7-30-2015

Picolinyl-Assisted Approaches to Stereocontrolled Glycosylation

Jagodige Prithika Yasomanee
University of Missouri-St. Louis, jpymwc@mail.umsl.edu

PICOLINYL-ASSISTED APPROACHES TO STEREOCONTROLLED GLYCOSYLATION

By

JAGODIGE P. YASOMANEE

Master of Science (Chemistry), University of Missouri-St. Louis, August 2011

Master of Science (Chemistry), Southern Illinois University-Edwardsville, May 2009

Bachelor of Science (Chemistry) Hons., University of Peradeniya, Sri Lanka, May 2004

A Dissertation

Submitted to the Graduate School of the

UNIVERSITY OF MISSOURI – ST. LOUIS

in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

June 27th, 2014

Dissertation Committee

Prof. Alexei V. Demchenko, Ph.D. (Chair)

Prof. Eike B. Bauer, Ph.D.

Prof. Cristina De Meo, Ph.D. (SIUE)

Prof. Stephen M. Holmes, Ph.D.

ABSTRACT

Picolinyl-Assisted Approaches to Stereocontrolled Glycosylation

Jagodige P. Yasomanee

Doctor of Philosophy, University of Missouri – St. Louis

Prof. Alexei V. Demchenko, Advisor

Although carbohydrates are the most abundant molecules on Earth, our current knowledge of these fascinating natural compounds is still limited. Some aspects that are already known include the carbohydrate involvement in damaging cellular processes such as bacterial and viral infections, development of tumors, metastasis, septic shock, etc. Consequently the development of effective methods for the synthesis, isolation, analysis, and investigation of complex carbohydrates has become critical in all areas of glycoscience. Among various focus areas, stereocontrolled glycosylation has emerged as a topic of particular importance. Yet, it remains a remarkable challenge to chemists because a new chirality center is formed during glycosylation. A failure to control the stereoselectivity of glycosylation reactions will typically lead to mixtures of 1,2-*cis* and 1,2-*trans* diastereomers. The aim of stereocontrolling of glycosylation has been approached in a variety of ways and the effect of a neighboring acyl participating group has been among the most powerful stereodirecting factors known to date for obtaining 1,2-*trans* glycosides.

The work presented herein is dedicated to broadening the scope of the stereodirected glycosylation using the concept of participating groups. Novel to this approach is the development of a well-rounded methodology that allows for synthesizing either 1,2-*cis* or 1,2-*trans* glycosides by simple switching of protecting groups. This is accomplished *via* novel glycosyl donors equipped either with picolinyl (2-pyridylmethyl ether) or picoloyl (2-pyridylcarbonyl ester) groups. A mechanistic understanding of various modes of action of these groups enhanced our ability to perform stereodirected glycosylations with exceptional stereoselectivity. This led to the development of a novel concept to stereocontrolled glycosylation that we named Hydrogen-bond-mediated Aglycone Delivery (HAD). The HAD concept has been extended to the synthesis of various linear and branched oligosaccharides and broadening of all aspects of the methodology. Furthermore, this study evolved into the development of a new type of glycosyl donors allowing for switchable stereoselectivity.

ACKNOWLEDGEMENTS

First and foremost I would like to express my sincere gratitude to my PhD advisor, Professor. Alexei V. Demchenko, who allowed me join the "Glycoworld" as the very first student who selected him as the second choice. His continuous and invaluable support, encouragements and patience never let me feel that I could have joined a better group; nevertheless, undoubtedly proven that he is well deserved to be selected as the first choice! I am grateful to all professors in my dissertation committee including Eike B. Bauer and Stephen M. Holmes from UMSL and Cristina De Meo from Southern Illinois University, Edwardsville (SIUE) for their comments and support. Thank you Dr. Archana R. Parameswar for training me patiently when I first joined the Glycoworld with limited synthetic skills.

My special thanks go to Dr. Rensheng Luo for his assistance with NMR spectroscopy, Prof. Rudolf Winter and Mr. Joe Kramer for mass spectrometry and Dr. Nigam Rath for crystal structure determination. I also would like to extend my thanks to all faculty and staff members in the Department of Chemistry and Biochemistry - UMSL for their continuous support in numerous ways throughout my PhD. UMSL graduate school is also greatly acknowledged for the financial support given to me through the Graduate School Dissertation Fellowship. I would like to convey my extended gratitude to my previous research supervisors Prof. Jayasundera. Bandara from Institute of Fundamental Studies, Sri Lanka and, Prof. Sadegh Khazaeli from SIUE for their invaluable support, guidance and, encouraging me to pursue my PhD. I also wish to thank all the past and current Glycoworld group members for their support and thoughts.

I am indebted to my parents for their boundless love, emotional support and trusting me on my capabilities to succeed. I wish to thank my brother who takes a good care of my parents and letting me focus on my studies with no worries. Finally, I would like to thank my husband Ananth for being with me during all the ups and downs and, pushing me forward. Certainly, without my parents' and your infinite love, care, understanding and great support my journey wouldn't be this successful!

LIST OF ABBREVIATIONS

Å ..... Angstrom

Ac ..... Acetyl

$AgBF_4$ ..... Silver tetrafluoroborate

$AgClO_4$ ..... Silver perchlorate

AgOTf ..... Silver trifluoromethanesulfonate

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

Bn ..... Benzyl

br……..Broad

Bz ..... Benzoyl

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

Bu_4NBr ..... Tetrabutylammonium bromide

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

d ..... Doublet

1,2-DCE 1,2-Dichloroethane

DCM ..... Methylene chloride

dd ..... Doublet of doublets

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

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

Et ..... Ethyl

EtOAc ..... Ethyl acetate

Et_2O ..... Diethyl ether

Gal ..... Galactose

Glc ..... Glucose

h ..... Hour(s)

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

HSEt .....*S*-Ethyl

HSPh ..... *S*-Phenyl

HTol .....*S*-Tolyl

Hz ..... Hertz

IDCP ..... Iodonium dicollidine perchlorate

m ..... Multiplet

Man ..... Mannose

min ..... Minute

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

Me ..... Methyl

MeOTf..... Methyl trifluoromethanesulfonate

MeI ..... Methyl iodide

MeCN ..... Acetonitrile

MeOH ..... Methanol

MS ..... Molecular sieves

NaCN……...Sodium cyanide

NaOH ..... Sodium hydroxide

NaOMe ..... Sodium methoxide

NIS ..... *N*-Iodosuccinimide

NMR ..... Nuclear magnetic resonance

Pent ..... Pentenoyl

Ph ..... Phenyl

Phth…… Phthalimido

Pic……... Picolinyl

Pico…..…….Picoloyl

ppm ..... Parts per million

R_f ..... Retention factor

rt ..... Room temperature

SBox ..... *S*-Benzoxazolyl

SBiz ..... *S*-Benzimidazolyl

STaz ..... *S*-Thiazolinyl

s ..... Singlet

t ..... Triplet

TBDMS ..... *tert*-Butyldimethylsilyl

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

TFA ..... Trifluoroacetic acid

TfOH ..... Trifluoromethanesulfonic (triflic) acid

TLC ..... Thin layer chromatography

TMS……Trimethylsilyl

TMSI……... Trimethylsilyl iodide

TMSOTf ..... Trimethylsilyl trifluoromethanesulfonate

Troc 2,2,2-Trichloroethoxycarbonyl

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CHAPTER 1

From stereocontrolled glycosylation to expeditious oligosaccharide synthesis

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Yasomanee, J. P.; Demchenko, A. V. From stereocontrolled glycosylation to expeditious oligosaccharide synthesis. *Trends Glycosci. Glycotechnol.* **2013**, *25,* 13-42.

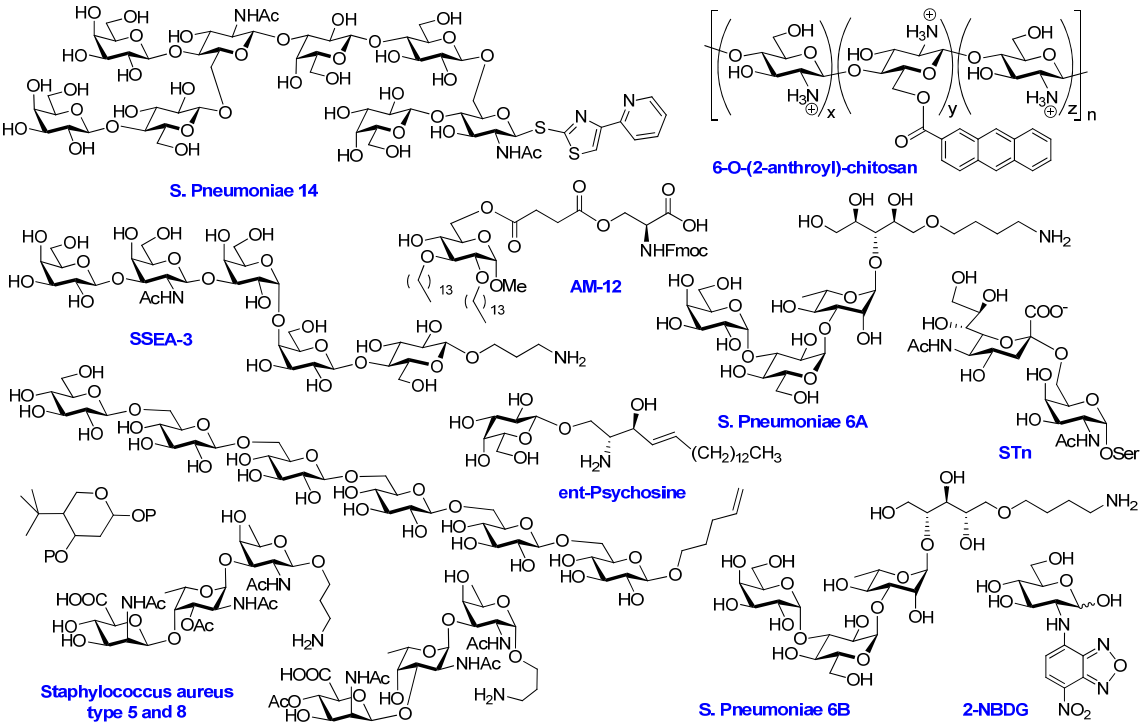
1.1. Introduction

Carbohydrates are involved in a wide range of fundamental biological processes and are often referred to as the "essential molecules of life".[1] Indeed, our life begins with fertilization, which is taking place *via* a very selective carbohydrate-protein recognition process.[2] Carbohydrates also help us to maintain healthy lifestyle because of their involvement into anti-inflammation, immunoresponse, joint lubrication, cell growth, antigenic determination, etc.[3] Thanks to the explosive growth of the field of glycosciences, the improved understanding of the roles of carbohydrates allows us to describe them as "molecules of death" due to their sizable contribution into harmful processes including bacterial and viral infections, development and growth of tumors, metastasis, tissue rejection, septic shock, congenital disorders, etc.[4] Many of these cellular processes are directly associated with the pathogenesis of deadly diseases of the 21st century.

One of the major focuses of the Glycoworld since 2001 has been set for the synthesis of biologically important and therapeutically relevant oligosaccharides associated with pathogenesis of cancer, pneumonia, septicemia, etc. Some targets that our laboratory synthesized over the past decade and some current targets are depicted in Figure 1.1.[5-17] These target molecules are very diverse in their composition: both common monosaccharides, such as glucose and galactose, as well as more rare or unusual sugars, such as sialic acid or "ManNAcA" are present therein. Some structures are plain oligosaccharides and others are conjugated with other biomolecules of the amino acid or lipid origin. Nevertheless, there is one common thing for all of these structures: all monomeric units are connected *via O*-glycosidic linkages. In spite of significant progress

that has emerged in the area of chemical glycosylation, chemical *O*-glycosylation remains challenging and inefficient, particularly when applied to the synthesis of difficult linkages. Therefore, the development of new methods for stereocontrolled synthesis of glycosidic linkages remains one of the major focuses of research in our laboratory.

Figure 1.1. Past and current synthetic targets in our laboratory.

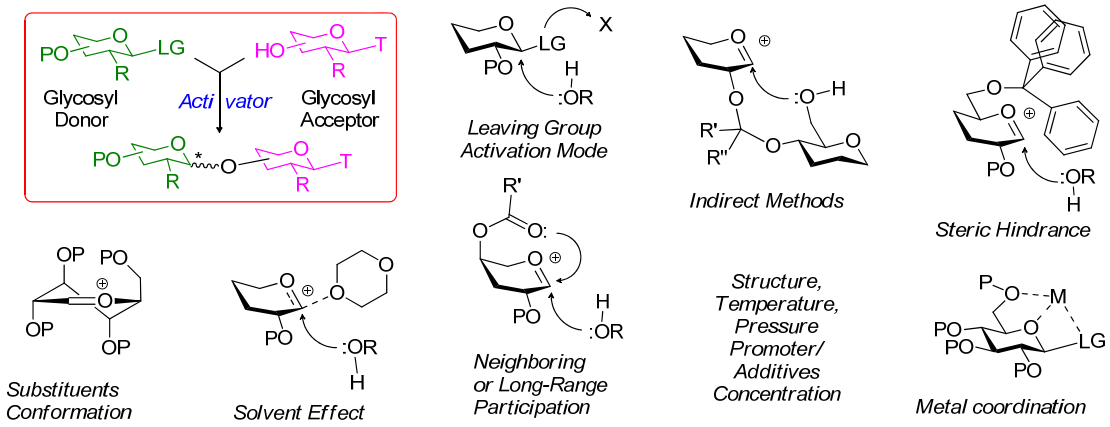


1.2 The development of new methods for chemical glycosylation

A majority of the biologically and therapeutically active carbohydrates are oligosaccharides (or glycoconjugates) in which monosaccharides are linked *via* *O*-glycosidic bonds. Chemically, this linkage is formed by a glycosylation reaction wherein a leaving group (LG) of the glycosyl donor is replaced with a hydroxyl moiety of the glycosyl acceptor (Scheme 1.1).[18] Other functional groups on both the donor and acceptor are temporarily masked with protecting groups (P, R, T). Since the new glycosidic

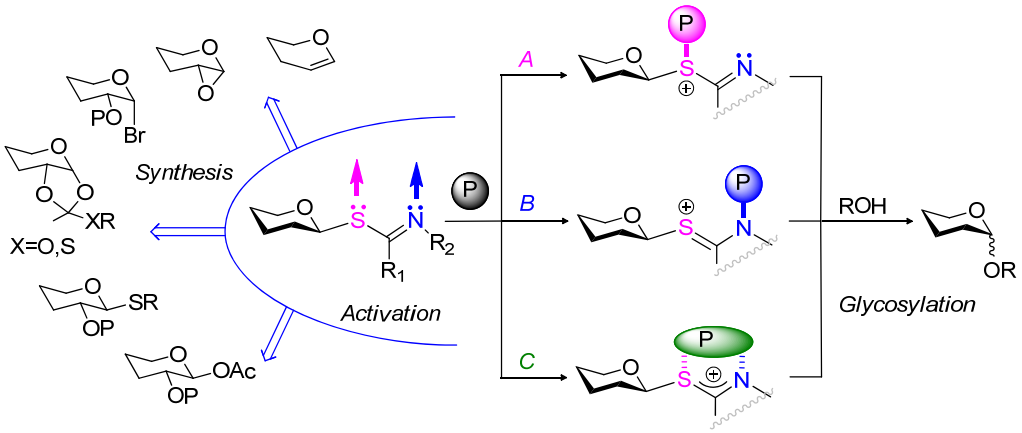
linkage creates a new chirality center, particular care has to be taken with regards to the stereoselectivity. Although mechanistic studies of the glycosylation reaction are still scarce, certain conventions have already been established.[19] Typical uncontrolled glycosylation leads to anomeric mixtures mixtures of 1,2-*cis/trans* diastereomers. If the use of an acyl-type substituent at C-2 is permitted, the synthesis of 1,2-*trans* glycosides becomes relatively straightforward although occasionally even participating acyl moieties fail in providing efficient participation *via* an acyloxonium intermediate.[20] In the instances where the use of an 2-*O*-acyl substituent is impossible or impractical, the synthesis of 1,2-*trans* glycosides becomes as challenging as the synthesis of 1,2-*cis* glycosides, for which no universal method is still available,[21,22] despite of a plethora of methods developed for their synthesis. Therefore, the major effort has been put into the investigation of various factors that may affect the stereoselectivity of glycosylations (Scheme 1.1). Other factors influence the stereoselectivity only up to certain extent and in spite of significant progress, chemical *O*-glycosylation remains among the top challenges of modern synthetic chemistry due to the requirement to achieve complete stereocontrol and the necessity to suppress side reactions.[18]

Scheme 1.1. Glycosylation reaction and factors affecting its stereoselectivity.



Although a typical glycosylation reaction follows monomolecular mechanism, the nature of a leaving group may also have an effect on the anomeric stereoselectivity, and these observations led to the development of a large number of different classes of glycosyl donors.[18] Early methods developed by Fischer[23] and Koenigs and Knorr[24] have been complemented by the development of other leaving groups, amongst which thioglycosides[25] and *O*-imidates[26] practically revolutionized the field of carbohydrate chemistry. These new glycosyl donors have been successfully applied to the synthesis of a large variety of natural compounds and unnatural mimetics thereof. Nevertheless, even these very widespread methods have drawbacks. For instance, *O*-imidates typically provide very high selectivity in glycosylations, although low stability of these groups makes it impossible to use them as building blocks in oligosaccharide synthesis. Conversely, thioglycosides are very stable and as a result fit into many modern strategies for oligosaccharide assembly. However, the stereoselectivity obtained with thioglycosides is often lower than that achieved with their *O*-imidoyl counterparts. Hence, our initial intention was to design a new class of a leaving group, some sort of a hybrid structure between classic thioglycosides and *O*-imidates.

Scheme 1.2. Synthesis and activation of glycosyl thioimidates.

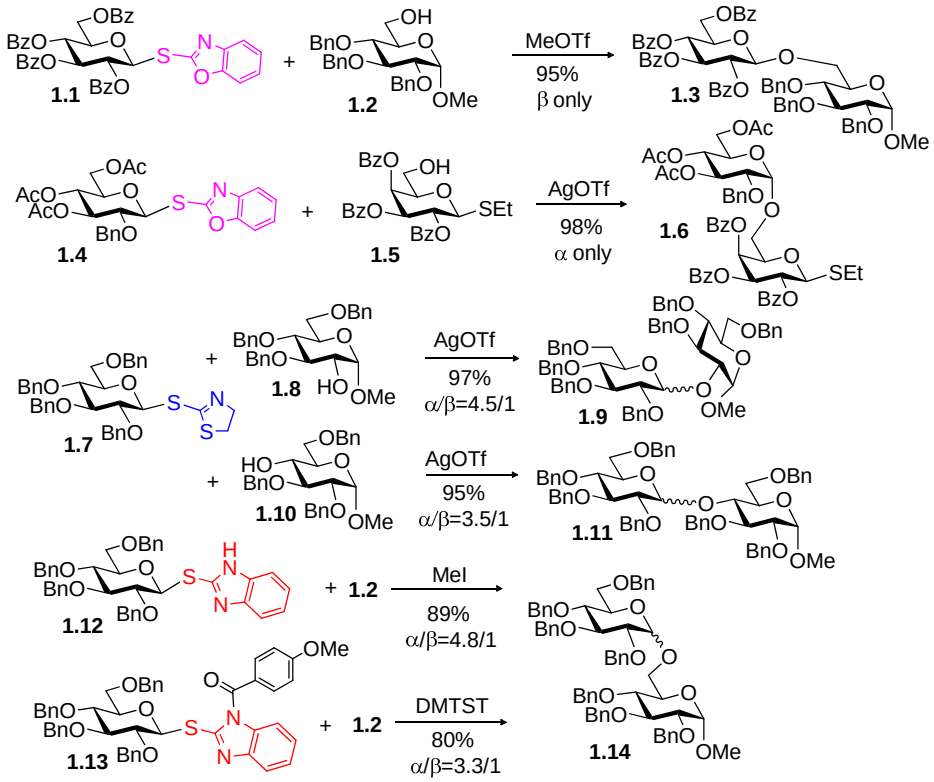


We had anticipated that glycosyl thioimidates, compounds with S-CR^1=NR^2 generic leaving group, would be universally applicable and may combine positive traits of other known glycosyl donors and would eventually create a new robust method for chemical glycosylation. We also assumed that thioimidates can be obtained *via* a variety of modes, all of which were later confirmed (Scheme 1.2), and that their reactivity and stability can be tuned to a wide range by varying electronic and/or steric properties of the R^1 and R^2 substituents. One of the most important reasons to select this platform for future studies was the belief that these polyfunctional leaving groups could be activated *via* a variety of modes depicted in Scheme 1.2. Thus, we assumed that thioimidates can be activated directly *via* the anomeric sulfur, or remotely, a concept proposed by Hanessian,[27] *via* the nitrogen atom with the use of electrophilic reagents. Additionally, metal coordination can also affect the leaving group ability of the thioimidoyl moiety and this could take place *via* the sulfur, the nitrogen or a combination of both reactivity centers. Extensive studies that have been conducted later on have confirmed the viability of the pathways proposed *vide infra*.

Over the last decade, the thioimidate method has evolved into a very robust methodology for glycosylation.[28,29] Particularly, with the introduction of novel *S*-benzoxazolyl (SBox) and *S*-thiazolinyl (STaz) leaving groups, it has become apparent that thioimidates can withstand many reaction conditions associated with protecting group manipulations.[30,31] In addition, thioimidates are easily accessible from a variety of simple precursors. This class of glycosyl donors can be typically glycosidated under a range of relatively mild activation conditions. Superior stereoselectivity in comparison to other glycosylation methods is often achieved, and thioimidoyl moiety could be

selectively activated in the presence of other types of leaving groups. All listed are important traits for both glycoside and oligosaccharide synthesis that are rarely found all in one class of a leaving group. *S*-benzimidazolyl (SBiz)[32] leaving group that was recently introduced among a series of other thioimidoyl leaving groups developed by us[28,33,34] and others[29,35-37] further enhances utility of this leaving group in glycosylation. Some illustrative examples of coupling reactions between glycosyl thioimidates and various glycosyl acceptors are shown in Scheme 1.3.

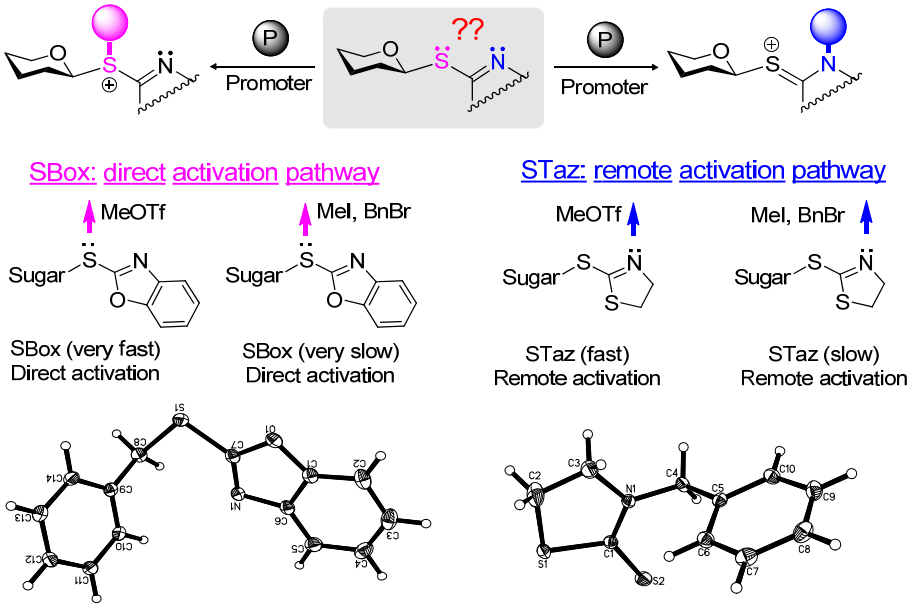
Scheme 1.3. SBox, STaz, and SBiz glycosyl donors in stereoselective glycoside synthesis.



Having extensively studied a variety of glycosyl thioimidates, it came to our attention that there is very little commonality between these seemingly similar leaving groups.

This called for further investigation of the activation pathway and during the course of this study we noticed that it is the structure of the leaving group rather than the nature of the activation reagent that determine the activation mode, either direct or remote. For instance, SBox glycosides are activated *via* the anomeric sulfur (direct activation) regardless of the activation conditions used: NIS/TfOH, AgOTf, or MeOTf.[38] More recent study with the SBiz glycosyl donors showed that these compounds also follow the direct activation pathway.[32] Further enrichments of the leaving group ability of glycosyl thioimidates require a thorough understanding about applicability of different promoters and their activation pathways.

Figure 1.2. Direct activation of SBox glycosides and remote activation of STaz glycosides.



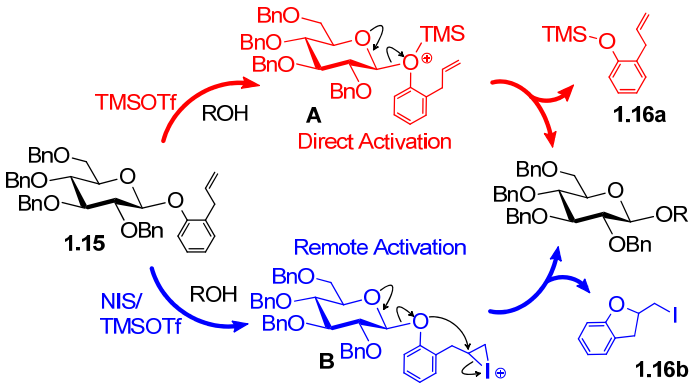
Very differently, STaz leaving group is activated *via* the remote nitrogen. Side-by-side comparisons of the SBox and STaz glycosyl donors under alkylation activation conditions (MeI, BnBr) allowed to determine the activation mode. The X–ray

crystallography of the departed aglycones clearly demonstrated the alkylation mode, Bn-SBox and Bn-NTaz (Figure 1.2).[39] The reactivity difference between slow activation of the SBox and fast activation of STaz was sufficient to develop a new orthogonal strategy based on these two seemingly similar leaving groups *vide infra*).

This observation of the differential activation of SBox and STaz leaving group gave us an idea of developing a new type of a leaving group that would be capable of both direct and remote activation pathways. Ideally, activation pathways should be differentiated by a simple change of the promoter/activator. In our opinion, if this kind of a leaving group were available, it could easily fit into selective or even orthogonal activation strategies along with other, common glycosyl donors. To the best of our knowledge, among a plethora of leaving groups developed, only glycosyl phosphites allow for the differential activation mode.[40-42] This trait, however, has not yet been employed in multi-step block oligosaccharide synthesis, perhaps due to the relatively unstable nature of this leaving group. With this line of thought, we have developed the *ortho*-allylphenyl (AP) leaving group and demonstrated that can be activated for chemical glycosylation *via* both direct anomeric (oxygen) and remote (*via* alkene) pathways.[43] Hung and co-workers came up with essentially the same idea and introduced the AP leaving group concomitantly.[44] The orthogonal-like activation of the AP moiety along with common thioglycosides allowed for executing efficient oligosaccharide assembly (*vide infra*). The two activation pathways were confirmed by isolating (*O*-allylphenoxy)trimethylsilane (**1.16a**) from TMSOTf-promoted reaction of **1.15** which takes place *via* the anomeric oxygen atom (direct activation) and 2-iodomethyl-2,3-

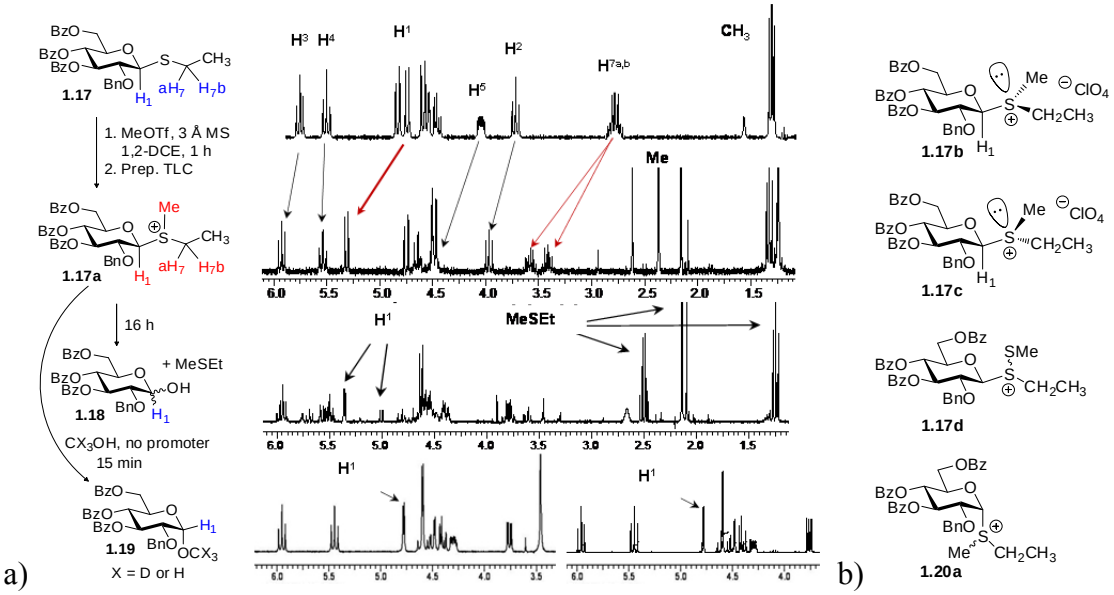
dihydrobenzofuran (**1.16b**) from NIS/TMSOTf-promoted reaction in which the activation with I^+ takes place *via* the remote allyl moiety (Scheme 1.4).[43]

Scheme 1.4. Direct and remote activation pathways of *ortho*-allylphenyl (AP) glycosides



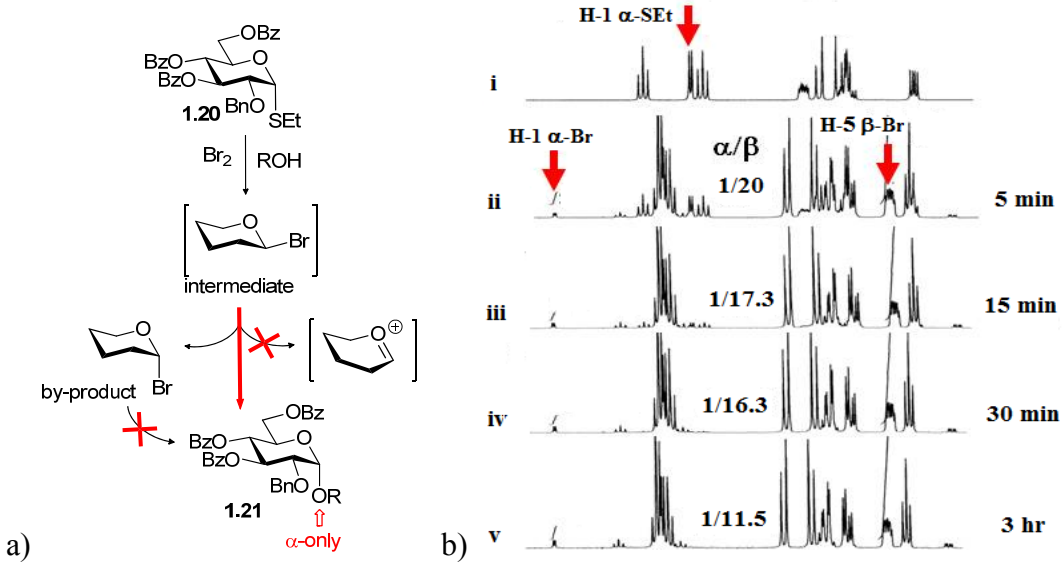
Having investigated the activation modes of thioimidates and developed a number of leaving groups, it came to our attention that very little is known about activation modes of common leaving groups in general. For instance, activation of thioglycosides has been proposed multiple times[25,45-48] although direct evidence of this activation had not been acquired prior to our recent study of sulfonium ions as intermediates of glycosylation.[49] Anomerically pure sulfonium salt **1.17a**, obtained by direct alkylation of superdisarmed thioglycoside **1.17** with MeOTf, can be isolated and characterized by NMR (Scheme 1.5a). A number of other anomeric sulfonium salts have been generated and characterized accordingly using MeI/$AgClO_4$ or dimethyl(methylthio)sulfonium triflate (DMTST, Scheme 1.5b).[49] It is our expectation that dedicated studies of the activation pathways and reaction mechanisms would lead to the development of highly stereocontrolled glycosylation methodologies.

Scheme 1.5. Direct synthesis of glycosyl sulfonium salts.



Other recent mechanistic work in our laboratory involved the investigation of the glycosidation of thioglycosides in the presence of bromine.[50] It was demonstrated that bromine-mediated glycosylation of thioglycoside **1.20** leads to exclusive α-selectivity in product **1.21** (Scheme 1.6a). This reaction was monitored by NMR, and this study demonstrated that β-bromide is the reactive intermediate that leads to the product **1.21** with complete stereoselectivity. The NMR experiment showed that β-bromide can undergo a relatively rapid anomerization into the α-linked counterpart (Scheme 1.6b), and if this anomerization is not suppressed, the yield of the glycosylation product can be low. Once formed, α-bromide is totally unreactive under the established reaction conditions, but it can be reactivated in the presence of mercury(II)-based promoters. Being primarily applicable to thioglycosides of the unreactive, superdisarmed series, this concept complements well-known *in-situ* anomerization procedure introduced by Lemieux and co-workers for reactive bromides[51] and further adapted to iodides by Gervay-Hague.[52,53]

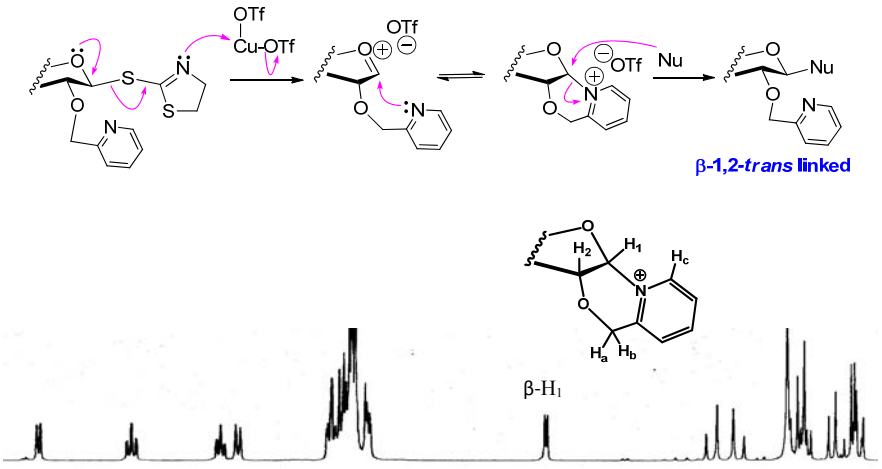
Scheme 1.6. Stereoselective glycosidation of superdisarmed thioglycoside 1.20 *via* reactive β-bromide intermediate.



