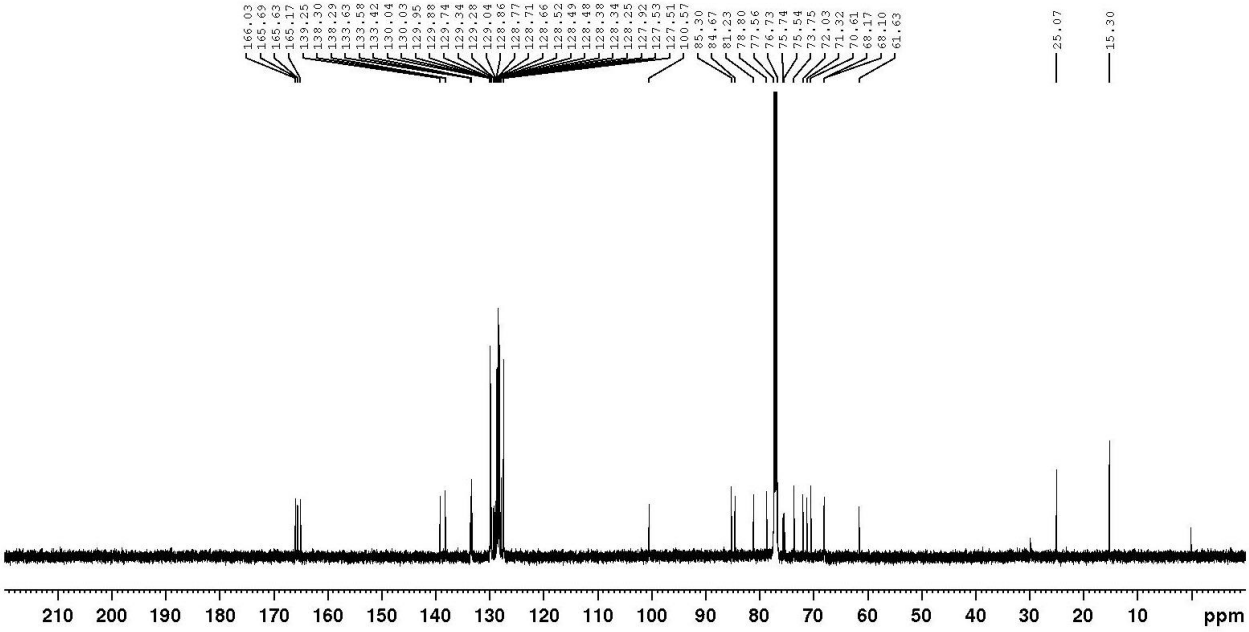



$CDCl_3$ 300 MHz

**Figure A-39:** $^1H$ NMR spectrum of Ethyl 4-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-O-benzyl-1-thio-β-D-glucopyranoside **(4.23**)

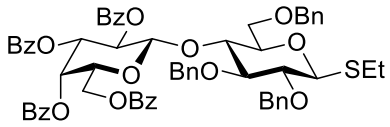



**4.23**

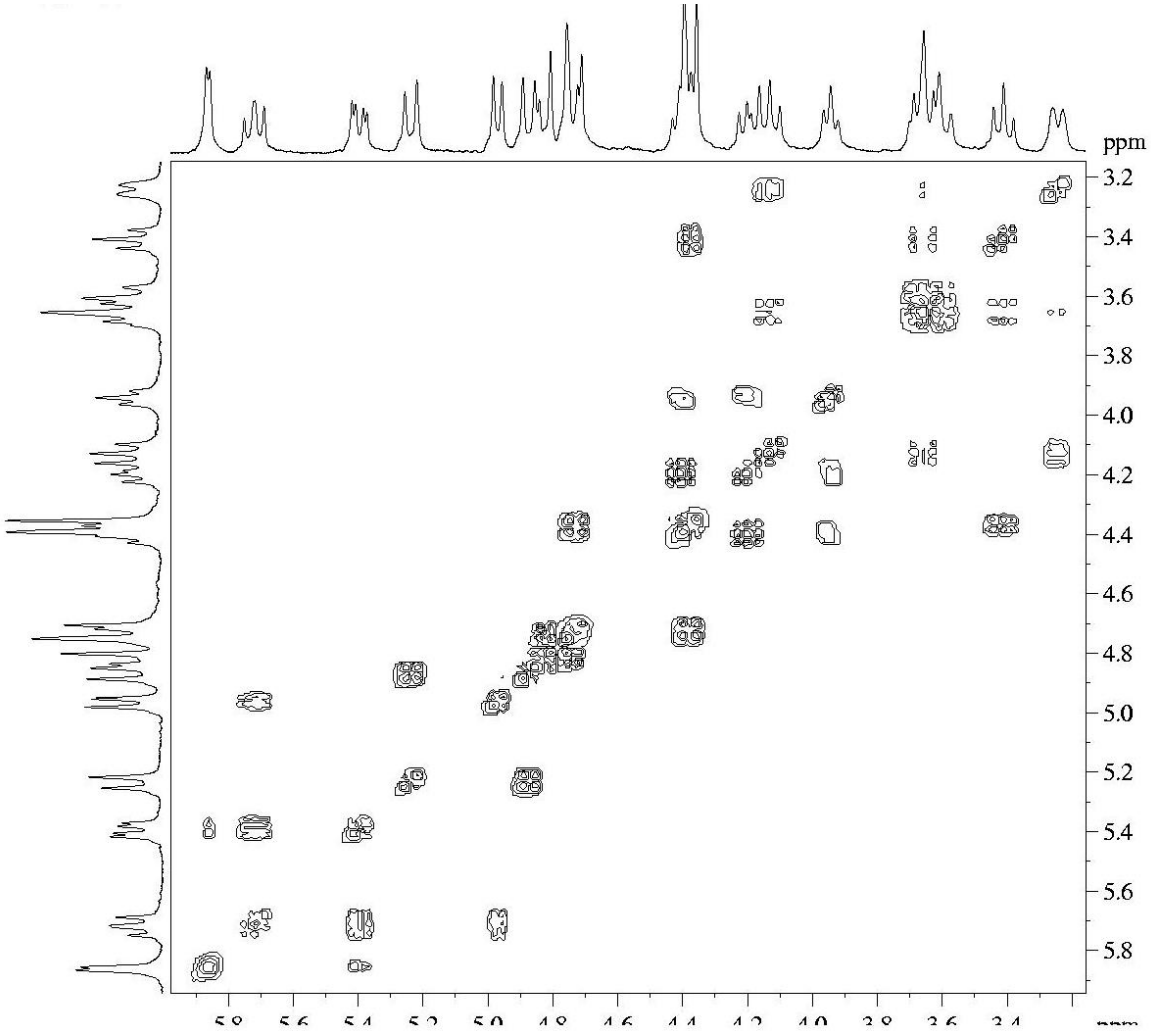



$CDCl_3$ 151 MHz

**Figure A-40:** $^{13}C$ NMR spectrum of Ethyl 4-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-O-benzyl-1-thio-β-D-glucopyranoside **(4.23**)

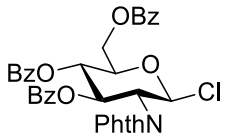



**4.23**

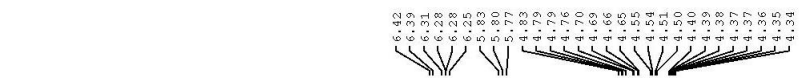


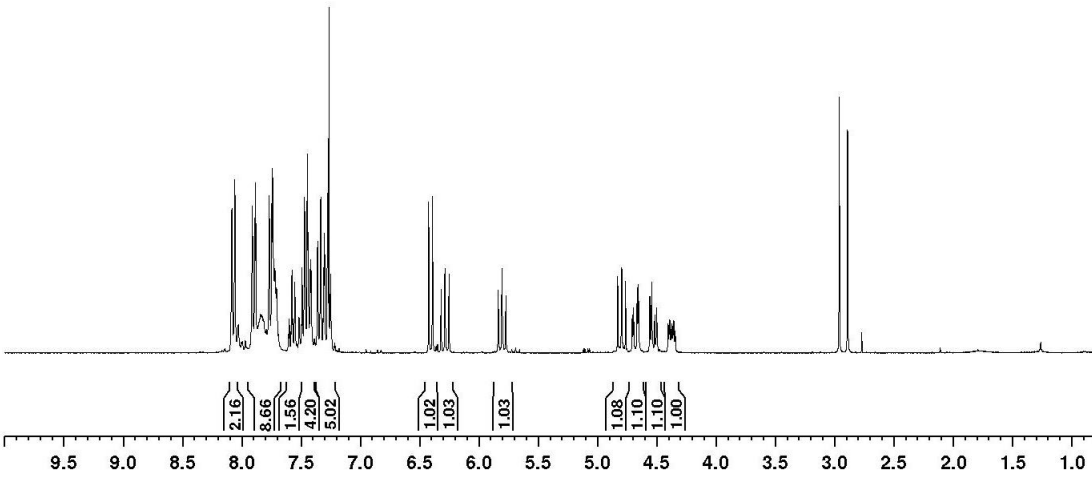

$CDCl_3$ 300 MHz

**Figure A-41:** 2-D NMR COSY spectrum of Ethyl 4-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-O-benzyl-1-thio-β-D-glucopyranoside **(4.23**)