Our laboratory has also introduced a complementary method for the synthesis of 1,2-*trans* glycosides. Differently from a vast variety of other approaches for 1,2-*trans* glycosylation based on the participating effect of the ester neighboring group (*vide supra*)[20] this method is based on an ether-type substituent. We demonstrated that 1,2-*trans* selectivity can be achieved with the use of a 2-*O*-picolinyl moiety, a novel neighboring group that is capable of efficient.[54] The participation mode was studied by a variety of techniques, and the six-membered intermediate shown in Scheme 1.7 was proven by extended 2D NMR experimentation. The compatibility of this protocol with glycosyl donors of the thioimidoyl, thioglycosyl, and trichloroacetimidoyl series has been shown.[55] The fact that picolinyl moiety also retains the glycosyl donor in the armed state, as opposed to disarming acyl participating moieties, was used as a basis for the development of the "inverse armed-disarmed" strategy (*vide infra*)[54,55] that allows to

obtain *trans-trans* and *trans-cis* patterned oligosaccharides and expands the scope of classic Fraser-Reid's armed-disarmed approach.[56] Currently we are working on expanding the application of picolinyl and picoloyl protecting group in stereocontrolled glycosidation reactions.[57]

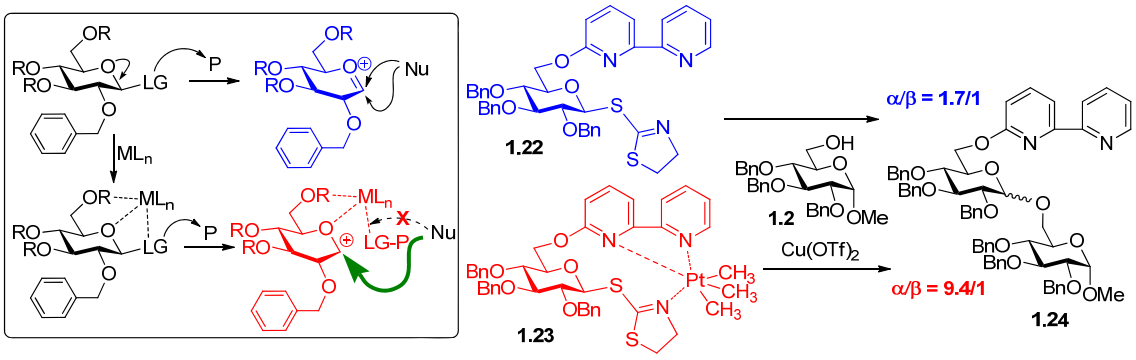
Scheme 1.7. Synthesis of 1,2-*trans* glycosides assisted by 2-*O*-picolinyl arming participating group.



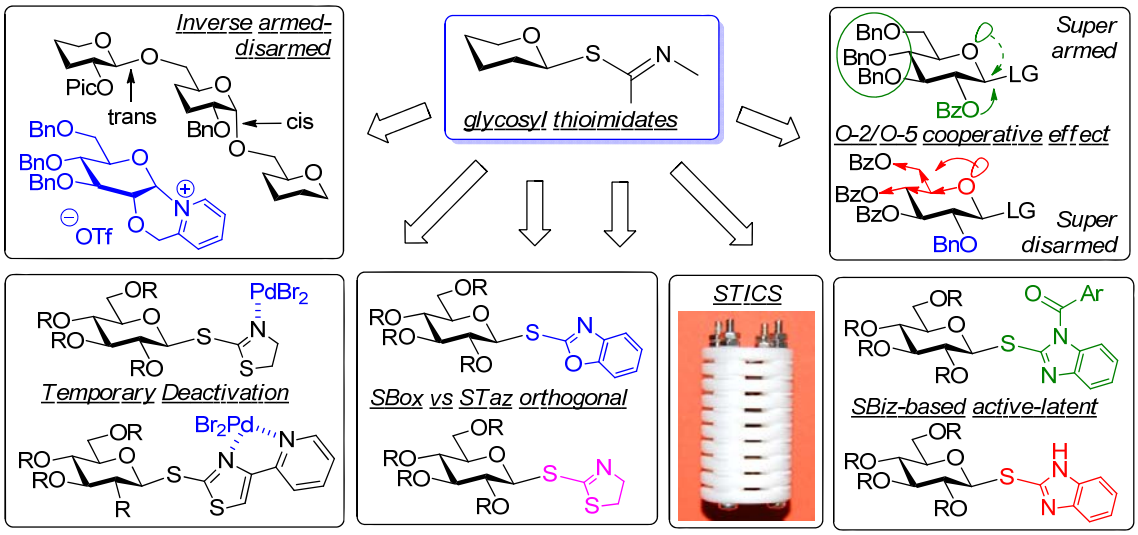
In our parallel study of investigating pyridyl-based protecting groups and their effect on the stereoselectivity of glycosylation, we observed that a multi-dentate metal coordination to the leaving group, along with a protecting group at *O*-6 and/or *O*-5, has a strong effect on the stereoselectivity of chemical glycosylation (Scheme 1.8). We showed that platinum(IV) complexation of 6-*O*-picolinyl or 6-*O*-bipyridyl to the leaving group, such as thiazolinyl shown in Scheme 1.8, has a pronounced effect on the stereoselectivity of glycosylation.[58] While the glycosidation of thioimidate donor **1.22** with acceptor **1.2** in the presence of $Cu(OTf)_2$ gave the disaccharide **1.24** with poor selectivity (α/β = 1.7/1), the complexed glycosyl donor counterpart **1.23** showed a significant 5-fold increase in 1,2-*cis* stereoselectivity (α/β = 9.4/1). In our opinion, this

result offers a very promising venue for further investigation of thioglycosyl and thioimidoyl donors as ligands for complexes with transition metals.[59]

Scheme 1.8. Effect of metal complexation on the stereoselectivity of glycosylation.



Scheme 1.9. Glycosyl thioimidates led to a discovery of a variety of new strategies and concepts for oligosaccharide synthesis.



These mechanistic studies along with the major effort to investigate glycosyl thioimidates resulted in the development of a number of robust methods for stereocontrolled glycosylation. Thioimidates easily fit into the existing strategies for

oligosaccharide synthesis and also allowed us to develop a variety of strategies that are unique to thioimidates. While working with thioimidates, we have also discovered some unusual trends and phenomena, such as the cooperative effect in glycosylation, which was later applied to building blocks of other series. Subsequent sections will emphasize methods, strategies, and phenomena that have been discovered mainly thanks to the unique structural features and reactivity pattern of glycosyl thioimidates (Scheme 1.9).

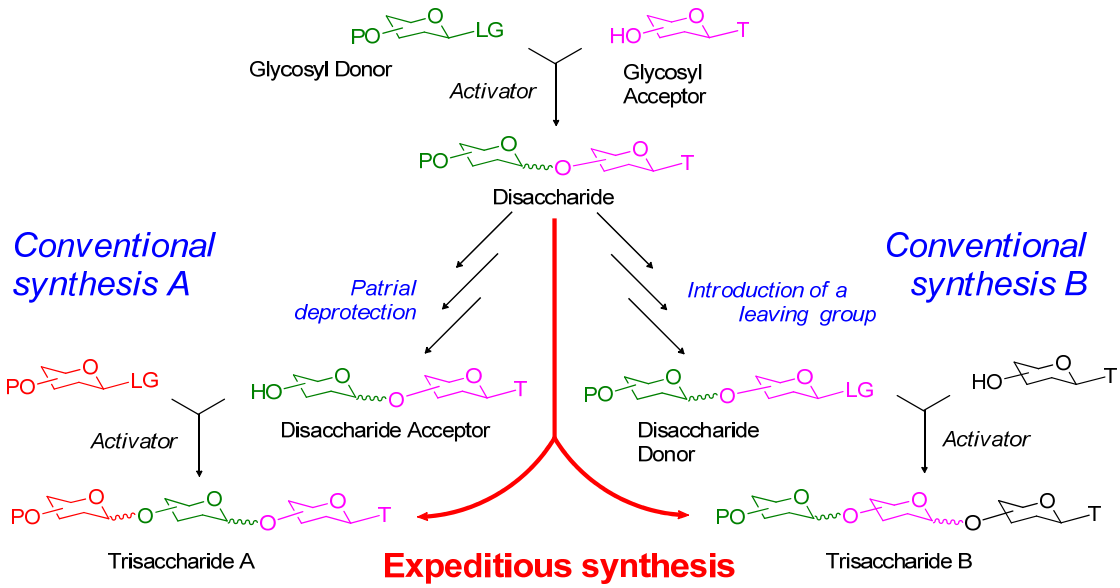
1.3 A strategic approach to the synthesis of oligosaccharide sequences

A single-step glycosylation is the only one challenge that researchers are working on the oligosaccharide synthesis face. In accordance with the traditional oligosaccharide synthesis, the disaccharide that has been formed as a result of the first glycosylation, needs to be converted into a glycosyl acceptor or glycosyl donor of the second generation.[60] This is usually accomplished *via* additional protecting and/or leaving group manipulations, respectively, that are required between each glycosylation step (Scheme 1.10). Resultantly, the synthesis becomes increasingly inefficient and often leads to a dramatic drop in yield, and as a consequence, the availability of oligosaccharides. One way to circumvent the necessity for additional synthetic steps is to execute an advantageous expeditious approach according to which building blocks are activated sequentially with no necessity for the interim protecting / leaving group reactivity. The differential reactivity of building blocks can be achieved *via* reactivity tuning by means of the protecting groups. Strategic placement of protecting groups leads to a differential reactivity of various building blocks that are then activated in accordance with their reactivity profile. Following the pioneering study by Fraser-Reid,[56] contributions from

Ley,[61] Wong[62] and others[63] led to a variety of very effective concepts based on the principle of chemoselective differentiation of reactivity. Usually, protecting groups in both reaction components and careful selection of mild reaction conditions have to be taken into consideration to allow direct chemoselective activation of the armed glycosyl donor over the disarmed glycosyl acceptor. The convenience of this approach is that the same leaving group can be used for all building blocks in the sequence.

Another general concept to expedite oligosaccharide synthesis is to achieve selective activation of different leaving groups, and it is practically independent on the nature of protecting groups. A number of selective activation techniques have been developed and selective activation, active-latent, and orthogonal strategies are only few to mention.[64] Our group studied both chemoselective and selective activation-based strategies.

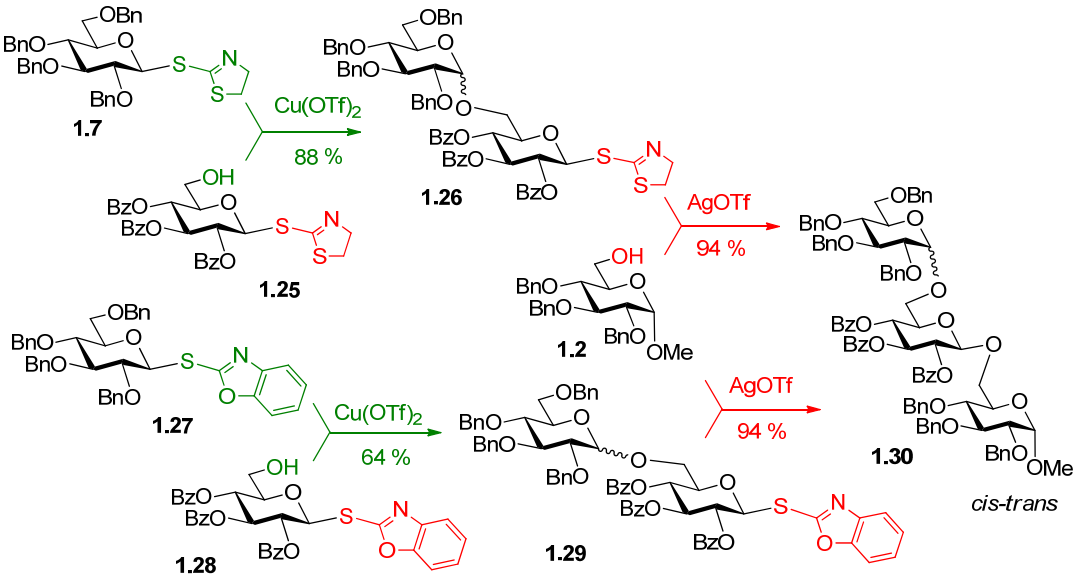
Scheme 1.10. Expeditious approach to streamlining oligosaccharide synthesis.



1.3.1 Chemoselective oligosaccharide synthesis

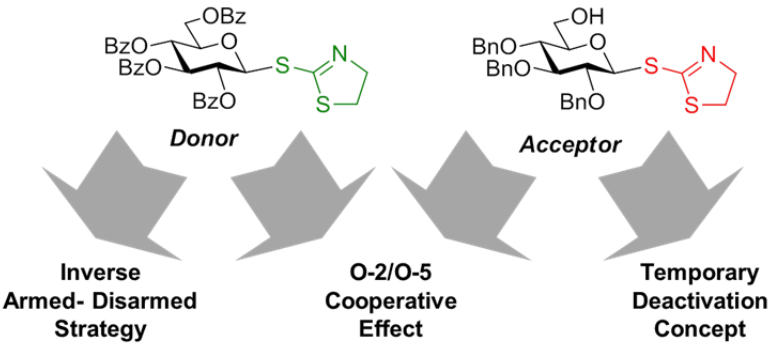
First described by Fraser-Reid, the armed disarmed strategy has attracted notable attention in the scientific world.[63] Many classes of leaving groups can be activated accordingly, and glycosyl thioimidates is no exception: it was determined that both SBox and STaz glycosides fit into the general concept of the armed-disarmed approach.[56,63,65-67] The activated (benzylated) thioimidates could be promoted over electronically disarmed (benzoylated) glycosyl acceptors equipped with the same leaving group in the presence of $Cu(OTf)_2$. For instance, as shown in Scheme 1.11, armed STaz donor **1.7** could be chemoselectively activated over the disarmed acceptor **1.25** in the presence of $Cu(OTf)_2$ leading to the formation of disaccharide **1.26**.[54] The disarmed STaz group of the latter can be also activated, but requires more powerful promoter AgOTf.

Scheme 1.11. Chemoselective activation of STaz and SBox building blocks in accordance with the classical armed-disarmed approach.



Resultantly, a *cis-trans* linked trisaccharide **1.30** was obtained in an excellent overall yield without any intermediate functional group manipulations. Similarly, armed SBox donor **1.27** was activated over disarmed SBox acceptor **1.28**,[68] but again only the *cis-trans* linked sequence was obtained. These results clearly represent the major limitation of the traditional armed-disarmed approach. As insightfully stated by Fraser-Reid, "protecting groups do more than protect"[65], protecting groups affect the reactivity, nevertheless they also determine the stereoselectivity of glycosylation. Therefore, 1,2-*trans* glycosides cannot be introduced by using conventions of the traditional armed-disarmed approach, which is a significant pit fall because *trans-trans* and *trans-cis* sequences are commonly found in a variety of natural oligosaccharide syntheses. Apparently, it is impossible to take the disarmed donor **1.31** and try to couple it with the armed acceptor **1.32** using traditional armed-disarmed approach. The cross-coupling would not happen, instead, the reactive glycosyl acceptor **1.32** will self-react either intra or inter-molecularly. This appealed to us as a significant challenge, and we approached it in a variety of modes.

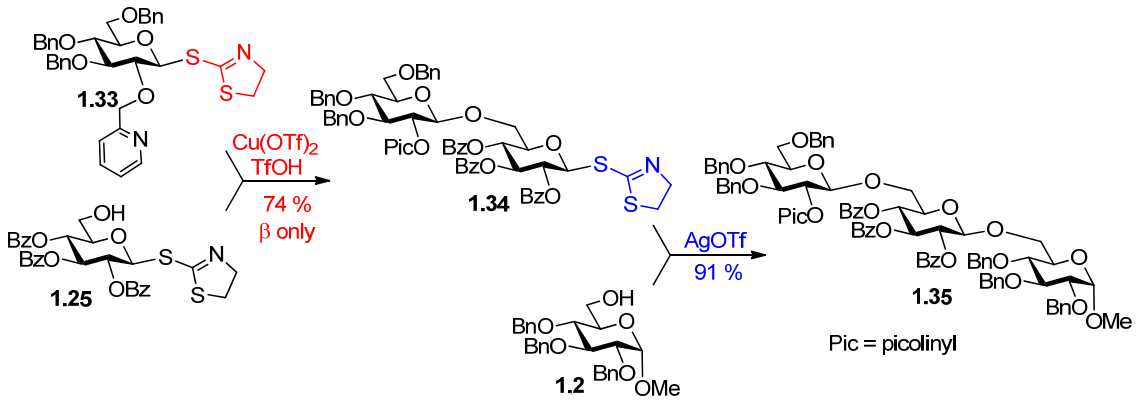
Scheme 1.12. Attempts to broaden the scope of the armed-disarmed concept.



First, by making modifications to the glycosyl donor we developed the inverse armed-disarmed approach (Scheme 1.12). Second, by modifying glycosyl acceptor we

introduced the temporary deactivation concept. Third, by careful reactivity tuning and studying differential protecting group pattern in both glycosyl donor and glycosyl acceptor counterparts we discovered the O-2/O-5-cooperative effect in glycosylation. All three concepts are discussed below. Concomitantly, a pre-activation-based strategy, which was invented to address essentially the same global challenge, was developed by Huang,[69,70] van der Marel[45,71] and others.

Scheme 1.13. Inverse armed-disarmed strategy with 2-*O*-picolinyl glycosyl donor.

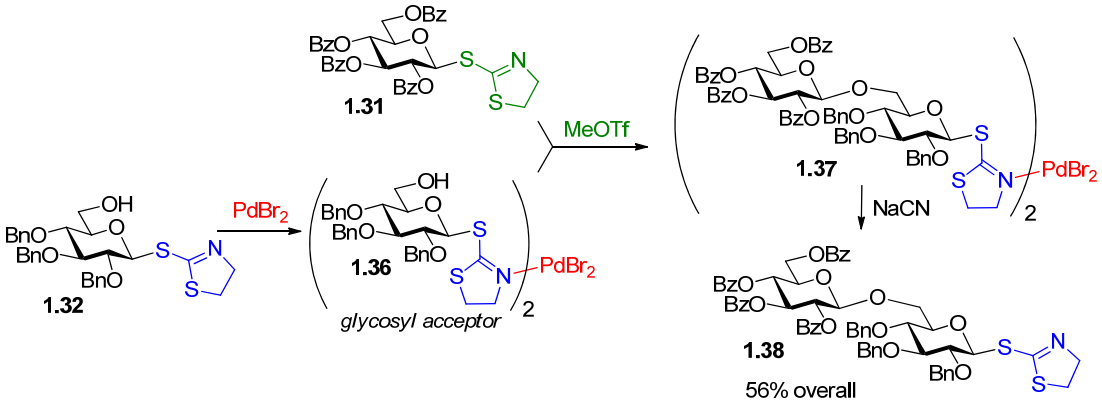


The inverse armed-disarmed concept was invented based on 2-*O*-picolinyl, a novel arming participating group. The application of the inverse strategy which allowed to expand chemoselective activation principle to the synthesis of *trans-trans* sequenced oligosaccharides.[54] For instance, when STaz donor **1.33** equipped with 2-*O*-picolinyl group was activated over the disarmed acceptor **1.25**, disaccharide **1.34** was obtained with complete 1,2-*trans* stereoselectivity (Scheme 1.13). This is the inverse outcome in comparison to the classical armed-disarmed approach resulting in 1,2-*cis* bond formation in the first step (*vide supra*, see Scheme 1.11). Subsequent activation of **1.34** with AgOTf yielded the *trans-trans*-linked trisaccharide **1.35**. A possibility of synthesizing a

trans-cis-linked trisaccharide using the picolinyl approach along with conventions of the cooperative effect was also demonstrated.[55]

During our studies we have observed that STaz leaving group can act as a ligand for transition metals to form stable non-ionizing complexes. Upon this complexation, reactivity of the STaz glycoside was reduced dramatically because the activation site the nitrogen was temporarily blocked by the metal.[72] This interesting observation allowed us to develop the temporary deactivation concept depicted in Scheme 1.14.

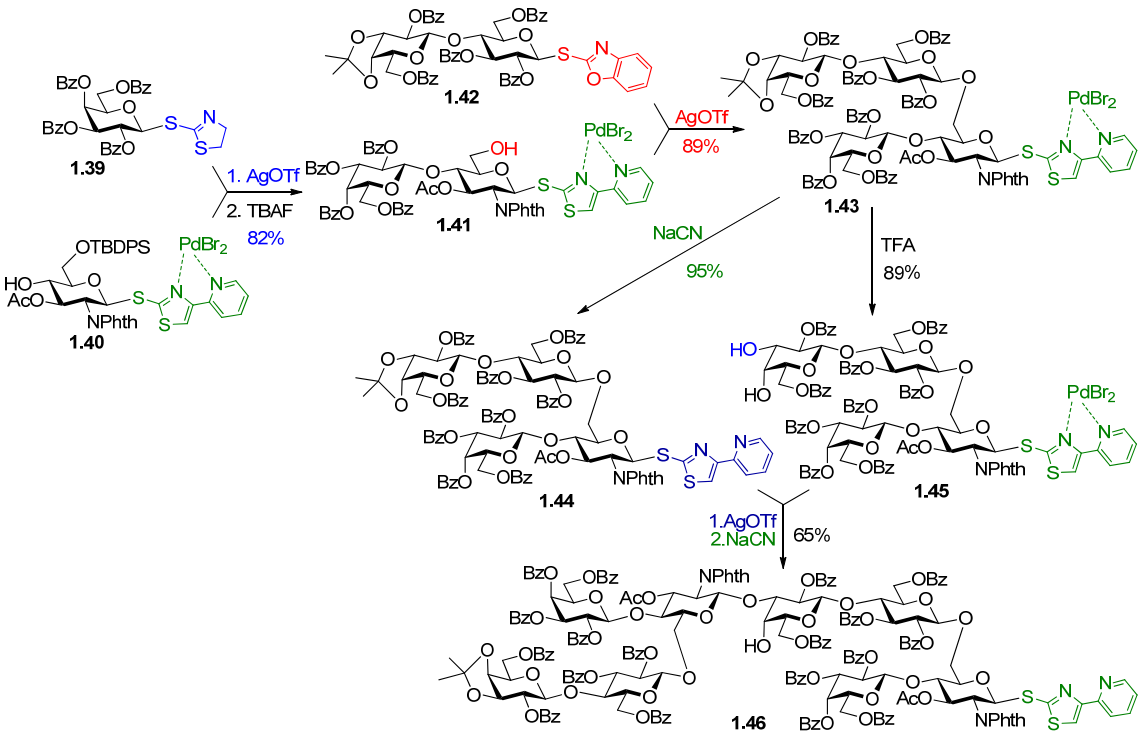
Scheme 1.14. Temporary deactivation concept.



First, the deactivated STaz acceptor **1.36** was obtained *via* metal complexation of the STaz moiety of the armed acceptor **1.32** with $PdBr_2$ to form stable, non-ionizing metal complex**.** This temporary deactivation (capping) of the STaz moiety in the acceptor **1.36** facilitated the successful activation of the "free" STaz leaving group of the disarmed glycosyl donor **1.31** in the presence of MeOTf to afford disaccharide **1.37**. Upon ligand exchange with NaCN "free" disaccharide **1.38** was obtained and could be used in further chain elongation directly.

The versatility of the temporary deactivation concept was demonstrated by the synthesis of octasaccharide **1.46** that consists of two repeating units of *Streptococcus pneumoniae* serotype 14 polysaccharide (Scheme 1.15).[10] A number of new leaving groups capable of efficient activation for glycosylation and also to form a stable bidentate complex with palladium(II) bromide. Amongst various leaving groups/ligands investigated, the (4-pyridin-2-yl)thiazole-2-yl thioglycoside (SPT) moiety was proven the most advantageous. As the first step of this synthesis, the "free" STaz donor **39** was activated over the complexed SPT acceptor **1.40** in the presence of AgOTf followed by desilylation with TBAF to achieve the disaccharide acceptor **1.41**.

Scheme 1.15. Synthesis of octasaccharide of *S. pneumonia* serotype 14 using the temporary deactivation strategy.

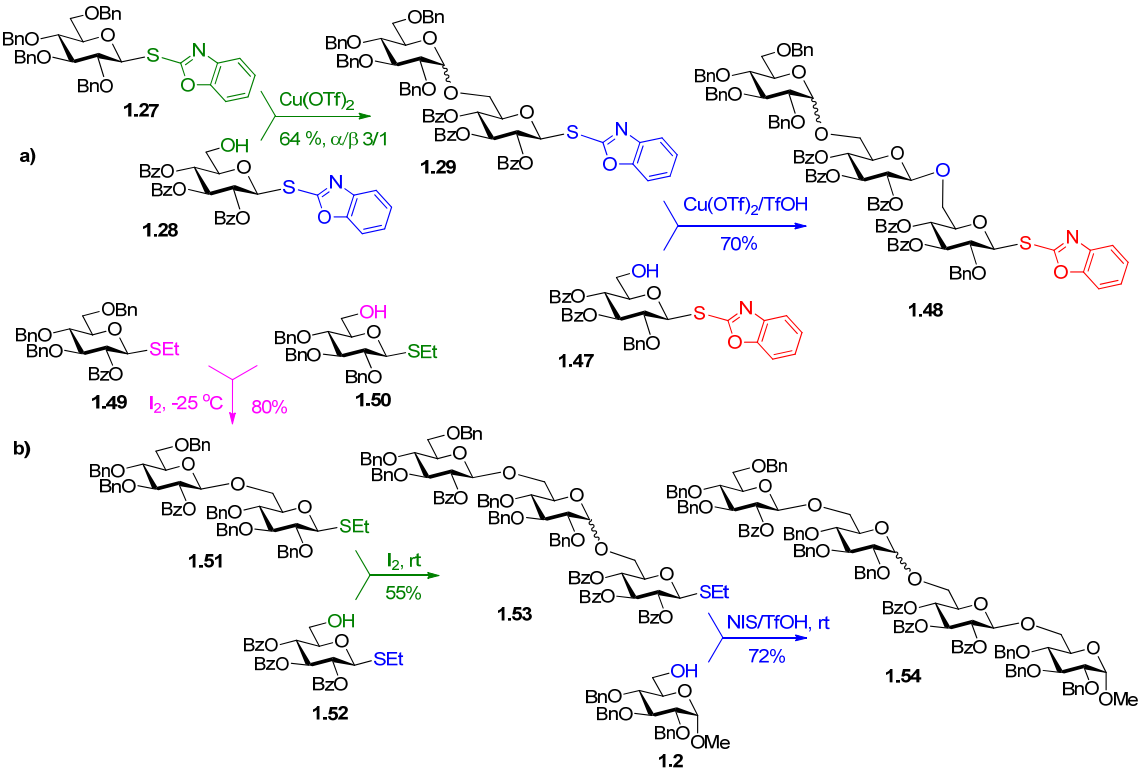


The latter was then reacted with SBox lactose donor **1.42** to obtain the pneumococcal tetrasaccharide repeating unit **1.43**. Subsequent decomplexation of one portion of **1.43** with NaCN gave donor **1.44,** meanwhile the treatment of another portion of **1.43** with dilute TFA afforded acceptor **1.45** with the deactivated SPT leaving group. Having these building blocks in hand, coupling of **1.44** and **1.45** in the presence of AgOTf followed by decomplexation yielded octasaccharide **1.46.**[10]

We also reported that a mixed protecting group pattern can have a rather unexpected effect on the reactivity of glycosyl donors and glycosyl acceptors. Upon investigating SBox glycosides containing an arming benzyl group at C-2 and disarming acyl groups at the remote positions, it was expected that reactivity would fall somewhere between that of the armed (per-benzylated) and the disarmed (per-benzoylated) glycosyl donors. However, the results acquired with the SBox glycosides of the D-gluco series revealed that these "mixed-patterned" glycosyl donors were the least reactive amongst the building blocks investigated.[68] This allowed for the chemoselective coupling between three different building blocks. Thus, the disarmed disaccharide **1.29** obtained by classic armed-disarmed approach from building blocks **1.27** and **1.28**, (Scheme 1.11), could be further chemoselectively activated over superdisarmed building block **1.47** in the presence of $Cu(OTf)_2$/TfOH to produce trisaccharide **1.48** as depicted in Scheme 1.16a.[68] We also reported that 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protected glycosyl donors are unusually reactive, "superarmed".[73,74] Thus, the superarmed glycosyl donor **1.49** was activated over "armed" acceptor **1.50** in the presence of iodine to provide disaccharide **1.51** (Scheme 1.16b). The latter was then glycosidated with the disarmed acceptor **1.52** to provide trisaccharide **1.53**, which in turn was glycosidated with glycosyl acceptor **1.2**

to obtain the target tetrasaccharide **1.54** in which monosaccharide residues are connected *via* alternating *trans-cis-trans* linkages.[75]

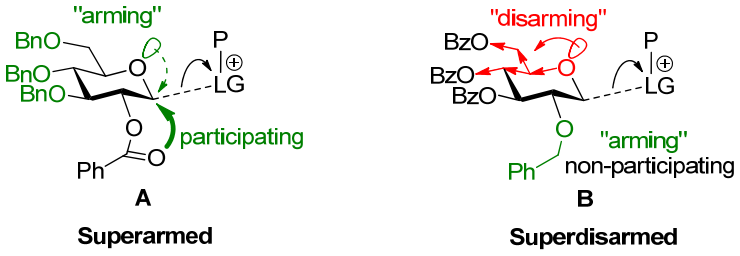
Scheme 1.16. Expansion of the armed-disarmed strategy to (a) superdisarmed 1.47 and (b) superarmed 1.49 building blocks.



Since Fraser-Reid's armed-disarmed concept rationale,[56,66] Ley's tuning reactivity studies,[61] and Wong's programmable oligosaccharide synthesis[62] all fail to predict this reactivity discrepancy, these unanticipated results were rationalized by the occurrence of the O-2/O-5 cooperative effect in glycosylation.[68] Thus, in addition to the "arming/disarming" nature of the protecting group at O-2, stabilization (or destabilization) of the glycosyl cation intermediate must also be taken into consideration. First, this stabilization can be achieved from the lone electron pair on the neighboring

endocyclic ring oxygen (O-5) like in the armed/superarmed glycosyl donor. Additionally, in the superdisarmed donors, the stabilization can be achieved by the anchimeric assistance from the C-2 acyl group (Figure 1.3), which is not available for the armed donors. Conversely, if electron withdrawing protecting groups are placed near the O-5 ring oxygen C-4 and C-6, like in the disarmed/superdisarmed donors, the electron density on O-5 will be decreased, effectively suppressing oxacarbenium ion formation. In this case, the ability of the system to stabilize *via* other internal modes becomes increasingly important and disarmed donors are partially stabilized *via* participation of the neighboring acyl group, which is not available in the case of superdisarmed donors (Figure 1.3).

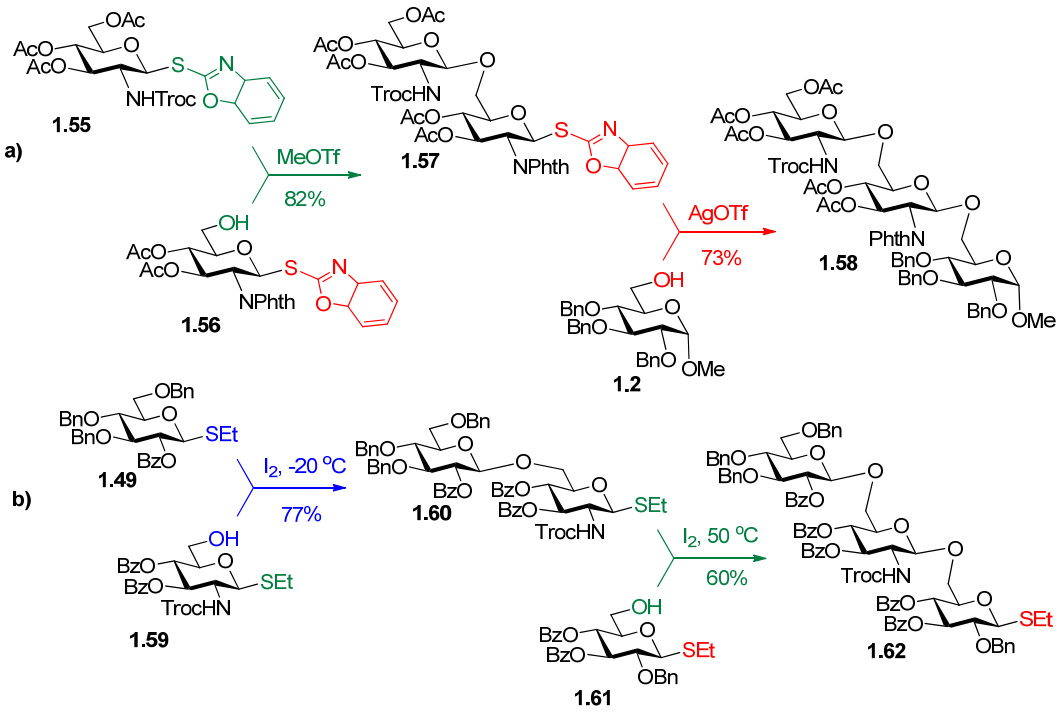
Figure 1.3. O-2/O-5 cooperative effect in glycosylation.



Our expanded work with SBox donors revealed the reactivity difference between the 2-*N*-trichloroethoxycarbonyl (Troc) and the 2-*N*-phthaloyl derivatives as well. We have observed that upon the glycosylation with MeOTf, the former is a more reactive donor than the latter. This armed-disarmed methodology could be used to synthesize 1,2-*trans*-linked oligosaccharides containing aminosugar residues as shown in Scheme 1.17a.[7] The activation of 2-*N*-Troc-protected glycosyl donor **1.55** over the 2-*N*-Phth-protected acceptor **1.56** in the presence of MeOTf resulted in the formation of

disaccharide **1.57**. The latter was then activated with AgOTf, a more powerful promoter, to give trisaccharide **1.58** upon coupling with acceptor **1.2**.

Scheme 1.17. Chemoselective synthesis of 2-amino-2-deoxy SBox glycosides.



Along similar lines, we also studied the reactivity difference of building blocks of the D-gluco and glucosamino series.[76] Competitive glycosylations clearly showed that the aminosugar reactivity with either NTroc or NPhth protection falls in between the superarmed and superdisarmed building blocks of the D-gluco series. For instance, the synthesis of trisaccharide **1.62** containing alternating neutral and aminosugar units was performed by a two-step chemoselective activation sequence. Thus, glycosidation of **1.49** with acceptor **1.59** was carried out in the presence of iodine at -20 °C to afford disaccharide **1.60** (Scheme 1.17b).[76] Subsequent chemoselective activation of the

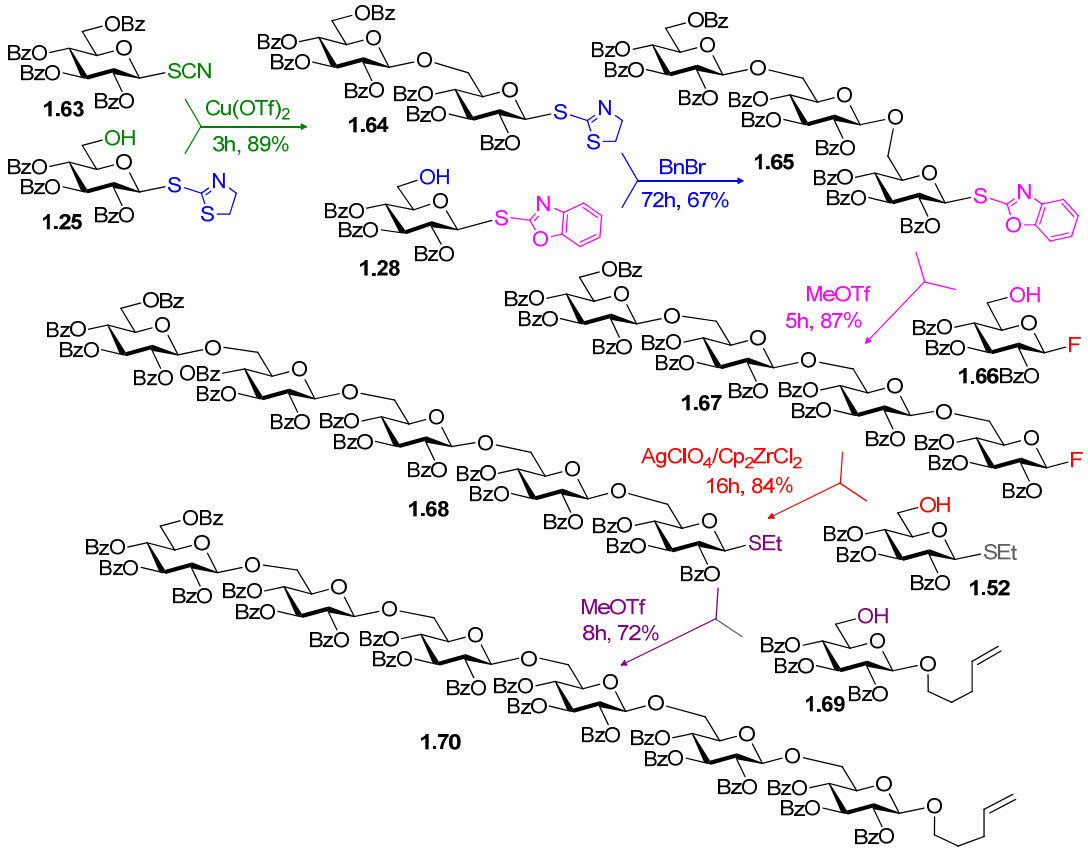
disaccharide donor **1.60** over superdisarmed acceptor **1.61** was successful in the presence of iodine at 50 ^{o}C to afford the target trisaccharide **1.62**.

1.3.2. Strategies based on selective activation

The selective activation strategy is easy to envisage. Practically, the leaving group of a glycosyl donor is activated over another type of a leaving group on a glycosyl acceptor. This sequence is then continued as long as there is a leaving group that would be compatible with the activation conditions for the previous stage. One-stage selective activations are routinely executed in oligosaccharide synthesis and two-step activations also become relatively available. Our recent review comprehensively discusses all recent advancements in this field.[64]

In our recent effort, we developed a selective activation strategy where six different leaving groups could be aligned for the synthesis of hexasaccharide **1.70** as depicted in Scheme 1.18.[17] First, the thiocyanate donor **1.63** was activated over STaz acceptor **1.25** in the presence of $Cu(OTf)_2$ to afford disaccharide **1.64**. Then, STaz disaccharide **1.64** was activated with benzyl bromide to couple with SBox acceptor **1.28**. The resulting trisaccharide **1.65** was glycosylated with fluoride acceptor **1.66** in the presence of MeOTf to produce tetrasaccharide **1.67**. Then, tetrasaccharide was reacted with SEt acceptor **1.52** in the presence of $AgClO_4/Cp_2ZrCl_2$ to obtain the pentasaccharide **1.68**. Finally, the *O*-pentenyl acceptor **1.69** was coupled with the pentasaccharide using MeOTf as an activator to afford hexasaccharide **1.70**.

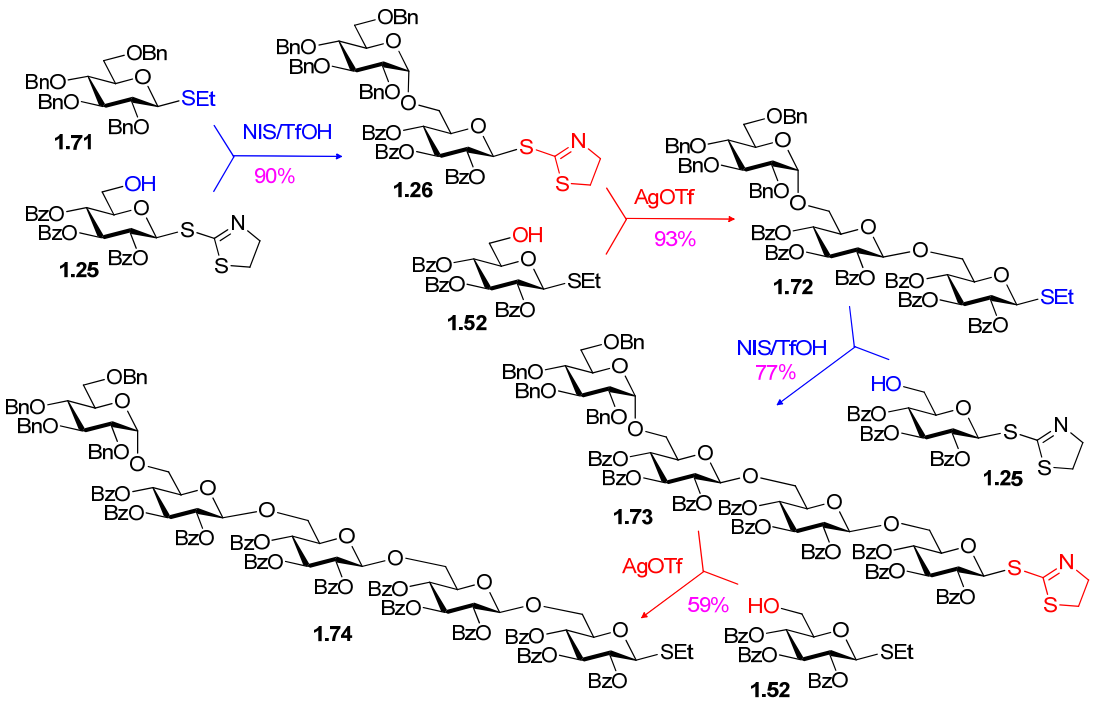
Scheme 1.18. Synthesis of hexasaccharide *via* five-step sequential selective activation.



The selective activation principle was also applied to the synthesis of oligosaccharides of *Streptococcus pneumonia* serogroup 6 and mimetics thereof for the development of synthetic vaccine components [8,9,11,12] and for the synthesis of a tumor associated glycosphingolipid SSEA-3 analog.[6] Nevertheless, the visible ease of the synthesis and straightforwardness does not imply that essentially the same selective activation sequence would be universally applicable. The selective activation of multiple leaving groups remains challenging and the synthesis of other target molecules may require additional extended study. To address this difficulty, the orthogonal approach

might be of general benefit because it requires only two types of leaving groups that can be independently activated in presence of each other. Discovered in 1994 by Kanie, Ito and Ogawa [77], original application of F and SPh leaving groups remained the only example of orthogonality in oligosaccharide synthesis[78-82] until our more recent study that begun in 2004 wherein we described STaz vs. SEt orthogonal activation. Thus, it was observed that the STaz leaving group remains inert in the presence of NIS in combination with *catalytic* amount of TfOH, common conditions for alkyl/aryl thioglycoside activation.[30] This finding led to the development of a promising combination of orthogonal leaving groups, wherein STaz is activated selectively with AgOTf, whereas ethyl thioglycosides are activated with NIS and catalytic TfOH.[30]

Scheme 1.19. Orthogonality of the STaz and SEt glycosides.

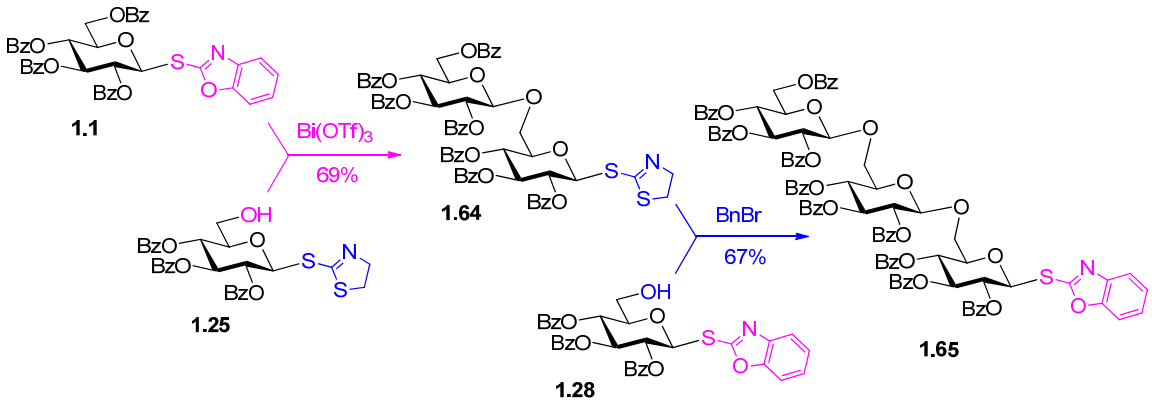


The synthesis of pentasaccharide **1.74** was executed as depicted in Scheme 1.19.[5] Thus, thioglycoside building blocks **1.71** and **1.72** were orthogonally activated with

NIS/cat. TfOH over STaz building block **1.25**. In turn, intermediates **1.26** and **1.73** bearing the anomeric STaz moiety were efficiently activated with AgOTf to glycosylate SEt acceptor **1.52**.

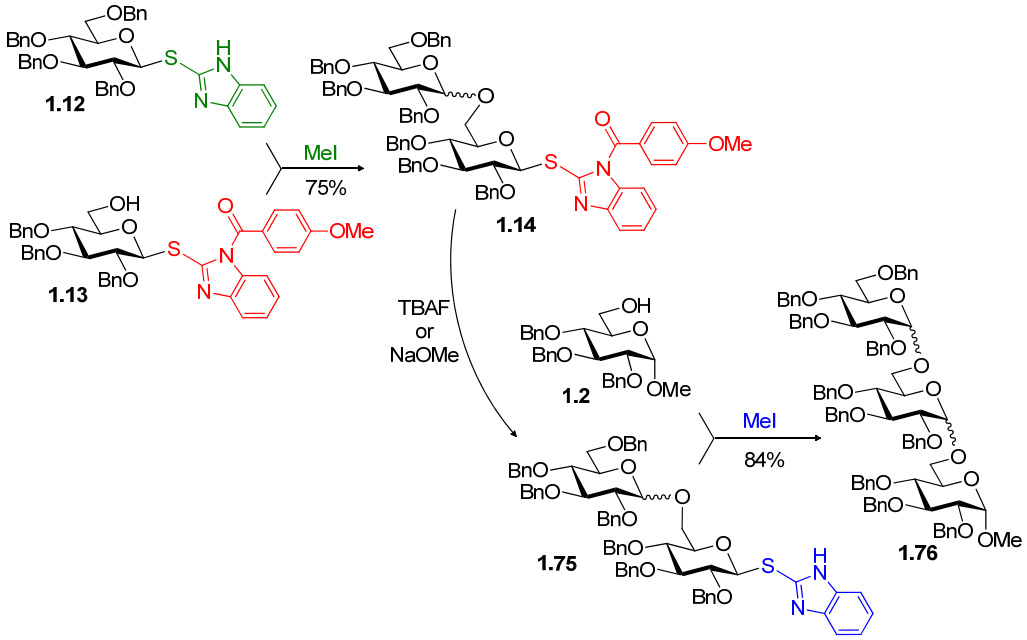
Our further studies have shown that even seemingly similar thioimidoyl leaving groups can be orthogonally activated over each other. The orthogonality of thioimidates is a unique feature of this methodology because conventional orthogonal activation requires two different classes of leaving groups. For instance, dedicated study of the SBox and STaz leaving groups allowed us to elucidate their activation pathways, direct for the SBox glycosides, and remote for the STaz derivatives. This allowed us to develop an orthogonal activation using these seemingly similar leaving groups. The key to differentiation of these two leaving groups is the choice of activator. For instance, the STaz was activated by mild alkylating agent benzyl bromide. Essentially the same reagent is extremely slow to benzylate the anomeric sulfur, the reaction that would be required for the activation of SBox see (Figure 1.2).

Scheme 1.20. Orthogonal activation of STaz and SBox leaving groups.



Conversely, SBox can be very readily activated with $Bi(OTf)_3$ whereas STaz remains inert. This finding was used in orthogonal activation according to which SBox glycosyl donor **1.1** was coupled with STaz acceptor **1.25** in the presence of $Bi(OTf)_3$ as depicted in Scheme 1.20.[39] Resulting disaccharide **1.64** equipped with the anomeric STaz group was then activated over SBox acceptor **1.28** using benzyl bromide to obtain trisaccharide **1.65**. Along similar lines, we determined the orthogonal-like character of glycosyl alkoxyimidates vs. SBox glycosides.[84]

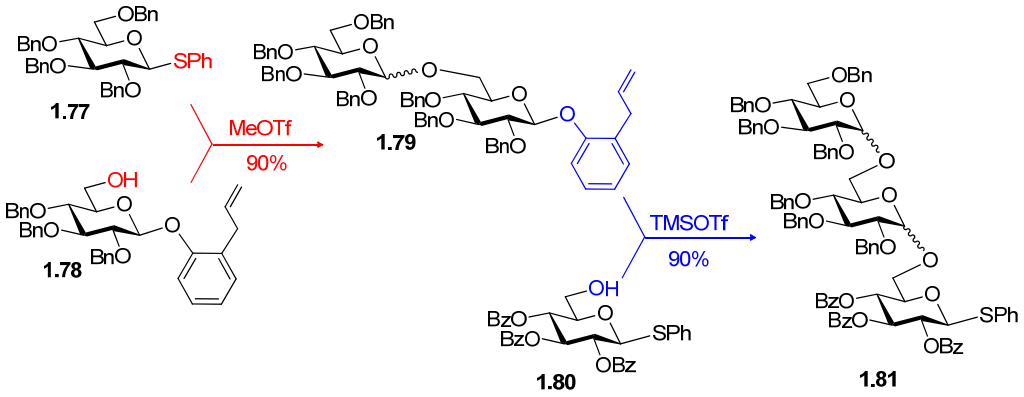
Scheme 1.21. Activation of SBiz vs. SBizAn in the active- latent fashion.



Recent studies from our laboratory have shown that *S*-benzimidazolyl (SBiz) glycosides can serve a promising new platform for further exploration of the active-latent strategy, a concept introduced by Roy,[85-87] and further developed by Fraser-Reid,[66,88] Boons,[89,90] Kim[91] and others.[92] We observed that a simple protection of the SBiz leaving group with anisoyl substituent significantly reduces its reactivity in the MeI-promoted

glycosylation. This finding allowed for direct activation of active SBiz donor **1.12** over the latent anisoylated SBiz glycosyl acceptor **1.13** to afford disaccharide **1.14** as shown in Scheme 1.21.[32] The latter was then treated with NaOMe or Bu_4NF to affect the deprotection of the anisoyl group. Thereby obtained active SBiz disaccharide **1.75** was then reacted with the acceptor **1.2** in the presence of MeI to afford the trisaccharide **1.76**. Our extended mechanistic study showed that the deactivation of donor **1.12** by means of the N-anisoyl group is due to the electron withdrawal effect.[32] Since the activation of the SBiz moiety follows the direct activation pathway, the anisoyl substituent reduces the nucleophilicity of the anomeric sulfur hence decreasing its reactivity in the presence of MeI. In contrast with well-known effect of disarming acyl groups on sugar oxygens, the disarming effect herein is achieved *via* the acylation of the leaving group.

Scheme 1.22. Orthogonal activation of the OAP and SPh leaving groups.



As aforementioned, allylphenyl (AP) leaving group was specifically designed to be compatible with either direct or remote activation pathways on demand. This unique feature of the AP glycosides was explored in the orthogonal activation with SPh glycosides. Iodonium-based reagents would activate both of these leaving groups,

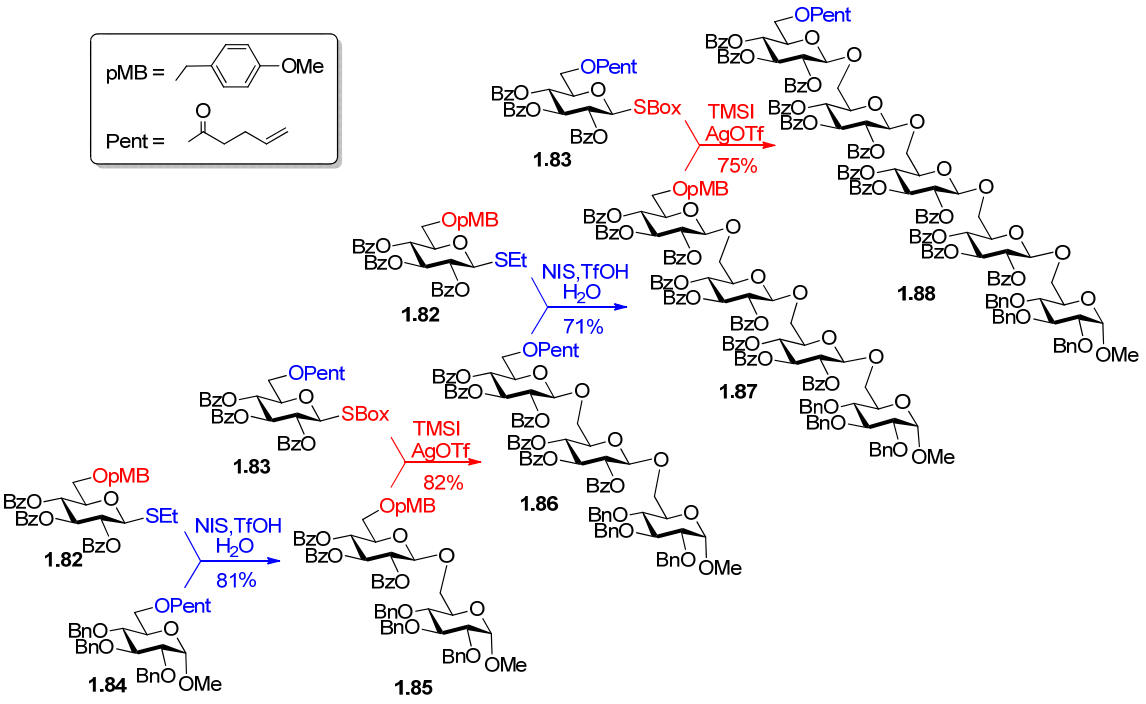
therefore we adopted alkylation conditions for the activation of SPh glycosides. Thus, SPh glycosyl donor **1.77** was coupled with the AP acceptor **1.78** in the presence of MeOTf to afford the disaccharide **1.79** as shown in the Scheme 1.22.[43] Subsequently, the AP disaccharide **1.79** was activated with TMSOTf for the coupling with SPh acceptor **1.80** to afford the trisaccharide **1.81**.

Recently, we discovered a novel concept for oligosaccharide assembly called the "reverse orthogonal strategy". It was designed to solve the major drawback of the traditional orthogonal approach – reduced reactivity and yields with increasing bulk of the oligosaccharide glycosyl donor. This drawback was particularly evident during the synthesis of longer oligosaccharide sequences. Unlike the classic concept based on orthogonal leaving groups, the reverse approach is based on orthogonal protecting groups, herein *p*-methoxybenzyl and 4-pentenoyl. The concept is based on the idea that a strategically placed temporary labile substituent would be removed during the glycosylation reaction. This strategic adjustment allowed us to perform efficient oligosaccharide assembly in the reverse direction elongation of glycosyl acceptor without additional steps between glycosylations.[93]

Although in principle, this approach can be executed with only one type of a leaving group, best yields were obtained with SEt glycoside with 6-*O*-*p*-methoxybenzyl (pMB) protection **1.82** and SBox glycoside with 6-*O*-pentenoyl (Pent) protection **1.83**. Coupling of glycosyl donor **1.82** with acceptor **1.84** was affected in the presence of NIS/TfOH/H_2O and led to the formation of disaccharide **1.85** (Scheme 1.23). The latter was then glycosylated with SBox donor **1.83** equipped with an *O*-pentenoyl group using TMSI/AgOTf promoter. The resulting trisaccharide **1.86** was then reacted with **1.82** to

afford tetrasaccharide **1.87**. In turn, tetrasaccharide **1.87** was coupled with SBox donor **1.83** to afford pentasaccharide **1.88** in a good over-all yield.

Scheme 1.23. Four-step synthesis of pentasaccharide 1.88 *via* the reverse orthogonal strategy.

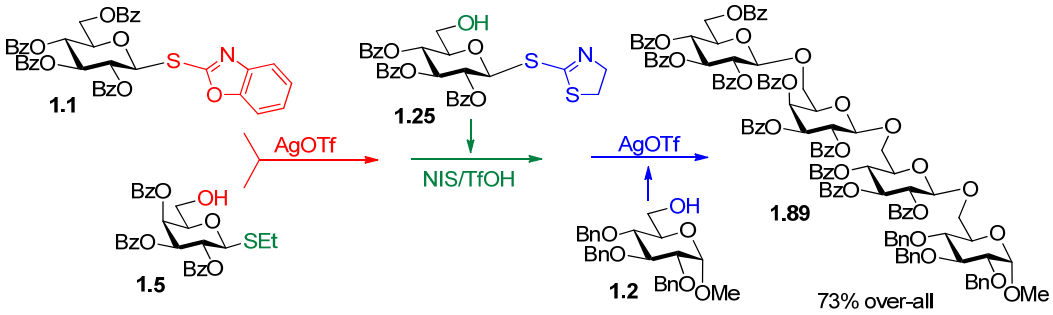


1.4 Innovative technologies for oligosaccharide synthesis

One-pot techniques for multi-step oligosaccharide synthesis combine two or more chemoselective glycosylation steps and offer arguably the shortest pathway to oligosaccharides. In fact, the sequential glycosylation reactions are performed in a single flask ("one-pot") and do not require isolation and purification of the intermediates. Many variations of the one-pot strategy have been developed.[62,70,71,94-102] Among those several classes of leaving groups have been investigated and thioimidates are no exception. We have shown that SBox, SEt and STaz building blocks can be activated sequentially to

synthesize tetrasaccharide **1.89** in one pot. First, the SBox donor **1.1** was activated over SEt galactose acceptor **1.5** with AgOTf (Scheme 1.24).[103] Upon completion of the coupling step, STaz glycosyl acceptor **1.25** was added to the reaction vessel along with NIS and catalytic TfOH to activate the formed SEt disaccharide intermediate. When the TLC analysis showed that reactants have been consumed, glycosyl acceptor **1.2** was added along with AgOTf promoter required to activate the STaz trisaccharide intermediate. Upon completion of the one-pot three-step sequence and purification by column chromatography, tetrasaccharide **1.89** was isolated in 73% yield overall accounting for about 90% yield per step.[103]

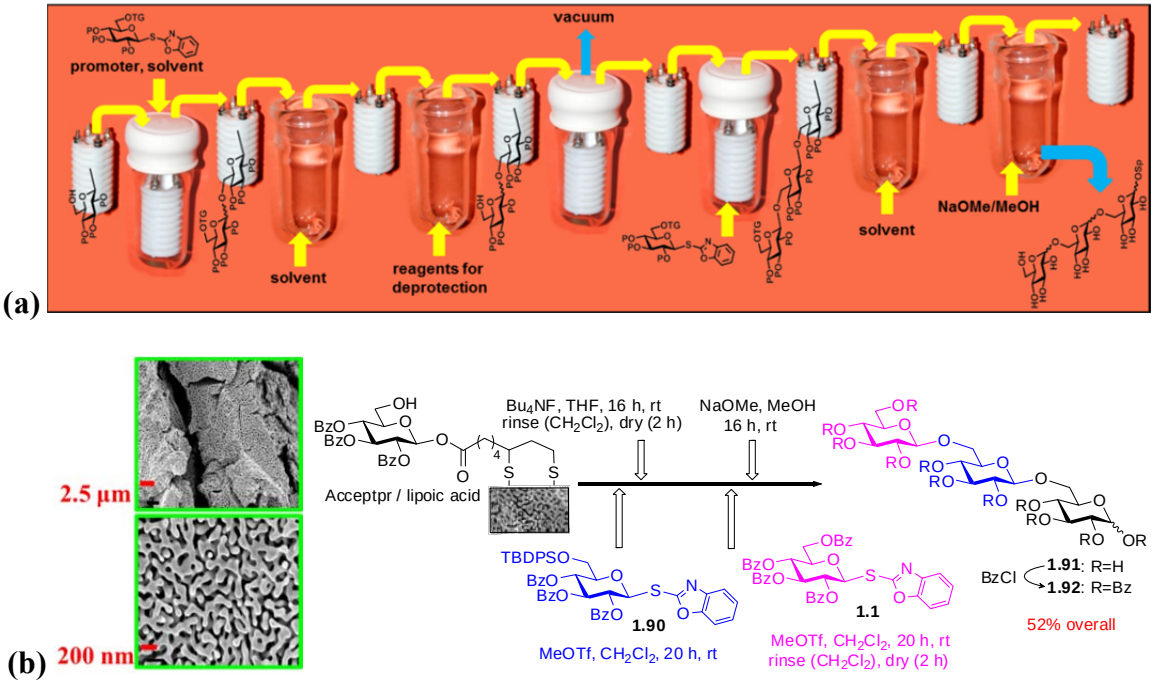
Scheme 1.24. Thioimidate-based one-pot oligosaccharide synthesis.



During our further studies carried out to expand the application of glycosyl thioimidates to oligosaccharide synthesis, we have shown that SBox building blocks can be used in polymer supported (Merrifield's resin or Tentagel) glycosylations following both glycosyl acceptor and glycosyl donor-bound approaches.[104] As an extension of this study, and in attempt to address major drawbacks of the polymer-supported synthesis, we established the Surface-Tethered Iterative Carbohydrate Synthesis (STICS), a novel approach to oligosaccharide synthesis using Nano-Porous Gold (NPG) as a solid support.[105]

NPG is a high-surface area, sponge-like nanomaterial, it can be utilized as a set of NPG plates (8 x 8 x 0.2 mm) assembled in a stacked Teflon mini reactor as shown in top figure in Scheme 1.25a. The glycosyl acceptor can be anchored to NPGs using thiolated linkers and the oligosaccharide assembly is accomplished *via* alternating glycosylation, washing, deprotection and drying steps as depicted in Scheme 1.25a. The 6-*O*-TBDPS-protected SBox glycosyl donor **1.90** was first coupled to the lipoic acid anchored acceptor in the presence of MeOTf. Then the tethered disaccharide was treated with Bu_4NF to deprotect the silyl group and allowed to react with donor **1.1** to obtain the trisaccharide **1.91**. Finally, the latter was cleaved from the NPG plate using NaOMe/MeOH followed by benzoylation to give trisaccharide **1.92** (Scheme 1.25b). Pictures in Scheme 1.25b are SEM images of NPG plates in two different bar scales (2.5 µm and 200 nm).

Scheme 1.25. STICS: Surface-Tethered Iterative Carbohydrate Synthesis.

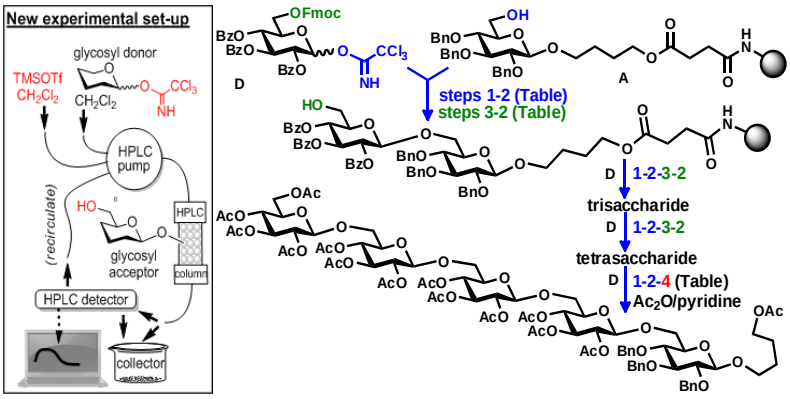


Over-all, STICS approach is a promising new concept for oligosaccharide synthesis that allows to address the following important drawbacks of the polymer-supported synthesis: limited use of the molecular sieves that are hard to separate for the polymer beads; extended time for resin swelling/drying, NPG surface only requires wetting; large volume of the waste solvent is generated when resin needs to be washed while the NPG is simply rinsed; reagent trapping/resin poisoning is not an issue with NPG because it does not trap any reagent and can be regenerated to bare surface by electrochemical methods if necessary; reusability of resin is a problem while gold is fully recoverable. The limitations of the STICS approach are similar to other standard drawbacks of the polymer-supported synthesis and include: difficulty to monitor the reaction and analyze intermediates, longer reaction times than those for reactions in solution and the requirement to use large (5-10 fold) excess of reagents.

Some notable drawbacks of the STICS technology that is using simple immersion technique have stimulated us to pursue a new experimental set-up based on an unmodified HPLC instrument. In brief, a glass Omnifit chromatography column was packed with the pre-swelled polymer resin or small NPG chips (see the left panel in Scheme 1.26). The column was then connected to the HPLC system consisting of a reciprocating pump containing three chambers, a variable UV range detector, and a computer with standard HPLC-operating software installed.[106] The column was packed with the glycosyl acceptor loaded on resin, purged with the solvent and then two separate solutions containing glycosyl donor and promoter were delivered concomitantly. After a relatively short reaction time, typically 30-60 min, the system was purged (washed) with solvent. At this time, the resin is loaded with the disaccharide derivative that can be either

cleaved off from the polymer support or the oligosaccharide elongation can be continued *via* alternating deprotection/glycosylation steps. Although we are still currently optimizing many aspects of the HPLC-assisted method, we have already applied this technology to the synthesis of small oligosaccharides containing various sugar moieties. Amongst these, we obtained a series of tri-, tetra-, and pentasaccharides consisting of glucose, galactose, and mannose units, all of which are major constituents of many natural mammalian and bacterial oligosaccharides and glycoconjugates. One example is illustrated here, the synthesis of a pentasaccharide (middle panel) and automation steps required to accomplish the synthesis (right panel, Scheme 1.26).