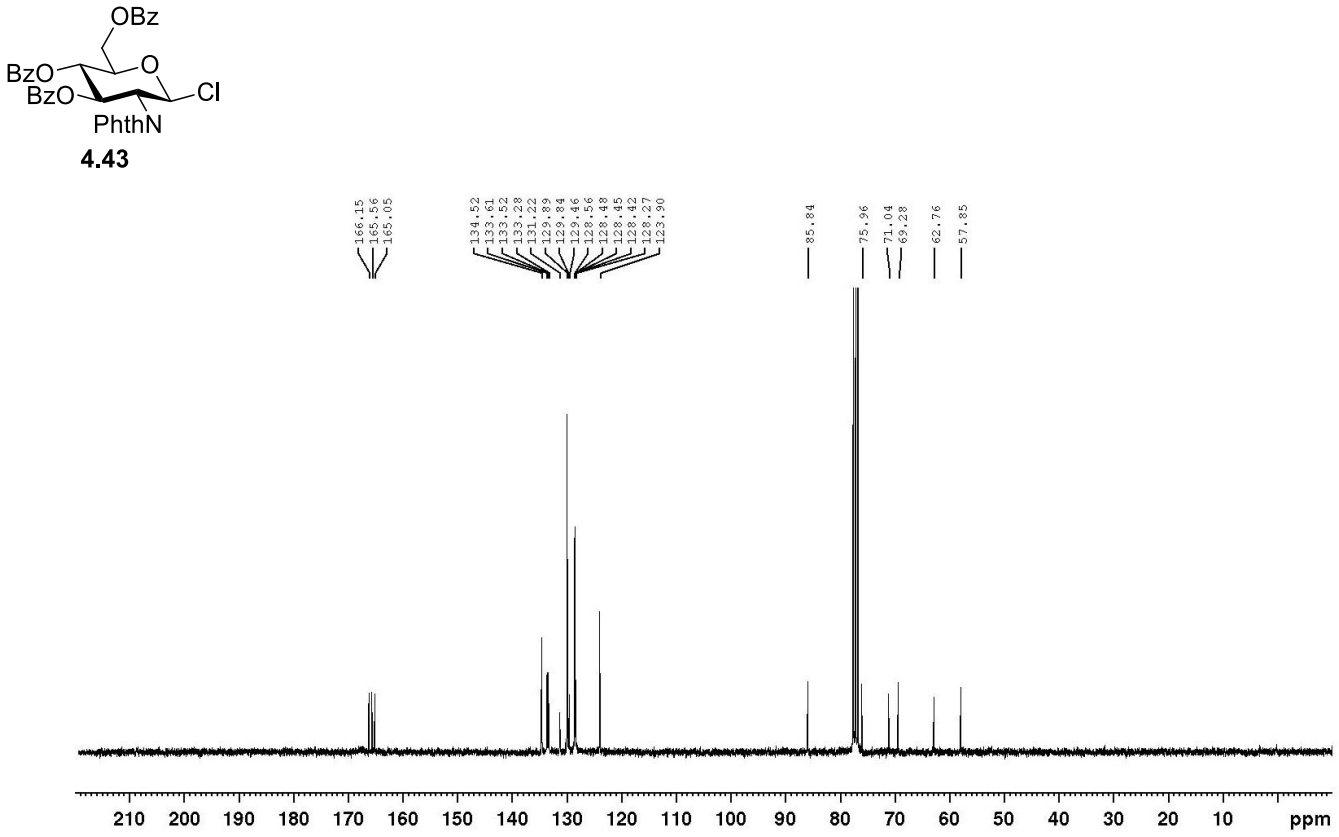

**4.43**





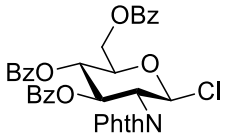

$CDCl_3$ 300 MHz

**Figure A-42:** $^1H$ NMR spectrum of 3,4,6-Tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride **(4.43).**

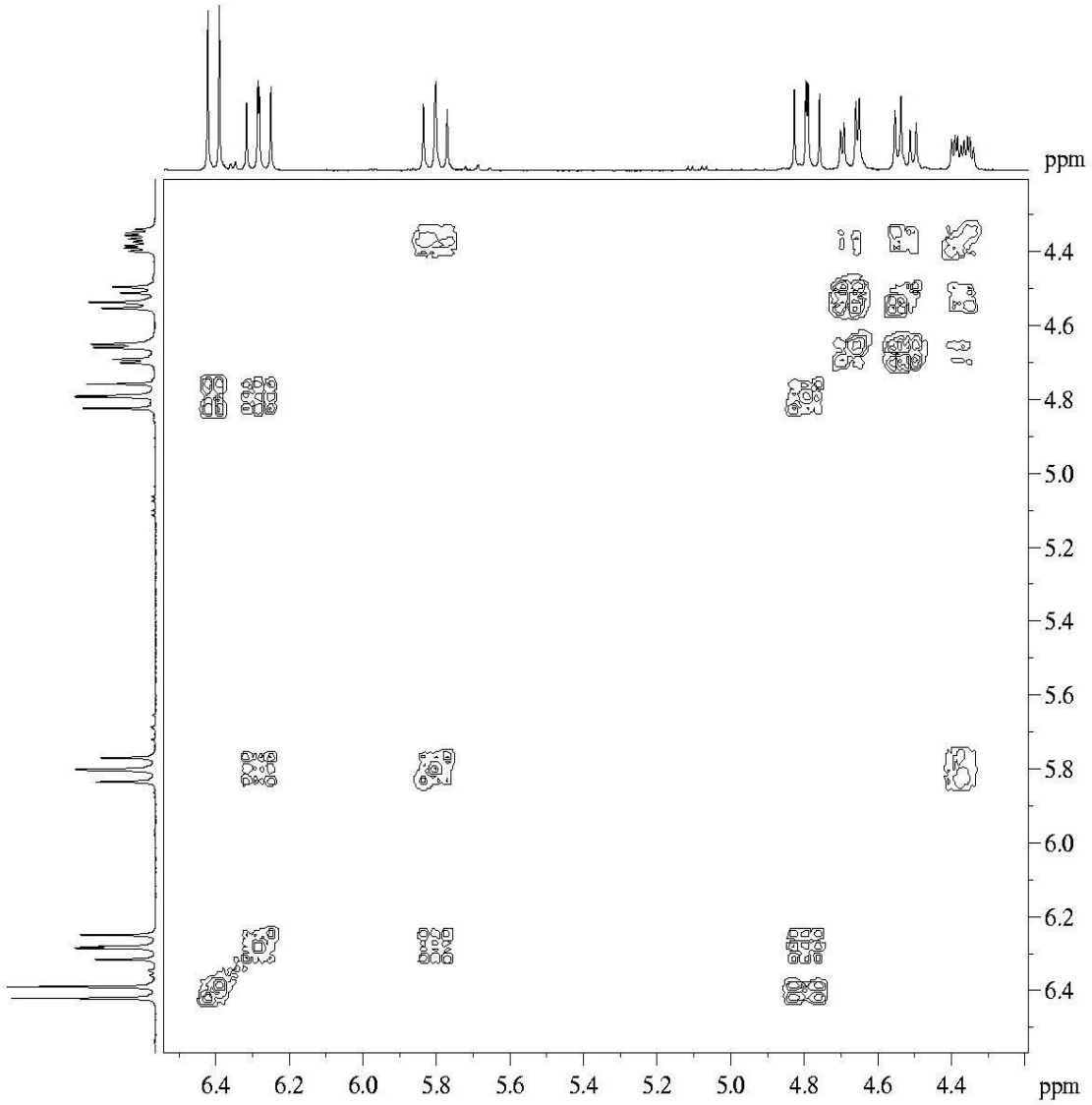



$CDCl_3$ 75 MHz

**Figure A-43:** $^{13}C$ NMR spectrum of 3,4,6-Tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride **(4.43).**

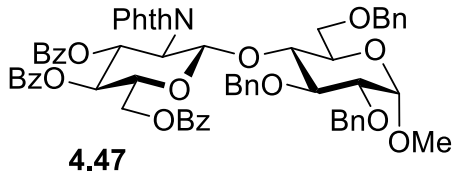



**4.43**

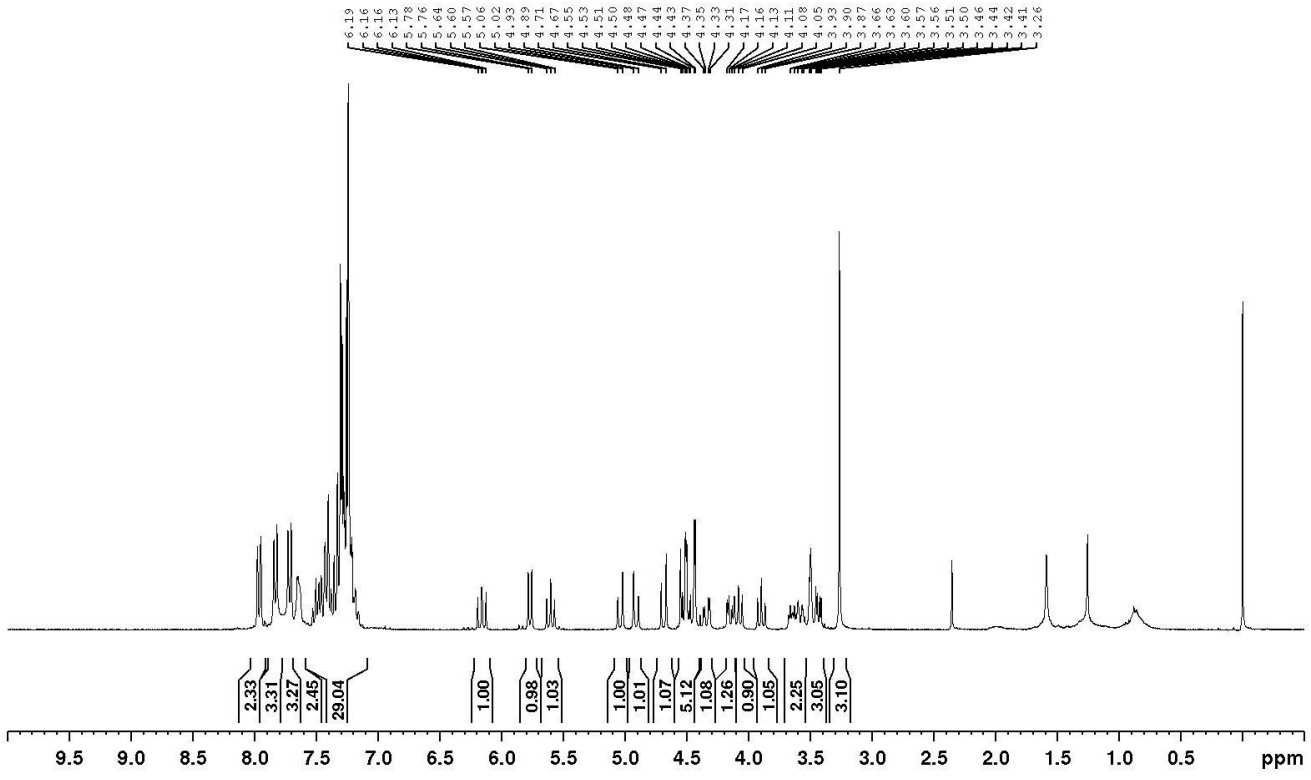



$CDCl_3$ 300 MHz

**Figure A-44:** 2-D NMR COSY spectrum of 3,4,6-Tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride **(4.43).**

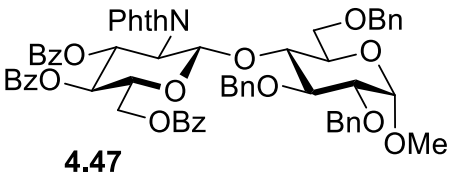



**4.47**

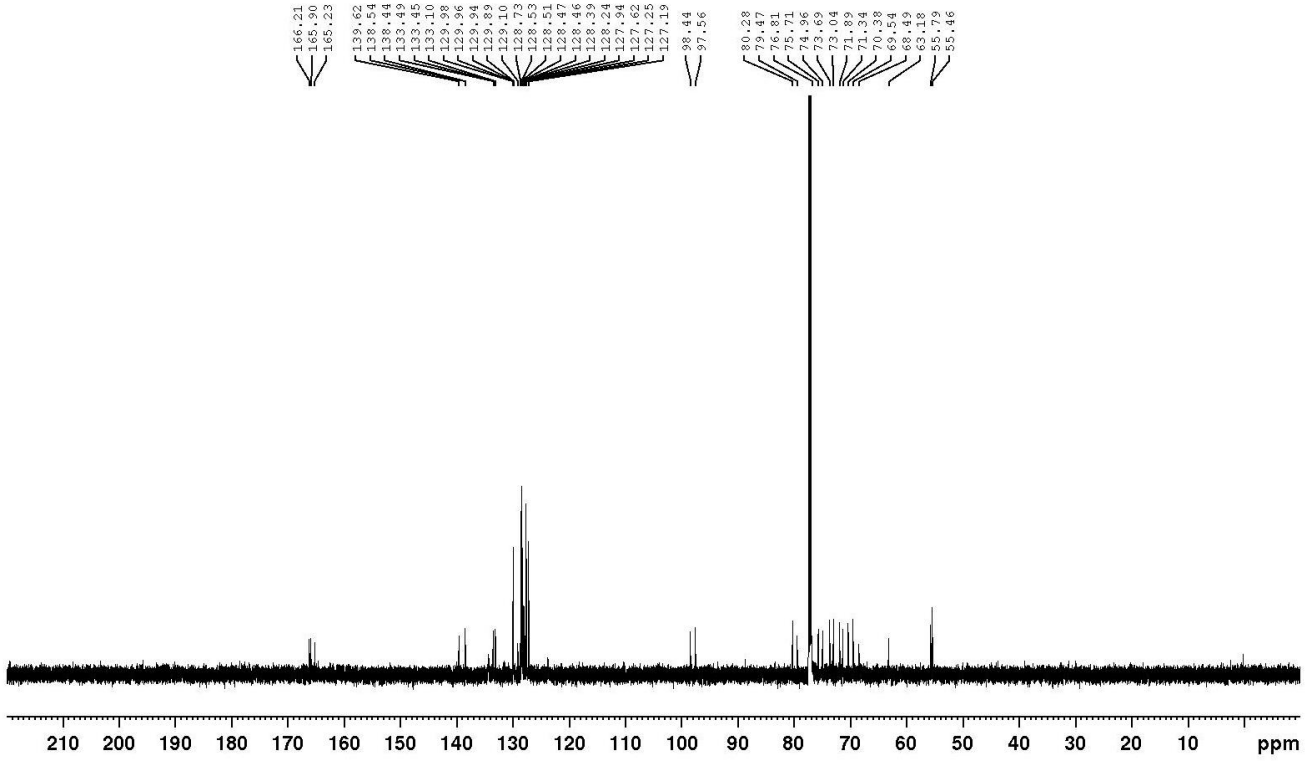



$CDCl_3$ 300 MHz

**Figure A-45:** $^1H$ NMR spectrum of Methyl 4-O-(3,4,6-tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside **(4.47)**

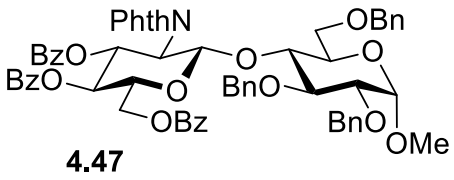



**4.47**

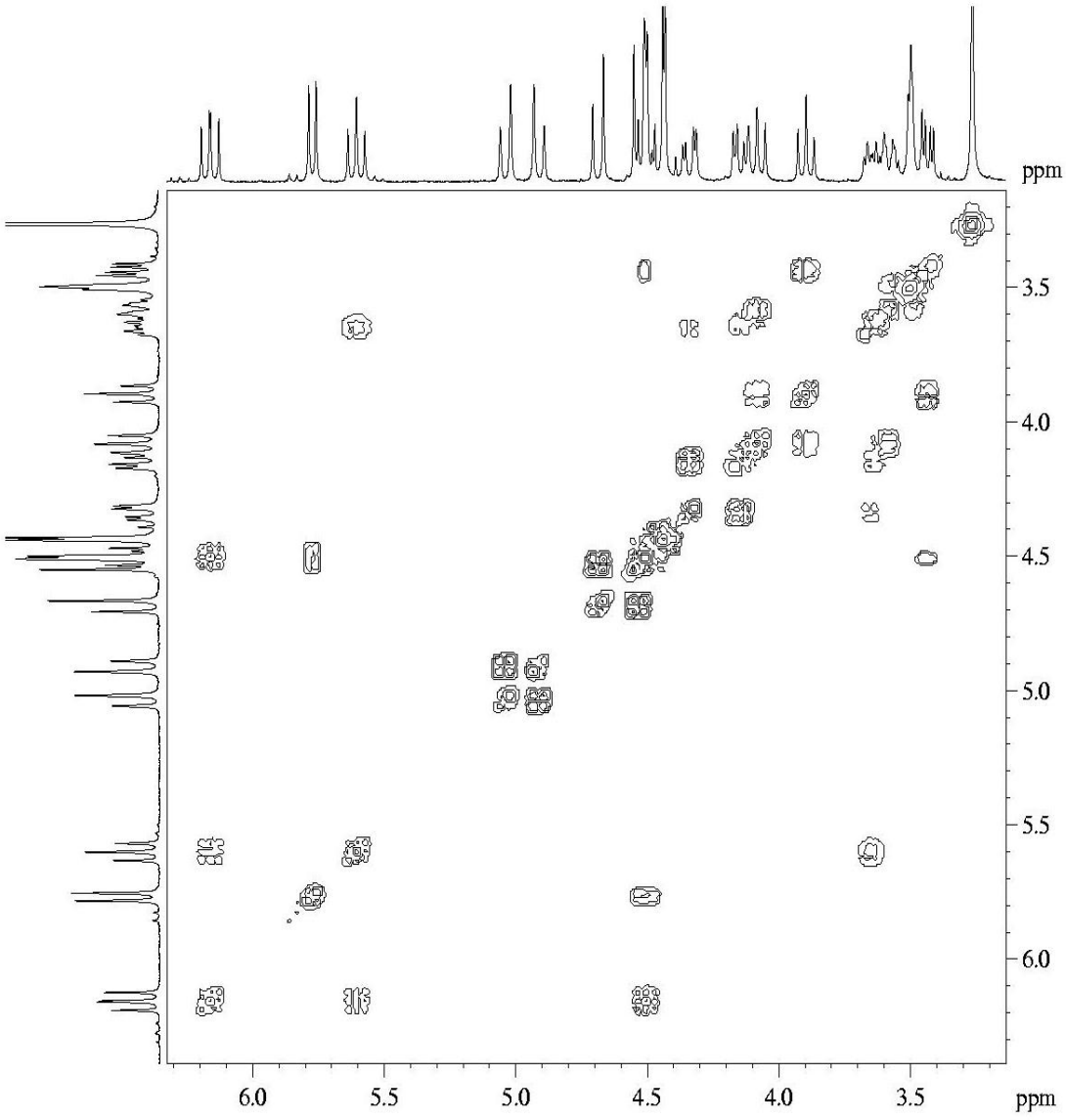



$CDCl_3$ 151 MHz

**Figure A-46:** $^{13}C$ NMR spectrum of Methyl 4-O-(3,4,6-tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside **(4.47)**

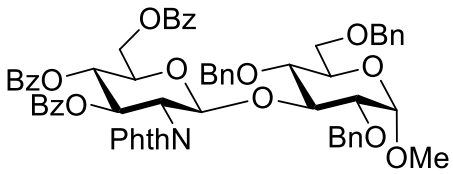



**4.47**

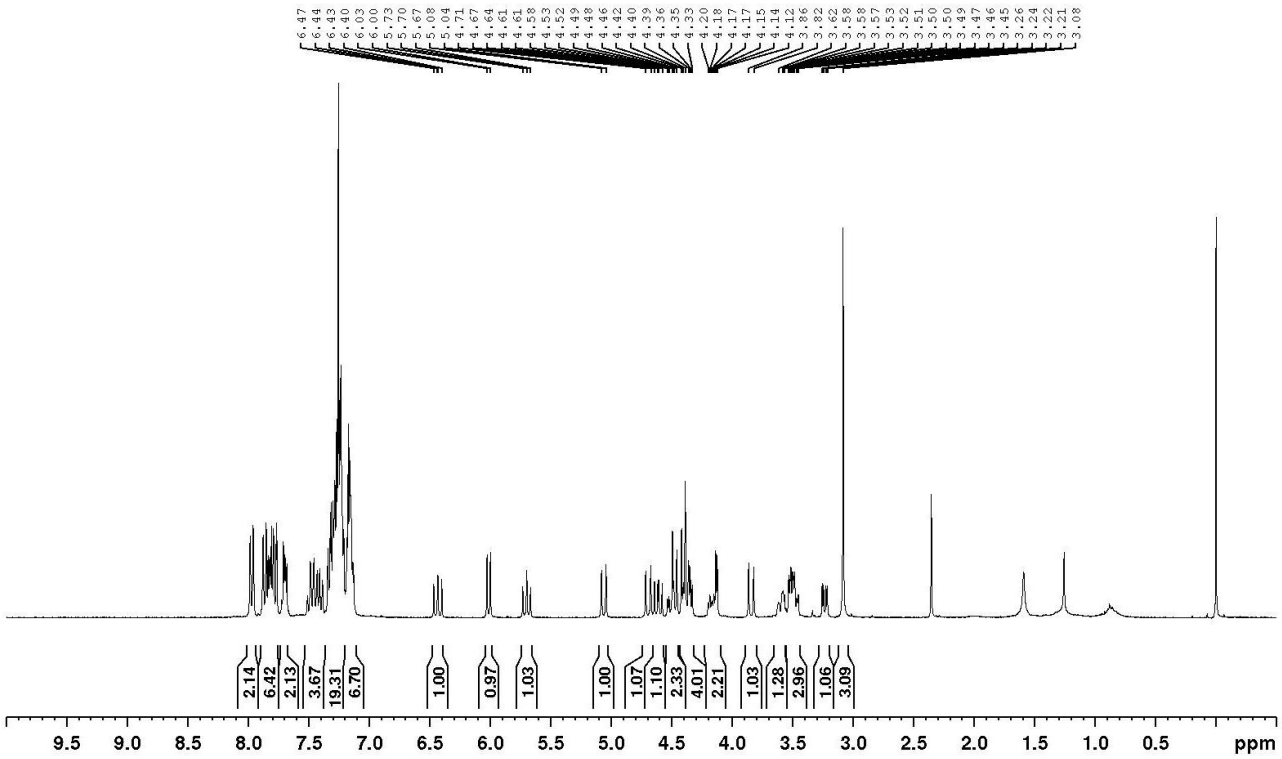



$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of Methyl 4-O-(3,4,6-tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside **(4.47)**

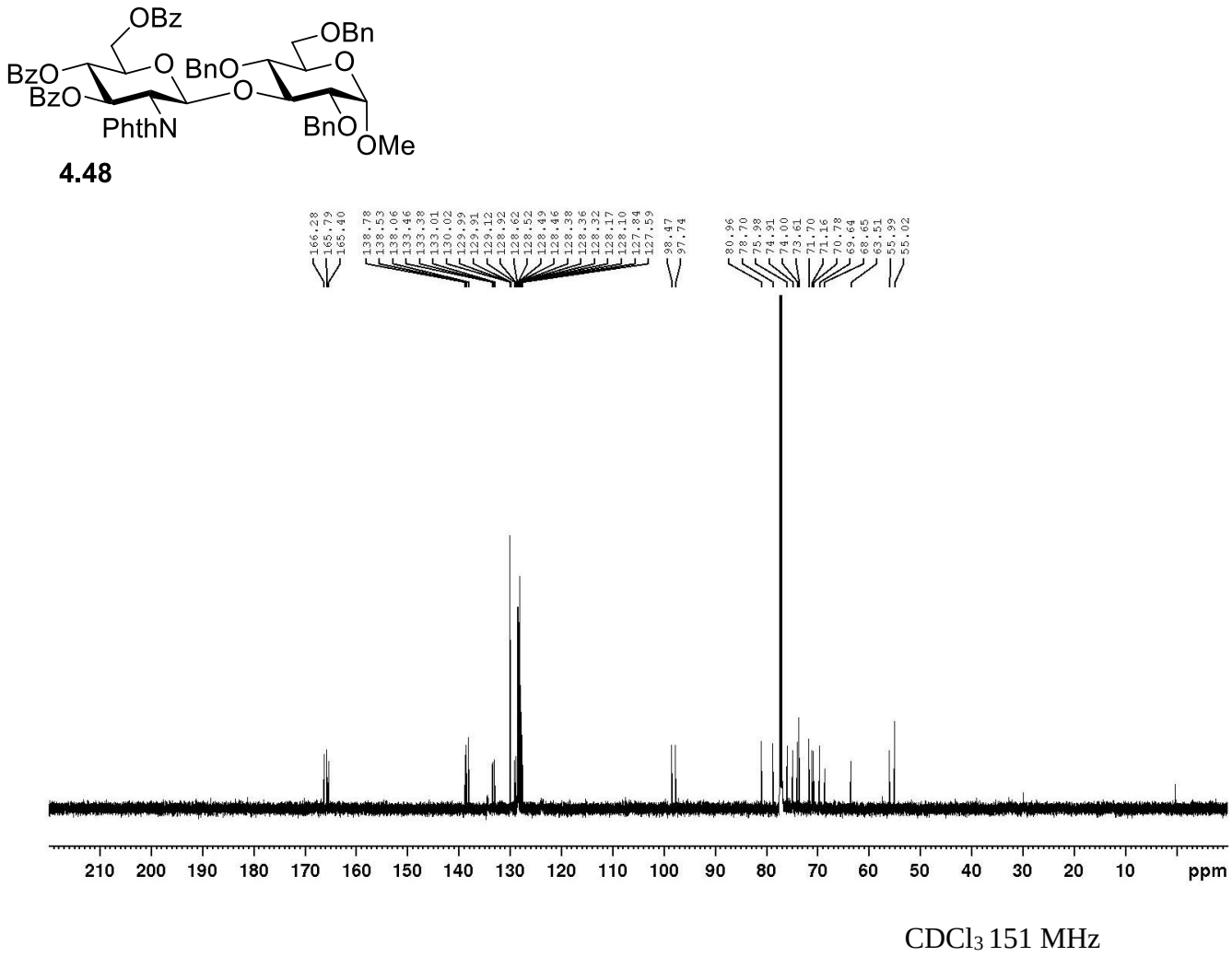



**4.48**



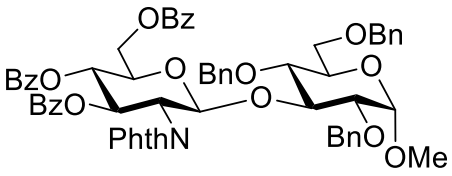

$CDCl_3$ 300 MHz

**Figure A-48:** $^1H$ NMR spectrum of Methyl 3-O-(3,4,6-tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,4,6-tri-O-benzyl-α-D-glucopyranoside **(4.48)**

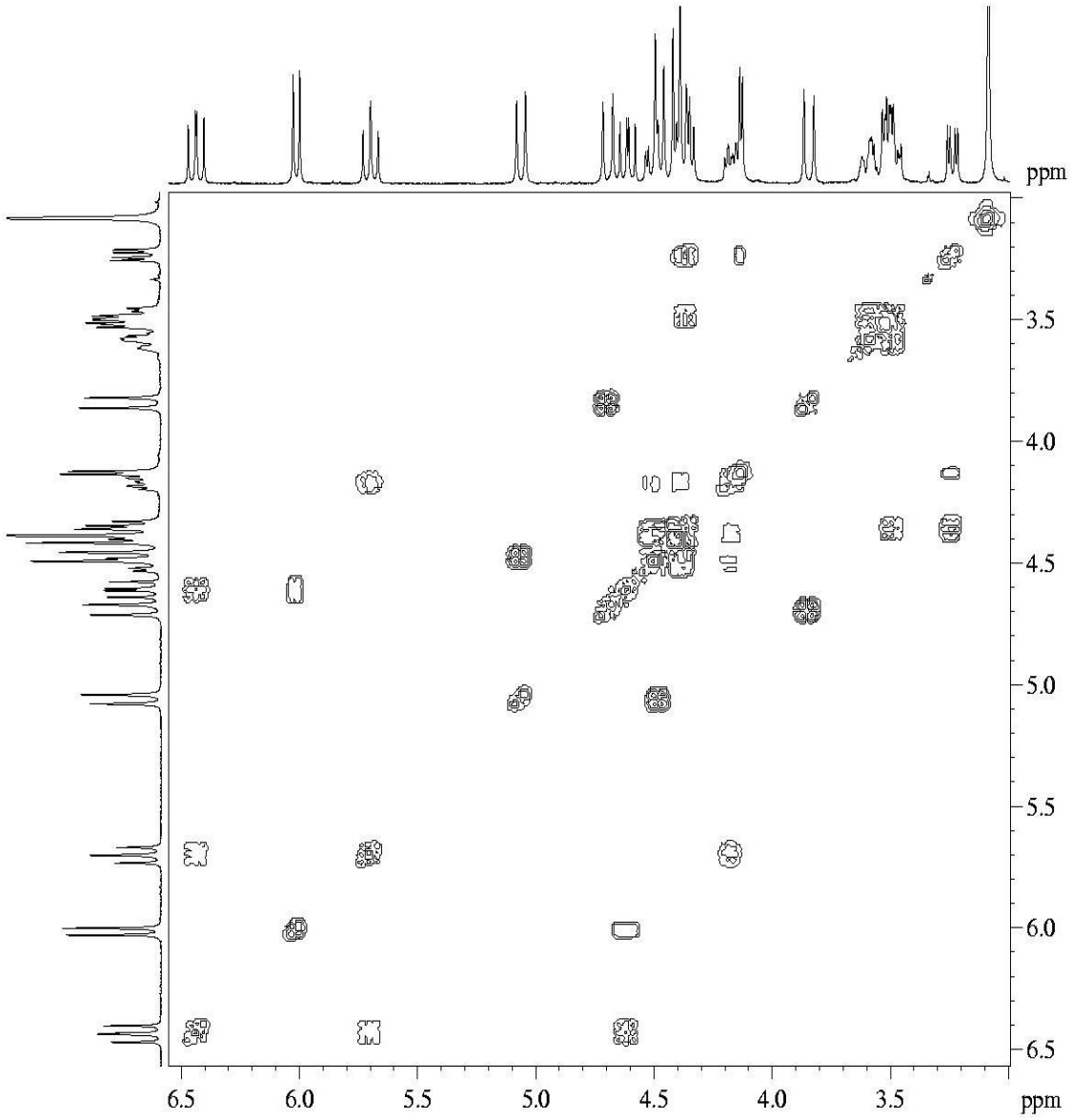



$CDCl_3$ 151 MHz

**Figure A-49:** $^{13}C$ NMR spectrum of Methyl 3-O-(3,4,6-tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,4,6-tri-O-benzyl-α-D-glucopyranoside **(4.48)**

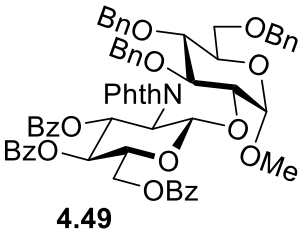



**4.48**

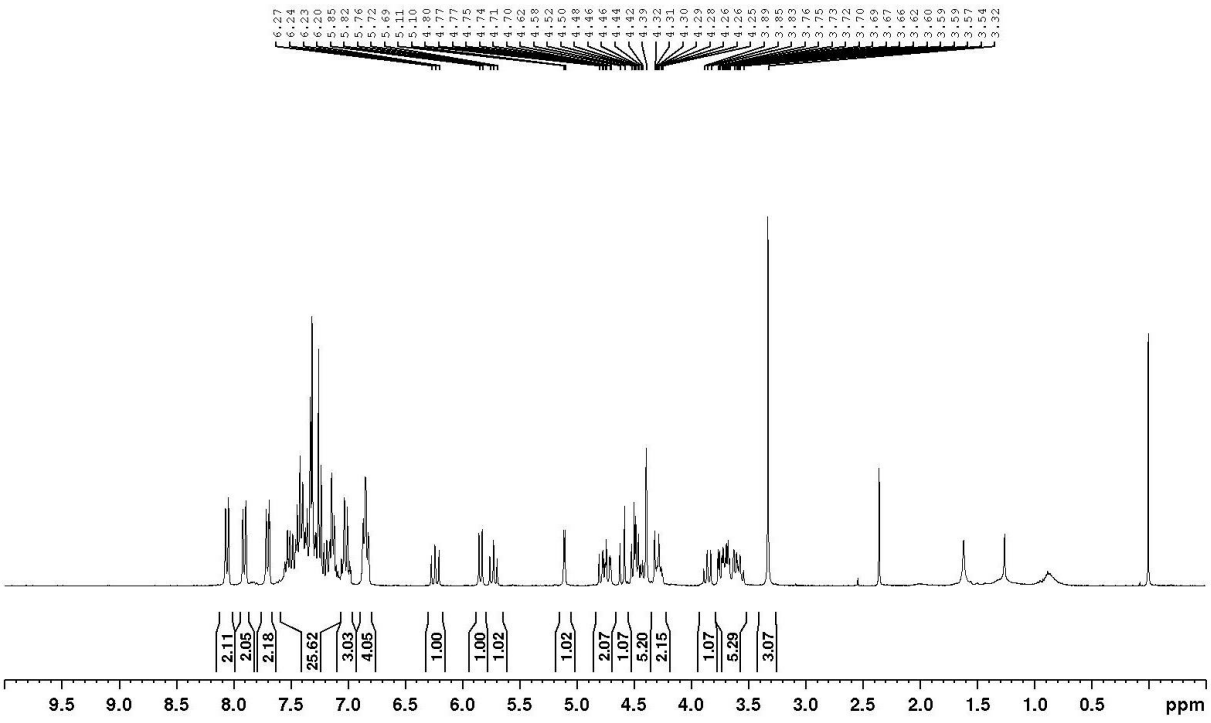



$CDCl_3$ 300 MHz

**Figure A-50:** 2-D NMR COSY spectrum of Methyl 3-O-(3,4,6-tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,4,6-tri-O-benzyl-α-D-glucopyranoside **(4.48)**




**4.49**




$CDCl_3$ 300 MHz

**Figure A-51:** $^1H$ NMR spectrum of Methyl 2-O-(3,4,6-tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3,4,6-tri-O-benzyl-α-D-glucopyranoside **(4.49)**

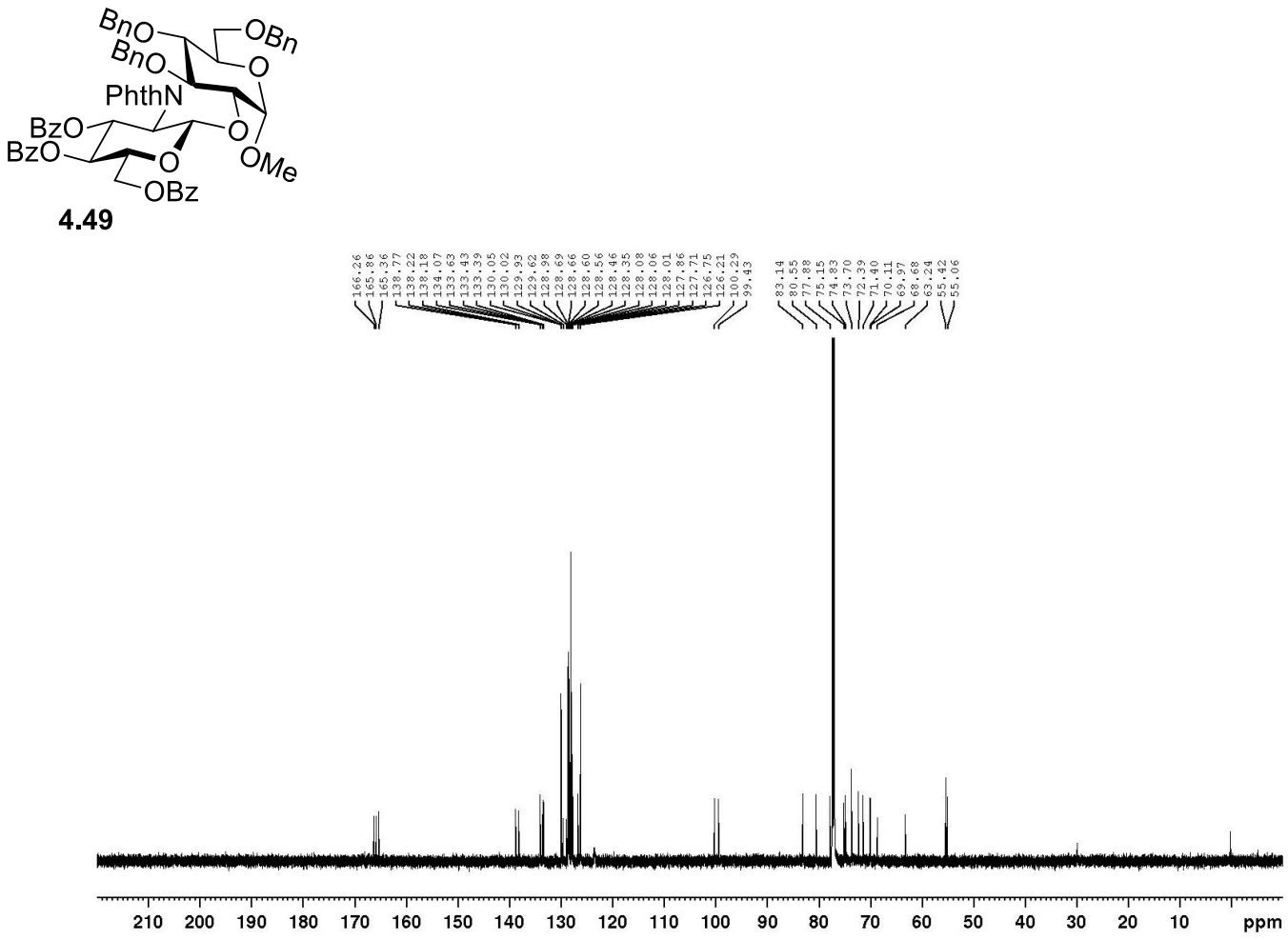
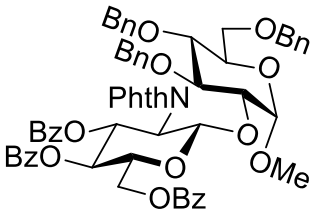
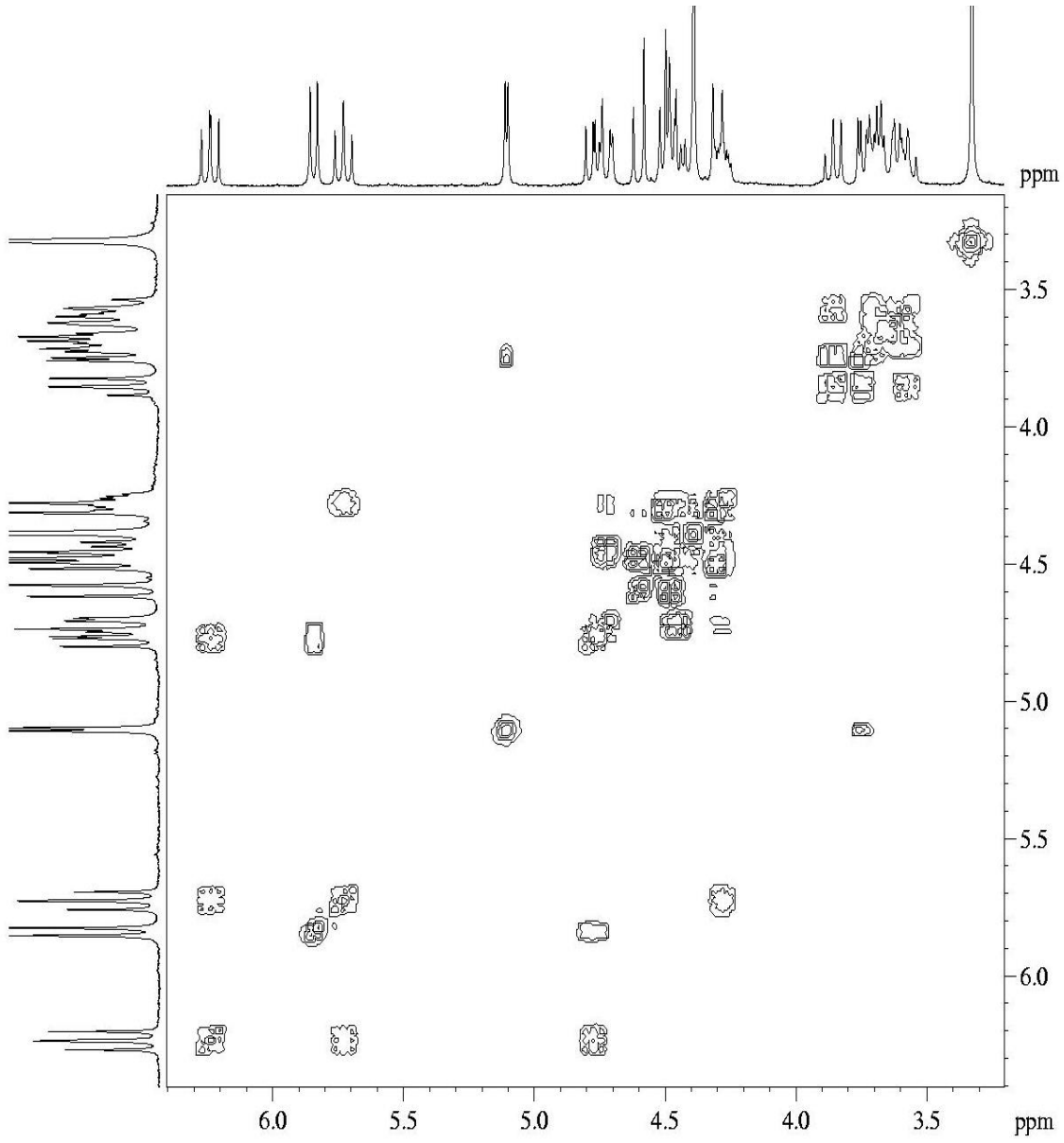