Scheme 1.26. HPLC-assisted automated oligosaccharide synthesis.



operation	action	flow rate, mL/min	total volume	time, min
1. Glycosylate (acceptor A)	Pump B: 39 mM D in CH_2Cl_2 Pump C: 0.28 M TMSOTf in CH_2Cl_2	0.3 B/C = 4/1	18 mL	60
2. Wash	Pump A: CH_2Cl_2	2.0	20 mL	10
3. Deprotect	Pump C: piperidine/ DMF (1/5, v/v)	0.5	2.5 mL	5
2. Wash	Pump A: CH_2Cl_2	2.0	20 mL	10
Repeat 1	As above,	0.3	18 mL	60
2	trisacccharide	2.0	20 mL	10
3	accceptor is	0.5	2.5 mL	5
2	obtained	2.0	20 mL	10
Repeat 1	As above,	0.3	18 mL	60
2	tetrasaccharide	2.0	20 mL	10
3	acceptor is	0.5	2.5 mL	5
2	obtained	2.0	20 mL	10
Repeat 1	Pentasaccharide	0.3	18 mL	60
2	is obtained	2.0	20 mL	10
4. Cleave off to get penta	Pump C: 0.1 M $NaOCH_3$ in CH_3OH/CH_2Cl_2	1.0	5 mL (recirc.)	60

All steps can be monitored using a standard HPLC detection system set up to record changes in the UV absorbance of the solution eluting off the column. A solution of reagents can be recirculated to reduce the amount of reagents and ensure complete conversion at each reaction step. In our opinion, the improved experimental set up offers the following advantages in comparison to that of conventional oligosaccharide synthesis on polymer and NPG supports: faster reaction times, real-time reaction monitoring using an HPLC detection system, and all steps and sequences can be automated using the

standard HPLC-managing computer software. Further optimization of the HPLC-based technology and its application to the NPG platform and biological targets described in the proposal are currently underway.

1.5. Conclusions and outlook

Oligosaccharide sequences are found in numerous natural compounds and constitute the core of many modern therapeutics. In spite of recent progress, chemical synthesis of even moderately complex oligosaccharides still requires significant resources, which makes these targets accessible only to a small circle of glycoscientists and questions the feasibility of their industrial production. The development of more efficient and dependable techniques for synthesis offers a high level of significance because reliable access to oligosaccharides is essential for further innovations and practical applications in all areas of glycobiology, glycomics, and glycomedicine.

The long-term goal of our research program is to make synthetic complex carbohydrates more accessible to general chemical, biochemical, medical and industrial audiences to keep pace with the exploding area of glycobiology. The achievement of the ultimate goal will be simplified by the development of new expeditious strategies for oligosaccharide synthesis and by the application of the new HPLC-based experimental set up. We have already applied, and are continuing to apply the developed strategies in the synthesis of important oligosaccharide and glycoconjugate targets for biomedical studies. As a result, it is our expectation that the methodological advances made in the synthetic field will boost innovations in the related fields of glycosciences.

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CHAPTER 2

The effect of remote picolinyl and picoloyl substituents on the stereoselectivity of chemical glycosylation

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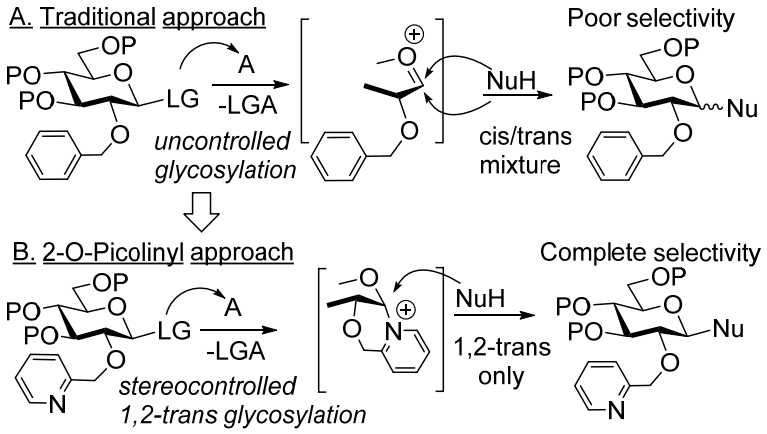
Yasomanee, J. P.; Demchenko, A, V. The effect of remote picolinyl and picoloyl substituents on the stereoselectivity of chemical glycosylation. *J. Am. Chem. Soc.* **2012**, *134*, 20097-20102.

2.1. Introduction

Complex carbohydrates consist of monosaccharide units, which are connected *via* O-glycosidic linkages into elaborate oligosaccharide networks.[1,2] Chemically, the O-glycosidic linkage is formed by a glycosylation reaction, which in the most general sense, is a promoter/activator (A) assisted monomolecular nucleophilic displacement of the leaving group (LG) of a glycosyl donor with a hydroxyl moiety of a glycosyl acceptor (NuH, Scheme 1).[3,4] Other functional groups on both glycosyl donor and acceptor are temporarily masked with protecting groups (P). Upon the leaving group departure, the flattened oxacarbenium ion is formed, which often leads to anomeric mixtures (Scheme 2.1A).[5] Therefore, particular care has to be taken with regards to the stereoselectivity of glycosylation.

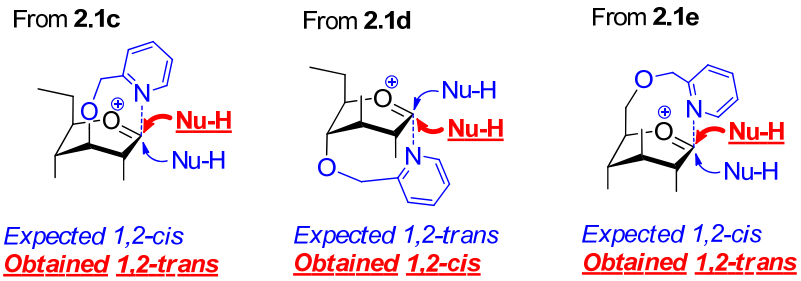
Scheme 2.1. Traditional glycoside synthesis using conventional 2-*O*-benzyl protection *vs.* 2-*O*-picolinyl-assisted 1,2-*trans*-glycosylation.



The aim of stereocontrolling of glycosylation has been approached in a variety of ways and the participation of a neighboring acyl-type group has been widely used to obtain 1,2-*trans* glycosides.[6] Recently, our group has expanded methods available for 1,2-*trans*

glycosylation by developing the neighboring 2-*O*-picolinyl (2-pyridylmethyl, Pic) participating group.[7,8] It was demonstrated that 2-*O*-picolinyl-assisted glycosylations proceed *via* a formal six-membered ring intermediate leading to the formation of 1,2-*trans* glycosides with complete stereocontrol (Scheme 2.1B). Other unconventional methods for participation-assisted or stereodirected glycosylation have also been recently introduced.[9-15]

Figure 2.1. Expected vs. detected stereoselectivity that was found to be always *syn* in respect to the remote picolinyl group.



2.2. Results and Discussion

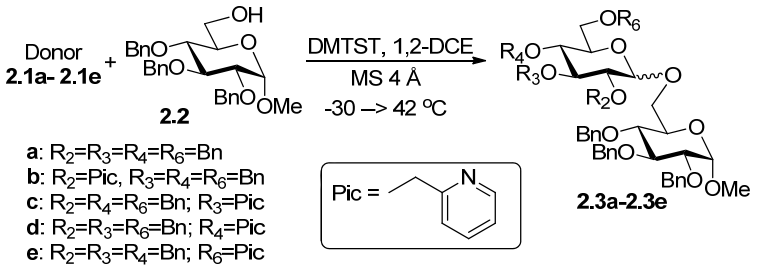
Upon discovering complete 1,2-*trans* stereoselectivity obtained *via* the 2-*O*-picolinyl participation, we decided to broaden the scope of this method and investigate whether a similar effect can be achieved with remote picolinyl groups. Herein, we report the study of a series of novel glycosyl donors equipped with picolinyl and picoloyl (2-pyridinecarbonyl, Pico) groups at remote positions (C-3, C-4, and C-6). The major emphasis of this study is to investigate the effect that these remote substituents may have on the stereoselectivity of glycosylation. As shown in Figure 2.1, our original expectation was to obtain *anti* substitution due to the anticipated participation of the remote Pic/Pico moieties.

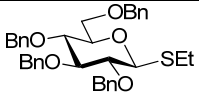
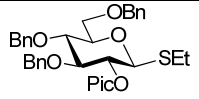
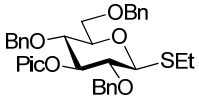
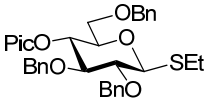
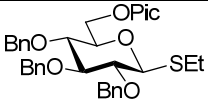
As the starting comparison point, known glycosyl donors per-*O*-benzylated and 2-*O*-picolinyl substituted thioglycosides, **2.1a**[16] and **2.1b**,[8] respectively, were coupled with glycosyl acceptor **2.2**[17] under reaction conditions that became standard for 2-*O*-picolinyl glycosyl donors: dimethyl(methylthio)sulfonium triflate (DMTST),[18] 1,2-dichloroethane, -30 → 42 ^{o}C.[8] Glycosidation of donor **2.1a** was non-stereoselective and the corresponding disaccharide **2.3a**[19] was isolated in 92% yield (α/β = 1/1.9, entry 1, Table 2.1). As expected, glycosidation of 2-*O*-picolinyl donor **2.1b** provided disaccharide **2.3b**[8] with anticipated complete β-stereoselectivity in 83% yield (entry 2). Rather unexpectedly, 3-*O*-picolinyl thioglycoside **2.1c** gave disaccharide **2.3c** in a relatively high 1,2-*trans* β-selectivity (84%, α/β=1/5.8, entry 3). In further probing positional isomers 4-*O*-picolinyl donor **2.1d** and 6-*O*-picolinyl donor **2.1e** (entries 4 and 5), we noticed that in all cases the product was preferentially forming in the *syn* orientation to that of the picolinyl substituent rather than *anti* as it was originally anticipated (Figure 2.1). Thus, 4-*O*-picolinyl donor **2.1d** (the substituent at C-4 is projecting below the ring) showed slight preference towards the formation of α-**2.3d** (α/β = 1.2/1, 88%, entry 4). Conversely, glycosidation of 6-*O*-picolinyl donor **2.1e** (substituent projecting above the ring) gave disaccharide **2.3e** with some β-stereoselectivity (α/β = 1/2.4, 93%, entry 5).

Clearly, the level of stereoselectivity observed in these preliminary experiments was not exceptionally high. Nevertheless, these results suggest that the nature of the remote picolinyl effect is perhaps of a more complex origin than the anticipated direct participation. It is possible that the remote picolinyl groups affect glycosylation reactions *via* a different mode than that observed for the neighboring 2-*O*-picolinyl group (complete 1,2-*trans* selectivity, *anti* in respect to picolinyl, *via* the direct participation).[7,8]

Intrigued by the unexpected preliminary results, we began a study that would improve our understanding of the mode by which the remote picolinyl substituents affect both 1,2-*cis* and 1,2-*trans* stereoselectivity of glycosylation.

Table 2.1. Comparative investigation of glycosyl donors 2.1a- 2.1e.

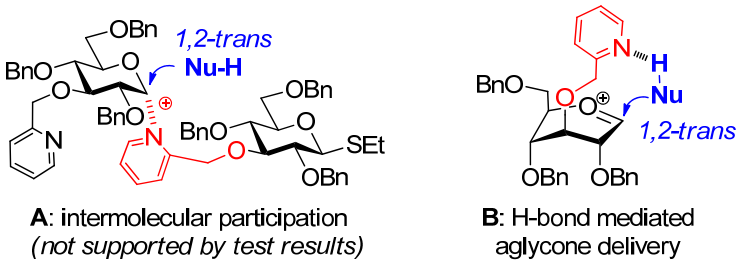


Entry	*Donor*	*Time*	*Yield*	*Product*	*α/β Ratio*
1	 **2.1a**	15 min	92%	**2.3a**	1 / 1.9
2	 **2.1b**	20 h	83%	**2.3b**	β only
3	 **2.1c**	4 h	84%	**2.3c**	1 / 5.8
4	 **2.1d**	4 h	88%	**2.3d**	1.2 / 1
5	 **2.1e**	5 h	93%	**2.3e**	1 / 2.4

One explanation for the stereoselectivity observed is through the intermolecular participation of the picolinyl nitrogen at the anomeric center that would result in shielding of one face of the oxacarbenium intermediate over another (Figure 2.2A). To

test the viability of this assumption we investigated glycosidations of standard per-*O*-benzylated thioglycoside **2.1a** in the presence of pyridine, which showed no significant

Figure 2.2. Possible rationalization for the stereoselectivity observed.



change in stereoselectivity. We also found that the stereoselectivity diminishes dramatically in case of glycosyl donors protected with 4,6-*O*-benzylidene (entry 5, Table 2.2). The induced rigidity of the pyranose ring should have no significant effect on intermolecular participation and would be more indicative of other modes of action. Therefore, in our opinion the intermolecular participation is not strongly supported by the experimental results.

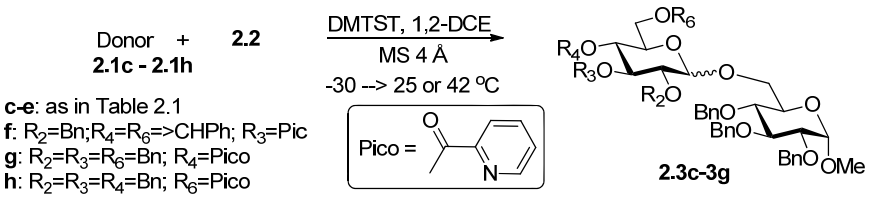
Another possibility is that instead of the anticipated direct participation at the anomeric center, the remote picolinyl moiety acts as a platform for a hydrogen bond mediated aglycone delivery (Figure 2.2B). In our opinion, this is the most relevant mechanism to explain the *syn* stereoselectivity observed in all preliminary glycosylations. The fact that stereoselectivity decreases in case of 4,6-*O*-benzylidene protected donor indicates that the conformational changes to form all-axial oxacarbenium intermediate[5,20-22] are necessary to ensure efficient *H*-bond mediated delivery. If the remote picolinyl group indeed acts as the *H*-bond acceptor for NuH, the benefit of such an action would be two-fold. First, the hydrogen bond tethering would provide enhanced (if not complete) facial selectivity by

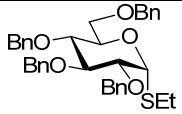
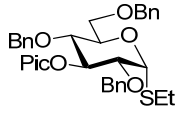
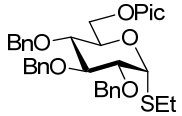
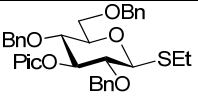
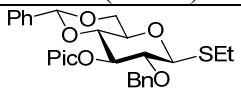
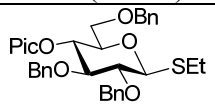
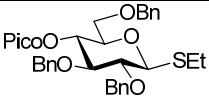
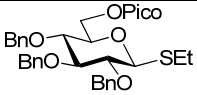
delivering the glycosyl acceptor from the same face[23] in respect to the *H*-bond acceptor (consistent with results described in Table 2.1). Second, picolinyl moiety would accelerate the entire reaction by positioning both reaction components in a close proximity to each other and also may facilitate deprotonation, the last essential step of the glycosylation of neutral aglycones.[3] It should be noted that intramolecular hydrogen bonding between picolinyl group and the neighboring acetamido group has been reported by Crich.[24]

To elucidate the reaction pathway and, consequently, improve the stereoselectivity of glycosylations we began a systematic study with the emphasis on acquiring the experimental evidence supporting the existence of the hydrogen bonding between the glycosyl acceptor and donor counterparts. Having assumed that the orientation of the anomeric substituent would be significant for the proposed *H-bond mediated aglycone delivery* to take place, we investigated donor α-**2.1c**. Indeed, nearly a 3-fold enhancement of β-selectivity (α/β = 1/14.5, entry 2, Table 2.2) was observed in comparison to that obtained with β-**2.1c** (α/β = 1/5.8, entry 3, Table 2.1). Even more dramatically, a 5-fold enhancement of β-selectivity was obtained with 6-*O*-picolinyl donor α-**2.1e** (α/β = 1/11.8, entry 3, Table 2.2) in comparison to that obtained with β-**2.1e** (α/β = 1/2.4, entry 5, Table 2.1). For comparison, the use of α- or β-**2.1a** showed practically no difference in stereoselectivity obtained (entry 1, Table 2.1 and entry 2, Table 2.2).

We also assumed that if the *H*-bonding between the donor and acceptor counterparts indeed were taking place in the reaction medium, the effect of dilution would help to enhance the stereoselectivity due to decreased probability of the non-stereoselective attack of unbound nucleophiles. In addition, we anticipated that high

Table 2.2. Refining the stereoselectivity obtained with picolinyl and picoloyl-protected donors 2.1c- 2.1g.



Entry	*Donor (conc.)*	*Time*	*Yield*	*Product*	*α/β Ratio*
1	 α-**2.1a** (50 mM)	15 min	96%	**2.3a**	1 / 1.3
2	 α-**2.1c** (50 mM)	3.5 h	89%	**2.3c**	1 / 14.5
3	 α-**2.1e** (50 mM)	4 h	71%	**2.3e**	1 / 11.8
4	 **2.1c** (5 mM)	3 h	85%	**2.3c**	1 / 15.6
5	**2.1c** (5 mM)	18 h[a]	64%	**2.3f**	1 / 7.1
6	 **2.1f** (5 mM)	20 h	77%	**2.3f**	1 / 2.1
7	 **2.1d** (5 mM)	5 h	86%	**2.3d**	5.3 / 1
8	 **2.1g** (5 mM)	4 h	73%	**2.3g**	>25 / 1
9	 **2.1h** (50 mM)	1.5 h	96%	**2.3h**	>1 / 25

[a] -Reaction was done at 50 °C starting from the beginning

dilution will have very minor effect on the rate of the reaction because the donor-acceptor pairs would be pre-assembled rather than separated by solvent molecules like in conventional glycosylations. To prove this concept, we performed a glycosylation between donor **2.1c** and acceptor **2.2** at a 10-fold dilution with 1,2-dichloroethane, 5 mM donor concentration *vs.* 50 mM in standard experiments. This coupling was even faster than that of the standard concentration (3 h *vs.* 4 h), and a 3-fold enhanced stereoselectivity was obtained under high dilution conditions (α/β = 1/5.8, entry 3, Table 2.1 *vs.* α/β = 1/15.6, entry 4, Table 2.2). Interestingly, applying much higher dilution, up to 50-fold (1 mM), even faster glycosidation of **2.1c** (2.5 h) was observed, whereas glycosidation of donor **2.1a** was practically ineffective. This result speaks very supportively of the postulated mechanism and is consistent with the occurrence of an *H*-bond tethering between glycosyl donor and acceptor counterparts. In this context, Yu and co-workers have recently reported a strong concentration effect on N-glycosylation, wherein it was attributed to the long-range participation effect.[25] Kononov and co-workers also observed very interesting correlation between concentration and stereoselectivity.[26] It should be noted that although the comparison of all reactions were performed at standard temperature of -30 → rt (or 42 ^{o}C), experiments at lower or ambient temperatures showed a very similar trend and very minor effect on stereoselectivity.

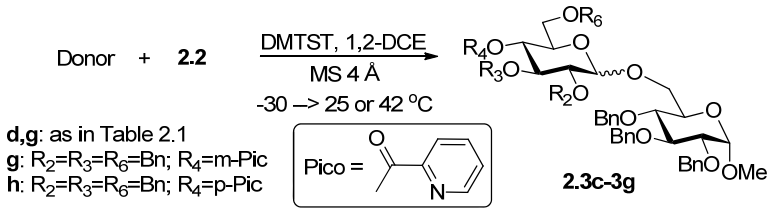
Conversely, we observed a significant loss of stereoselectivity if the reactions were performed at 50 ^{o}C from the beginning. A result of particular interest was obtained in the high dilution experiments wherein reaction at 50 ^{o}C was significantly slower (incomplete at 18 h) than those at -30 ^{o}C or ambient temperature (3 h) and much less stereoselective

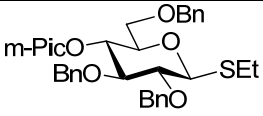
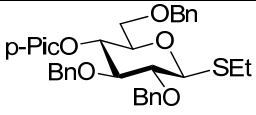
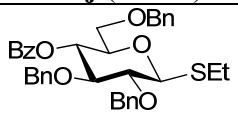
(entry 5, Table 2.2). On the other hand, introduction of rigidity to the glycosyl donor *via* 4,6-*O*-benzylidene also reduced the stereoselectivity greatly, both in 5mM and 50 mM glycosylations, indicating that the ring flexibility also plays an important role in observed stereoselectivity through aglycone delivery. (entry 6, Table 2.2).

At this stage, we also incorporated a series of glycosyl donors equipped with *O*-picoloyl (2-pyridinecarbonyl, Pico) substituent.[27,28] In general, these glycosyl donors showed comparable stereoselectivity and the dilution effect trend to that observed with the picolinyl substituent. On one occasion, however, a significant enhancement in 1,2-*cis* stereoselectivity was observed when the picoloyl substituent was used instead of picolinyl at the C-4 position. While reactions with 4-*O*-picolinyl donor **2.1d** performed at high dilution gave unexceptional stereoselectivity of α/β = 5.3/1 (entry 7, Table 2.2), 4-*O*-picoloyl donor **2.1g** led to disaccharide **2.3g** with complete α-stereoselectivity (entry 8). Further study of the 6-*O*-picoloyl substituent in donor **2.1h** showed excellent 1,2-*trans* stereoselectivity and the resulting disaccharide **2.3h** was obtained as pure β-linked diastereomer (entry 9). In our opinion, the set of data summarized in Table 2.2 provides a strong evidence of the *syn* delivery effect of picolinyl and picoloyl substituents while offering a practical new methodology for highly stereoselective synthesis of both 1,2-*trans* and 1,2-*cis* linked disaccharides. Although picoloyl substituent is a weaker *H*-bond acceptor than its picolinyl counterpart, very comparable results have been observed with these two groups. In our opinion, the strength of the *H*-bonding is not the deciding factor for excellent stereoselectivity. It is possible that the key importance of the *H*-bonded acceptor is to provide right geometry for the aglycone delivery. Arguably, preferential

trans-ester conformation of picoloyl group may offer the beneficial orientation for the *H*-bonding mediated delivery.

Table 2.3. The effect of non-assisting protecting groups at C-4 on stereoselectivity.[a]



Entry	*Donor (conc.)*	*Time*	*Yield*	*Product*	*α/β Ratio*
1	**2.1d** (5 mM)	5 h	86%	**2.3d**	5.3 / 1
2	**2.1g** (5 mM)	4 h	73%	**2.3g**	>25 / 1
3	 **2.1i** (5 mM)	10 h	82%	**2.3i**	1.5 / 1
4	 **2.1j** (5 mM)	10 h	74%	**2.3j**	1.3 / 1
5	 **2.1k** (5 mM)	5 h	93%	**2.3k**	1 / 2.6

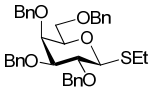
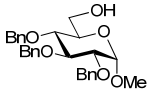
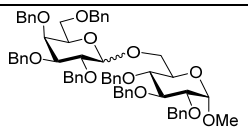
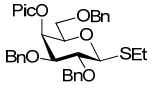
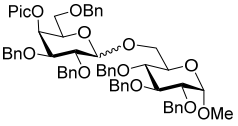
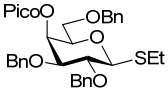
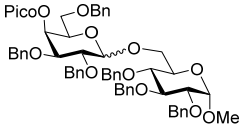
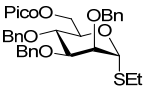
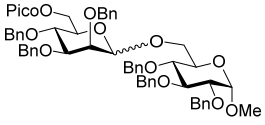
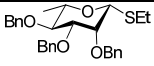
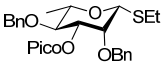
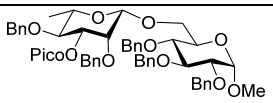
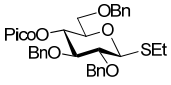
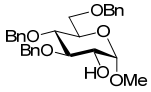
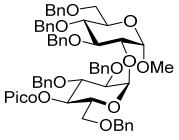
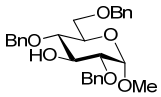
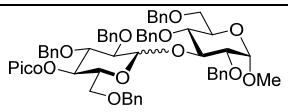
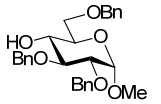
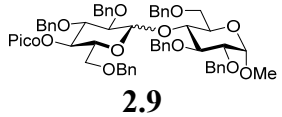
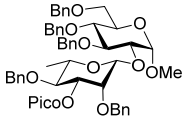
[a] -Reactions with *m*- and *p*-picoloyl protected donors were sluggish, low yielding, and non-stereoselective (no experimental data has been provided)

The stereodirecting effect of other possible isomers of picolinyl, 3-pyridylmethyl (*m*-picolinyl) and 4-pyridylmethyl (*p*-picolinyl), was also tested for comparison. In this context, non-stereoselective reactions were observed with glycosyl donors **2.1i** and **2.1j** equipped with *m*-picolinyl and *p*-picolinyl groups at C-4 respectively (entries 3 and 4, Table 2.3). Correspondingly, glycosidation of donors equipped with *m*-picoloyl (3-pyridinecarbonyl) and *p*-picoloyl (4-pyridinecarbonyl) were sluggish and non-stereoselective. To elucidate whether or not this enhancement of stereoselectivity is due

to an electron-withdrawing (or a remote participating) effect of the carbonyl group, we tested the corresponding 4-*O*-benzoylated donor **2.1k**. This glycosylation was modestly β-stereoselective indicating that the carbonyl group effect by itself is of very minor, if any, influence (entry 5).

Encouraged by these results, we decided to expand the scope of the *H*-bond mediated stereoselective glycosylations to a broader range of substrates and investigated a variety of sugar series, common galactose, mannose, and rhamnose, as well as secondary glycosyl acceptors. The abbreviated results with the emphasis on the synthesis of traditionally challenging 1,2-*cis* linkages[29,30] are listed in Table 2.4. Complete β-stereoselectivity obtained in galactosylation with 4-*O*- picolinyl/picoloyl glycosyl donors (**2.1m**/**1n**) is also noteworthy (entries 2 and 3, Table 2.4). This directing effect represents a dramatic change in comparison to the non-stereoselective glycosidation of per-*O*-benzylated galactosyl donor **2.1l**. Most remarkably, the high β-stereoselectivity obtained with 4-*O*-picoloyl ester differs drastically from that reported by Boons and co-workers in studying a series of 4-*O*-acylated galactosyl donors wherein high α-selectivity was achieved.[31] This result is also very indicative of the existence of the *H*-bond mediated glycosylation. Although not particularly high, yet respectable β-stereoselectivity (α/β = 1/9.5) was recorded for β-mannosylation with **2.1o** in the presence of NIS/TfOH (entry 4). We also obtained complete β-stereoselectivity upon rhamnosylation with 3-*O*-picoloyl donor **2.1q** (entry 6) whereas, per-benzylated rhamnosyl donor **2.1p** showed no selectivity (entry 5). Secondary glycosyl acceptors **2.4**,[32] **2.6**,[33] and **2.8**[34] were glycosylated with glucosyl donor **2.1g** equipped with 4-*O*-picoloyl substituent to provide consistently high α-stereoselectivity, particularly at a 10-fold dilution (5 mM, entries 7-

Table 2.4. Broadening the scope of the pic/pico-assisted glycosylation.[a]

Entry	*Donor*	*Acceptor,*	*Conc.*	*Time*	*Yield*	*Product*	*α/β Ratio*
1	 **2.1l**	 **2.2**	50 mM	45 min	87%	 **2.3l**	1 / 1.0
2	 **2.1m**	**2.2**	5 mM	3 h	83%	 **2.3m**	>1 / 25
3	 **2.1n**	**2.2**	50 mM 5 mM	1 h 1.5 h	96% 95%	 **2.3n**	1 : 24 >1 / 25
4	 **2.1o**	**2.2**	5 mM 5 mM	4 h 2.5 h[b]	86% 87%	 **2.3o**	1 / 4.5 1 / 9.5
5	 **2.1p**	**2.2**	50mM	45 min	85%	**2.3p**	1.1 / 1
6	 **2.1q**	**2.2**	50 mM	15 min	94%	 **2.3q**	>1 / 25
7	 **2.1g**	 **2.4**	50 mM	5 h	93%	 **2.5**	>25 / 1
8	**2.1g**	 **2.6**	50 mM 5 mM	6 h 16 h	87% 81%	 **2.7**	10 / 1 >25 / 1
9	**2.1g**	 **2.8**	50 mM 5 mM	16 h 24 h	94% 81%	 **2.9**	12 / 1 21 / 1
10	**2.1q**	**2.4**	50 mM	1 h	90%	 **2.10**	>1/ 25

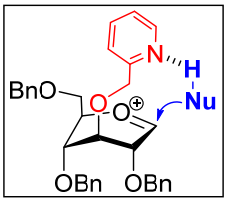
[a] Unless noted otherwise, the reactions were performed under standard conditions: DMTST, 1,2-dichloroethane, -30 → 25 °C; [b] Performed in the presence of NIS/TfOH

9). Similarly, **2.1q** also showed near complete β-selectivity upon rhamnosylation with secondary acceptor **2.4** (entry 10) at 50 mM concentration.

Fortified with these results we attempted to obtain further sustaining evidence for the existence of the intermolecular *H*-bonding and its key involvement into the glycosylation process. The outcome of the following experiments, along with previously discussed factors, is summarized in Figure 2.3. First, consistently with the documented phenomenon that hydrogen bonding can be disturbed by the addition of DMSO,[35] reactions in the presence of DMSO were much less stereoselective with both α- and β-directing glycosyl donors. The contribution of glycosyl sulfoxonium ion intermediates that could be forming in the presence of DMSO,[36] remains to be investigated. However, in our opinion, simple formation of other activated species may not have the direct effect on the stereoselectivity of *H*-bond mediated glycosylation.

Figure 2.3. A survey of effects that reduce stereoselectivity by disrupting the *H*-bonding.

Standard glycosidation of donor **2.1c:** α/β = 1/15.6 (5 mM)



Modification	α/β
4,6-*O*-benzylidene	1/2.1
heat at 50 °C	1/7.1
added DMSO (1 equiv.)	1/4.9
excess DMTST (6 equiv.)	1/9.8
added TfOH (1 equiv.)	1/8.1
replace H with TMS	1/2.0

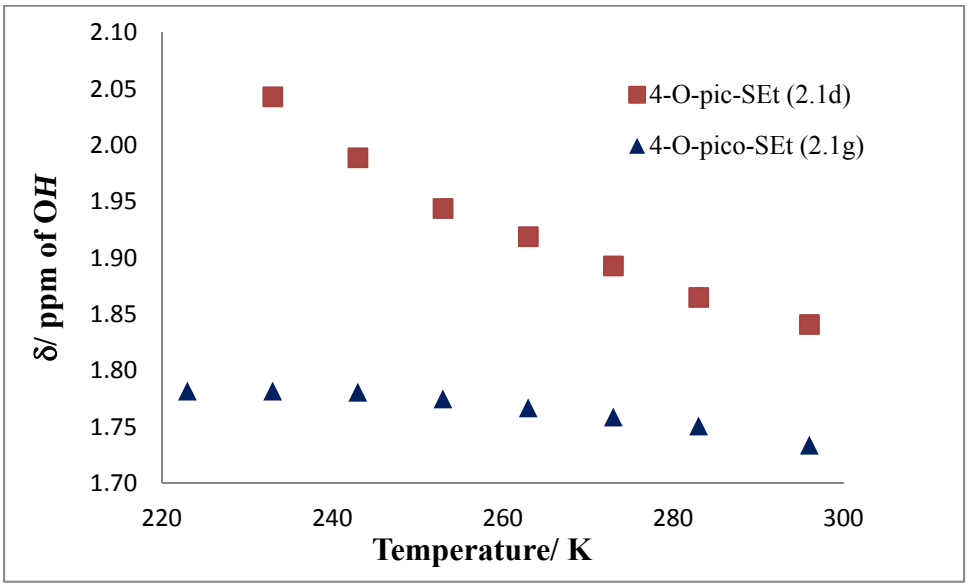
Decrease of selectivity was also detected by using m- and p-picolinyl/picoloyl groups, donor preactivation or by concomitant addition of acceptor and promoter

Second, a significant loss of stereoselectivity was observed when reactions were performed in the presence of a large excess of DMTST (6 equiv. to donor). Also, the

addition of TfOH (1 equiv. in respect to the donor) along with DMTST (2 equiv.) significantly decreased the stereoselectivity. The effect of excess electrophilic reagents in the reaction medium is arguably due to blocking the *H*-bond acceptor (pyridyl nitrogen) with SMe^+ released from DMTST or by protonation. This effect was observed both under 50 mM and 5 mM reaction conditions.

Third, the use of TMS-protected counterpart of glycosyl acceptor **2.2** gave very low stereoselectivity for both α- and β-directing glycosyl donors. This result clearly confirms the essentiality of acceptor proton and the presence of hydrogen bonding for the enhanced *syn*-selectivity. It is possible that these reactions still proceed *via* sequential TMS-deprotection followed by glycosylation, but the generated acceptor has no time to establish *H*-bonding with the donor. Our further study showed that it is essential to premix the donor and acceptor counterparts (1 h standard time) before adding DMTST.

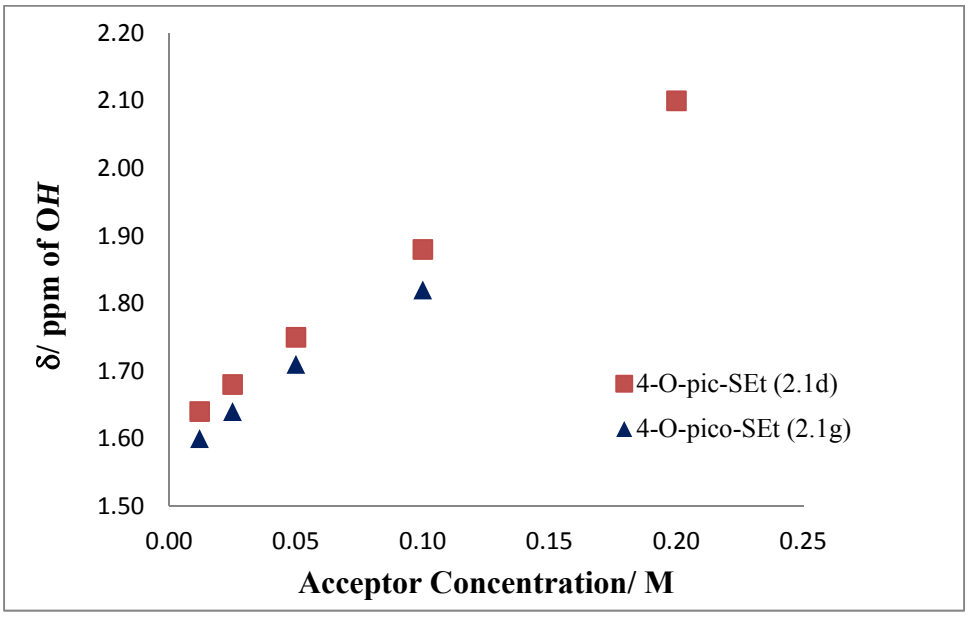
Figure 2.4. Temperature dependence of *OH* chemical shift of acceptor 2.2 in the presence of equimolar amount of donor 2.1d (or 2.1f) in 0.05 M solution.