**Figure A-52:** $^{13}C$ NMR spectrum of Methyl 2-O-(3,4,6-tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3,4,6-tri-O-benzyl-α-D-glucopyranoside **(4.49)**

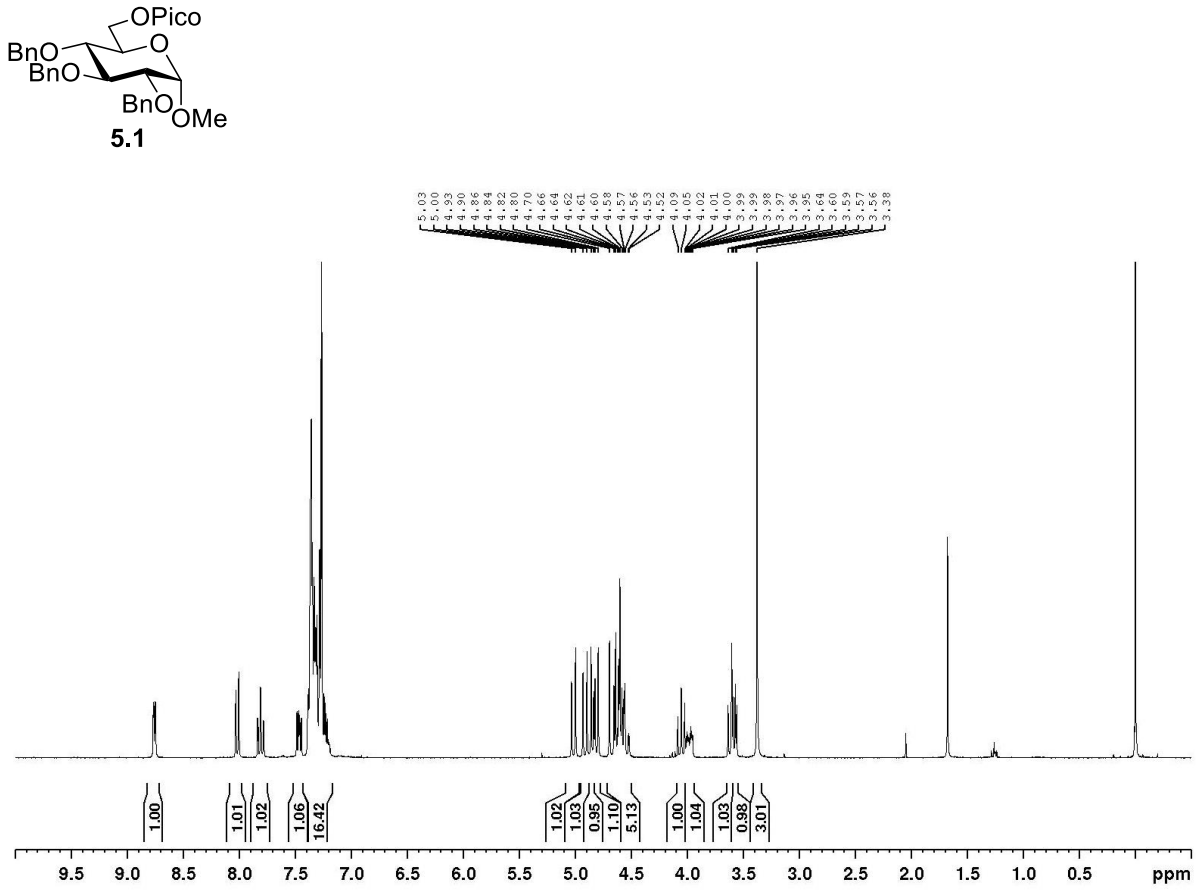



**4.49**



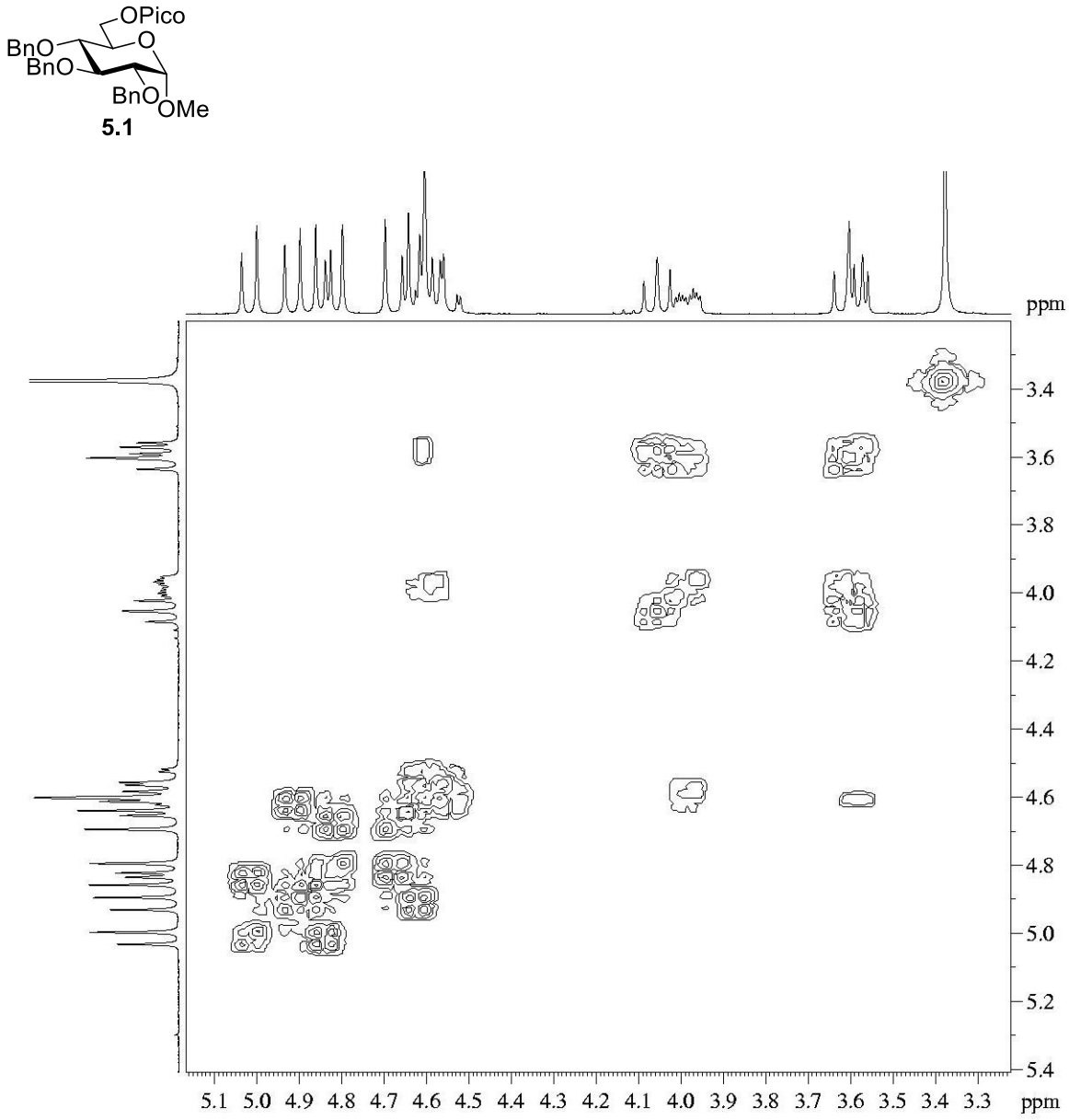

$CDCl_3$ 300 MHz

**Figure A-53:** 2-D NMR COSY spectrum of Methyl 2-O-(3,4,6-tri-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3,4,6-tri-O-benzyl-α-D-glucopyranoside **(4.49)**



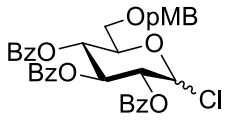

$CDCl_3$ 300 MHz

**Figure A-51:** $^1H$ NMR spectrum of Methyl 2,3,4-tri-O-benzyl-6-O-picoloyl-α-D-glucopyranoside **(5.1)**

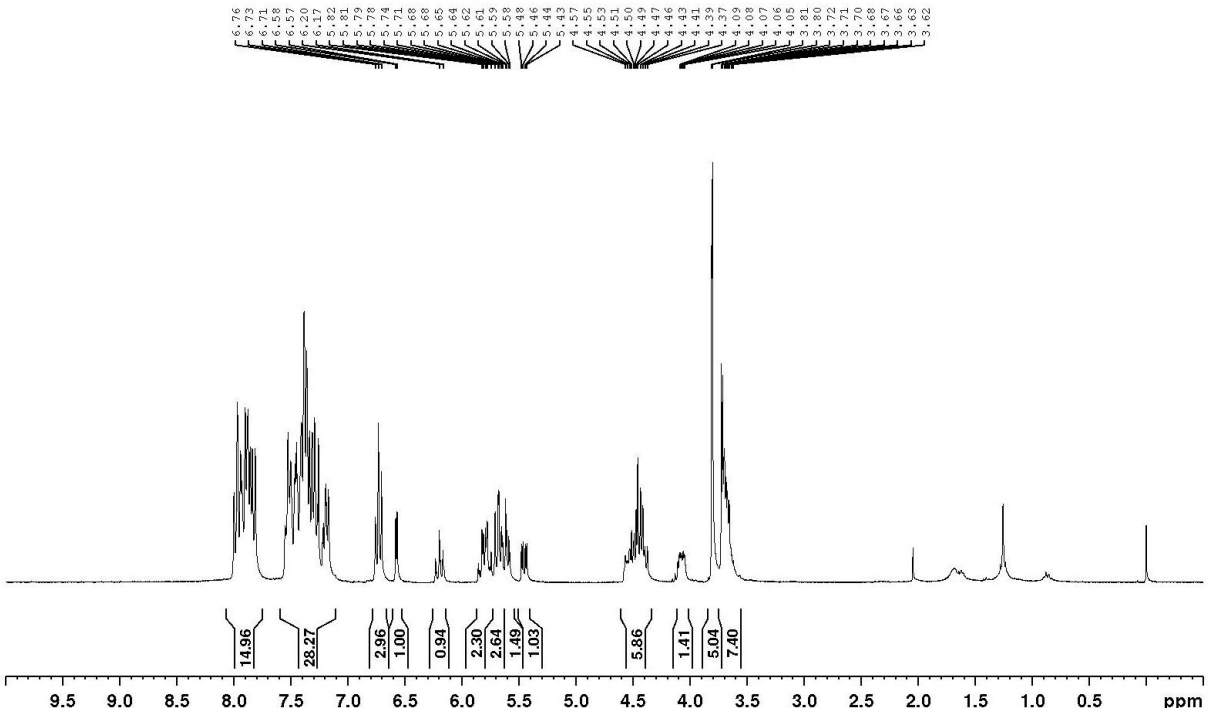



$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of Methyl 2,3,4-tri-O-benzyl-6-O-picoloyl-α-D-glucopyranoside **(5.1)**

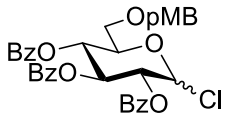



**5.3**
α:β 1:1.4

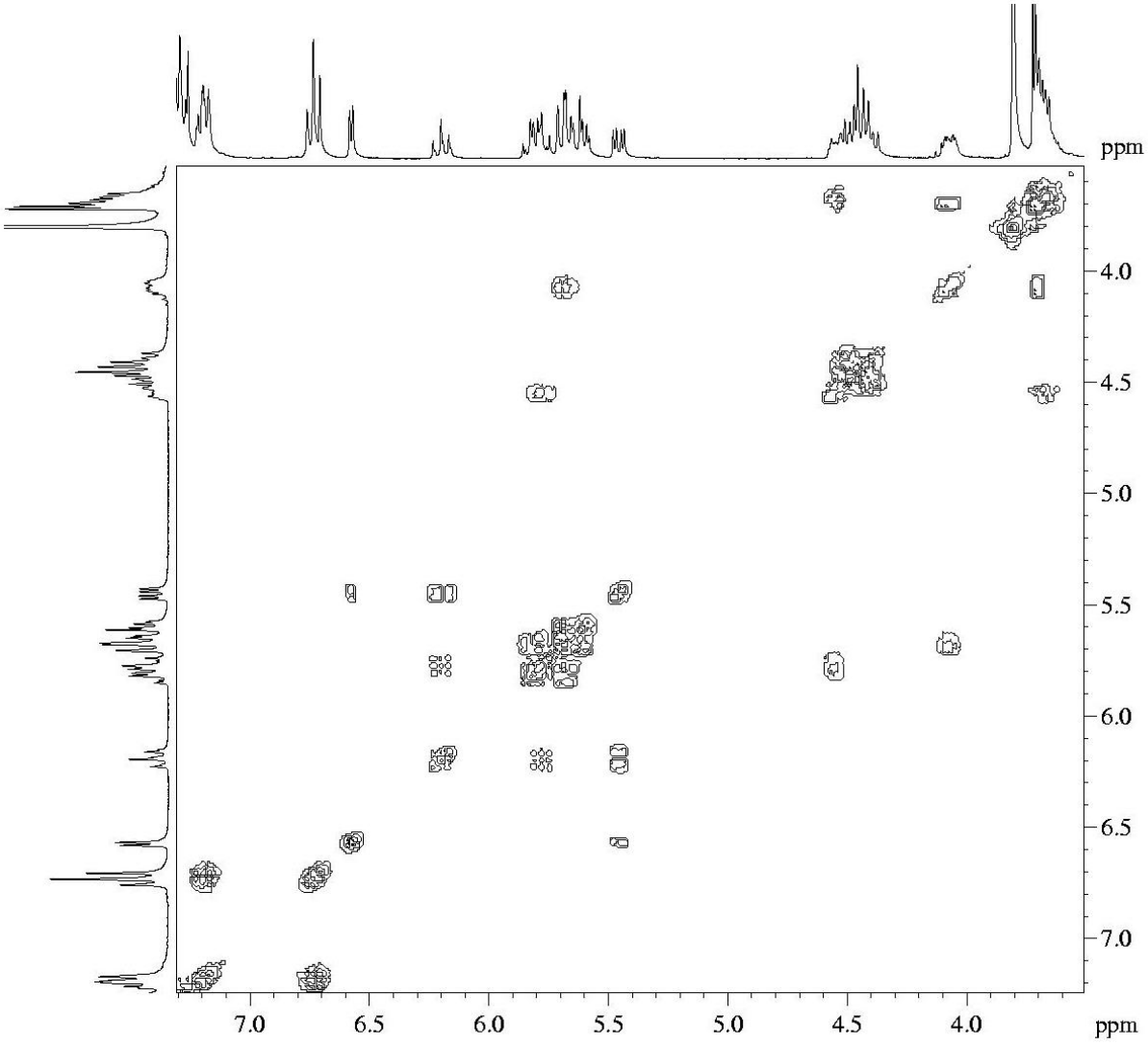



$CDCl_3$ 300 MHz

**Figure A-51:** $^1$H NMR spectrum of 2,3,4-Tri-*O*-benzoyl-6-O-*p*-methoxybenzyl-α/β-D-glucopyranosyl chloride **(5.3)**

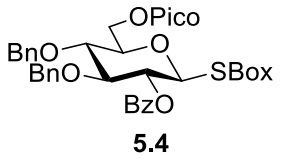



**5.3**
α:β 1:1.4

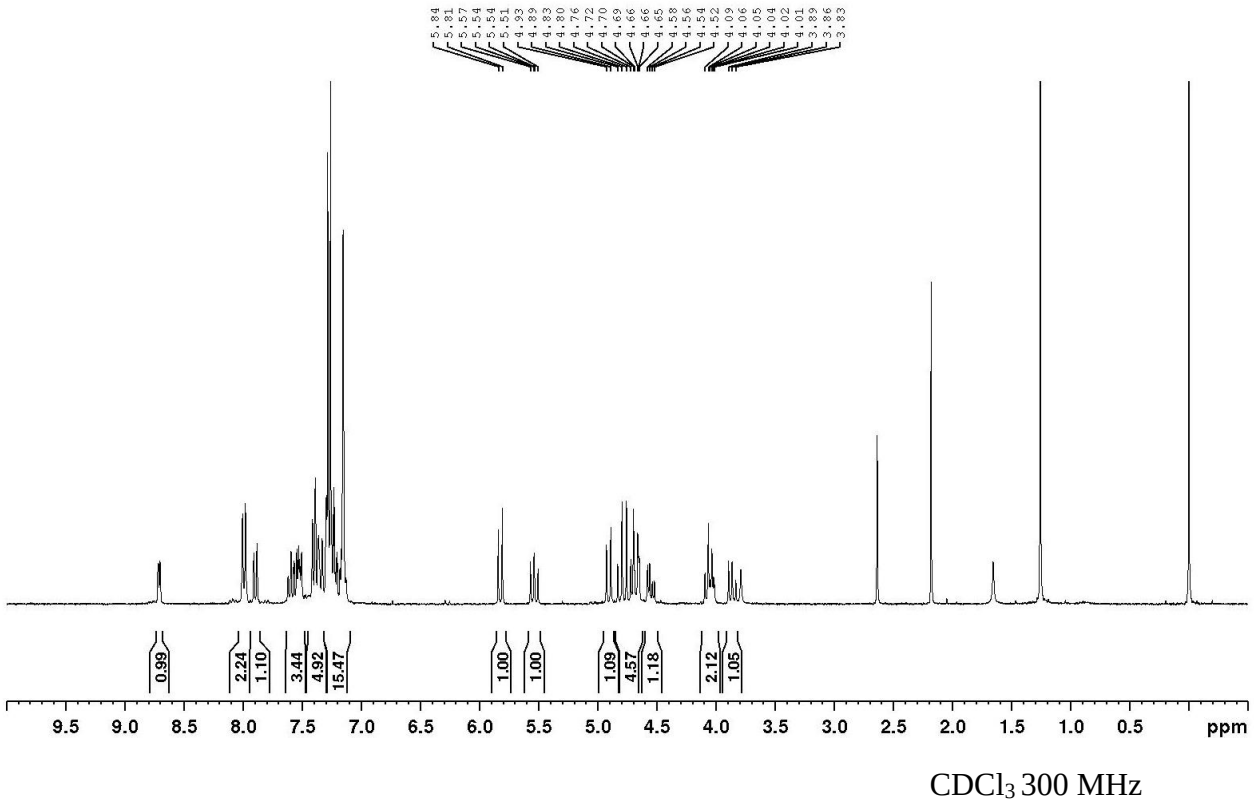



$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of 2,3,4-Tri-*O*-benzoyl-6-O-*p*-methoxybenzyl-α/β-D-glucopyranosyl chloride **(5.3)**

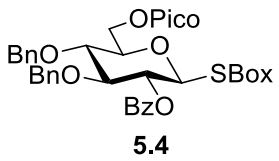



**5.4**

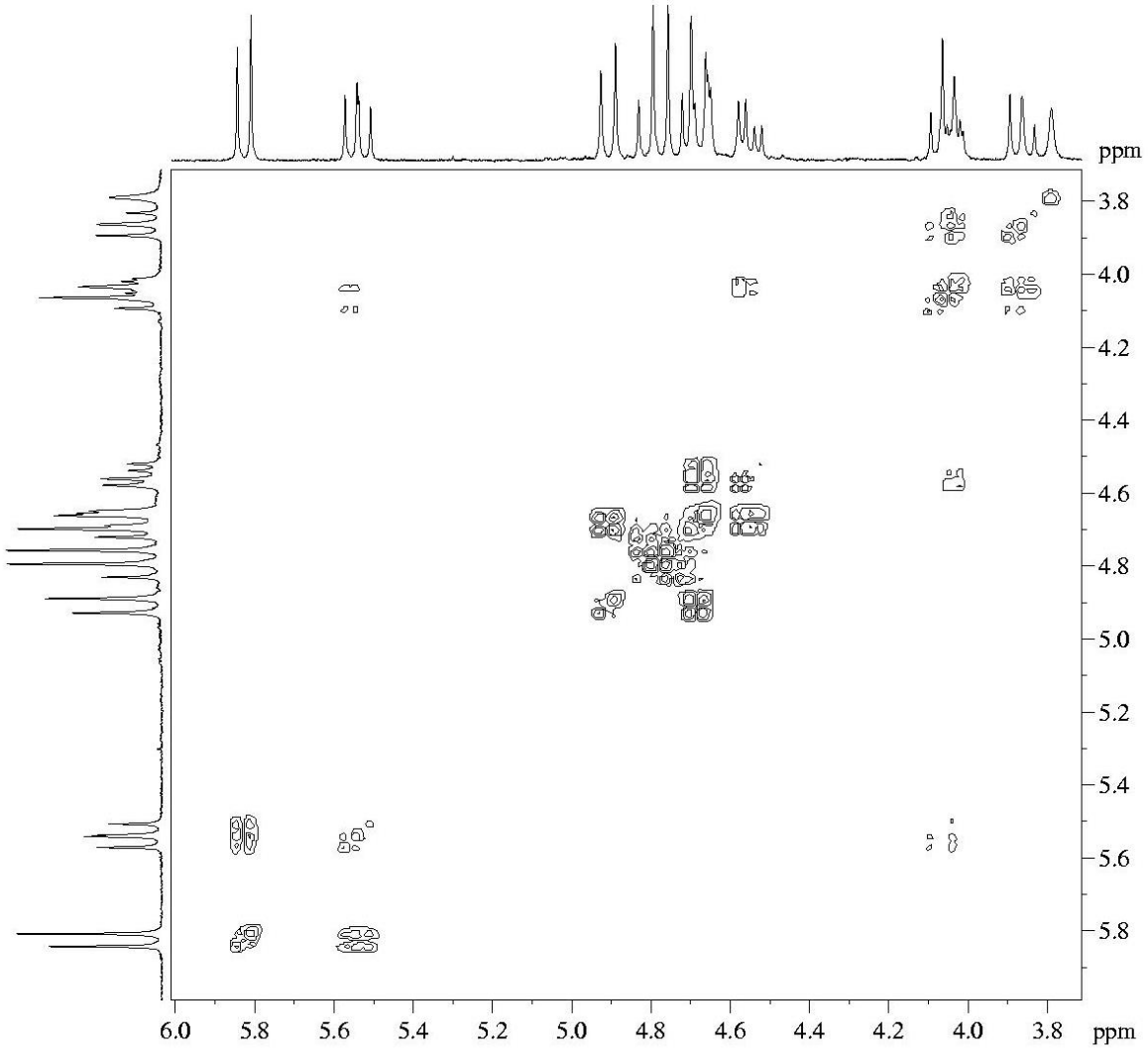



$CDCl_3$ 300 MHz

**Figure A-51:** $^1$H NMR spectrum of Benzoxazolyl 3,4-di-O-benzyl-2-O-benzoyl-6-O-picoloyl-1-thio-β-D-glucopyranoside **(5.4)**

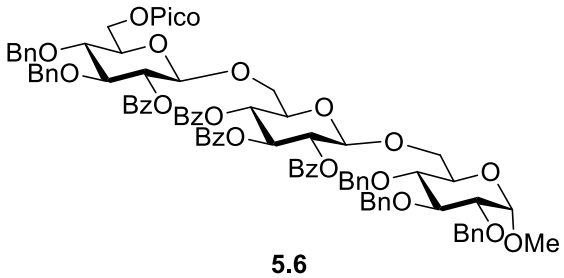



**5.4**

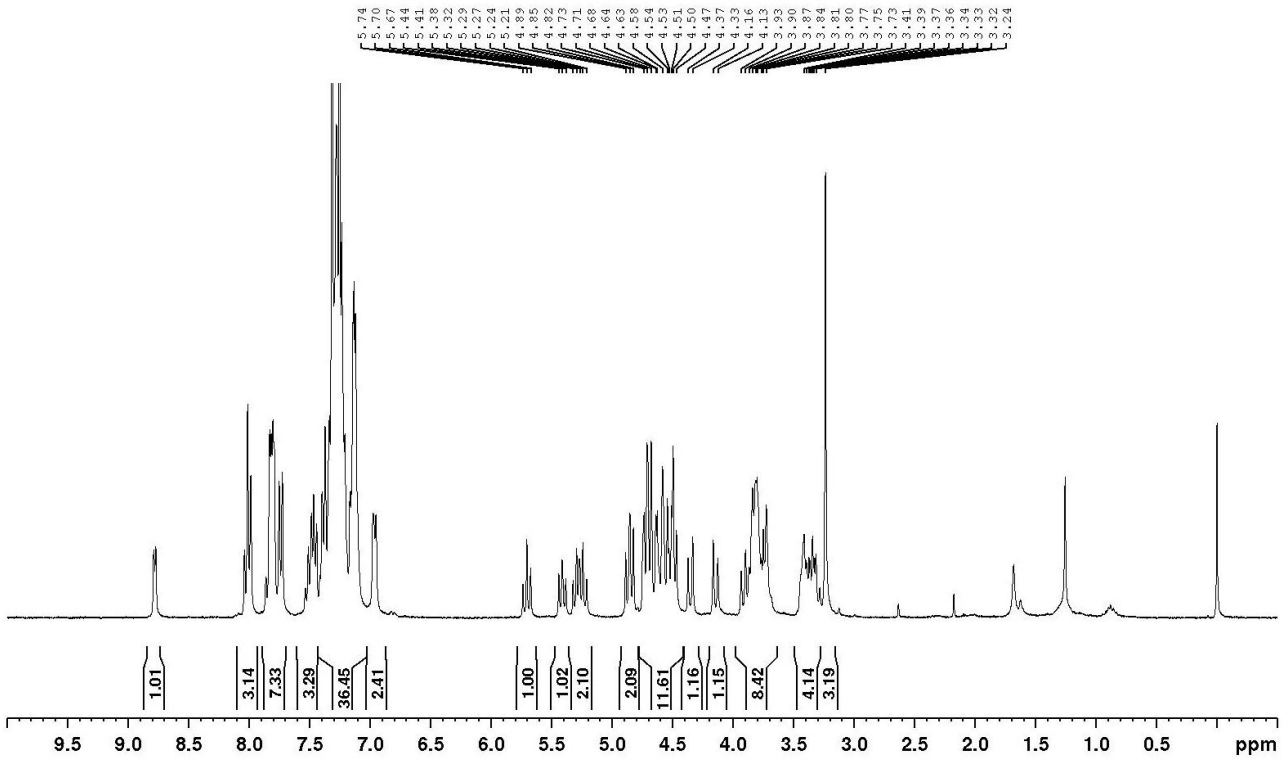



$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of Benzoxazolyl 3,4-di-O-benzyl-2-O-benzoyl-6-O-picoloyl-1-thio-β-D-glucopyranoside **(5.4)**

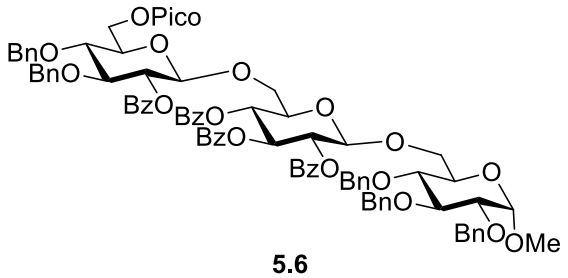



**5.6**

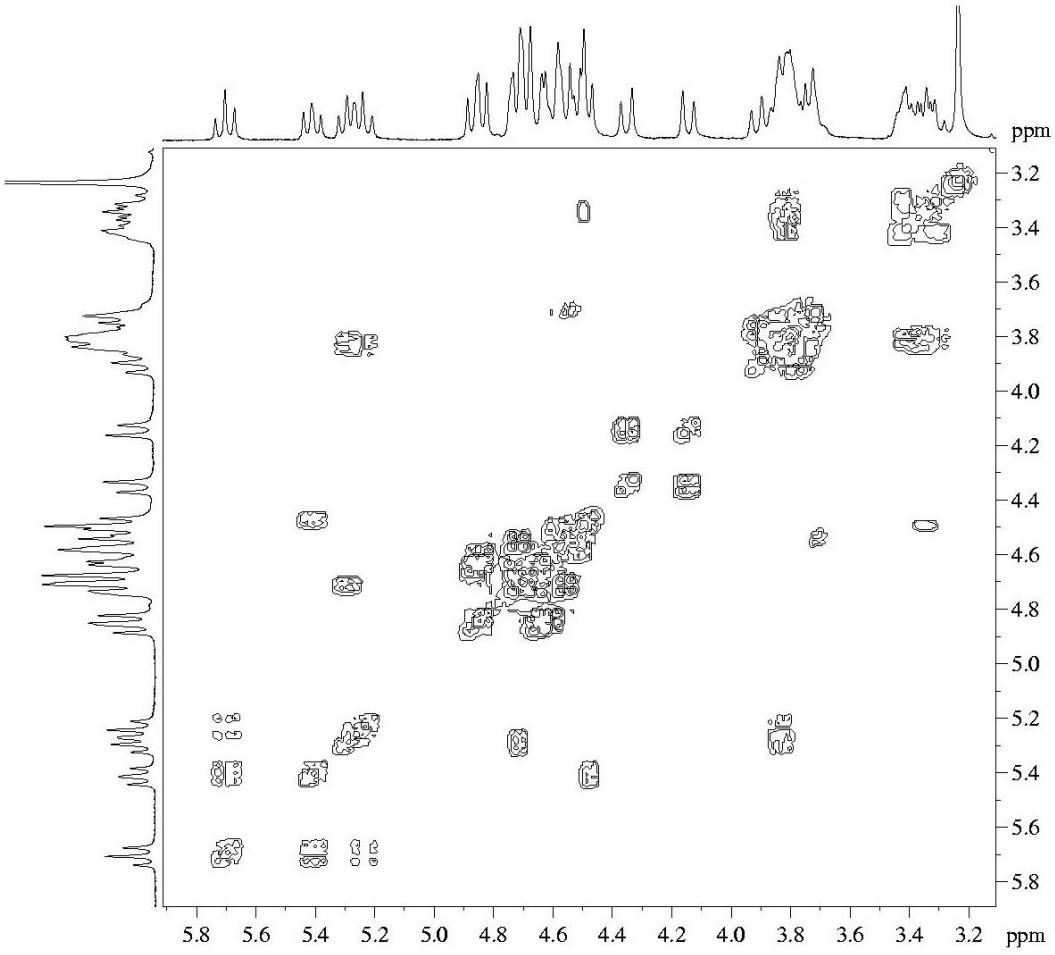



$CDCl_3$ 300 MHz

**Figure A-51:** $^1$H NMR spectrum of Methyl *O*-(3,4-di-*O*-benzyl-2-O-benzoyl-6-O-picoloyl-β-D-glucopyranosyl)-(1→6)-O-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-glucopyranoside **(5.6)**