Alternatively, if the donor is preactivated before the addition of the acceptor or acceptor and DMTST are added concomitantly, no stereoselectivity is observed.

Fourth, inspired by previous studies by Vasella[37,38] and Crich[24] we have determined the reduced temperature coefficient for equimolar **2.2**/ **2.1d** and **2.2**/ **2.1g** combinations in CDCl3 to be -3.1 ppbK^{-1} and -0.9 ppbK^{-1}, respectively, at the linear regression region of the $\Delta\delta/\Delta T$ plots for δ_{OH} at 50 mM concentration (Figure 2.4).[24,37,38] This data provides an indication that the *H*-bonding may exist between glycosyl acceptor and donor. We have also observed a linear dependence of δ_{OH} in ^{1}H NMR spectra of **2.2** recorded at different concentrations for equimolar acceptor-donor pairs in $CDCl_3$ at rt (Figure 2.5). The linear dependence obtained for both 4-picolinyl donor **2.1d** and 4-*O*-picoloyl donor **2.1g** is very indicative of the intermolecular hydrogen bonding, as previously shown by Vasella[37,39] and Crich[24] for substituted 2-aminosugars.

Figure 2.5. Concentration dependence of OH chemical shift of acceptor 2.2 in the presence of donor 2.1d (or 2.1f) at 24℃.



Last, we found that the stereoselectivity diminishes dramatically in case of glycosyl donors protected with 4,6-*O*-benzylidene (entry 6, Table 2.2). It is possible that the induced rigidity of the pyranose ring prevents conformational changes necessary to form the all-axial oxacarbenium intermediate.[5,20-22] This result indicates that the conformational flexibility of the pyranose ring might be essential to ensure efficient H-bond-mediated aglycone delivery.

2.3. Conclusions

We discovered that remote O-picolinyl and O-picoloyl groups can mediate glycosylation reactions by providing high or even complete facial selectivity for the attack of the glycosyl acceptor. In our opinion, the set of data presented herein provides a strong evidence for the hydrogen bond-mediated aglycone delivery while providing a practical new methodology for stereoselective glycosylation. The applicability of this approach was demonstrated and found to be consistently effective with various sugar series including glucose, galactose, mannose, and rhamnose as well as with both primary and secondary glycosyl acceptors. Further application of this new stereoselective glycosylation reaction to other targets and the synthesis of oligosaccharides along with further investigation of the mechanism and kinetic profile of this reaction are currently underway in our laboratory.

2.4. Experimental Section

2.4.1. General Remarks

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. AgOTf was co-evaporated with toluene (3 x 10 mL) and dried in vacuo for 2-3 h directly prior to application. Optical rotations were measured at 'Jasco P-1020' polarimeter. Unless noted otherwise, ^{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 MHz. Two-dimensional heteronuclear *J*-resolved spectra (HETERO2DJ)[40-42] were recorded in $CDCl_3$ at 600 MHz.

2.4.2. Synthesis of Glycosyl Donors

Ethyl 2,3,4,6-Tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (2.1a). The title compound was synthesized according to the standard procedure and the analytical data for **2.1a** was essentially the same as reported previously.[16]

Ethyl 2,3,4,6-Tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (α-2.1a). The title compound was synthesized according to the standard procedure and the analytical data for α-**2.1a** was essentially the same as reported previously.[43]

Ethyl 3,4,6-Tri-*O*-benzyl-2-*O*-picolinyl-1-thio-β-D-glucopyranoside (2.1b). The title compound was synthesized according to the standard procedure and the analytical data for **2.1b** was essentially the same as reported previously.[8]

Ethyl 2,4,6-Tri-*O*-benzyl-3-*O*-picolinyl-1-thio-β-D-glucopyranoside (2.1c). To a solution of ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside[44] (1.0 g, 2.48 mmol) in DMF (10 mL) NaH (60% in mineral oil, 0.2 g, 5.00 mmol) and picolinyl bromide hydrobromide (0.94 g, 3.73 mmol) were added at rt. The reaction mixture was stirred for 1.5 h, quenched with ice-water (~10 mL, 30 min) and then extracted with ethyl acetate /diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~150 mL) was washed with cold water (3 × 30 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1f**) as a white amorphous solid in 90% yield (1.1g, 2.23 mmol). Analytical data for **2.1f**: R_f = 0.58 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{26}$ -50.4 (*c* = 1.0, $CHCl_3$); ^{1}H-NMR: δ, 1.21 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.65 (m, 2H, SCH_2CH_3), 3.35 (m, 1H, H-5), 3.41 (dd, 1H, $J_{2,3}$ = 8.3 Hz, H-2), 3.59-3.71 (m, 2H, H-4, 6a), 3.73 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.24 (dd, 1H, $J_{5,6b}$ = 5.0 Hz $J_{6a,6b}$ = 10.4 Hz, H-6b), 4.47 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.76 (dd,

2H, ^{2}J = 10.2 Hz, CH_2Ph), 4.92 (dd, 2H, ^{2}J = 13.4 Hz, CH_2Ph), 5.44 (s, 1H, >C*H*Ph), 6.90-7.50 (m, 13H, aromatic), 8.40 (d, 1H, aromatic) ppm; ^{13}C-NMR: δ, 15.2, 25.3, 68.8, 70.3, 75.6, 76.0, 81.4, 81.5, 83.7, 85.9, 101.3, 121.6, 122.3, 126.1 (×2), 128.0, 128.3 (×2), 128.5 (×4), 129.1, 136.6, 137.2, 137.9, 149.0, 158.8 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{28}H_{32}NO_5S$ 494.2001, found 494.2005.

To a stirring mixture of **2.1f** (0.5 g, 1.00 mmol) in CH_2Cl_2 (10 mL), water (150 μL) and trifluoroacetic acid (TFA)/CH_2Cl_2 (1/9, v/v, 1.0 mL) were added at rt. The reaction mixture was stirred for 3 h, then neutralized with Et_3N (3 mL) and then diluted with dichloromethane (200 mL) and washed with cold water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and cold water (20 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (methanol - dichloromethane gradient elution) to afford ethyl 2-*O*-benzyl-3-*O*-picolinyl-1-thio-β-D-glucopyranoside as a white amorphous solid in 92% yield (0.38 g, 0.93 mmol). Analytical data: R_f = 0.40 (methanol/dichloromethane, 1/9, v/v); $[\alpha]_D^{25}$ -34.6 (*c* = 1.0, $CHCl_3$); ^{1}H-NMR: δ, 1.25 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.70 (m, 2H, SCH_2CH_3), 3.28-3.42 (m, 3H, H-2, 5, OH), 3.52 (dd, 1H, $J_{3,4}$ = 8.7 Hz, H-3), 3.67 (dd, 1H, $J_{4,5}$ = 9.1 Hz, H-4), 3.78 (dd, 1H, $J_{5,6b}$ = 5.5 Hz, $J_{6a,6b}$ = 11.7 Hz, H-6b), 3.93 (dd, 1H, $J_{5,6a}$ = 3.4 Hz, H-6a), 4.46 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.71 (d, 1H, ^{2}J = 10.6 Hz, ½ CH_2Ph), 4.81-4.98 (m, 3H, 1½ CH_2Ph), 7.05-7.70 (m, 8H, aromatic), 8.51 (d, 1H, *J* = 4.9 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.1, 24.9, 62.9, 71.0, 74.0, 75.4, 79.9, 81.4, 85.0, 89.1, 121.6, 122.8, 127.8, 128.1 (×2), 128.3 (×2), 137.3, 138.1, 148.6, 158.0 ppm; HR FAB MS $[M+Na]^+$ calcd for $C_{21}H_{27}NO_5SNa$ 428.1508, found 428.1912.

To a solution of ethyl 2-*O*-benzyl-3-*O*-picolinyl-1-thio-β-D-glucopyranoside (0.38 g, 0.93 mmol) in DMF (5.0 mL), NaH (60% in mineral oil, 0.19 g, 4.69 mmol) and benzyl bromide (0.33 mL, 2.79 mmol) were added at rt. The reaction mixture was stirred for 2 h, then quenched with ice water (15 mL, 30 min) and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 30 mL). The combined organic extract (~90 mL) was washed with cold water (3 × 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound as a white amorphous solid in 87% yield (0.48 g, 0.82 mmol). Analytical data for **2.1c**: R_f = 0.47 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{25}$ +0.10 (*c* = 1.2, $CHCl_3$); ^{1}H NMR: δ, 1.24 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.68 (m, 2H, SCH_2CH_3), 3.36-3.47 (m, 2H, H-2, 4), 3.52-3.74 (m, 4H, H-3, 5, 6a, 6b), 4.39 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.49 (dd, 2H, ^2J = 12.2 Hz, CH_2Ph), 4.59 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 4.73 (dd, 2H, ^2J = 10.1 Hz, CH_2Ph), 4.95 (dd, 2H, ^2J = 12.8 Hz, CH_2Ph), 7.05-7.70 (m, 18H, aromatic), 8.48 (d, 1H, *J* = 4.8 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.3, 25.2, 69.2, 73.6, 75.2, 75.6, 76.3, 78.0, 79.2, 81.7, 85.2, 87.1, 121.5, 122.4, 127.8, 127.9 (×2), 128.0, 128.3 (×2), 128.5 (×7), 128.6 (×2), 136.7, 138.0, 138.1, 138.3, 149.3, 158.7 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{40}NO_5S$ 586.2627, found 586.2612.

Ethyl 2,4,6-Tri-*O*-benzyl-3-*O*-picolinyl-1-thio-α-D-glucopyranoside (α-2.1c). To a solution of ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-glucopyranoside[44] (1.0 g, 2.48 mmol) in DMF (10 mL), NaH (60% in mineral oil, 0.2 g, 5.00 mmol) and picolinyl bromide hydrobromide (0.94 g, 3.73 mmol) were added at rt. The reaction mixture was

stirred for 1 h, then quenched with ice water (20 mL, 30 min) and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~ 150 mL) was washed with cold water (3 × 30 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/ hexane gradient elution) to give ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-picolinyl-1-thio-α-D-glucopyranoside as a white amorphous solid in 91% yield (1.1g, 2.26 mmol). Analytical data: R_f = 0.53 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ +175.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.27 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.54 (m, SCH_2CH_3), 3.64 (dd, 1H, $J_{4,5}$ = 9.2 Hz, H-4), 3.74 (m, 1H, H-6b), 3.83-3.40 (m, 2H, H-2, 3), 4.18-4.36 (m, 2H, H-5, 6a), 4.71 (dd, 2H, ^2J = 11.8 Hz, CH_2Ph), 4.99 (dd, 2H, ^2J = 14.0 Hz, CH_2Ph), 5.40 (d, 1H, $J_{1,2}$ = 5.4 Hz, H-1), 5.54 (s, 1H, >C*H*Ph), 7.00-7.65 (m, 13H, aromatic), 8.47 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 15.0, 23.9, 62.9, 69.0, 72.7, 75.8, 79.0, 81.9, 84.1, 101.6, 121.6, 122.2, 126.3 (×2), 128.0, 128.2 (×2), 128.4 (×2), 128.5 (×2), 129.1, 136.5, 137.4, 137.8, 148.9, 159.3 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{28}H_{32}NO_5S$ 494.2001, found 494.1963.

To a stirred solution of ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-picolinyl-1-thio-α-D-glucopyranoside (0.5 g, 1.00 mmol) in CH_2Cl_2 (10 mL), water (150 μL) and 10% TFA/CH_2Cl_2 (1/9, v/v, 1.0 mL) were added at rt. The reaction mixture was stirred for 3 h, neutralized with Et_3N (~3 mL) and then diluted with CH_2Cl_2 (200 mL) and washed with cold water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and water (20 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (methanol - dichloromethane gradient elution) to afford ethyl 2-*O*-benzyl-3-*O*-picolinyl-1-thio-α-D-glucopyranoside as a white

amorphous solid in 91% yield (0.37 g, 0.91 mmol). Analytical data: R_f = 0.44 (methanol/ dichloromethane, 1/9, v/v); $[\alpha]_D^{22}$ +99.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.23 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.51 (m, 2H, SCH_2CH_3), 2.90 (br. s, 1H, OH), 3.61-3.94 (m, 5H, H-2, 3, 4, 6a, 6b), 4.02(m, 1H, H-5), 4.67 (dd, 1H, ^2J = 11.8 Hz, CH_2Ph), 4.94 (dd, 2H, ^2J = 15.2 Hz, CH_2Ph), 5.38 (d, 1H, $J_{1,2}$ = 5.2 Hz, H-1), 7.05-7.80 (m, 8H, aromatic), 8.48 (d, 1H, *J* = 4.6 Hz, aromatic) ppm; ^{13}C NMR: δ, 14.8, 23.6, 62.9, 70.9, 72.0, 72.2, 73.6, 79.3, 82.9, 84.6, 121.6, 122.8, 128.0, 128.1 (×2), 128.5 (×2), 137.3, 138.0, 148.6, 158.5 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{21}H_{28}NO_5S$ 406.1688, found 406.1697.

To a solution of ethyl 2-*O*-benzyl-3-*O*-picolinyl-1-thio-α-D-glucopyranoside (0.37 g, 0.91 mmol) in DMF (5 mL), NaH (60% in mineral oil, 0.18 g, 4.56 mmol) and benzyl bromide (0.33 mL, 2.73 mmol) were added at rt. The reaction mixture was stirred for 2 h, then quenched with ice water (15 mL, 30 min) and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 30 mL). The combined organic extract (~90 mL) was washed with cold water (3 × 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound as a white amorphous solid in 85% yield (0.45 g, 0.77 mmol). Analytical data for α-**2.1c**: R_f = 0.49 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{25}$ +128.9 (*c* = 1.0, $CHCl_3$); NMR: δ, 1.23 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.47 (m, 2H, SCH_2CH_3), 3.30-3.94 (m, 5H, H-2, 3, 4, 6a, 6b), 4.15 (m, 1H, H-5), 4.53 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.56 (dd, 2H, ^2J = 10.2 Hz, CH_2Ph), 4.59 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 4.96 (dd, 2H, ^2J = 12.9 Hz, CH_2Ph), 5.37 (d, 1H, $J_{1,2}$ = 4.7 Hz, H-1), 6.92-7.63 (m, 18H, aromatic), 8.47 (d, 1H, *J* = 4.8 Hz, aromatic) ppm; ^{13}C NMR: δ, 14.8, 23.7, 68.5, 70.4, 72.2, 73.5, 75.0, 76.2, 77.5, 79.2, 83.0, 83.1, 121.6,

122.2, 127.7, 127.8, 127.9, 128.0 (×4), 128.1 (×2), 128.3 (×2), 128.4 (×4), 136.4, 137.8, 137.9, 138.2, 149.1, 158.9 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{40}NO_5S$ 586.2627, found 586.2735.

Ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-picolinyl-1-thio-β-D-glucopyranoside (2.1d). To a solution of ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[45] (0.5 g, 1.01 mmol) in DMF (5 mL), NaH (60% in mineral oil, 0.12 g, 3.03 mmol) and picolinyl bromide hydrobromide (0.51 g, 2.02 mmol) were added at rt. The reaction mixture was stirred for 2.5 h, then quenched with ice water (15 mL, 30 min) and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~150 mL) was washed with cold water (3 × 15 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound as a white amorphous solid in 88% yield (0.51 g, 0.87 mmol). Analytical data for **2.1d**: R_f = 0.48 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ +1.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.31 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.75 (m, 2H, SCH_2CH_3), 3.44 (dd, 1H, $J_{2,3}$ = 8.9 Hz, H-2), 3.50 (m, 1H, H-5), 3.60-3.79 (m, 4H, H-3, 4, 6a, 6b), 4.46 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.54 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.72 (dd, 2H, ^2J = 11.4 Hz, CH_2Ph), 4.84 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 4.90 (dd, 2H, ^2J = 12.6 Hz, CH_2Ph), 7.05-7.65 (m, 18H, aromatic), 8.51 (d, 1H, *J* = 4.8 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.3, 25.1, 69.3, 73.5, 75.6, 75.8, 75.9, 78.7, 79.2, 81.8, 85.1, 121.5, 122.5, 127.6, 127.8 (×3), 128.0 (×2), 128.4 (×4), 128.5 (×3), 128.5 (×2), 136.6, 138.1, 138.3, 138.5, 149.2, 158.3 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{40}NO_5S$ 586.2627, found 586.2619.

Ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-picolinyl-1-thio-β-D-glucopyranoside (2.1e). To a solution of ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[46] (0.5 g, 1.01 mmol) in DMF (5 mL), NaH (60% in mineral oil, 0.12 g, 3.03 mmol) and picolinyl bromide hydrobromide (0.51 g, 2.02 mmol) were added at rt. The reaction mixture was stirred for 2.5 h, then quenched with ice water (15 mL, 30 min) and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~150 mL) was washed with cold water (3 × 15 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound as a white amorphous solid in 87% yield (0.52 g, 0.89 mmol). Analytical data for **2.1e**: R_f = 0.42 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{24}$ +4.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.33 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.78 (m, 2H, SCH_2CH_3), 3.47 (dd, 1H, $J_{2,3}$ = 8.7 Hz, H-2), 3.53 (m, 1H, H- 5), 3.66 (dd, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 3.72 (dd, 1H, $J_{3,4}$ = 8.6 Hz, H-3), 3.78 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, H-6a), 3.84 (dd, 1H, $J_{5,6b}$ = 1.9 Hz, H-6b), 4.50 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.70 (d, 2H, ^2J = 4.4 Hz, CH_2Ph), 4.74 (dd, 2H, ^2J = 9.7 Hz, CH_2Ph), 4.83 (dd, 2H, ^2J = 10.2 Hz, CH_2Ph), 4.91 (dd, 2H, ^2J = 13.2 Hz, CH_2Ph), 7.05-7.50 (m, 17H, aromatic), 7.66 (dd, 1H, *J* = 7.7 Hz, aromatic), 8.53 (d, 1H, *J* = 4.8 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.3, 25.1, 70.0, 74.3, 75.2, 75.7, 75.9, 78.0, 79.1, 81.9, 85.2, 86.8, 121.4, 122.4, 127.8, 127.9 (×2), 128.0 (×2), 128.1 (×2), 128.5 (×4), 128.6 (×4), 136.7, 138.1 (×2), 138.6, 149.1, 158.7 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{40}NO_5S$ 586.2627, found 586.2695.

Ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-picolinyl-1-thio-α-D-glucopyranoside (α-2.1e). To a solution of ethyl 2,3,4-tri-*O*-benzyl-1-thio-α-D-glucopyranoside[47] (0.5 g, 1.01 mmol) in DMF (5 mL), NaH (60% in mineral oil, 0.12 g, 3.03 mmol) and picolinyl bromide hydrobromide (0.51 g, 2.02 mmol) were added at rt. The reaction mixture was stirred for 2 h, then quenched with ice water (15 mL) and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~150 mL) was washed with cold water (3 × 15 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound as a white amorphous solid in 94% yield (0.56 g, 0.95 mmol). Analytical data for α–**2.1e**: R_f = 0.38 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{24}$ +146.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.32 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.59 (m, 2H, SCH_2CH_3), 3.72 (dd, 1H, $J_{4,5}$ = 8.5 Hz, H-4), 3.78 (dd, 1H, $J_{5,6a}$ = 1.8 Hz, $J_{6a,6b}$ = 10.8 Hz, H- 6a), 3.85-3.93 (m, 2H, H-2, 6b), 3.94 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 4.29 (m, 1H, H-5), 4.69 (dd, 2H, ^2J = 13.6 Hz, CH_2Ph), 4.75 (dd, 2H, ^2J = 11.5 Hz, CH_2Ph), 4.77 (dd, 2H, ^2J = 11.0 Hz, CH_2Ph), 4.92 (dd, 2H, ^2J = 10.8 Hz, CH_2Ph), 5.47 (d, 1H, $J_{1,2}$ = 4.8 Hz, H-1), 7.10-7.50 (m, 17H, aromatic), 7.65 (dd, 1H, *J* = 7.7 Hz, aromatic), 8.54 (d, 1H, *J* = 4.2 Hz, aromatic) ppm; ^{13}C NMR: δ, 14.9, 23.8, 69.5, 70.5, 72.4, 74.3, 75.1, 75.8, 77.6, 79.6, 82.7, 83.2, 121.3, 122.4, 127.7, 127.8, 127.9 (×2), 128.0, 128.2 (×4), 128.5 (×6), 136.6, 137.9, 138.4, 138.8, 149.0, 158.4 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{40}NO_5S$ 586.2627, found 586.2702.

Ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (2.1g). To a solution of ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[47] (0.5 g, 1.01 mmol) in

CH_2Cl_2 (10 mL), picolinic acid (0.19 g, 1.52 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.31 g, 1.52 mmol), and 4-dimethylaminopyridine (25 mg, 0.20 mmol) were added at rt. The reaction mixture was stirred for 15 min under argon, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with brine (2 x 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 give the title compound as a white amorphous solid in 89% yield (0.54 g, 0.90 mmol). Analytical data for **2.1g**: R_f = 0.44 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ -38.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.50 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.95 (m, 2H, SCH_2CH_3), 3.74 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2), 3.80-3.85 (m, 2H, H- 6a, 6b), 4.02 (m, 1H, H-5), 4.10 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 4.63 (s, 2H, CH_2Ph), 4.74 (d, 1H, $J_{1,2}$ =9.8 Hz, H-1), 4.92 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 5.01 (dd, 2H, ^2J =10.3 Hz, CH_2Ph), 5.58 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 7.15-7.65 (m, 16H, aromatic), 7.89 (dd, 1H, *J* = 7.7 Hz, aromatic), 8.14 (d, 1H, *J* = 7.7 Hz, aromatic), 8.87 (d, 1H, *J* = 3.9 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.1, 24.9, 69.6, 72.3, 73.4, 75.4, 77.2, 81.5, 83.6, 85.1, 125.5, 126.9, 127.3, 127.4, 127.5 (×2), 127.8 (×2), 127.9, 128.1 (×5), 128.3 (×3), 136.9, 137.7, 137.8, 137.9, 147.4, 149.7, 164.1 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{38}NO_6S$ 600.2420, found 600.2427.

Ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-picoloyl-1-thio-β-D-glucopyranoside (2.1h). To a solution of ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[46] (0.5 g, 1.01 mmol) in CH_2Cl_2 (10 mL), picolinic acid (0.19 g, 1.52 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.31 g, 1.52 mmol), and 4-dimethylaminopyridine (25 mg, 0.20 mmol) were added at rt.

The reaction mixture was stirred 10 min under argon, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with brine (2 x 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 give the title compound as a white amorphous solid in 87% yield (0.53 g, 0.88 mmol). Analytical data for **2.1h**: R_f = 0.47 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{24}$ +18.7 (*c* = 1.2, $CHCl_3$); ^{1}H NMR: δ, 1.23 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.69 (m, 2H, SCH_2CH_3), 3.46 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 3.63 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 3.70 (m, 1H, H-5), 3.72 (dd, 1H, $J_{3,4}$ = 8.6 Hz, H-3), 4.51 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.53-4.68 (m, 3H, H-6a, 6b, ½ CH_2Ph), 4.73 (d, 1H, ^2J = 10.2 Hz, ½ CH_2Ph), 4.80-5.00 (m, 4H, 2 × CH_2Ph), 7.10-7.50 (m, 16H, aromatic), 7.78 (dd, 1H, *J* = 7.7 Hz, aromatic), 8.02 (d, 1H, *J* = 7.8 Hz, aromatic), 8.81 (dd, 1H, *J* = 4.7 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.3, 25.2, 64.6, 75.2, 75.7, 76.0, 77.0, 78.0, 81.9, 85.2, 86.7, 125.2, 127.0, 127.9 (×2), 128.0, 128.1, 128.2 (×2), 128.4 (×2), 128.5 (×2), 128.6 (×4), 137.0, 137.7, 137.9, 138.3, 147.9, 150.1, 164.7 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{38}NO_6S$ 600.2420, found 600.2430.

Ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-(pyrid-3-ylmethyl)-1-thio-β-D-glucopyranoside (2.1i). NaH (60% in mineral oil, 40.8 mg, 1.02 mmol) and 3-(bromomethyl)pyridine hydrobromide (191.8 mg, 0.76 mmol) were added to a solution of ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[45] (250 mg, 0.51 mmol) in DMF (3 mL) and the resulting mixture was stirred for 6.5 h at rt. After that, the reaction mixture was poured into ice-water (10 mL), stirred for 30 min, and extracted with ethyl acetate/ diethyl ether

(1/1, v/v, 3 × 30 mL). The combined organic extract (~90 mL) was washed with cold water (3 × 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/ hexane gradient elution) to give the title compound in 89% yield (265 mg, 0.45 mmol) as a white amorphous solid. Analytical data for **2.1i**: R_f = 0.38 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{21}$ +5.0 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.93 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.83 (m, 2H, SCH_2CH_3), 3.45-3.58 (m, 2H, H-2, 5), 3.67-3.85 (m, 4H, H-3, 4, 6a, 6b), 4.53 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.64 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 4.72 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.90 (dd, 2H, ^2J = 10.6 Hz, CH_2Ph), 4.92 (dd, 2H, ^2J = 11.7 Hz, CH_2Ph), 7.15-7.52 (m, 17H, aromatic), 8.44 (d, 1H, *J* = 0.9 Hz, aromatic), 8.55 (d, 1H, *J* = 4.7 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.3, 25.1, 68.9, 72.4, 73.6, 75.6, 75.8, 78.0, 79.0, 81.9, 85.2, 86.7, 123.4, 127.7 (× 2), 127.8 (× 3), 127.9 (× 2), 128.0, 128.4 (× 2), 128.5(× 3), 128.6 (× 2), 133.6, 135.5, 138.0, 138.1, 138.5, 149.2 (× 2) ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{40}NO_5S$ 586.2627, found 586.2673.

Ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-(pyrid-4-ylmethyl)-1-thio-β-D-glucopyranoside (2.1j). NaH (60% in mineral oil, 40.8 mg, 1.02 mmol) and 4-(bromomethyl)pyridine hydrobromide (191.8 mg, 0.76 mmol) were added to a solution of ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[45] (250 mg, 0.51 mmol) in DMF (3 mL) and the resulting mixture was stirred for 6 h at rt. After that, the reaction mixture was poured into ice-water (10 mL), stirred for 30 min, and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 30 mL). The combined organic extract (~90 mL) was washed with cold water (3 × 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and

concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/ hexane gradient elution) to give the title compound 91% yield (269 mg, 0.45 mmol) as a white amorphous solid. Analytical data for **2.1j**: R_f = 0.35 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{21}$ +2.5 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.39 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.82 (m, 2H, SCH_2CH_3), 3.45-3.56 (m, 2H, H-2, 4), 3.62-3.85 (m, 4H, H-5, 6a, 6b), 4.53 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.61 (dd, 2H, ^2J = 12.2 Hz, CH_2Ph), 4.71 (dd, 2H, ^2J = 12.9 Hz, CH_2Ph), 4.88 (dd, 2H, ^2J = 11.1 Hz, CH_2Ph), 4.88 (dd, 2H, ^2J = 10.2 Hz, CH_2Ph), 7.05-7.52 (m, 17H, aromatic), 8.53 (d, 2H, *J* = 5.7 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.3, 25.2, 69.0, 73.1, 73.6, 75.6, 75.9, 78.3, 79.0, 82.0, 85.3, 86.7, 121.7 (× 2), 127.8 (× 3), 127.9 (× 3), 128.1, 128.5 (× 4), 128.6 (× 4), 138.0, 138.1, 138.4, 147.4, 149.9 (× 2) ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{40}NO_5S$ 586.2627, found 586.2681.

Ethyl 4-*O*-Benzoyl-2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2.1k). The title compound was synthesized according to standard procedures and the analytical data for **2.1k** was essentially same as previously reported.[48]

Ethyl 2,3,4,6-Tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (2.1l). The title compound was synthesized according to the standard procedure and the analytical data for **2.1l** was essentially the same as reported previously.[49]

Ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-picolinyl-1-thio-β-D-galactopyranoside (2.1m). To a solution of ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside[50] (0.5 g, 1.01 mmol) in DMF (5 mL), NaH (60% in mineral oil, 0.12 g, 3.03 mmol) and picolinyl bromide

hydrobromide (0.51 g, 2.02 mmol) were added at rt. The reaction mixture was stirred for 1.5 h, then quenched with ice water (15 mL, 30 min) and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~150 mL) was washed with cold water (3 × 15 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound as a white amorphous solid in 90% yield (0.53 g, 0.90 mmol). Analytical data for **2.1m**: R_f = 0.46 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ -5.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.31 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.75 (m, 2H, SCH_2CH_3), 3.54-3.75 (m, 4H, H-3, 5, 6a, 6b), 3.82 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 4.06 (d, 1H, $J_{4,5}$ = 2.8 Hz, H-4), 4.39-4.53 (m, 3H, H-1, CH_2Ph), 4.67-4.53 (m, 4H, 2 × CH_2Ph), 4.88 (d, 1H, ^2J = 10.2 Hz, ½ CH_2Ph), 5.12 (d, 1H, ^2J = 13.4 Hz, ½ CH_2Ph), 7.05-7.80 (m, 18H, aromatic), 8.51 (d, 1H, *J* = 4.8 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.2, 25.0, 68.6, 72.8, 73.7, 75.2, 75.8, 75.9, 77.1, 78.5, 83.7, 85.5, 121.7, 122.3, 127.8, 127.9 (×4), 128.1 (×2), 128.5 (×6), 128.6 (×2), 136.7, 137.8, 138.3, 138.4, 148.6, 159.2 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{40}NO_5S$ 586.2627, found 586.2612.

Ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-galactopyranoside (2.1n). To a solution of ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside[50] (0.5 g, 1.01 mmol) in CH_2Cl_2 (10 mL), picolinic acid (0.19 g, 1.52 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.31 g, 1.52 mmol), and 4-dimethylaminopyridine (25 mg, 0.20 mmol) were added at rt. The reaction mixture was stirred 10 min under argon, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with brine (2 x

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 give the title compound as a colorless syrup in 91% yield (0.55 g, 0.90 mmol). Analytical data for **2.1n**: R_f = 0.56 (ethyl acetate/ hexane, 1/1, v/v); $[\alpha]_D^{25}$ +23.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.35 (t, 3H, *J* = 7.5 Hz, SCH_2CH_3), 2.80 (m, 2H, SCH_2CH_3), 3.53-3.69 (m, 2H, H-6a, 6b), 3.69 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 3.76 (dd, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 3.87 (dd, 1H, H-5), 4.47 (dd, 2H, ^2J = 11.7 Hz, CH_2Ph), 4.57 (d, 1H, $J_{1,2}$ = 9.3 Hz, H-1), 4.58 (d, 1H, ^2J = 11.3 Hz, ½ CH_2Ph), 4.80 (dd, 1H, ^2J = 10.2 Hz, CH_2Ph), 4.89 (d, 1H, ^2J = 11.3 Hz, ½ CH_2Ph), 5.97 (dd, 1H, $J_{4,5}$ = 2.8 Hz, H-4), 7.10-7.50 (m, 16H, aromatic), 7.79 (dd, 1H, aromatic), 8.07 (d, 1H, *J* = 7.8 Hz, aromatic), 8.81 (dd, 1H, *J* = 4.8 Hz, aromatic) ppm; ^{13}C NMR: δ, 15.2, 25.1, 68.2, 68.5, 72.1, 73.8, 75.9, 76.0, 77.9, 81.1, 85.6, 125.5, 127.8 (×2), 127.9, 128.1 (×2), 128.4 (×11), 137.0, 137.5, 137.6, 138.1, 147.6, 150.3, 163.9 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{38}NO_6S$ 600.2420, found 600.2431.

Ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-picoloyl-1-thio-α-D-mannopyranoside (2.1o). To a solution of ethyl 2,3,4-tri-*O*-benzyl-1-thio-α-D-mannopyranoside[51] (0.5 g, 1.01 mmol) in CH_2Cl_2 (10 mL), picolinic acid (0.19 g, 1.52 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.31 g, 1.52 mmol), and 4-dimethylaminopyridine (25 mg, 0.20 mmol) were added at rt. The reaction mixture was stirred 10 min under argon, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with brine (2 x 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 give the title compound as colorless syrup in 91% yield (0.55 g, 0.92 mmol). Analytical data for **2.1o**: R_f = 0.39 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{24}$ +93.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.18 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.52 (m, 2H, SCH_2CH_3), 3.82-3.93 (m, 2H, H-2, 3), 4.03 (dd, 1H, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 4.28 (m, 1H, H-5), 4.50-4.70 (m, 7H, H-6a, 6b, 2 ½ CH_2Ph), 4.90 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 5.34 (s, 1H, H-1), 7.05-7.60 (m, 17H, aromatic), 7.92 (d, 1H, *J* = 7.8 Hz, aromatic), 8.64 (d, 1H, *J* = 1.7 Hz, aromatic) ppm; ^{13}C NMR: δ, 14.8, 25.2, 64.1, 70.1, 71.7, 71.8, 74.1, 74.8, 76.2, 80.1, 81.6, 124.9, 126.5, 127.4 (×2), 127.5 (×3), 127.6 (×2), 127.8 (×2), 128.1 (×5), 128.2 (×2), 136.5, 137.8 (×2), 147.5, 149.7, 164.2 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{35}H_{38}NO_6S$ 600.2420, found 600.2426.