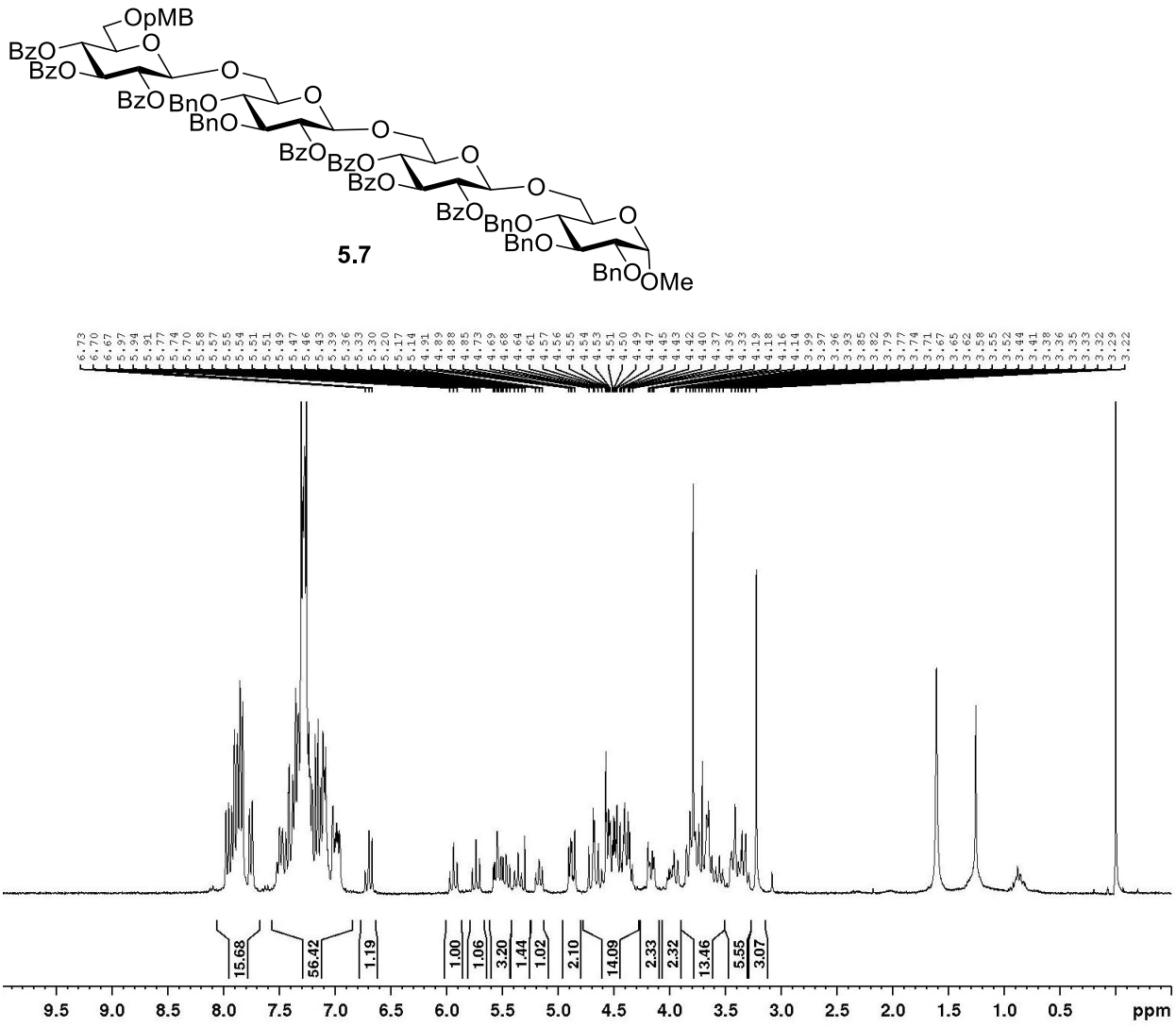



**5.6**



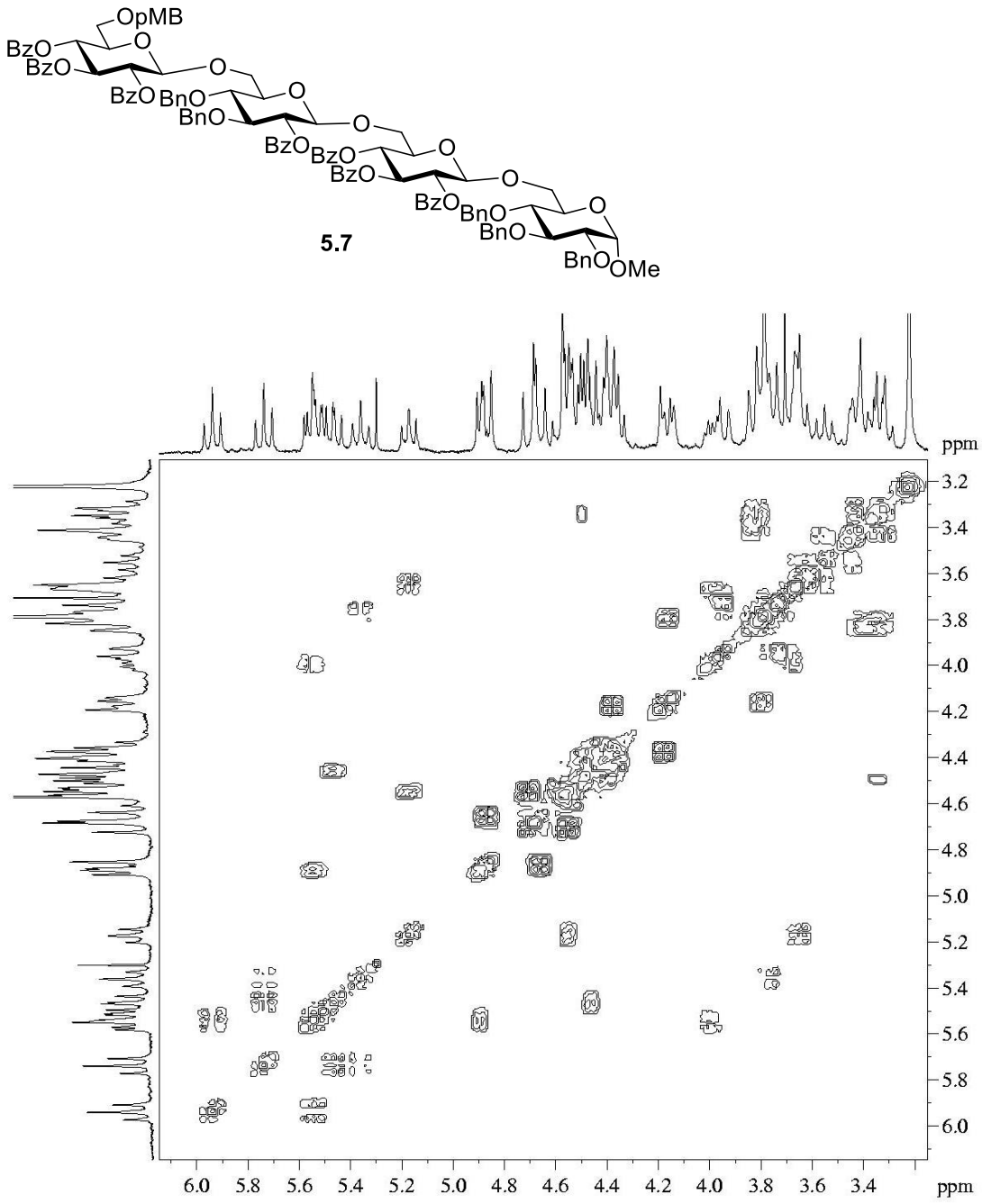

$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of Methyl *O*-(3,4-di-*O*-benzyl-2-O-benzoyl-6-O-picoloyl-β-D-glucopyranosyl)-(1→6)-O-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-glucopyranoside **(5.6)**



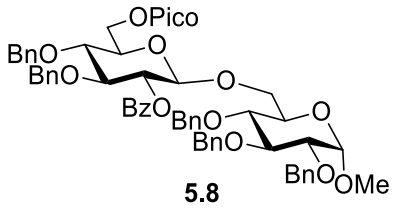

$CDCl_3$ 300 MHz

**Figure A-51:** $^1H$ NMR spectrum of Methyl *O*-(2,3,4-tri-*O*-benzoyl-6-O-*p*-methoxybenzyl-β-D-glucopyranosyl)-(1→6)-O-(3,4-di-*O*-benzyl-2-O-benzoyl-β-D-glucopyranosyl)-(1→6)-O-(2,3,4-tri-O-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-glucopyranoside **(5.7)**

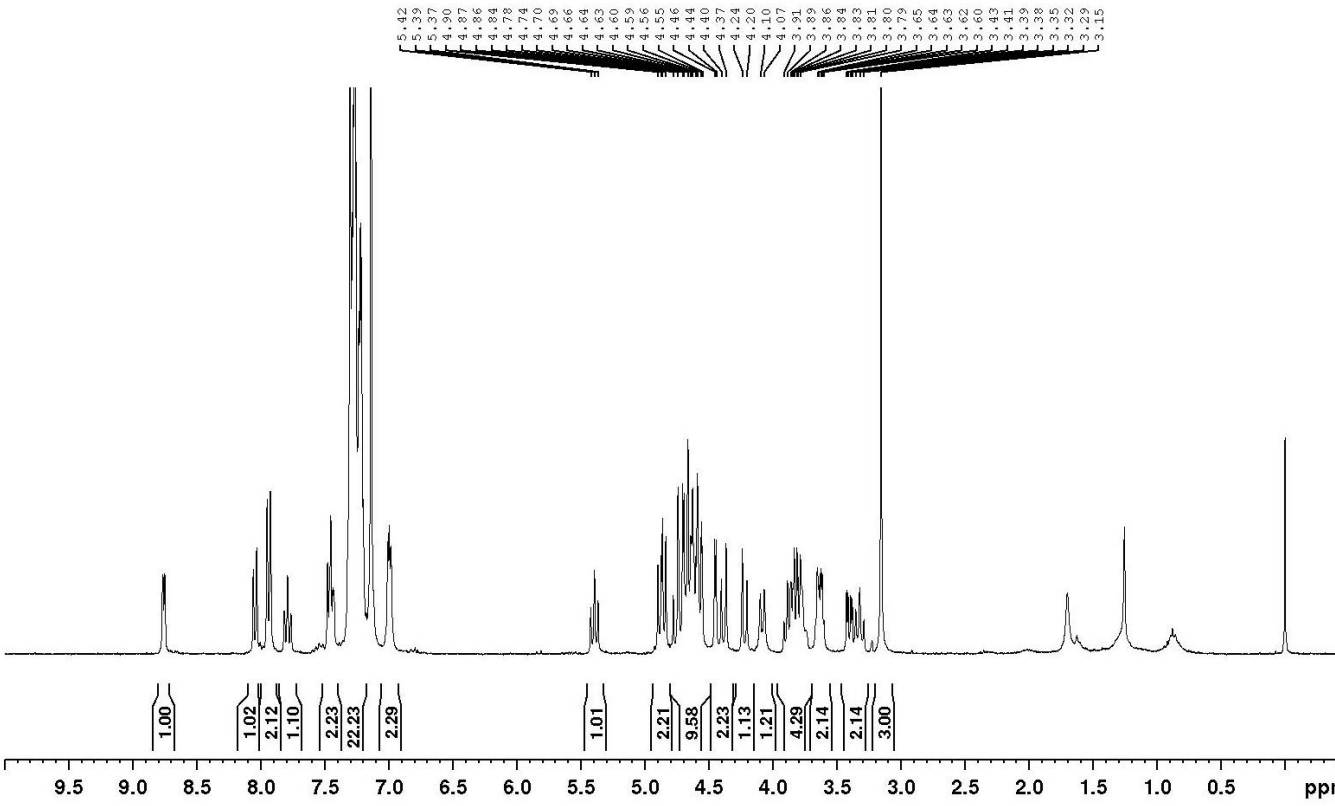



$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of Methyl *O*-(2,3,4-tri-*O*-benzoyl-6-O-*p*-methoxybenzyl-β-D-glucopyranosyl)-(1→6)-O-(3,4-di-*O*-benzyl-2-O-benzoyl-β-D-glucopyranosyl)-(1→6)-O-(2,3,4-tri-O-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-glucopyranoside **(5.7)**

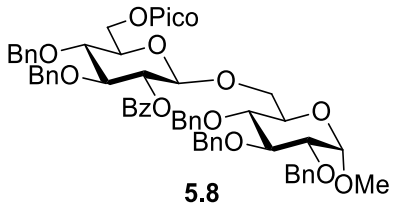



**5.8**

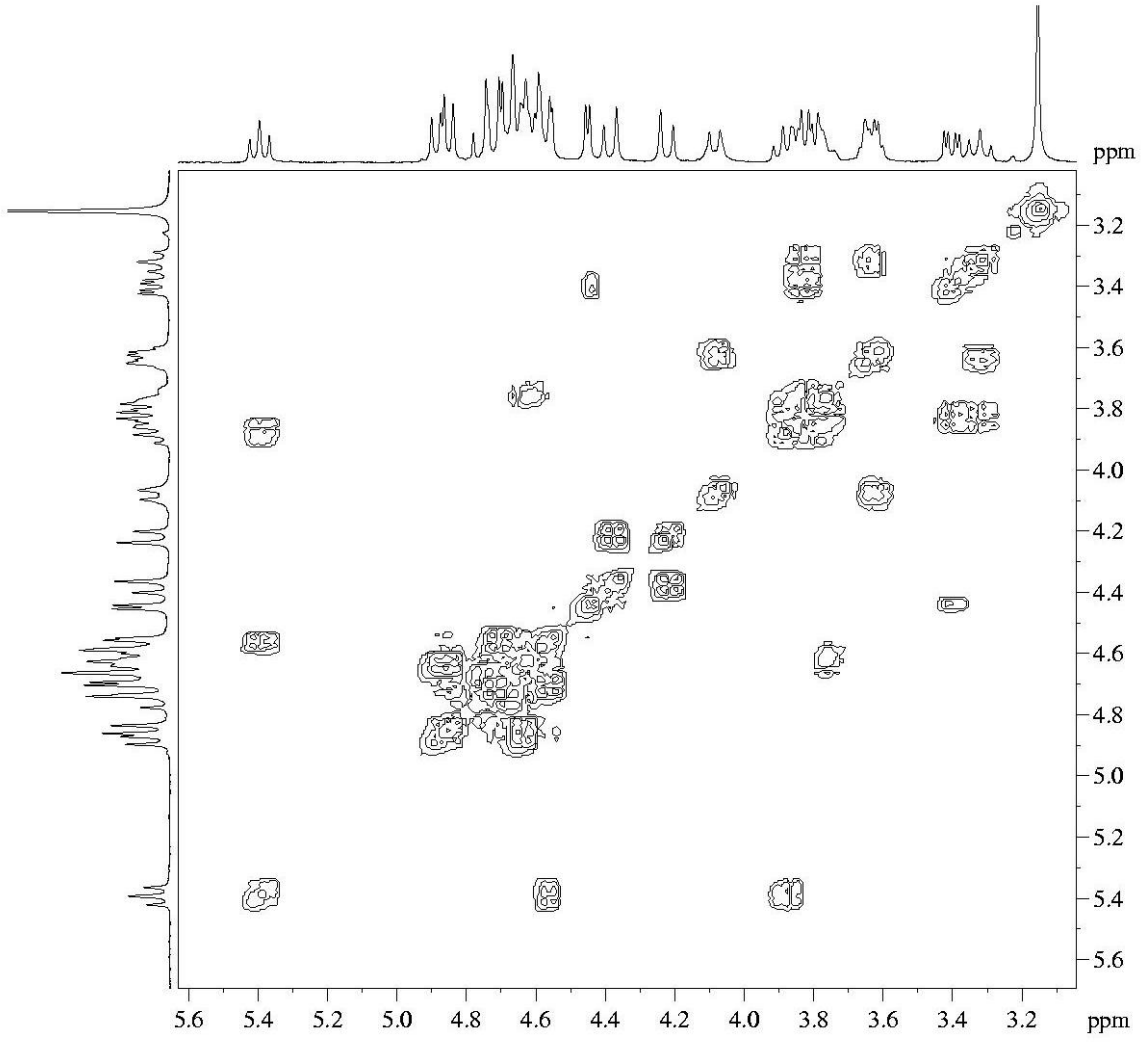



$CDCl_3$ 300 MHz

**Figure A-51:** $^1$H NMR spectrum of Methyl 6-*O*-(3,4-di-*O*-benzyl-2-O-benzoyl-6-O-picoloyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **(5.8)**

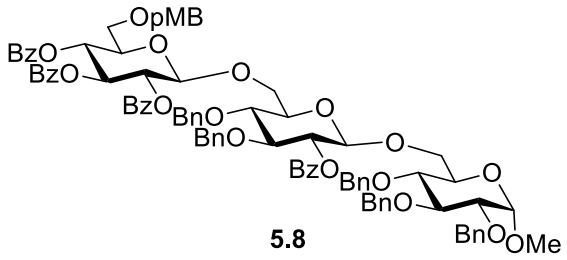



**5.8**

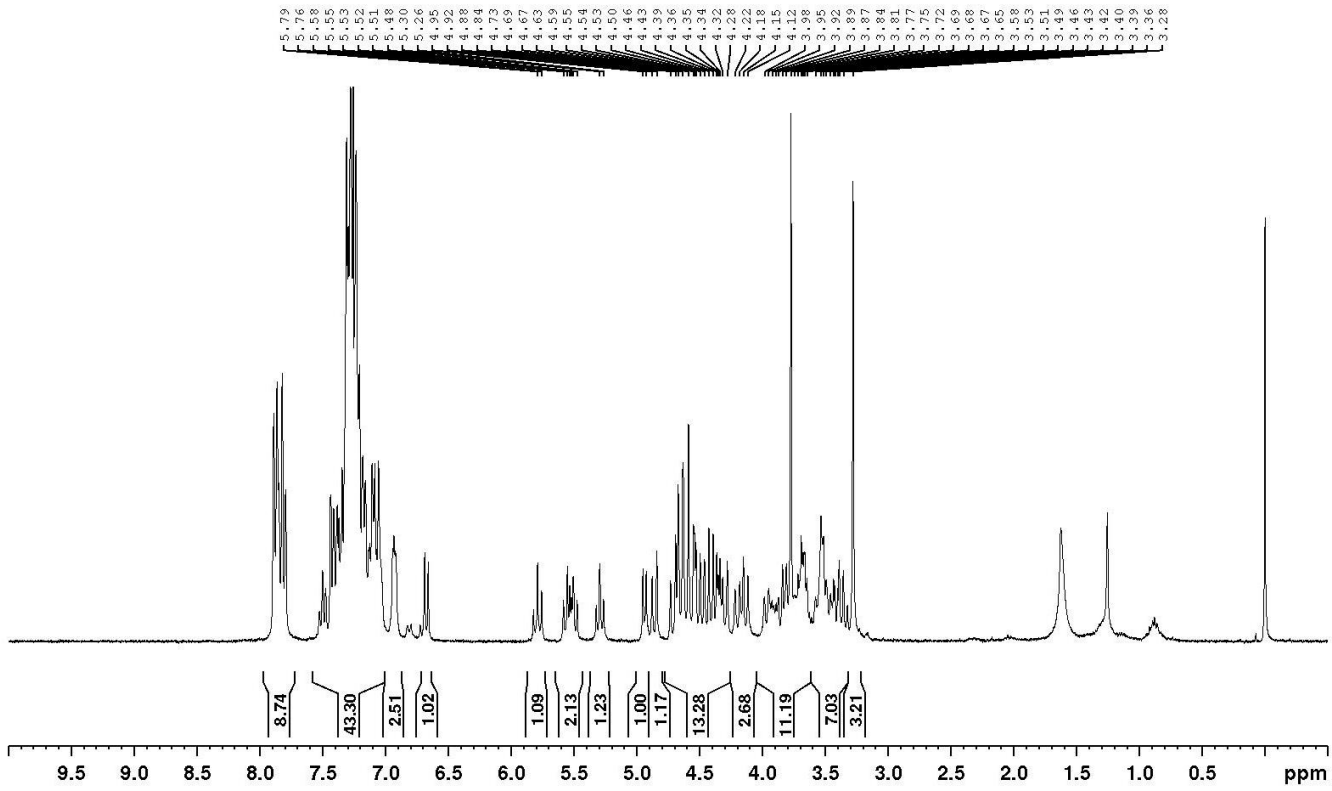



$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of Methyl 6-*O*-(3,4-di-*O*-benzyl-2-O-benzoyl-6-O-picoloyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **(5.8)**

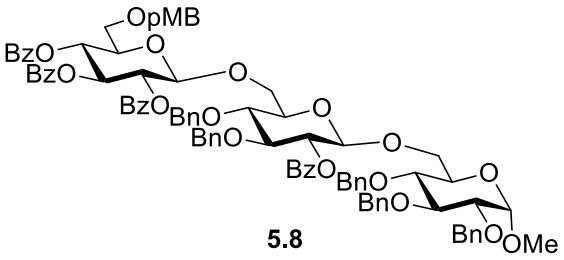



**5.8**

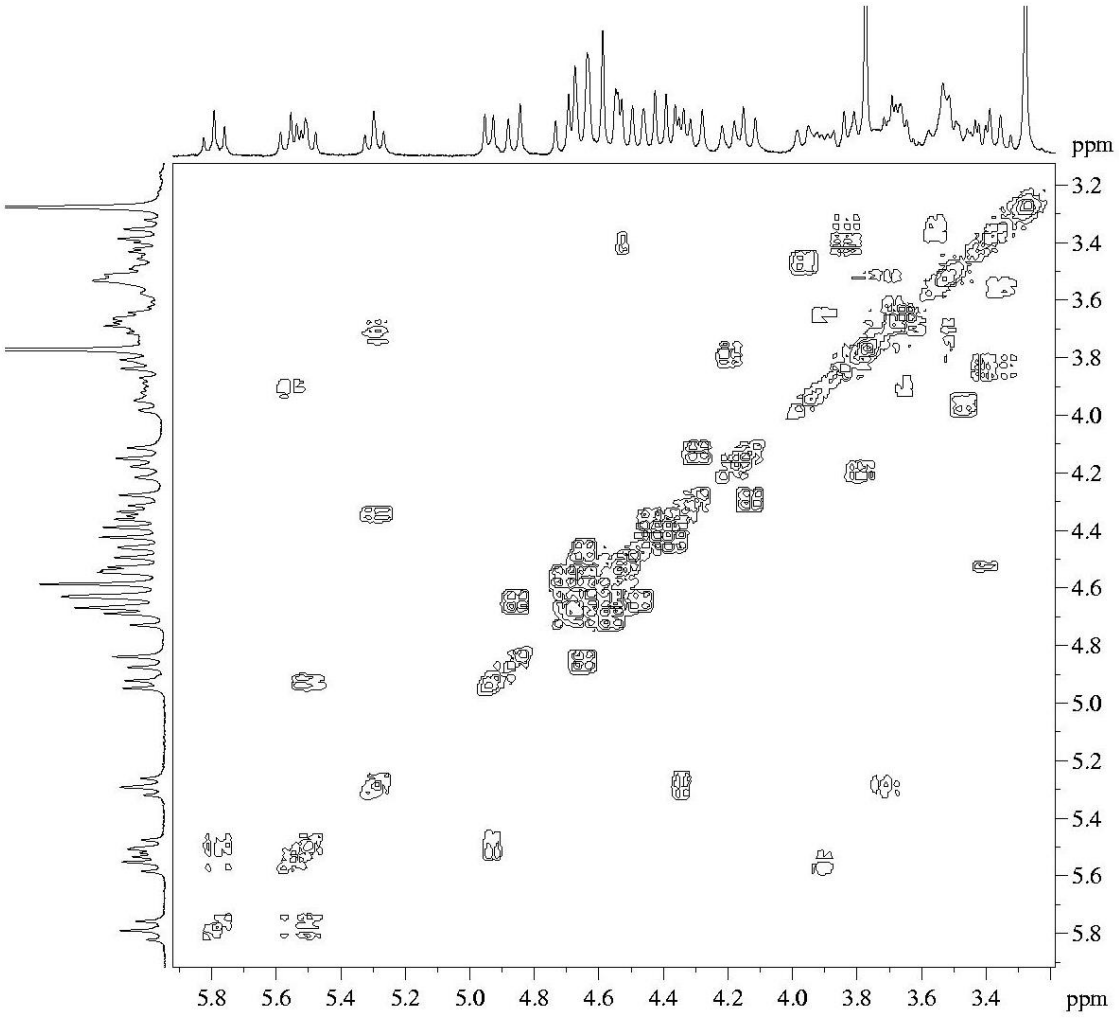



$CDCl_3$ 300 MHz

**Figure A-51:** $^1H$ NMR spectrum of Methyl *O*-(2,3,4-tri-*O*-benzoyl-6-O-*p*-methoxybenzyl-β-D-glucopyranosyl)-(1→6)-O-(3,4-di-*O*-benzyl-2-O-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-glucopyranoside **(5.9)**

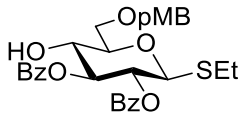



**5.8**

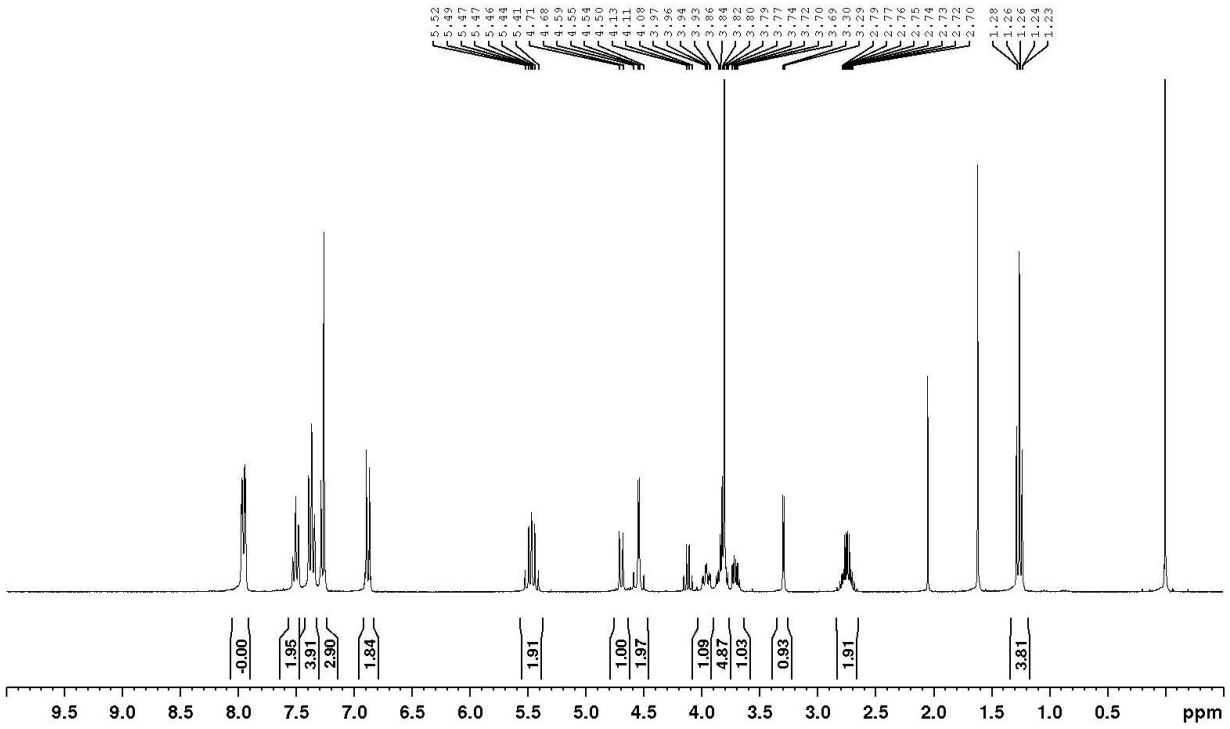



$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of Methyl *O*-(2,3,4-tri-*O*-benzoyl-6-O-*p*-methoxybenzyl-β-D-glucopyranosyl)-(1→6)-O-(3,4-di-*O*-benzyl-2-O-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-glucopyranoside **(5.9)**