Ethyl 2,3,4-Tri-*O*-benzyl-1-thio-β-L-rhamnopyranoside (2.1p). NaH (60% in mineral oil, 0.43 g, 10.8 mmol) and benzyl bromide (0.86 mL, 7.2 mmol) were added to a solution of ethyl 1-thio-β-L-rhamnopyranoside[52] (**S7**, 0.25 g, 1.2 mmol) in DMF (5.0 mL) and the resulting mixture was stirred for 2 h at rt. After that, the reaction mixture was poured into ice-water (30 mL), stirred for 30 min, and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~150 mL) was washed with cold water (3 × 15 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/ hexane gradient elution) to give the title compound in 89% yield (0.51 g, 1.1 mmol) as a white amorphous solid. Analytical data for **2.1p**: R_f = 0.61 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{22}$ +80.8 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.27 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 1.35 (d, 3H, $J_{5,6}$ = 6.2 Hz, C-6), 2.68 (q, 2H,

J = 7.4 Hz, SCH_2CH$_3$), 3.33 (m, 1H, H-5), 3.55 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 3.67 (dd, 1H, $J_{4,5}$ = 9.2 Hz, H-4), 3.96 (d, 1H, $J_{2,3}$ = 2.5 Hz, H-2), 4.51 (s, 1H, H-1), 4.60- 4.75 (m, 3H, 1½ CH_2Ph), 4.89 (dd, 2H, ^2J = 11.6 Hz, CH_2Ph), 4.93 (d, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 7.15-7.55 (m, 15H, aromatic) ppm; ^{13}C NMR: δ, 15.2, 18.3, 25.9, 72.3, 75.1, 75.6, 76.5, 77.3, 80.1, 84.3, 84.4, 127.7 (× 3), 127.8, 127.9, 128.2 (× 2), 128.3 (× 2), 128.5 (× 4), 128.6 (× 2), 138.4, 138.5 (× 2) ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{29}H_{35}O_4S$ 479.2256, found 479.2586.

Ethyl 2,4-Di-*O*-benzyl-3-*O*-picoloyl-1-thio-β-L-rhamnopyranoside (2.1q). 2,6-Lutidine (0.79 mL, 7.2 mmol) was added to a soln. of ethyl 2,3-*O*-isopropylidene-1-thio-β-L-rhamnopyranoside[52] (0.9 g, 3.6 mmol) in anhydrous THF (10 mL) and the resulting mixture was stirred under argon for 10 min at rt. After that, the mixture was cooled to -78 ^{o}C, TBDMSOTf (5.5 mmol, 1.2 mL) was added. The resulting reaction mixture was stirred for 15 min at -78 ^{o}C and the volatiles were evaporated *in vacuo*. The residue was diluted with CH_2Cl_2 (~200 mL) and washed with 20% aq. $NaHCO_3$ (40 mL) and water (3 x 40 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 ethyl 4-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-thio-β-L-rhamnopyranoside in 89% yield (1.2 g, 2.7 mmol) as a white amorphous solid. Analytical data: R_f = 0.69 (ethyl acetate/hexane, 1/4, v/v); $[\alpha]_D^{22}$ +62.3 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 0.03, 0.09 (2s, 6H, 2 × Si(CH$_3$)$_3$), 0.84 (s, 9H, 3 × C(CH$_3$)$_3$), 1.18-1.35 (m, 6H, C-6, SCH$_2$CH_3), 1.31, 1.50 (2s, 6H, 2 × C(CH$_3$)$_2$), 2.71 (q, 2H, J = 7.5 Hz, SCH_2CH$_3$), 3.10-3.25 (m, 1H, H-5), 3.38 (dd, 1H, $J_{4,5}$ = 9.1 Hz, H-4),

3.89 (dd, 1H, $J_{3,4}$ = 6.6 Hz, H-3), 4.20 (dd, 1H, $J_{2,3}$ = 5.6 Hz, H-2), 4.77 (d, 1H, $J_{1,2}$ = 2.1 Hz, H-1) ppm; ^{13}C NMR: δ -4.9, -3.9, 14.9, 18.2, 18.4, 25.9, 26.0 (× 3), 26.6, 28.2, 75.8, 76.0, 76.6, 80.7, 80.9, 110.1 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{17}H_{35}O_4SSiNa$ 363.2025, found 363.2113.

To a stirring mixture of ethyl 2,3-*O*-isopropylidene-4-*O*-*tert*-butyldimethylsilyl-1-thio-β-L-rhamnopyranoside (0.42 g, 1.2 mmol) in CH_2Cl_2 (10 mL), water (150 μL) and a soln. of TFA in CH_2Cl_2 (1/9, v/v, 1.2 mL) were added at rt. The reaction mixture was stirred for 30 min, then neutralized with Et_3N (~3.0 mL), diluted with CH_2Cl_2 (~200 mL) and washed with water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and water (3 x 20 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (methanol - dichloromethane gradient elution) to afford ethyl 4-*O*-*tert*-butyldimethylsilyl-1-thio-β-L-rhamnopyranoside in 83% yield (0.31 g, 0.9 mmol) as a white amorphous solid. Analytical data: R_f = 0.36 (ethyl acetate/hexane, 3/7, v/v); $[\alpha]_D^{22}$ +63.0 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 0.05, 0.10 (2s, 6H, 2 × $Si(CH_3)_3$), 0.85 (s, 9H, 3 × $C(CH_3)_3$), 1.20-1.35 (m, 6H, C-6, SCH_2CH_3), 2.51 (br. s, 1H, OH), 2.67 (m, 2H, SCH_2CH_3), 3. 22 (m, 1H, H-5), 3.32-3.45 (m, 2H, H-3, 4), 3.96 (s, 1H, H-2), 4.59 (d, 1H, $J_{1,2}$ = 0.9 Hz, H-1) ppm; ^{13}C NMR: δ, -4.4, -3.6, 15.2, 18.4, 18.5, 25.4, 26.1 (× 3), 72.7, 75.0, 75.5, 77.4, 83.8 ppm; $^1J_{C1,H1}$ = 151.7 Hz; HR-FAB MS $[M+Na]^+$ calcd for $C_{14}H_{30}O_4SSiNa$ 345.1532, found 345.1687.

NaH (60% in mineral oil, 0.23 g, 5.8 mmol) and benzyl bromide (0.46 mL, 3.9 mmol) were added to a solution of ethyl 4-*O*-*tert*-butyldimethylsilyl-1-thio-β-L-rhamnopyranoside (0.31 g, 0.96 mmol) in DMF (5.0 mL) and the resulting mixture was

stirred for 1.5 h at rt. After that, the reaction mixture was poured into ice-water (~20 mL), stirred for 30 min, and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~150 mL) was washed with cold water (3 × 15 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give ethyl 2,4-di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-1-thio-β-L-rhamnopyranoside in 81% yield (0.39 g, 0.78 mmol) as a white amorphous solid. Analytical data: R_f = 0.66 (ethyl acetate/hexane, 1/4, v/v); $[\alpha]_D^{21}$ +47.8 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 0.00, 0.05 (2s, 6H, $Si(CH_3)_3$), 0.85 (s, 9H, $C(CH_3)_3$), 1.10-1.25 (m, 6H, C-6, SCH_2CH_3), 2.60 (q, 2H, *J* = 7.4 Hz, SCH_2CH_3), 3. 22 (m, 1H, H-5), 3.44 (dd, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 3.63-3.72 (m, 2H, H-2, 3), 4.42-4.56 (m, 2H, H-1, ½ CH_2Ph), 4.78 (d, 1H, ^2J = 11.3 Hz, ½ CH_2Ph), 4.79 (dd, 2H, ^2J = 11.2 Hz, CH_2Ph), 7.15-7.45 (m, 10H, aromatic) ppm; ^{13}C NMR: δ, -4.7, -4.0, 15.2, 18.1, 18.2, 25.8, 26.1 (× 3), 75.4, 75.8, 76.4, 77.7, 80.7, 82.0, 84.4, 127.4, 127.6, 127.8 (× 4), 128.1 (× 2), 128.2 (× 2), 138.4, 138.8 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{28}H_{42}O_4SSiNa$ 525.2573, found 525.2463.

1M soln. of *tert*-butylammonium fluoride in THF (0.5 mL, 0.5 mmol) was added to a solution of ethyl 2,4-di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-1-thio-β-L-rhamnopyranoside (0.25 g, 0.50 mmol) in THF (3.0 mL) and the resulting mixture was stirred for 30 min at rt. After that, the reaction mixture was neutralized with Et_3N (~0.5 mL), diluted with CH_2Cl_2 (~150 mL) and washed with cold water (15 mL), sat. aq. $NaHCO_3$ (15 mL), and water (3 x 15 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 ethyl 2,4-

di-*O*-benzyl-1-thio-β-L-rhamnopyranoside in 93% yield (0.18 g, 0.46 mmol) as a white amorphous solid. Analytical data: R_f = 0.43 (ethyl acetate/hexane, 3/7, v/v); $[\alpha]_D^{21}$ +132.3 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.30 (t, 3H, *J* = 7.5 Hz, SCH_2CH_3), 1.37 (d, 3H, $J_{5,6}$= 5.7 Hz, C-6), 2.17 (d, 1H, *J* = 8.7 Hz, OH), 2.74 (q, 2H, *J* = 7.4 Hz, SCH_2CH_3), 3.25-3.37 (m, 2H, H-4, 5), 3.64 (m, 1H, H-3), 3.86 (d, 1H, $J_{2,3}$ = 3.2 Hz, H-2), 4.57 (d, 1H, $J_{1,2}$ = 0.6 Hz, H-1), 4.73 (dd, 2H, ^2J = 11.1 Hz, CH_2Ph), 4.82 (dd, 2H, ^2J = 11.5 Hz, CH_2Ph), 7.16-7.50 (m, 10H, aromatic) ppm; ^{13}C NMR: δ, 15.2, 18.4, 26.1, 75.3, 75.6, 76.1, 76.2, 80.9, 81.9, 84.3, 128.0, 128.2 (× 3), 128.5 (× 2), 128.6 (× 2), 128.7 (× 2), 138.2, 138.4 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{22}H_{28}O_4SNa$ 411.1606, found 411.1713.

Picolinic acid (95 mg, 0.77 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (197 mg, 1.03 mmol), and 4-dimethylaminopyridine (12.6 mg, 0.10 mmol) were added to a solution of ethyl 2,4-di-*O*-benzyl-1-thio-β-L-rhamnopyranoside (200 mg, 0.52 mmol) in CH_2Cl_2 (6.0 mL) and the resulting mixture was stirred under argon for 45 min at rt. The reaction mixture was diluted with CH_2Cl_2 (~100 mL) and washed with 20% brine solution (2 x 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 give the title compound in 90% yield (229 mg, 0.46 mmol) as a colorless syrup. Analytical data for **2.1q**: R_f = 0.44 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{22}$ +122.0 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.31 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 1.42 (d, 3H, $J_{5,6}$ = 6.1 Hz, C-6), 2.74 (q, 2H, *J* = 7.5 Hz, SCH_2CH_3), 3.51 (m, 1H, H-5), 3.90 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 4.21 (d, 1H, $J_{2,3}$ = 3.2 Hz, H-2), 4.63-4.87 (m, 5H, H-1, 2 × CH_2Ph), 5.22 (dd, 1H, $J_{3,4}$ = 9.8 Hz, H-3), 7.02-7.50 (m, 12H, aromatic), 7.75 (m, 1H, aromatic), 7.91 (m, 1H, aromatic), 7.87 (d, 1H, *J* = 4.0 Hz,

aromatic) ppm; ^{13}C NMR: δ, 15.2, 18.3, 25.9, 75.3, 75.7, 76.3, 78.0, 78.3, 78.5, 84.2, 125.2, 127.1, 127.6, 127.7, 128.0 (× 2), 128.1 (× 2), 128.3 (× 2), 128.5 (× 2), 136.9, 137.8, 138.0, 147.5, 150.1, 164.4 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{28}H_{32}O_5$ 494.2001, found 494.2005.

2.4.3. Synthesis of Disaccharides

General procedure for glycosylation in the presence of DMTST. A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $(ClCH_2)_2$ (2.6 mL, 50 mM or 26 mL, 5 mM) was stirred under argon for 1 h. The mixture was cooled to -30 °C, DMTST[18] (0.26 mmol) was added, and the resulting mixture was allowed to warm to rt over a period of 1 h. The external heating was then applied and the reaction mixture was stirred at 42 °C for the time specified in tables. *Alternative procedure involved stirring at rt as indicated in tables*. Upon completion, Et_3N (0.3 mL) was added and the resulting mixture was stirred for 30 min. The mixture was then diluted with CH_2Cl_2 (10 mL), the solid was filtered off, and the residue was washed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 20% aq. $NaHCO_3$ (10 mL) and water (3 x 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). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (2.3a). The title compound was obtained as a white amorphous solid from glycosyl donor **2.1a** and acceptor **2.2** in 92% (α/β = 1/1.9, 50 mM) and 85% yield (α/β = 1/1, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for **3a** was in accordance with that reported previously.[19]

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-picolinyl-β-D-glucopyranosyl)-α-D-glucopyranoside (2.3b). The title compound was obtained as a white amorphous solid from glycosyl donor **2.1b** and acceptor **2.2** in 83% yield (β only, 50 mM). Analytical data for **2.3b** was essentially the same as reported previously.[7]

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,4,6-tri-*O*-benzyl-3-*O*-picolinyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (2.3c). The title compound was obtained as a white amorphous solid from glycosyl donor **1c** and acceptor **2.2** in 84% (α/β = 1/5.8, 50 mM) and 85% yield (α/β = 1/15.6, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for **β**-isomer of **3c**: R_f = 0.63 (ethyl acetate/hexane, 1/1, v/v); ^{1}H NMR: δ, 3.25 (s, 3H, OCH_3), 3.28-3.66 (m, 9H, H-2, 2', 3', 4, 4', 5, 6a, 6a', 6b'), 3.76 (m, 1H, H-5'), 3.92 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.11 (dd, 1H, $J_{5,6b}$ = 1.8 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6b), 4.27 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.49 (dd, 2H, ^2J = 13.2 Hz, CH_2Ph), 4.53 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.54 (dd, 2H, ^2J = 9.8 Hz, CH_2Ph), 4.58 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 4.64 (dd, 2H, ^2J = 12.4 Hz, CH_2Ph), 4.75 (dd, 2H, ^2J = 9.8 Hz, CH_2Ph), 4.80 (dd, 2H, ^2J = 10.8 Hz, CH_2Ph), 4.93 (dd, 2H, ^2J = 12.9 Hz, CH_2Ph), 7.00-7.90 (m, 32H, aromatic), 7.47 (dd, 1H, J = 7.7 Hz, aromatic), 8.46 (dd, 1H,

J = 4.1 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.3, 68.6, 69.0, 70.0, 73.3, 73.5, 74.8, 74.9, 75.0, 75.0 (× 2), 75.5, 76.2, 77.8, 78.1, 79.8, 81.7, 82.0, 85.3, 98.1, 103.8, 121.4, 122.2, 127.5, 127.6, 127.7 (× 5), 127.8, 127.9 (× 3), 128.0 (× 2), 128.1 (× 2), 128.2 (× 2), 128.3 (× 2), 128.4 (× 9), 128.5 (× 2), 136.5, 138.0, 138.2, 138.3 (× 2), 138.4, 138.9, 149.1, 158.7 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{65}NO_{11}Na$ 1010.4455, found 1010.4442.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picolinyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (2.3d). The title compound was obtained as a white amorphous solid from glycosyl donor **2.1d** and acceptor **2.2** in 88% (α/β = 1.2/1, 50 mM) and 86% yield (α/β = 5.3/1, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for **α** isomer of **2.3d**: R_f = 0.59 (ethyl acetate/hexane, 1/1, v/v); ^{1}H NMR: δ, 3.31 (s, 3H, OCH_3), 3.39 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.45-3.83 (m, 9H, H-2', 4, 4', 5, 5', 6a, 6a', 6b, 6b'), 3.92 (dd, 1H, $J_{3',4'}$ = 9.2 Hz, H-3'), 3.94 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.44 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.60 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.51 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.56-4.67 (m, 2H, CH_2Ph), 4.69 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.71 (dd, 2H, ^2J = 10.8 Hz, CH_2Ph), 4.76 (dd, 1H, ^2J = 10.8 Hz, ½ CH_2Ph), 4.84-4.98 (m, 5H, H-1', 2 × CH_2Ph), 7.05-7.56 (m, 33H, aromatic), 8.47 (d, 1H, *J* = 4.8 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.4, 66.3, 68.7, 70.4, 70.5, 72.6, 73.6 (× 2), 75.2, 75.6, 75.7, 75.9, 78.0, 78.3, 80.2, 80.3, 81.5, 82.3, 97.5, 98.2, 121.3, 122.3, 127.6, 127.7, 127.8 (× 4), 128.0 (× 4), 128.1, 128.2 (× 4), 128.3 (× 2), 128.4 (× 5), 128.6 (× 8), 136.6, 138.1, 138.4, 138.6, 138.8, 139.0, 149.1,

158.8 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{65}NO_{11}Na$ 1010.4455, found 1010.4476.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-picolinyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (2.3e). The title compound was obtained as a white amorphous solid from glycosyl donor **1e** and acceptor **2.2** in 93% (α/β = 1/2.4, 50 mM) and 84% yield (α/β = 1.1/1, 5 mM) under regular and high dilution reaction conditions, respectively. Selected analytical data for **β**-isomer of **3e**: R_f = 0.44 (ethyl acetate/hexane, 1/1, v/v); ^{1}H NMR: δ, 3.36 (s, 3H, OCH_3), 4.22 (dd, 1H, $J_{5,6b}$ = 1.7 Hz, $J_{6a,6b}$ = 10.6 Hz, H-6b), 4.24 (dd, 1H, $J_{5',6b'}$ = 5.0 Hz, $J_{6a',6b'}$ = 10.5 Hz, H-6b'), 4.39 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1') ppm; ^{13}C NMR: δ, 98.2, 104.0 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{65}NO_{11}Na$ 1010.4455, found 1010.4523.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-picolinyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (2.3f). The title compound was obtained as a white amorphous solid from glycosyl donor **2.1f** and acceptor **2.2** in 76% (α/β = 1/2.4, 50 mM) and 77% yield (α/β = 1/2.1, 5 mM) under regular and high dilution reaction conditions, respectively. Selected analytical data for **β–**isomer of **2.3f**: R_f = 0.64 (ethyl acetate/hexane, 1/1, v/v); ^{1}H NMR: δ, 3.34 (s, 3H, OCH_3), 3.35-3.41 (m, 1H, H-6'a), 3.50-3.58 (m, 3H, H-2, 2', 4), 3.67-3.74 (m, 2H, H-4', 6a), 3.75-3.82 (m, 3H, H-3', 5, 5'), 4.00 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 4.13 (dd, 1H, $J_{5,6b}$ = 1.9 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6b), 4.32 (dd, 1H, $J_{5',6b'}$ = 5.0 Hz, $J_{6a',6b'}$ = 10.5 Hz, H-6b'), 4.47 (d, 1H, $J_{1',2'}$ = 8.2 Hz, H-1'), 4.61(d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.62 (dd, 2H, ^2J = 11.2 Hz, CH_2Ph), 4.63-4.72 (m, 2H,

C*H*$_2$Ph), 4.77-4.84 (m, 2H, C*H*$_2$Ph), 4.88-4.95 (m, 2H, C*H*$_2$Ph), 5.00 (dd, 2H, ^2J = 13.5 Hz, C*H*$_2$Ph), 5.53 (s, 1H, >C*H*Ph), 7.05 (m, 28H, aromatic), 8.50 (m, 1H, aromatic) ppm; ^{13}C NMR: δ, 55.4, 62.7, 66.2, 68.9 (× 2), 69.9, 73.6, 75.1, 75.5, 75.8, 75.9, 78.0, 79.9, 81.4, 81.9, 82.1, 98.3, 101.4, 104.2, 121.7, 122.4, 126.2 (× 2), 126.3, 127.7, 127.8 (× 2), 128.1 (× 6), 128.3 (× 2), 128.4 (× 2), 128.5 (× 2), 128.6 (× 5), 128.7, 129.2, 136.7, 137.3, 138.2, 138.3, 138.5, 138.9, 148.9, 159.0 ppm. Selected analytical data for **α–**isomer of **2.1f**: R_f = 0.64 (ethyl acetate/hexane, 1/1, v/v); ^{1}H NMR: δ, 3.35 (s, 3H, OCH$_3$), 3.43 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.6 Hz, H-3), 3.56-3.66 (m, 3H, H-2', 4, 4'), 3.69-3.74 (m, 1H, H-5'), 3.65- .74 (m, 2H, H-4', 6a), 3.75- 3.83 (m, 1H, H-5), 3.91 (m, 1H, H-6a'), 3.97- 4.06 (m, 2H, H-3, 3'), 4.22 (dd, 1H, $J_{5',6b'}$ = 4.9 Hz, $J_{6a',6b'}$ = 10.2 Hz, H-6b'), 4.44- 5.08 (m, 12H, H-1, 1', 5 x C*H*$_2$Ph), 5.53 (s, 1H, >C*H*Ph), 7.05 (m, 28H, aromatic), 8.50 (m, 1H, aromatic) ppm; ^{13}C NMR: δ, 55.4, 62.5, 66.5, 69.3, 70.6,72.9, 75.2, 75.6, 75.9, 77.8, 79.0, 79.4, 80.2, 82.1, 82.2, 82.3, 98.2 (× 2), 101.6 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{54}H_{58}NO_{11}$ 896.4010, found 896.4050.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (2.3g). The title compound was obtained as a colorless syrup from glycosyl donor **2.1g** and acceptor **2.2** in 85% (α/β = 2.8/1, 50 mM) and 73% yield (α/β > 25/1, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for **2.3g**: R_f = 0.50 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{23}$ +42.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.30 (s, 3H, OCH$_3$), 3.38 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.42-3.60 (m, 2H, H-6a', 6b'), 3.55-3.67 (m, 2H, H-4, 2'), 3.69-3.82 (m, 3H, H- 5, 6a, 6b), 3.93 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 4.03 (m, 1H, H- 5'), 4.07 (dd, 1H, $J_{3',4'}$ = 9.5 Hz, H-

3'), 4.37 (dd, 2H, ^2J = 10.5 Hz, CH_2Ph), 4.50 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 4.60 (s, 2H, CH_2Ph), 4.62 (dd, 2H, ^2J = 10.1 Hz, CH_2Ph), 4.65 (dd, 2H, ^2J = 11.4 Hz, CH_2Ph), 4.74 (dd, 2H, ^2J = 11.1 Hz, CH_2Ph), 4.83 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 5.00 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1'), 5.34 (dd, 1H, $J_{4',5'}$ = 9.7 Hz, H-4'), 6.85-7.70 (m, 31H, aromatic), 7.67 (dd, 1H, J = 7.7 Hz, aromatic), 7.82 (d, 1H, J = 7.8 Hz, aromatic), 8.66 (d, 1H, J = 3.3 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.3, 66.1, 68.9, 70.7, 72.0, 72.7, 73.6, 73.7, 75.1, 75.2, 75.9, 77.4, 77.9, 78.6, 79.9, 80.3, 82.3, 97.5, 98.1, 125.6, 127.0, 127.4, 127.5, 127.7, 127.8 (× 3), 127.9 (× 2), 128.1 (× 4), 128.2 (× 7), 128.3 (× 2), 128.5 (× 3), 128.6 (× 6), 137.0, 138.0, 138.3, 138.4, 138.5, 138.6, 139.0, 147.9, 150.0, 164.1 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{63}O_{12}NNa$ 1024.4248, found 1024.4273.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranosyl)-α-D-glucopyranoside (2.3h). The title compound was obtained as a colorless syrup from glycosyl donor **2.1h** and acceptor **2.2** in 96% (α/β > 1/25, 50 mM) and 92% yield (α/β > 1/25, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for **2.3h**: R_f = 0.57 (ethyl acetate/hexane, 3/2, v/v); $[\alpha]_D^{23}$ +32.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.27 (s, 3H, OCH_3), 3.46-3.57 (m, 3H, H-2, 2', 6b), 3.59-3.71 (m, 4H, H-3', 4, 4', 5'), 3.76 (m, 1H, H-5), 3.94 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.11 (dd, 1H, $J_{5,6b}$ = 1.5 Hz, $J_{6a,6b}$ = 9.3, H-6b), 4.37 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.44 (d, 1H, ^2J = 11.2 Hz, ½ CH_2Ph), 4.48-4.69 (m, 6H, H-1, 6a', 6b', 1½ CH_2Ph), 4.70- 4.85 (m, 4H, 2 × CH_2Ph), 4.93 (dd, 4H, ^2J = 10.6 Hz, 2 × CH_2Ph), 7.05-7.52 (m, 31H, aromatic), 7.73 (dd, 1H, J = 7.7 Hz, aromatic), 7.99 (d, 1H, J = 7.7 Hz, aromatic), 8.72 (d, 1H, J = 3.9 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.4, 64.5, 68.8, 69.9, 73.1, 73.6, 75.1, 75.2, 75.3,

75.9, 76.1, 77.4, 78.1, 79.9, 82.1, 82.2, 85.0, 98.2, 104.0, 125.4, 127.1, 127.8 (× 5), 128.0 (× 3), 128.1 (× 2), 128.2 (× 4), 128.3 (× 2), 128.4 (× 2), 128.5 (× 2), 128.6 (× 4), 128.7 (× 6), 137.0, 137.9, 138.3, 138.4, 138.5 (× 2), 139.0, 147.9, 150.2, 164.8 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{63}O_{12}NNa$ 1024.4248, found 1024.4246.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-(pyrid-3-ylmethyl)-α/β-D-glucopyranosyl)-α-D-glucopyranoside (2.3i). The title compound was obtained as a white amorphous solid from glycosyl donor **2.1i** and acceptor **2.2** by in 87% (α/β = 1.1/1, 50 mM) and 82% yield (α/β = 1.5/1, 5 mM) under regular and high dilution reaction conditions, respectively. Selected analytical data for **2.3i**: R_f = 0.45 (acetone/toluene, 3/17, v/v). Selected ^{1}H NMR data for β-isomer of **2.3i**: δ, 3.34 (s, 3H, OCH_3), 3.41 (m, 1H, H-5'), 3.48- 3.58 (m, 3H, H-2, 2', 4), 3.59-3.88 (m, 6H, H-3', 4', 5, 6a, 6'a, 6'b), 3.97-4.40 (m, 1H, H-3), 4.19 (dd, 1H, $J_{6a, 6b}$ = 11.2 Hz, H-6b), 4.36 (d, 1H, $J_{1',2'}$ = 7.6 Hz, H-1'), 4.39 (d, 1H, ^2J = 11.2 Hz, ½ CH_2Ph), 4.90-5.40 (m, 14H, H-1, 6½ x CH_2Ph), 7.10-7.50 (m, 32H, aromatic), 8.28-8.56 (m, 2H, aromatic) ppm. Selected ^{1}H NMR data for α-isomer of **2.3i**: δ, 3.37 (s, 3H, OCH_3), 3.45 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2), 3.48-3.58 (m, 2H, H-2', 5'), 3.59-3.88 (m, 7H, H- 4, 4', 5, 6a, 6b, 6'a, 6'b), 3.94 (dd, 1H, $J_{3',4'}$ = 9.0 Hz, H-3'), 3.97-4.40 (m, 1H, H-3), 4.40 (d, 1H, ^2J = 12.3 Hz, ½ CH_2Ph), 4.90-5.40 (m, 15H, H-1, 1', 6½ x CH_2Ph), 7.10-7.50 (m, 32H, aromatic), 8.28-8.56 (m, 2H, aromatic) ppm. Selected ^{13}C NMR data for the sugar region of α/β-**2.3i**: δ, 55.3, 55.4, 66.3, 68.3, 68.8, 68.9, 70.0, 70.2, 70.5, 72.4 (× 2), 72.5, 73.6 (× 2), 73.7 (× 2), 75.0, 75.1 (× 3), 75.7, 75.9 (× 2), 76.0, 77.4, 77.9, 78.1, 78.2, 79.9, 80.2, 80.3, 81.7, 82.2, 82.3 (× 2), 84.9, 97.4, 98.2

(× 2), 104.0 ppm. HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{65}NO_{11}Na$ 1010.4455, found 1010.4521.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-(pyrid-3-ylmethyl)-α/β-D-glucopyranosyl)-α-D-glucopyranoside (2.3j). The title compound was obtained as a white amorphous solid from glycosyl donor **2.1j** and acceptor **2.2** in 82% (α/β = 1/1.6, 50 mM) and 74% yield (α/β = 1.3/1, 5 mM) under regular and high dilution reaction conditions, respectively. Selected analytical data of **2.3j**: R_f = 0.49 (acetone/toluene, 3/17, v/v). Selected ^{1}H NMR data for β-isomer of **2.3j**: δ, 3.34 (s, 3H, OCH_3), 3.43 (m, 1H, H-5'), 3.45- 3.60 (m, 7H, H-2, 2', 4, 5, 6b, 6'a, 6'b), 3.84-3.89 (m, 1H, H-3), 4.01 (m, 1H, H-3), 4.19 (dd, 1H, $J_{6a,\ 6b}$ = 10.9 Hz, H-6b), 4.35- 4.41 (m, 2H, H-1', ½ CH_2Ph), 4.48-5.40 (m, 14H, H-1, 6½ x CH_2Ph), 6.90-7.55 (m, 32H, aromatic), 8.45-8.55 (m, 2H, aromatic) ppm. Selected ^{1}H NMR data for α-isomer of **2.3j**: δ, 3.38 (s, 3H, OCH_3), 3.45-3.60 (m, 6H, H-2, 2', 4, 4', 6a', 6b'), 3.84-3.89 (m, 1H, H-5'), 3.95 (dd, 1H, $J_{3',4'}$ = 9.1 Hz, H-3'), 4.01 (m, 1H, H-3), 4.36-4.41 (m, 1H, ½ CH_2Ph), 4.48-5.40 (m, 15H, H-1, 1', 6½ x CH_2Ph), 6.90-7.55 (m, 32H, aromatic), 8.45-8.55 (m, 2H, aromatic) ppm. Selected ^{13}C NMR data for the sugar region of α/β-**2.3j**: δ, 55.3, 55.4, 66.4, 68.3, 68.8, 68.9, 70.0, 70.2, 70.5, 72.5, 73.0, 73.1, 73.6 (× 3), 73.7, 75.0 (× 3), 75.1, 75.7, 75.9 (× 2), 76.0, 77.4, 77.9, 78.2, 78.3, 79.9, 80.1, 80.3, 81.6, 82.1, 82.2, 82.3, 84.8, 97.4, 98.2 (× 2), 104.0 ppm. HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{65}NO_{11}Na$ 1010.4455, found 1010.4732.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-*O*-benzoyl-2,3,6-tri-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (2.3k). The title compound was obtained as a colorless syrup from glycosyl donor **2.1k** and acceptor **2.2** in 97% (α/β = 1/2.5, 50 mM) and 93% yield (α/β > 1/2.6, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for the title compound was in accordance with that reported previously.[48]

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (2.3l). The title compound was obtained as a white amorphous solid from glycosyl donor **2.1l** and acceptor **2.2** in 87% yield (α/β = 1/1.0, 50 mM). Analytical data for **2.3l** was in accordance with that reported previously.[36,53]

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picolinyl-β-D-galactopyranosyl)-α-D-glucopyranoside (2.3m). The title compound was obtained as a white amorphous solid from glycosyl donor **2.1m** and acceptor **2.2** in 89% (α/β = 1/10, 50 mM) and 83% yield (α/β > 1/25, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for **2.3m**: R_f = 0.54 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{23}$ +19.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.23 (s, 3H, OCH_3), 3.35-3.64 (m, 7H, H-2, 3', 4, 5, 5', 6a, 6a'), 3.71-3.81 (m, 2H, H-2', 3), 3.85-3.96 (m, 2H, H-4', 6b'), 4.07 (dd, 1H, $J_{5,6b}$ = 1.6 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6b), 4.22 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1'), 4.37 (s, 2H, CH_2Ph), 4.51 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.53 (dd, 2H, ^2J = 11.2 Hz, CH_2Ph), 4.63 (dd, 2H, ^2J = 12.2 Hz, CH_2Ph), 4.70 (d, ^2J = 10.2 Hz, CH_2Ph), 4.77 (dd, 2H, ^2J = 10.6 Hz, CH_2Ph), 4.79 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 4.83 (dd, 2H, ^2J = 13.3 Hz, CH_2Ph), 7.00-

7.55 (m, 33H, aromatic), 8.40 (d, 1H, J = 4.7 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.3, 68.5, 68.8, 70.1, 72.9, 73.4, 73.5, 73.7, 75.0, 75.1, 75.3, 75.8, 76.0, 78.2, 79.3, 80.0, 82.0, 82.2, 98.1, 104.5, 121.8, 122.2, 127.5, 127.7 (× 3), 127.8 (× 4), 127.9, 128.0 (× 3), 128.1 (× 2), 128.2 (× 2), 128.3 (× 2), 128.4 (× 2), 128.5 (× 8), 128.6 (× 4), 136.6, 137.9, 138.3, 138.4, 138.5, 138.8, 139.0, 148.6, 159.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{65}NO_{11}Na$ 1010.4455, found 1010.4503.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-β-D-galactopyranosyl)-α-D-glucopyranoside (2.3n). The title compound was obtained as a colorless syrup from glycosyl donor **2.1n** and acceptor **2.2** in 96% (α/β = 1/24, 50 mM) and 95% yield (α/β > 1/25, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for **2.3n**: R_f = 0.43 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{23}$ +36.9 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.25 (s, 3H, OCH_3), 3.41-3.72 (m, 8H, H-2, 2', 3', 4, 5', 6a, 6a', 6b'), 3.75 (m, 1H, H-5), 3.91 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.09 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6b}$ = 1.8 Hz, H-6b), 4.26 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-1'), 4.37 (dd, 2H, ^2J = 11.8 Hz, CH_2Ph), 4.52 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 4.54 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.64 (dd, 2H, ^2J = 12.3 Hz, CH_2Ph), 4.65 (dd, 2H, ^2J = 11.5 Hz, CH_2Ph), 4.73 (dd, 2H, ^2J = 10.8 Hz, CH_2Ph), 4.79 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 5.79 (dd, 1H, $J_{4',5'}$ = 2.7 Hz, H-4'), 7.05-7.45 (m, 33H, aromatic), 7.69 (dd, 1H, J = 7.7 Hz, aromatic), 7.95 (d, 1H, J = 7.8 Hz, aromatic), 8.70 (d, 1H, J = 3.4 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.4, 68.2, 68.4, 69.0, 70.1, 72.3, 72.5, 73.6, 73.9, 75.0, 75.5, 75.8, 78.0, 78.9, 79.6, 80.0, 82.2, 98.3, 104.5, 125.7, 127.1, 127.6, 127.7 (× 2), 127.8 (× 3), 127.9, 128.1 (× 5), 128.2 (× 2), 128.3 (× 2), 128.4 (× 4), 128.5 (× 7), 128.6 (× 2), 137.0, 137.7, 137.8, 138.3, 138.5, 138.6,

139.0, 147.8, 150.4, 164.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{63}O_{12}NNa$ 1024.4248, found 1024.4271.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside (2.3o). The title compound was obtained as a colorless syrup from glycosyl donor **2.1o** and acceptor **2.2** in 89% (α/β > 1/3.5, 50 mM) and 86% yield (α/β > 1/4.5, 5 mM) under regular and high dilution reaction conditions, respectively. Alternatively, the title compound was prepared as follows. A mixture of glycosyl donor **2.1o** (0.13 mmol), glycosyl acceptor **2.2** (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $(ClCH_2)_2$ (2.6 mL, 50 mM or 26 mL, 5 mM) was stirred under an argon for 1 h. The mixture was cooled to -30 °C, NIS (0.26 mmol) and TfOH (0.026 mmol) were added, and the reaction mixture was allowed to warm to rt and stirred until the completion (see tables). The resulting mixture was diluted with CH_2Cl_2 (~10 mL), the solid was filtered off and the residue was washed with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 10% aq. $Na_2S_2O_3$ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to afford the title compound in 91% (α/β = 1/5.3, 50 mM) and 87% yield (α/β = 1/9.5, 5 mM). Analytical data for **β–**isomer of **2.3o**: R_f = 0.46 (ethyl acetate/hexane, 3/2, v/v); ^{1}H NMR: δ, 3.20 (s, 3H, OCH_3), 3.31 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 3.36- 3.47 (m, 3H, H-2, 3', 6a), 3.53 (m, 1H, H-5'), 3.65-3.77 (m, 2H, H- 5, 2'), 3.84-3.96 (m, 2H, H-3, 4'), 4.06 (dd, 1H, $J_{5,6b}$ = 1.7 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6b), 4.13 (s, 1H, H-1'), 4.45-4.58 (m, 3H, H-1, 6a', 6b'), 4.51 (dd, 2H, ^2J = 4.4 Hz, CH_2Ph), 4.56 (dd, 2H, ^2J

= 11.3 Hz, CH_2Ph), 5.63 (dd, 2H, ^2J = 12.3 Hz, CH_2Ph), 5.71 (dd, 2H, ^2J = 10.8 Hz, CH_2Ph), 5.77 (dd, 2H, ^2J = 12.3 Hz, CH_2Ph), 5.82 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 7.05-7.43 (m, 31H, aromatic), 7.49 (dd, 1H, J = 7.8 Hz, aromatic), 7.90 (d, 1H, J = 7.8 Hz, aromatic), 8.64 (d, 1H, J = 3.9 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.2, 65.2, 68.6, 69.9, 71.8, 73.5, 73.7, 73.9, 74.0, 74.8, 75.0, 75.4, 76.0, 77.9, 80.0, 82.2, 82.3, 98.0, 101.8 ($^1J_{C1,H1}$ = 165.2 Hz, $^1J_{C1',H1'}$ = 154.6 Hz), 125.6, 126.9, 127.6, 127.7, 127.8 (× 3), 127.9 (× 2), 128.0, 128.2 (× 3), 128.2 (× 2), 128.4 (× 5), 128.5 (× 2), 128.6 (× 8), 128.7 (× 2), 137.1, 138.1, 138.2 (× 2), 138.4, 138.9, 139.0, 150.1, 164.8 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{63}O_{12}NNa$ 1024.4248, found 1024.4293

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-α/β-L-rhamnopyranosyl)-α-D-glucopyranoside (2.3p). The title compound was obtained as a colorless syrup from glycosyl donor **2.1p** and acceptor **2.2** in 85% yield (α/β = 1.1/1, 50 mM). Analytical data for **2.3p**: R_f = 0.59 (ethyl acetate/hexane, 2/3, v/v). Selected ^{1}H NMR data for β-isomer of **2.3p**: δ, 1.36 (d, 1H, $J_{5',6'}$ = 5.9 Hz, C-6'), 3.27 (s, 3H, OCH_3), 3.30-3.36 (m, 1H, H-5'), 3.42-3.52 (m, 2H, H-2, 3'), 3.57-3.73 (m, 3H, H-4, 4', 6a), 3.75 (m, 1H, H-5), 3.93-4.20 (m, 2H, H-2', 3), 4.29 (dd, 1H, $J_{5,6b}$ = 3.5 Hz, $J_{6a,6b}$ = 11.2 Hz, H-6b), 4.44 (s, 1H, H-1'), 4.36- 5.02 (m, 13H, H-1, 6 x CH_2Ph), 7.15-7.50 (m, 30H, aromatic) ppm; Selected ^{1}H NMR data for α-isomer of **2.3p**: δ, 1.31 (d, 3H, $J_{5',6'}$ = 5.9 Hz, C-6'), 3.20-3.85 (m, 4H, H-4, OCH_3), 3.42-3.52 (m, 2H, H-2, 3'), 3.57-3.73 (m, 3H, H-5, 5', 6a), 3.81-3.86 (m, 2H, H-4', 6b), 3.93-4.20 (m, 1H, H-3), 4.36-5.02 (m, 14H, H-1, 1', 6 x CH_2Ph), 7.15-7.50 (m, 30H, aromatic). Selected ^{13}C NMR data for the sugar region of α/β-**2.3p**: δ,18.1, 18.2, 55.2, 55.4, 66.2, 67.4, 68.2, 70.0, 70.2, 71.5, 72.2, 72.5, 72.9, 73.5, 73.7, 74.2, 74.4,

75.1, 75.2, 75.4, 75.6, 75.7, 75.9, 76.0, 77.4, 78.0 (× 2), 79.9, 80.0, 80.1, 80.4, 80.8, 82.1 (× 2), 97.9, 98.4, 98.5, 101.6 ppm. HR-FAB MS $[M+Na]^+$ calcd for $C_{55}H_{60}NaO_{10}$ 903.4084, found 903.4221.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,4-di-*O*-benzyl-3-*O*-picoloyl-β-L-rhamnopyranosyl)-α-D-glucopyranoside (2.3q). The title compound was obtained as a colorless syrup from glycosyl donor **2.1q** and acceptor **2.2** in 94% yield (α/β > 1/25, 50 mM). Analytical data for **2.3q**: R_f = 0.47 (acetone/toluene, 3/17, v/v); $[\alpha]_D^{22}$ +79.9 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.33 (d, 3H, $J_{5,6}$ = 6.0 Hz, C-6), 3.30 (s, 3H, OCH_3), 3.36-3.50 (m, 2H, H-2, 5'), 3.56 (dd, 1H, m, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 3.62-3.73 (m, 2H, H-5, 6a), 3.77 (dd, 1H, $J_{4',5'}$ = 9.4 Hz, H-4'), 3.92 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.11 (d, 1H, $J_{2',3'}$ = 3.2 Hz, H-2'), 4.20 (dd, 1H, $J_{5,6b}$ = 3.3 Hz, $J_{6a,6b}$ = 11.3 Hz, H-6b), 4.53-4.79 (m, 9H, H-1, 1', 3½ CH_2Ph), 4.85 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 4.85 (dd, 1H, ^2J = 12.2 Hz, ½ CH_2Ph), 6.78-7.45 (m, 26H, aromatic), 7.70 (dd, 1H, J = 7.7 Hz, aromatic), 7.85 (d, 1H, J = 7.8 Hz, aromatic), 8.46 (d, 1H, J = 4.1 Hz, aromatic) ppm; ^{13}C NMR: δ, 18.1, 55.4, 67.6, 70.2, 72.0, 73.6, 74.9, 75.4 (× 2), 75.6, 75.9, 77.3, 78.0, 78.7, 80.2, 82.0, 98.3, 101.2 ($^1J_{C1,H1}$ = 167.5 Hz, $^1J_{C1',H1'}$ = 155.1 Hz), 125.4, 127.1, 127.6, 127.7, 127.8, 127.9, 128.0 (× 2), 128.1 (× 2), 128.2 (× 2), 128.3 (× 2), 128.3 (× 3), 128.4 (× 3), 128.5 (× 5), 128.6 (× 2), 137.0, 138.2, 138.3, 138.4, 138.5, 139.0, 147.8, 150.2, 164.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{54}H_{57}NaO_{11}$ 918.3829, found 918.3774.

Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (2.5). The title compound was obtained as a

colorless syrup from glycosyl donor **2.1g** and acceptor **2.4** in 93% yield (α/β > 25/1, 50 mM). Analytical data for **2.5**: R_f = 0.40 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{23}$ +79.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.30 (dd, 1H, $J_{5',6b'}$ = 3.8 Hz, $J_{6a',6b'}$ = 11.0 Hz, H-6b'), 3.41 (m, 1H, H-6a'), 3.45 (s, 3H, OCH_3), 3.57-3.83 (m, 5H, H-2, 4, 5, 6a, 6b), 3.87 (dd, 1H, $J_{2',3'}$ = 9.8 Hz, H-2'), 4.08 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.15 (dd, 1H, $J_{3',4'}$ = 9.2 Hz, H-3'), 4.25 (m, 1H, H-5'), 4.37 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.56 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.60 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 4.73 (dd, 2H, ^2J = 11.8 Hz, CH_2Ph), 4.74 (dd, 2H, ^2J = 13.5 Hz, CH_2Ph), 4.91 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 4.94 (d,1H, $J_{1',2'}$ = 3.4 Hz, H-1'), 4.95 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.46 (dd, 1H, $J_{4',5'}$ = 9.8 Hz, H-4'), 6.65-7.70 (m, 33H, aromatic), 8.70 (d, 1H, *J* = 4.6 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.1, 68.3, 68.7, 68.9, 70.4, 71.5, 73.2, 73.6, 73.7, 75.2, 75.3, 75.5, 75.8, 78.2, 79.1, 79.3, 81.0, 94.8, 96.7, 126.8, 127.5 (× 2), 127.7 (× 2), 127.9 (× 2), 128.0 (× 2), 128.1 (× 4), 128.2 (× 2), 128.3 (× 5), 128.5 (× 4), 128.6 (× 4), 137.0, 137.9 (× 2), 138.1, 138.3 (× 2), 138.4 (× 2), 138.9, 147.8, 150.1, 163.7 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{63}O_{12}NNa$ 1024.4248, found 1024.4248.

Methyl 2,4,6-Tri-*O*-benzyl-3-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (2.7). The title compound was obtained as a colorless syrup from glycosyl donor **2.1g** and acceptor **2.6** in 87% (α/β = 10/1, 50 mM) and 81% yield (α/β > 25/1, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for **2.7** R_f = 0.44 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{23}$ +53.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.36 (s, 3H, OCH_3), 3.41 (dd, 1H, $J_{6a',6b'}$ = 10.9 Hz, H-6b'), 3.58 (dd, 1H, $J_{5',6a'}$ = 2.5 Hz, H-6a'), 3.63-3.93 (m, 6H, H-2, 2', 4, 5, 6a, 6b), 4.31

(dd, 1H, $J_{3',4'}$ = 9.4 Hz, H-3'), 4.33 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.49 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.59 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.64 (m, 2H, H-1, 5'), 4.69 (dd, 2H, ^2J = 11.8 Hz, CH_2Ph), 4.73 (dd, 2H, ^2J = 11.7 Hz, CH_2Ph), 4.76 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 4.78 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 5.56 (dd, 1H, $J_{4',5'}$ = 10.1 Hz, H-4'), 5.69 (d,1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 7.05-7.60 (m, 31H, aromatic), 7.80 (dd, 1H, J = 7.7 Hz, aromatic), 7.90 (d, 1H, J = 7.8 Hz, aromatic), 8.79 (d, 1H, J = 3.2 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.3, 68.7, 68.8, 69.0, 69.0, 69.6, 72.3, 73.3, 73.7, 73.8, 74.1, 75.4, 77.5, 78.1, 78.5, 79.1, 79.5, 79.9, 97.7 (× 2), 125.5, 127.0, 127.3 (× 2), 127.5 (× 2), 127.8, 128.0, 128.1 (× 5), 128.2 (× 3), 128.3 (× 6), 128.4 (× 2), 128.5 (× 4), 128.6 (× 4), 128.9 (× 2), 137.0, 138.1 (× 2), 138.2, 138.4, 138.5 (× 2), 148.2, 150.1, 164.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{63}O_{12}NNa$ 1024.4248, found 1024.4239.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (2.9). The title compound was obtained as a colorless syrup from glycosyl donor **2.1g** and acceptor **2.8** in 94% (α/β = 12/1, 50 mM) and 81% yield (α/β = 21/1, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for α-isomer of **2.9**: R_f = 0.47 (ethyl acetate/hexane, 1/1, v/v); ^{1}H NMR: δ, 3.36-3.54 (m, 5H, H-6a', 6b', OCH_3), 3.58- 3.67 (m, 2H, H-2, 2'), 3.72 (dd, 1H, $J_{5,6b}$ = 3.8 Hz, $J_{6a,6b}$ = 10.7 Hz, H-6b), 3.87 (m, 1H, H-5), 4.00 (dd, 1H, $J_{5,6a}$ = 1.6 Hz, $J_{6a,6b}$ = 10.7 Hz, H-6a), 4.08 (dd, 1H, $J_{4,5}$ = 8.3 Hz, H-4), 4.12-4.24 (m, 3H, H-3, 3', 5'), 4.39 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.48-4.71 (m, 7H, H-1, 3 × CH_2Ph), 4.76 (d, 1H, ^2J = 12.2 Hz, ½ CH_2Ph), 4.81 (d, 1H, ^2J = 11.3 Hz, ½ CH_2Ph), 4.99 (dd, 2H, ^2J = 11.5 Hz, CH_2Ph), 5.43 (dd, 1H, $J_{4',5'}$ = 9.7 Hz, H-4'), 5.57 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 7.05-7.60

(m, 31H, aromatic), 7.80 (dd, 1H, *J* = 7.8 Hz, aromatic), 7.98 (d, 1H, *J* = 7.9 Hz, aromatic), 8.77 (d, 1H, *J* = 4.0 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.4, 69.0, 69.4, 69.6, 69.9, 72.3, 73.4 (× 2), 73.6, 73.7, 74.9, 75.3, 75.4, 79.2, 79.4, 80.1, 81.8, 97.7, 98.0, 125.6, 127.3, 127.5, 127.6, 127.7, 127.8, 127.9 (× 4), 128.0 (× 2), 128.1, 128.3 (× 4), 128.4 (× 8), 128.5 (× 2), 128.6 (× 2), 137.0, 138.0, 138.1, 138.3, 138.4 (× 2), 139.3, 148.0, 150.0, 164.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{61}H_{63}O_{12}NNa$ 1024.4248, found 1024.4242.

Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-(2,4-di-*O*-benzyl-3-*O*-picoloyl-β-L-rhamnopyranosyl)-α-D-glucopyranoside (2.10). The title compound was obtained as colorless syrup from glycosyl donor **2.1q** and acceptor **2.4** in 90% yield (α/β > 1:25, 50 mM). Analytical data for **2.10**: R_f = 0.49 (acetone/toluene, 3/17, v/v); $[\alpha]_D^{22}$ +65.4 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.45 (d, 1H, $J_{5',6'}$ = 6.1 Hz, C-6'), 3.42-3.55 (m, 4H, H-5', OCH_3), 3.68-3.87 (m, 4H, H-4, 5, 6a, 6b), 3.56 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 3.62-3.73 (m, 2H, H-5, 6b), 3.77 (dd, 1H, $J_{4',5'}$ = 9.4 Hz, H-4'), 3.91(dd, 1H, $J_{4',5'}$ = 9.5 Hz, H-4'), 3.95-4.18 (m, 2H, H-2, 3), 4.20 (d, 1H, $J_{2',3'}$ = 3.2 Hz, H-2'), 4.61 (dd, 2H, ^2J = 12.2 Hz, CH_2Ph), 4.70 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 4.76 (dd, 1H, ^2J = 12.8 Hz, ½ CH_2Ph), 4.78 (s, 1H, H-1'), 4.79 (dd, 2H, ^2J = 10.8 Hz, CH_2Ph), 4.79 (dd, 2H, ^2J = 10.8 Hz, CH_2Ph), 4.85 (dd, 2H, ^2J = 12.8 Hz, CH_2Ph), 4.92 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 5.12-5.25 (m, 2H, H-3', CH_2Ph), 6.90-7.65 (m, 26H, aromatic), 7.82 (dd, 1H, *J* = 7.5 Hz, aromatic), 7.97 (d, 1H, *J* = 7.8 Hz, aromatic), 8.84 (d, 1H, *J* = 4.5 Hz, aromatic) ppm; ^{13}C NMR: δ, 18.2, 55.3, 68.7, 70.2, 72.2, 73.7, 74.7, 75.2, 75.3, 75.5, 75.7, 77.3 (× 2), 78.2, 78.8, 81.1, 97.6, 99.1 ($^1J_{C1,H1}$ = 166.9 Hz, $^1J_{C1',H1'}$ = 152.6 Hz), 125.4, 127.1, 127. 5 (× 2), 127.8, 127.9 (×

2), 128.0 (× 2), 128.1 (× 5), 128.3 (× 2), 128.5 (× 9), 128.6 (× 2), 137.0, 138.2 (× 2), 138.4, 138.6, 139.2, 147.8, 150.2, 164.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{54}H_{57}NaO_{11}$ 918.3829, found 918.3891.

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CHAPTER 3

Hydrogen bond-mediated aglycone delivery: adventures in the synthesis of linear and branched α-glucans

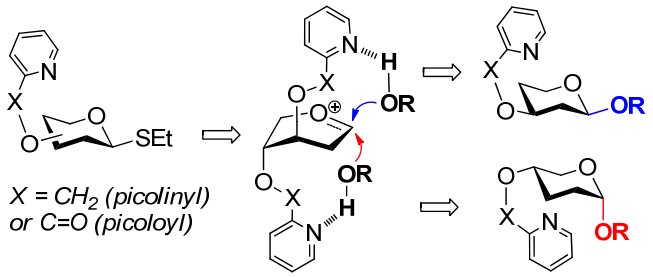
3.1. Introduction

Glycosylation reactions are challenging for chemists because of the necessity to obtain high stereoselectivity of substitutions at the anomeric carbon, and only pure anomers are needed for biological studies or pharmaceutical development.[1] A failure to control stereoselectivity of glycosylations leads to mixtures of 1,2-*cis* and 1,2-*trans* diastereomers, which are hard to separate at the glycoside or disaccharide stage, and are practically impossible at the oligosaccharide stage. Resultantly, stereocontrolled glycosylation has emerged as an important area of modern glycosciences that inspires many scientists and has led to many breakthroughs.[2-26] The aim of stereocontrolling of glycosylations has been approached in a variety of ways, and the effect of a neighboring participating group, particularly that of an acyl substituent, has been among the most powerful stereodirecting factors known to date.[27-29] For instance, if such an acyl participating group is used at the neighboring C-2 position, good or even complete 1,2-*trans* selectivity can often be achieved.[30] Boons and co-workers developed a chiral auxiliary group that is capable of participating from the opposite face of the ring leading to 1,2-*cis*-linked products with high stereoselectivity.[31,32]

Previously, our group introduced 2-*O*-picolinyl (2-pyridylmethyl, Pic) participating group that can be used to obtain 1,2-*trans* glycosides. We demonstrated that these reactions proceed *via* the six membered ring intermediate that in all case provided complete 1,2-*trans* or *anti*-selectivity in respect to the 2-*O*-picolinyl group.[33,34] Our further attempt to broaden the scope of this method led to investigation of the picolinyl group at remote positions, C-3, C-4, and C-6. Rather unexpectedly, we obtained very high *syn*-stereoselectivities in respect to the picolinyl substituent, which was an

indication of a different mode of action by which remote picolinyl substituents influence stereoselectivity of glycosylation. To explain the stereoselectivity observed, we acquired experimental evidence consistent with a new concept that we call H-bond-mediated Aglycone Delivery (HAD).[35] The nucleophile, hydroxyl of the glycosyl acceptor, forms the hydrogen bond with the picolinyl nitrogen of the glycosyl donors and then gets delivered to form the glycosidic linkage from the same face [36] with respect to that of the picolinyl group (Scheme 3.1). This typically results in more rapid rates of glycosylations in comparison to that of the corresponding benzylated glycosyl donors. This difference was particularly evident for experiments performed at low concentrations (5 mM of glycosyl acceptor).[35]

Scheme 3.1. H-bond-mediated Aglycone Delivery (HAD) *via* the remote picolinyl/picoloyl substituents



3.2. Results and Discussion

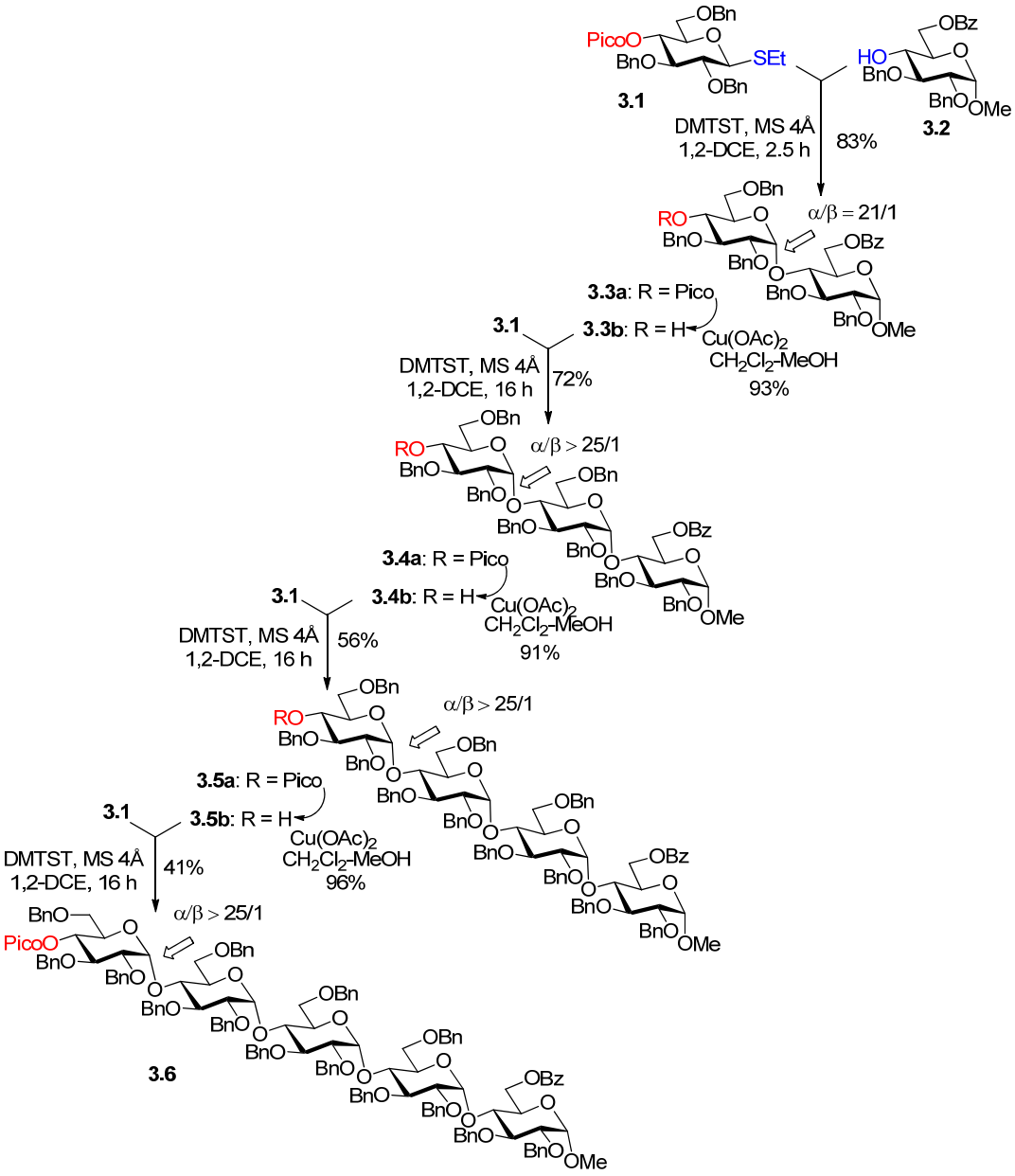
Using O-picolinyl and structurally similar 4-*O*-picoloyl (2-pyridinecarbonyl, Pico) substituents, we already obtained a range of different linkages ranging from relatively accessible 1,2-*trans* glycosides to much more challenging 1,2-*cis* glycosides of the D-gluco,[35] D-manno, and L-rhamno series.[35] Yang and co-workers applied the same principle to 2-quinolinecarbonyl-assisted synthesis of β-arabinofuranosides.[37] As an

extension of the earlier study, we decided to investigate whether HAD can be suitable for connecting multiple 1,2-*cis* linked residues. Among other challenging targets, α-glucosides are arguably most abundant, yet the synthesis of oligosaccharides with multiple α-glucose residues may become a major endeavor for chemists.

We first approached the synthesis of a linear pentasaccharide connected *via* α-(1→4)-linkages postulating that 4-*O*-picoloyl could be used both as the stereodirecting group and as the temporary substituent. Picoloyl can be selectively removed with copper(II) acetate,[38] reaction conditions under which many protecting groups used in carbohydrate chemistry are stable.[39-44]

The synthesis depicted in Scheme 3.2 began with the glycosylation of acceptor **3.2**[45] with 4-*O*-picoloylated ethyl thioglycoside donor **3.1**. This reaction was performed in the presence of DMTST (2 equiv.) and -30 °C → rt, conditions that became standard for the HAD approach. Resultantly, disaccharide **3.3a** was obtained in 83% yield and a high stereoselectivity of α/β = 21/1. The diastereomers were separated using column chromatorgraphy, and the anomerically pure **3.3a** was treated with $Cu(OAc)_2$ to give 4'-OH acceptor **3.3b**. The latter was glycosylated with donor **3.1** under standard HAD glycosylation conditions to afford trisaccharide **3.4a** in 72% yield and complete α-stereoselectivity, conservatively reported as α/β > 25/1 in Scheme 3.2. Depicoloylation of trisaccharide **3.4a** gave glycosyl acceptor **3.4b**, which was coupled with glycosyl donor **3.1** to afford tetrasaccharide **3.5a** in 56% yield and complete α-selectivity. Subsequent depicoloylation gave acceptor **3.5b** and coupling with donor **3.1** produced pentasaccharide **3.6** in 41% yield with complete α-selectivity.

Scheme 3.2. Pentasaccharide synthesis *via* sequential picoloyl-mediated glycosylation-deprotection

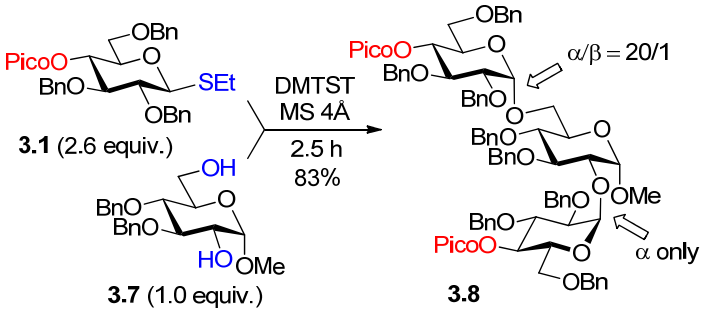


Evidently, over the course of this synthesis, the deprotection efficiency remains high (yields 91-93%), whereas glycosylation yields drop steadily. We explain this by the increased bulk of the acceptor and the inability of the glycosyl donor to maintain strong

H-bonding essential for rapid reactions and high stereoselectivity. Our attempt to "push" the reaction by adding more DMTST resulted in higher yields, but the stereoselectivity dropped. This is because excess DMTST "blocks" the picoloyl nitrogen and makes it unavailable to perform HAD. Nevertheless, the stereoselectivities remained complete, and the synthesis wherein the same substituent can be used both for controlling the stereoselectivity and as the selectively removable protecting group offers a useful strategy for streamlining the synthesis of 1→4-linked α-glucans.

Subsequently, we turned our attention to investigating whether this methodology would offer a viable access to branched oligosaccharides, common in many mamalian and baterial systems. In particular, we became interested in synthesizing the trisaccharide repeating unit of *Lactobacillus* spp. G-77 consisting of primary (1→6) and secondary (1→2) α-gluco linkages.[46-48] Concomitant α-glucosylation of 2,6-diol acceptor **3.7**[49] with excess of glycosyl donor **3.1** (2.6 equiv.) under standard HAD conditions afforded branched trisaccharide **3.8** in 83% yield and a nearly complete stereoselectivity (Scheme 3.3).

Scheme 3.3. Synthesis of trisaccharide 3.8 representing the repeating unit by *Lactobacillus* spp. G-77

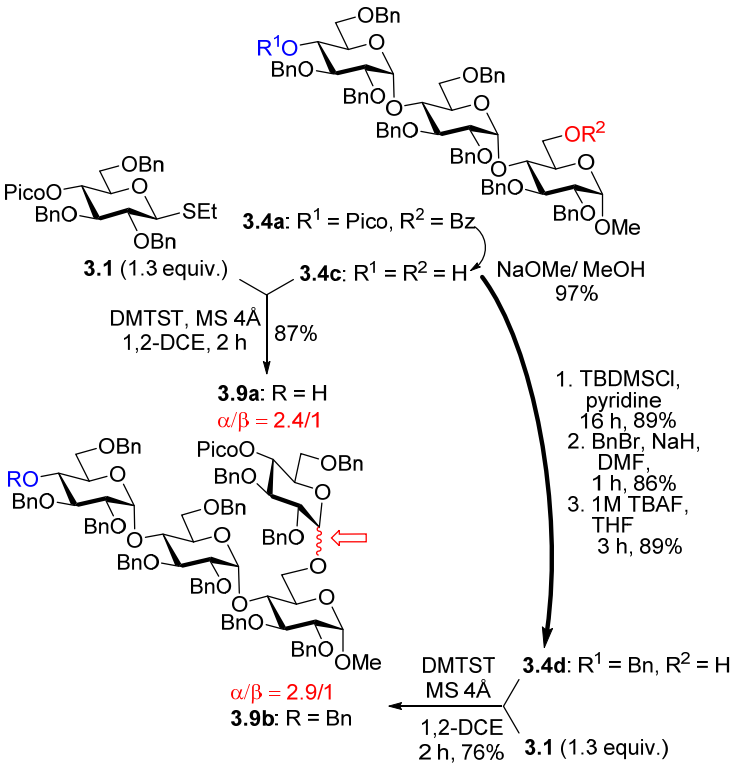


Another target that has drawn our attention is a 4,6-branched glycogen-like fungal cell wall α-glucan motif from *Pseudallescheria boydii*, which showed potential activity towards fungal phagocytosis and activation of innate immune responses.[50,51] This stucture inspired other synthetic work in the area, and chiral auxiliary-assisted synthesis by Boons and co-workers has emerged.[31,32,52,53] For our synthesis of the 4,6-branching motif we adapted trisaccharide **3.4a** obtained en route to pentasaccharide **3.6**. Compound **3.4a** was treated with 2M NaOMe in MeOH to affect concomitant removal of 6-*O*-benzoyl and 4"-*O*-picoloyl protecting groups (Scheme 3.4). The resulting 4",6-diol acceptor **3.4c** was glycosylated with glycosyl donor **3.1** (1.3 equiv.) under standard HAD conditions to obtain the target branched tetrasaccharide **3.9a** in 87% yield. The coupling was entirely regioselective at the primary position and no side products resulting from glycosylation of 4"-hydroxyl were obtained under these reaction conditions. In contrast to all other glycosylations with 4-*O*-picoloylated donor **3.1**, this glycosylation gave poor stereoselectivity (α/β = 2.4/1), but pure α-linked tetrasaccharide **3.9a** could still be isolated in 61% yield with tedious separation by column chromatography.

It occurred to us that having an additional hydroxyl group in the acceptor unit may result in the formation of other H-bonds that would cause slower reactions and, possibly, lower stereoselectivity. To rule out this possibility, we protected 4"-hydroxyl of glycosyl accetor **3.4c** *via* sequential 6-*O*-silylation, 4"-*O*-benzylation, and desylalation as shown on the bypass route on Scheme 3.4. The reprotection sequence was rather uneventful and glycosyl acceptor **3.4d** bearing 6-hydroxyl was obtained in 88% overall yield. Coupling of donor **3.1** with acceptor **3.4d** under HAD conditions produced tetrasacchaaride **3.9b** in 76% yield. Unfortunately, the stereoselectivity of this coupling

was still low (α/β = 2.9/1) and represented only a very marginal improvement in comparison to that obtained for tetrasaccharide **3.9a**. The observed low stereoselectivity from both mono and diol-acceptors led us to conclude that the presence of other hydroxyl does not the deciding affect or the stereoselectivity of HAD. Arguably, other factors, such as double stereodifferentiation, or simply low facial accessibility of 6-hydroxyl of trisaccharides acceptors **3.4c** or **3.4d** with donor **3.1** could be also responsible for this rather disappointing result.