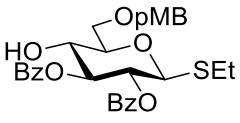



**5.10**

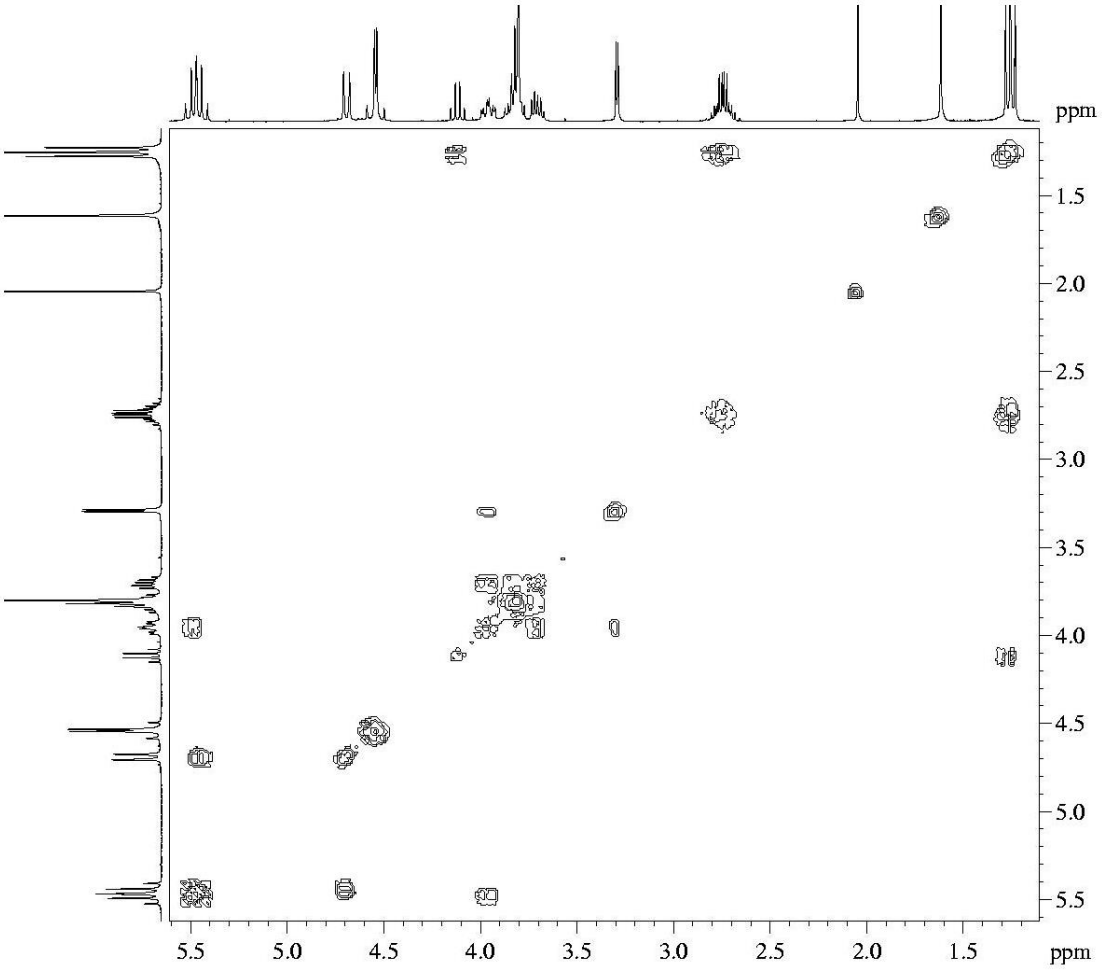



$CDCl_3$ 300 MHz

**Figure A-51:** $^1$H NMR spectrum of 2,3-di-O-benzoyl-6-O-p-methoxybenzyl-1-thio-β-D-glucopyranoside (**5.10)**

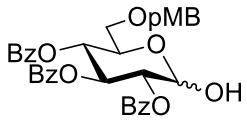



**5.10**



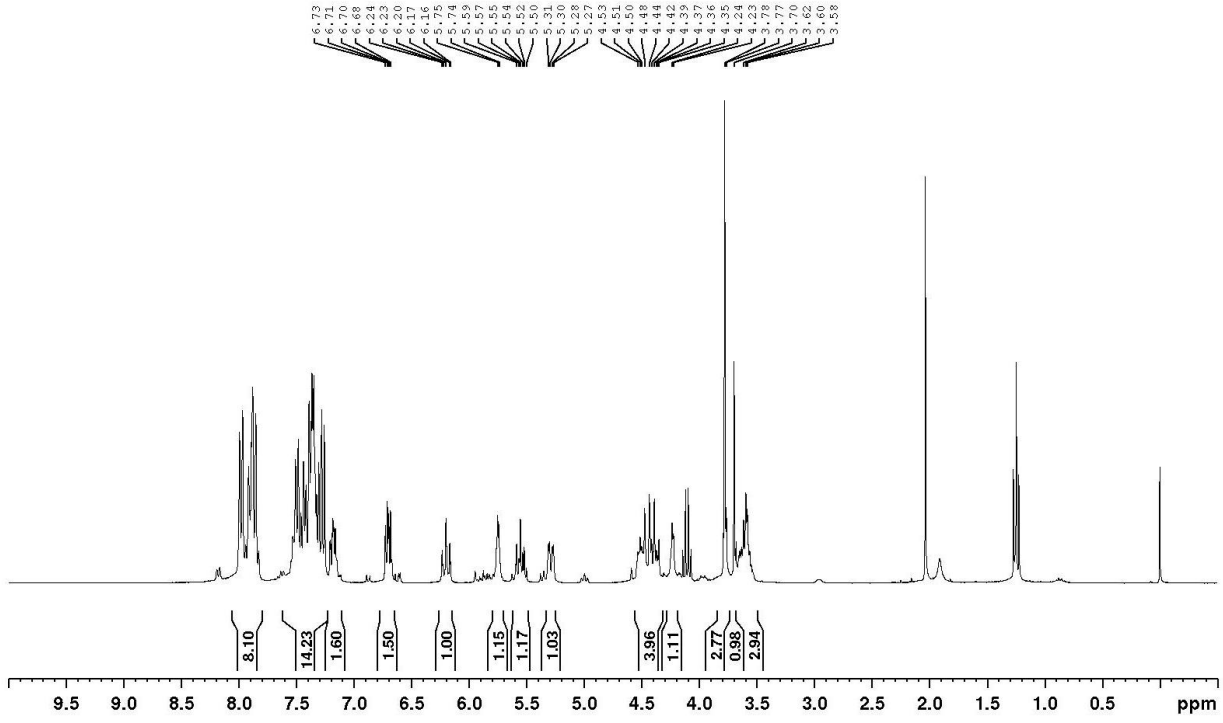

$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of 2,3-di-O-benzoyl-6-O-p-methoxybenzyl-1-thio-β-D-glucopyranoside (**5.10)**




**5.12**

α:β 2.9:1




$CDCl_3$ 300 MHz

**Figure A-51:** $^1$H NMR spectrum of 2,3,4-tri-*O*-benzoyl-6-O-*p*-methoxybenzyl-D-glucopyranose (**5.12)**

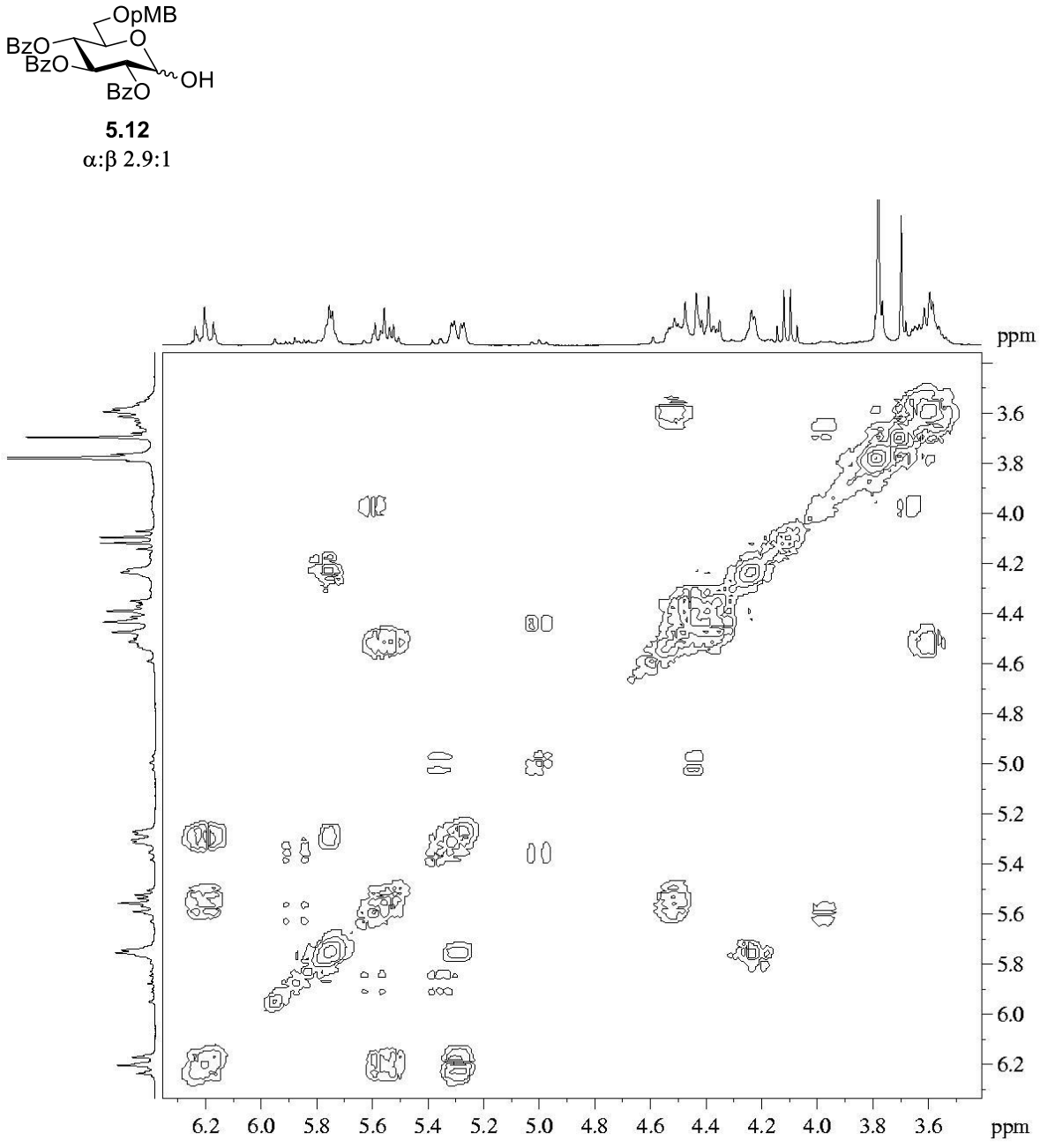
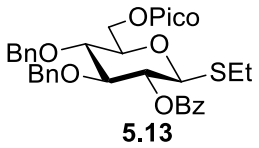
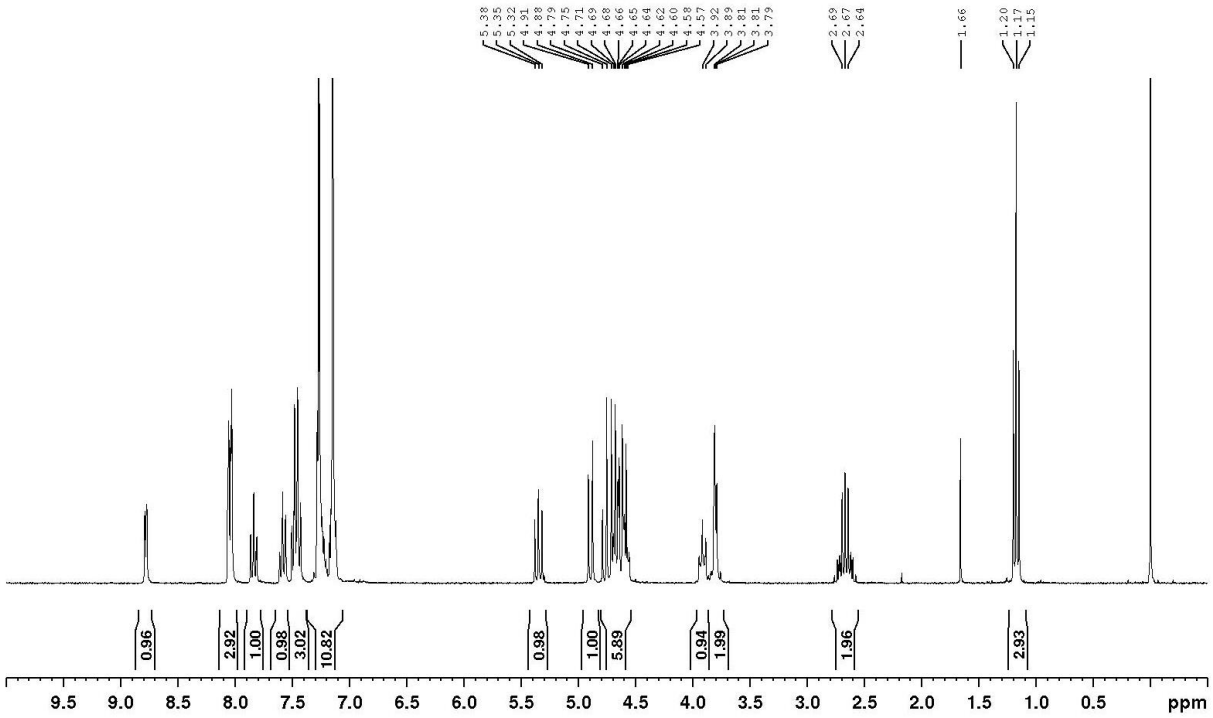



**Figure A-47:** 2-D NMR COSY spectrum of 2,3,4-tri-*O*-benzoyl-6-O-*p*-methoxybenzyl-D-glucopyranose (**5.12)**

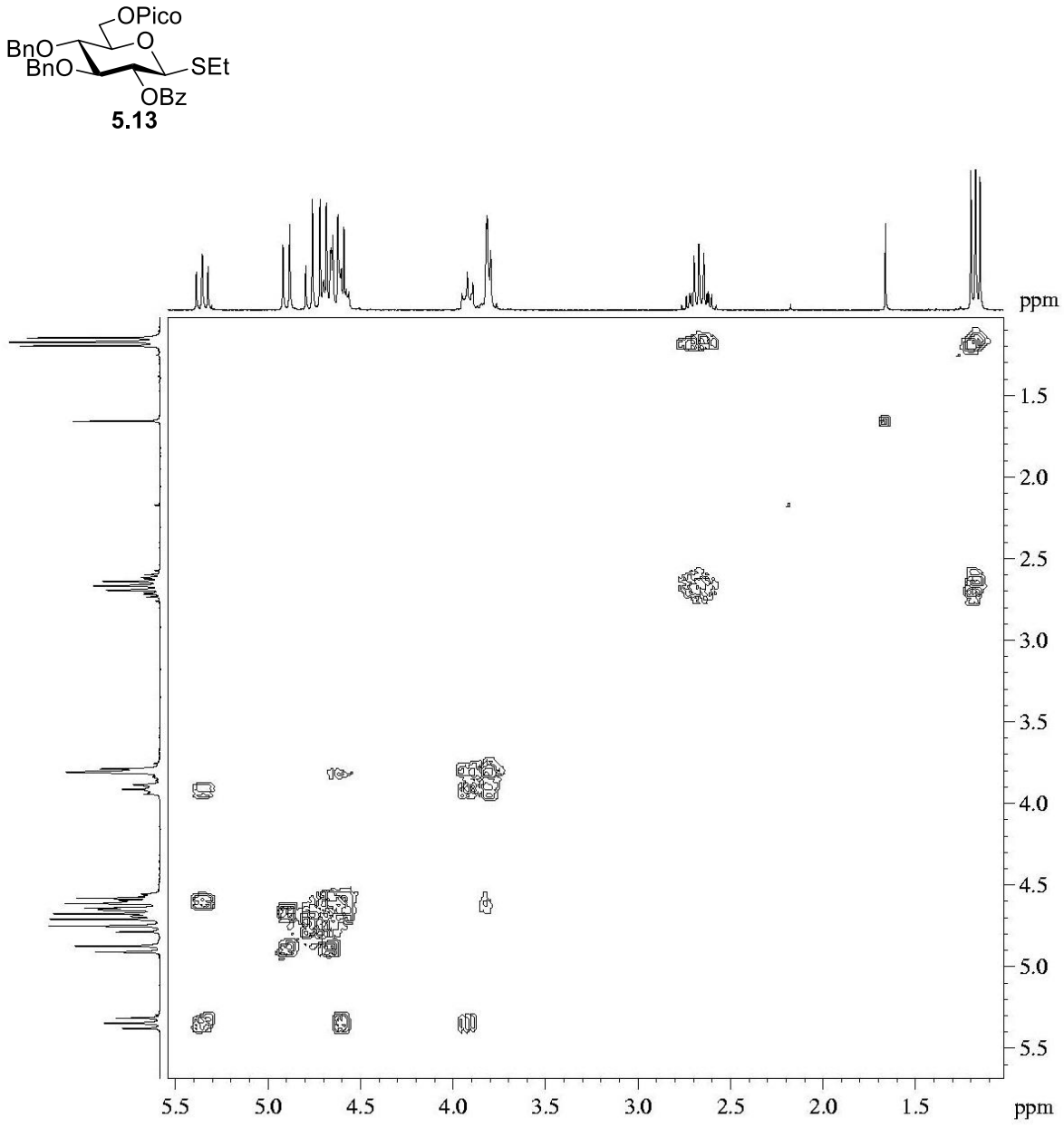



**5.13**




$CDCl_3$ 300 MHz

**Figure A-51:** $^1$H NMR spectrum of Ethyl 3,4-di-O-benzyl-2-O-benzoyl-6-O-picoloyl-1-thio-β-D-glucopyranoside **(5.13)**




$CDCl_3$ 300 MHz

**Figure A-47:** 2-D NMR COSY spectrum of Ethyl 3,4-di-O-benzyl-2-O-benzoyl-6-O-picoloyl-1-thio-β-D-glucopyranoside **(5.13)**