Scheme 3.4. Low selectivity observed in the synthesis of branched α-glucans 3.9a and 3.9b

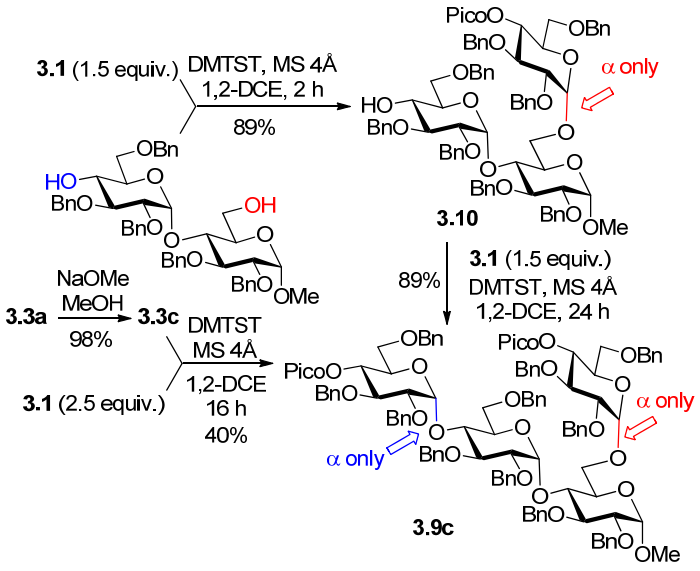


Since the stereoselectivity was poor in the final step of the tetrasaccharide **3.9a** synthesis, at this point we decided to investigate whether other classes of glycosyl donors

would provide superior selectivity in comparison to that obtained with the ethyl thioglycoside donor **3.1**. Disappointingly, and somewhat surprizingly, glycosyl donors of all other common series including aryl thioglycosides, O-imidates and S-imidates, all gave lower stereoselectivity. In glycosyl donors with nitrogen-containing leaving groups (O,S-imidates) we relate reduced stereoselectivity to the fact that glycosyl acceptor may form H-bonding with the leaving group rather than with the picoloyl nitrogen. The origin of lower stereoselectivity observed within S-phenyl/tolyl series remains illusive. It may well be related to lower reactivity of these glycosyl donors in comparison to that of S-ethyl donors in the presence of DMTST. This may lead to DMTST interfering with picololyl, hence blocking the nitrogen atom from forming the hydrogen bond with glycosyl acceptor. The full experimental account of this work will be presented in the Chapter 4.

To reduce the influence of the steric bulk that might have prevented giving high stereoselectivities during the synthesis of tetrasaccharides **3.9a** and **3.9b**, we altered our strategy as follows. Disaccharide **3.3a** was treated with 2M MeONa in methanol to affect concomitant debenzoylation and depicoloylation to afford 4‘,6-diol **3.3c** (Scheme 3.5). The coupling of glycosyl acceptor **3.3c** with donor **3.1** under the HAD condition proceeded regio and, most importantly, stereoselectively providing the trisaccharide **3.10** in 89% yield as a pure α-anomer. Subsequent glycosylation of the 4‘-hydroxyl in trisaccharide acceptor **3.10** with donor **3.1** was also sucessful and the branched tetrasaccharide sequence **3.9c** was obtained in 89% yield with complete α-stereoselectivity.

Scheme 3.5. Stepwise and one-pot synthesis of the branched tetrasaccharide 3.9c



We also attempted glycosylation of the diol acceptor **3.3c** with excess glycosyl donor **3.1** (2.5 equiv.). In this case, we also achieved complete stereoselectivity for the formation of both glycosidic linkages, but the desired tetrasaccharide **3.9c** was obtained in only 40% yield. All attempts to "push" the reaction with the use of extra DMTST led to higher yields albeit scrambled stereoselectivity.

3.3. Conclusions

This chapter discussed the application of the H-bond-mediated aglycone delivery (HAD) method on the synthesis of α-glucans, which are abundant in nature, but represent a notable synthetic challenge to chemists. The synthesis of linear oligosaccharide sequences was accomplished with complete stereoselectivity in all glycosylations up to the pentasaccharide. The efficacy of HAD may diminish with the increased bulk of the glycosyl acceptor, which may be an important factor to consider when attempting

syntheses of longer oligosaccharide sequences. The synthesis of branched structures were shown to be more challenging, particularly with bulky trisaccharide acceptors. The fact that some other types of leaving groups may give lower selectivity than that observed with *S*-ethyl glycosides requires further refinement and may enhance the utility of this method.

3.4. Experimental Section

3.4.1. General Remarks

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. AgOTf was co-evaporated with toluene (3 x 10 mL) and dried in vacuo for 2-3 h directly prior to application. Optical rotations were measured at 'Jasco P-1020' polarimeter. Unless noted otherwise, ^{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 MHz, 125 MHz or 150 MHz. Two-dimensional heteronuclear J-resolved spectra (HETERO2DJ)[54-56] were recorded in $CDCl_3$ at 600 MHz.

3.4.2. Synthesis of Glycosyl Donors

Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (3.1). The title compound was synthesized according to the reported procedure and the analytical data for **3.1** was essentially the same as reported previously.[35]

3.4.3. Synthesis of Oligosaccharides

General procedure for glycosylation in the presence of DMTST (commonly referred to as "HAD conditions"). A mixture of a glycosyl donor (0.13-0.15 mmol for mono- or 0.25 mmol for diglycosylations), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $(ClCH_2)_2$ (2.6 mL or 26 mL for 10x dilution) was stirred under argon for 1 h. The mixture was cooled to -30 °C and DMTST (0.26-0.50 mmol) was added. The resulting mixture was allowed to warm to rt over a period of 1 h and the reaction mixture was stirred at rt for the time specified in Schemes. Upon completion, Et_3N (0.3 mL) was added and the resulting mixture was stirred for 30 min. The mixture was then diluted with CH_2Cl_2 (10 mL), the solid was filtered off, and the residue was washed sucessively with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq. $NaHCO_3$ (10 mL) and water (3 x 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^{1}H-NMR spectra.

Methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3.3a). The title compound was obtained as a colorless syrup from glycosyl donor **3.1** (0.30 g, 0.50 mmol) and methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (**3.2**,[57] 0.19 g, 0.39 mmol) in the presence of DMTST in accordance with the general procedure in 83% yield (0.33 g, α/β = 21/1). Analytical data for **3.3a**: R_f = 0.42 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{23}$ +53.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.31-3.54 (m, 5H, H-6a', 6b', OCH_3), 3.58-3.75 (m, 2H, H-2, 2'), 4.02-4.26 (m, 5H, H-3, 3', 4, 5, 5'), 4.30 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.53 (d, 1H, ^2J = 12.0 Hz, ½ CH_2Ph), 4.57-4.78 (m, 7H, H-1, 6a, 6b, 2 x CH_2Ph), 4.81 (d, 1H, ^2J = 11.2 Hz, ½ CH_2Ph), 4.99 (dd, 2H, ^2J = 11.5 Hz, CH_2Ph), 5.51 (dd, 1H, $J_{4',5'}$ = 9.8 Hz, H-4'), 5.71 (d, 1H, $J_{1',2'}$ = 3.7 Hz, H-1'), 7.00-7.70 (m, 29H, aromatic), 7.80 (dd, 1H, *J* = 7.7 Hz, aromatic), 7.79-8.15 (m, 2H, aromatic), 8.77 (d, *J* = 4.7 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.5, 64.1, 64.4 (×2), 70.0, 71.9, 73.6, 73.7, 73.8, 74.9, 75.1, 75.4, 79.2, 79.3, 80.4, 81.6, 97.8, 98.0, 125.7, 126.9 (×2), 127.0, 127.3, 127.4, 127.5, 127.7 (×3), 127.9 (×2), 128.0 (×2), 128.1, 128.2 (×4), 128.3 (×2), 128.4 (×2), 128.5 (×3), 128.6 (×2), 130.0 (×2), 130.1, 133.3, 137.0, 137.8, 138.0, 138.1, 138.2, 139.1, 147.8, 150.0, 163.9, 166.3 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{61}H_{62}O_{13}N$ 1016.4221, found 1016.4263.

Methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3.3b). To a stirred solution of **3.3a** (0.30 g, 0.30 mmol) in CH_2Cl_2 (3.0 mL), methanol (300 μL) and $Cu(OAc)_2$ (88.4 mg, 0.44 mmol) were added and the resulting mixture was stirred under argon for 16 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (~50 mL) and washed with sat. aq. $NaHCO_3$ (10 mL), and water (2 x

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 the title compound as a colorless syrup in 93% yield (0.25 g, 0.28 mmol). Analytical data for **3.3b**: R_f = 0.48 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{23}$ +61.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 2.72 (br. s, 1H, O*H*), 3.34 (s, 3H, OCH_3), 3.38-3.50 (m, 3H, H-2', 6a', 6b'), 3.54 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{3,4}$ = 9.2 Hz, H-2), 3.58-3.63 (m, 2H, H-4', 5'), 3.76 (dd, 1H, $J_{3',4'}$ = 8.7 Hz, H-3'), 3.93-4.13 (m, 3H, H-3, 4, 5), 4.26 (dd, 2H, ^2J = 12.2 Hz, CH_2Ph), 4.42-4.64 (m, 7H, H-1, 6a, 6b, 2 x CH_2Ph), 4.76 (dd, 2H, ^2J = 11.2 Hz, CH_2Ph), 4.87 (dd, 2H, ^2J = 11.6 Hz, CH_2Ph), 5.69 (d, 1H, $J_{1',2'}$ = 3.8 Hz, H-1'), 7.00-7.57 (m, 28H, aromatic), 7.95-8.05 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 55.3, 63.8, 68.1, 69.4, 71.2, 71.3, 73.2, 73.4, 73.5 (×2), 74.5, 75.4, 78.8, 80.4, 81.4, 81.8, 97.3, 97.6, 126.7 (×2), 127.2, 127.6 (×4), 127.7, 127.9 (×2), 128.0, 128.2 (×2), 128.3 (×6), 128.4 (×2), 128.5 (×6), 129.8 (×2), 129.9, 133.2, 137.8 (×2), 137.9, 138.7, 138.9, 166.2 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{55}H_{59}O_{12}$ 911.4007, found 911.4031.

Methyl 2,3-di-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3.3c). A solution of 1N NaOMe in MeOH (1.0 mL, 1.0 mmol of NaOMe) was added to a stirred suspension of **3.3a** (130 mg, 0.13 mmol) in dry methanol (4.0 mL) and the resulting mixture was stirred for 1 h at rt. The reaction mixture was then neutralized with Dowex (H^+), filtered, washed successively with MeOH, and concentrated *in vacuo* to afford crude **3.3c** as a colorless syrup in 98% yield (101 mg, 0.13mmol). Analytical data for **3.3c**: R_f = 0.55 (ethyl acetate/hexane, 3/2, v/v); $[\alpha]_D^{22}$ +50.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 2.50 (br. s, 1H, 4'-OH), 3.05 (br. s, 1H, 6-OH), 3.43

(s, 3H, OCH_3), 3.45-3.54 (m, 2H, H-2', 4'), 3.58-3.67 (m, 2H, H-2, 6a), 3.71-3.92 (m, 5H, H-3, 5, 5', 6a', 6b'), 3.96-4.24 (m, 3H, H-3, 4, 6b), 4.52- 4.75 (m, 8H, H-1, 3½ x C*H*$_2$Ph), 4.92 (d, 1H, ^2J = 11.4 Hz, ½ C*H*$_2$Ph), 4.98 (dd, 2H, ^2J = 12.0 Hz, C*H*$_2$Ph), 5.81 (d, 1H, $J_{1',2'}$ = 3.8 Hz, H-1'), 7.15-7.55 (m, 25H, aromatic) ppm; ^{13}C NMR: δ, 55.3, 61.0, 69.5, 70.3, 70.7, 71.9, 72.1, 73.3 (×2), 73.7, 74.1, 75.3, 78.8, 80.3, 81.5, 81.9, 97.2, 97.9, 126.4 (×2), 127.1, 127.5 (×2), 127.7, 127.9 (×2), 128.0 (×2), 128.1 (×2), 128.3 (×2), 128.4 (×5), 128.6 (×4), 128.7 (×2), 137.5, 137.9 (×2), 138.6, 139.2 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{48}H_{55}O_{11}$ 807.3744, found 807.3761.

Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (3.4a). The title compound was obtained as a colorless syrup from glycosyl donor **3.1** (0.24 g, 0.34 mmol) and acceptor **3.3b** (0.24 g, 0.26 mmol) in 72% yield (0.27 g, 0.19 mmol, 93% based on the acceptor recovery, α/β > 25/1). Analytical data for **3.4a**: R_f = 0.57 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{24}$ +51.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.24-3.38 (m, 5H, H-6a", 6b", OCH_3), 3.39-3.38 (m, 5H, H-2, 2', 2", 5', 6a'), 3.72-3.83 (m, 2H, H-4', 6b'), 3.89-4.15 (m, 6H, H-3, 3', 3", 4, 5, 5"), 4.24 (dd, 2H, ^2J = 12.0 Hz, C*H*$_2$Ph), 4.26-4.58 (m, 10H, H-1, 6a, 4 x C*H*$_2$Ph), 4.59-5.00 (m, 7H, H-6b, 3 x C*H*$_2$Ph), 5.32-5.44 (m, 2H, H-1", 4"), 5.57 (d, 1H, $J_{1',2'}$ = 3.7 Hz, H-1'), 6.90-7.51 (m, 44H, aromatic), 7.55-8.05 (m, 4H, aromatic), 8.63 (d, 1H, *J* = 3.4 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.5, 64.1, 68.5, 68.7, 69.2, 69.6, 71.7, 72.1, 73.4, 73.5, 73.6 (×2), 73.7, 74.6, 74.9, 75.4, 75.9, 79.1, 79.3, 79.4, 79.5, 80.4, 81.2, 81.2, 81.8, 97.5, 97.9, 98.1, 125.6, 126.9 (×2), 127.0 (×2), 127.2, 127.4 (×2), 127.5 (×2), 127.7 (×4), 127.8 (×2), 127.9 (×2),

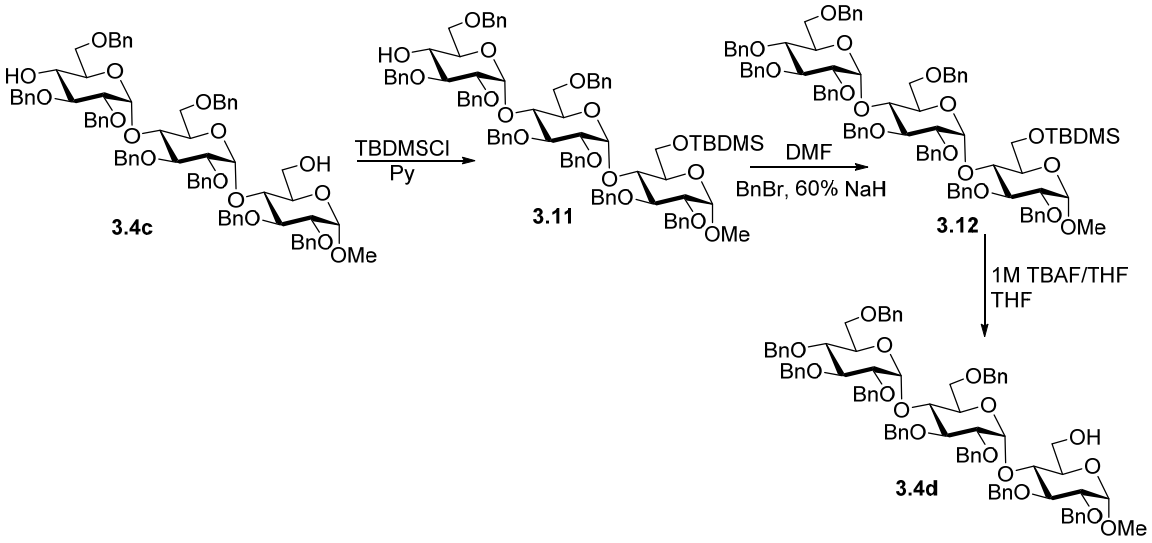
128.0 (×4), 128.2 (×5), 128.3 (×8), 128.4 (×6), 128.6, 128.7 (×3), 128.8, 129.2, 129.9, 130.2, 133.2, 137.0, 138.0, 138.1 (×2), 138.3, 138.5 (×2), 139.1 (×2), 164.1, 166.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{88}H_{89}O_{18}NNa$ 1470.5977, found 1470.6012.

Methyl *O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (3.4b). To a stirred solution of **3.4a** (100 mg, 0.07 mmol) in CH_2Cl_2 (2.0 mL), methanol (200 μL) and $Cu(OAc)_2$ (21 mg, 0.10 mmol) were added and the resulting mixture was stirred under argon for 16 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (~40 mL) and washed with sat. aq. $NaHCO_3$ (10 mL), and water (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 the title compound as a colorless syrup in 91% yield (84 mg, 0.50 mmol). Analytical data for **3.4b**: R_f = 0.56 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{22}$ +87.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 2.61 (d, 1H, *J* = 3.1 Hz, 4”-OH), 3.27- 3.82 (m, 14H, H-2, 2’, 2”, 3”, 4”, 5’, 5”, 6a’, 6a”, 6b’, 6b”, OCH_3), 3.88-4.12 (m, 5H, H-3, 3’, 4, 4’, 5), 4.19-4.56 (m, 10H, H-1, 6a, 3 x C*H*$_2$Ph), 4.57-4.70 (m, 4H, H-6b, 1½ x C*H*$_2$Ph), 4.71-4.84 (m, 4H, 2 C*H*$_2$Ph), 4.94 (d, 1H, ^2J = 11.6 Hz, ½ C*H*$_2$Ph), 5.44 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1’), 5.57 (d, 1H, $J_{1'',2''}$ = 3.6 Hz, H-1”), 6.95-7.55 (m, 43H, aromatic), 7.95 (d, 2H, *J* = 7.3 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.4. 64.2, 68.3, 69.0, 69.6, 70.9, 71.4, 71.6, 73.0, 73.3, 73.5 (×2), 73.6, 74.0, 74.2, 74.3, 74.8, 75.4, 79.1 (×3), 79.3, 80.3, 81.3, 81.5, 81.8, 97.2, 97.5, 97.7, 126.7 (×2), 126.9 (×2), 127.5, 127.7 (×4), 127.8, 128.0 (×2), 128.1, 128.3 (×7), 128.4 (×10), 128.5 (×2), 128.6 (×8), 128.7 (×2), 129.1 (×2), 129.9,136.1, 137.9, 138.0,

138.1, 138.2, 138.4, 135.9, 139.0 (×2), 166.5 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{82}H_{87}O_{17}$ 1343.5943, found 1343.5901.

Methyl *O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-α-D-glucopyranoside (3.4c). A solution of 1N NaOMe in MeOH (1.0 mL, 1.0 mmol of NaOMe) was added to a stirred suspension of **3.4a** (115 mg, 0.08 mmol) in dry methanol (4.0 mL) and the resulting mixture was stirred for 1 h at rt. The reaction mixture was then neutralized with Dowex (H^+), filtered, washed successively with MeOH, and concentrated *in vacuo* to yield crude **3.4c** as a colorless syrup in 97% yield (96 mg, 0.08 mmol). Analytical data for **3.4c**: R_f = 0.47 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{24}$ +54.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 2.33, 3.17 (2 br. s, 2H, 2 x OH), 3.34-3.45 (m, 4H, H-2", OCH_3), 3.48-3.65 (m, 9H, H-2, 2', 3", 4", 5", 6a, 6a', 6a", 6b"), 3.68-3.88 (m, 4H, H-4', 5, 6b, 6b'), 3.91-4.18 (m, 4H, H-3, 3', 4, 5'), 4.38-4.92 (m, 16H, H-1, 7½ x C*H*$_2$Ph), 5.06 (d, 1H, ^2J = 12.0 Hz, ½ C*H*$_2$Ph), 5.50 (d, 1H, $J_{1",2"}$ = 3.4 Hz, H-1"), 5.72 (d, 1H, $J_{1',2'}$ = 3.8 Hz, H-1'), 6.90-7.50 (m, 40H, aromatic) ppm; ^{13}C NMR: δ, 55.4. 60.9, 69.6, 69.7, 70.5, 71.2 (×2), 71.3, 72.3, 73.1, 73.3, 73.4, 73.7, 73.8, 73.9, 74.0, 74.3, 74.5, 78.9, 79.1, 80.3, 81.3 (×2), 82.1, 97.0 (×2), 98.1, 126.7 (×4), 127.2, 127.3, 127.7 (×2), 127.8 (×2), 127.9 (×2), 128.0 (×3), 128.2, 128.3 (×2), 128.4 (×8), 128.5 (×6), 128.6 (×6), 128.7 (×2), 137.6, 137.9 (×2), 138.0, 138.1, 138.8, 138.9, 139.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{75}H_{82}O_{16}Na$ 1261.5501, found 1261.5527.

Methyl *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-α-D-glucopyranoside (3.4d).



TBDMSCl (10.9 mg, 0.07 mmol) and 4-dimethylaminopyridine (0.9 mg, 0.007 mmol) were added to a solution of **3.4c** (60 mg, 0.05 mmol) in pyridine (3.0 mL) and the resulting mixture was stirred under argon for 16 h at rt. After that, pyridine was evaporated and co-evaporated with toluene (2×5 mL). The residue was dissolved in CH_2Cl_2 (~50 mL) and washed with cold water (10 mL), 1N HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), and water (2×10 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 give methyl *O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-α-D-glucopyranoside (**3.11**) in 89% yield (57 mg, 0.04 mmol) as colorless syrup. Analytical data for **3.11**: R_f = 0.47 (ethyl acetate/hexane, 3/7, v/v); $[\alpha]_D^{25}$ +54.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 0.03, 0.04 (2 s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 2.52 (br. s, 1H, OH),

3.34-3.47 (m, 5H, H-2", 6a", OCH_3), 3.48-3.60 (m, 3H, H-2, 2', 6b"), 3.61-3.81 (m, 5H, H-3", 4", 5", 6a", 6b"), 3.82-3.96 (m, 5H, H-4, 5, 5', 6b, 6b'), 3.98-4.14 (m, 3H, H-3, 3', 4'), 4.39 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.42-4.63 (m, 8H, H-1, 3½ x CH_2Ph), 4.65-4.76 (m, 3H, 1½ x CH_2Ph), 4.87 (d, 1H, ^2J = 11.4 Hz, ½ CH_2Ph), 4.91 (d, 1H, ^2J = 11.9 Hz, ½ CH_2Ph), 4.92 (dd, 2H, ^2J = 11.6 Hz, CH_2Ph), 5.63 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 5.69 (d, 1H, $J_{1",2"}$ = 3.5 Hz, H-1"), 7.00-7.45 (m, 40H, aromatic), ppm; ^{13}C NMR: δ, -4.9, -4.8, 18.7, 26.3 (×3), 55.1, 63.0, 69.2, 69.9, 70.6, 71.1, 71.2, 71.7, 72.6, 72.9, 73.2, 73.5 (×2), 73.6, 73.7, 74.2, 74.6, 75.5, 79.2, 79.7, 80.4, 81.5, 81.9 (×2), 96.5, 97.0, 97.6, 126.7, 127.0 (×2), 127.6 (×5), 127.7 (×2), 127.9 (×6), 128.0 (×3), 128.3 (×2), 128.4 (×11), 128.5 (×2), 128.6 (×7), 138.0, 138.1, 138.2, 138.3, 138.6, 139.0, 139.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{81}H_{96}O_{16}SiNa$ 1375.6365, found 1375.6284.

To a solution of **3.11** (55 mg, 0.04 mmol) in DMF (5.0 mL) NaH (60% in mineral oil, 4.8 mg, 0.12 mmol) and benzyl bromide (10 μL, 0.08 mmol) were added and the resulting mixture was stirred for 1.5 h at rt. The reaction mixture was poured into ice-water (~5 mL, 30 min) and stirred for 30 min and extracted with ethyl acetate/diethyl ether (1/1, v/v, 3 × 20 mL). The combined extract (~60 mL) was washed with cold water (3 × 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to give methyl *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-α-D-glucopyranoside (**3.12**) as a white amorphous solid in 86% (54.9 mg, 0.035 mmol). Analytical data for **3.12**: R_f = 0.58 (ethyl

acetate/hexane, 3/7, v/v); $[\alpha]_D^{24}$ +58.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 0.02, 0.03 (2 s, 6H, $Si(CH_3)_2$), 0.86 (s, 9H, $SiC(CH_3)_3$), 3.35-3.43 (m, 4H, H-6a", OCH_3), 3.45-3.59 (m, 4H, H-2, 2', 2", 6b"), 3.62-3.79 (m, 4H, H-4", 5, 5", 6a), 3.82-3.96 (m, 5H, H-3", 4, 5', 6a', 6b,), 3.97-4.12 (m, 4H, H-3, 3', 4', 6b'), 4.27 (d, 1H, ^2J = 12.01 Hz, ½ CH_2Ph), 4.42 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 4.44-4.56 (m, 8H, H-1, 3½ x CH_2Ph), 4.64 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.73-4.84 (m, 5H, 2½ x CH_2Ph), 4.89 (d, 1H, ^2J = 12.1 Hz, ½ CH_2Ph), 5.00 (d, 1H, ^2J = 11.6 Hz, ½ CH_2Ph), 5.62 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 5.66 (d, 1H, $J_{1",2"}$ = 3.6 Hz, H-1"), 7.00- 7.45 (m, 45H, aromatic), ppm; ^{13}C NMR: δ, -4.9, -4.8, 18.7, 26.3 (×3), 55.1, 63.1, 68.4, 69.3, 71.2 (×2), 71.3, 73.0, 73.1, 73.3, 73.5, 73.6, 73.7 (×2), 74.3, 74.6, 75.1, 75.7, 77.8, 79.7 (×2), 80.4, 81.8, 81.9, 82.3, 96.6, 97.2, 97.6, 126.7 (×2), 127.0 (×2), 127.1, 127.3, 127.6 (×5), 127.7 (×3), 127.8, 127.9 (×2), 128.0 (×8), 128.1, 128.2 (×3), 128.3 (×2), 128.4 (×8), 128.5 (×3), 128.6 (×4), 138.0, 138.2 (×2), 138.5, 138.6, 138.8, 139.0, 139.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{88}H_{102}O_{16}SiNa$ 1465.6835, found 1465.6801.

A 1 M soln. of *tert*-butylammonium fluoride in THF (85 μL, 0.085 mmol) was added to a solution of **3.12** (54 mg, 0.034 mmol) in THF (2.0 mL) and the resulting mixture was stirred for 3 h at rt. After that, the reaction mixture was neutralized with Et_3N (~0.1 mL), diluted with CH_2Cl_2 (~30 mL), and washed with cold water (5 mL), sat. aq. $NaHCO_3$ (5 mL), and water (3 x 5 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 the title compound **3.4d** in 94% yield (47.1 mg, 0.03 mmol) as a colorless syrup. Analytical data for **3.4d**: R_f = 0.58

(ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{24}$ +51.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.19 (br. dd, 1H, OH), 3.39 (s, 3H, OCH_3), 3.37-3.66 (m, 9H, H-2, 2', 2", 5, 5", 6a', 6a", 6b', 6b"), 3.68-3.88 (m, 4H, H-3", 4', 4", 6a), 3.90-4.18 (m, 5H, H-3, 3', 4, 5', 6b), 4.35-4.90 (m, 18H, H-1, 8½ x CH_2Ph), 5.05 (d, 1H, ^2J = 11.9 Hz, ½ CH_2Ph), 5.49 (d, 1H, $J_{1",2"}$ = 3.5 Hz, H-1"), 5.71 (d, 1H, $J_{1',2'}$ = 3.8 Hz, H-1'), 6.90-7.90 (m, 45 H, aromatic) ppm; ^{13}C NMR: δ, 55.4. 60.9, 68.4, 69.5, 70.5, 71.1, 71.5, 72.4, 73.4 (×3), 73.7 (×2), 74.0, 74.1, 74.3, 75.2, 75.7, 77.9, 78.8, 79.5, 80.2, 81.2, 82.0, 82.1, 97.1, 97.3, 98.1, 126.6 (×2), 126.7 (×2), 127.2, 127.3, 127.6, 127.7 (×5), 127.8 (×3), 127.9, 128.0 (×4), 128.1 (×4), 128.2 (×3), 128.4 (×8), 128.5 (×5), 128.6 (×5), 137.4, 138.0 (×2), 138.1 (×2), 138.5, 138.8, 138.9, 139.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{82}H_{88}O_{16}Na$ 1351.5970, found 1351.5943.

Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (3.5a). The title compound was obtained as a colorless syrup from glycosyl donor **3.1** (56 mg, 0.09 mmol) and acceptor **3.4b** (84 mg, 0.06 mmol) in 56% (63 mg, 0.03 mmol, 79% with the acceptor recovery, α/β = 23/1). Analytical data for **3.5a**: R_f = 0.51 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{24}$ +72.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.33 (dd, 1H, $J_{6a''',5'''}$ = 3.4 Hz, $J_{6a''',6b'''}$ = 10.7 Hz, H-6a'''), 3.35-3.44 (m, 4H, H-6b''', OCH_3), 3.46-3.63 (m, 5H, H-2, 2' 2", 2"', 5', 6a'), 3.47-3.93 (m, 4H, H-4', 6b', 6a", 6b"), 3.97-4.17 (m, 7H, H-3', 3", 3"', 4", 5, 5" 5"'), 4.23 (d, 1H, ^2J = 12.0 Hz, ½ CH_2Ph), 4.30-4.44 (m, 7H, 3½ x CH_2Ph), 4.45-4.63 (m, 8H, H-1, 6a, 3 x CH_2Ph), 4.68-4.74 (m, 3H, H-6b, CH_2Ph), 4.81-4.94 (m, 5H, 2½ x

C*H*$_2$Ph), 5.01 (d, 1H, ^2J = 11.4 Hz, ½ C*H*$_2$Ph), 5.42 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.45 (dd, 1H, $J_{4''',5'''}$ = 9.7 Hz, H-4'''), 5.60 (d, 1H, $J_{1''',2'''}$ = 3.5 Hz, H-1'''), 5.62 (d, 1H, $J_{1'',2''}$ = 3.7 Hz, H-1''), 6.95-7.85 (m, 60H, aromatic), 7.92 (d, 1H, J = 7.9 Hz, aromatic), 8.04 (d, 2H, J = 7.4 Hz, aromatic), 8.72 (d, 1H, J = 4.2 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.5, 64.1, 68.5, 68.8, 69.0, 69.2, 69.5, 71.2, 71.7, 72.3, 73.2, 73.3, 73.5 (×3), 73.6 (×2), 73.7, 74.5, 74.6, 74.9 (×2), 75.3 (×2), 79.1, 79.4, 79.5, 79.7, 80.4, 81.4, 81.5, 81.8, 97.3, 97.5, 97.7, 97.8, 125.6, 126.9 (×3), 127.0 (×4), 127.2 (×2), 127.4 (×2), 127.5 (×3), 127.7 (×5), 127.8 (×3), 127.9 (×3), 128.0 (×4), 128.2 (×5), 128.3 (×6), 128.4 (×8), 128.5 (×7), 128.6, 128.7 (×2), 130.1 (×3), 133.2, 137.0, 138.0, 138.1, 138.2 (×3), 138.4, 138.5, 138.6, 139.1, 139.2 (×2), 148.2, 150.0, 164.2, 166.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{115}H_{117}O_{23}NNa$ 1902.7914, found 1902.7853.

Methyl *O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (3.5b). To a stirred solution of **3.5a** (63 mg, 0.04 mmol) in CH_2Cl_2 (2.0 mL), methanol (100 μL) and $Cu(OAc)_2$ (10 mg, 0.05 mmol) were added and the resulting mixture was stirred under argon for 16 at rt. The reaction mixture was then diluted with CH_2Cl_2 (~30 mL) and washed with sat. aq. $NaHCO_3$ (6 mL), and water (2 x 6 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethylacetate-hexane gradient elution) to afford the title compound as a colorless syrup in 96% yield (57 mg, 0.04 mmol). Analytical data for **3.5b**: R_f = 0.52 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{24}$ +65.8 (c = 1.0, $CHCl_3$); ^{1}H NMR:

δ, 2.55 (d, 1H, J = 2.6 Hz, OH), 3.32-4.17 (m, 25H, H-2, 2', 2", 2"', 3, 3', 3", 3"', 4, 4', 4", 4"', 5, 5', 5", 5"', 6a', 6a", 6a"', 6b', 6b", 6b"', OCH_3), 4.26-4.77 (m, 18H, H-1, 6a, 6b, 7½ x CH_2Ph), 4.79-5.05 (m, 7H, 3½ x CH_2Ph), 5.40 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1'), 5.64 (1H, $J_{1",2"}$ = 3.7 Hz, H-1"), 5.69 (1H, $J_{1"',2"'}$ = 3.5 Hz, H-1"'), 6.95- 7.60 (m, 58H, aromatic), 8.02 (d, 2H, J = 8.5 Hz, aromatic), 8.72 (d, 1H, J = 4.2 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.5, 64.1, 68.5, 68.9, 69.9, 70.5, 71.0, 71.7, 72.1, 73.0 (×2), 73.4 (×2), 73.5, 73.6, 73.7, 74.1, 74.5, 74.7, 74.9, 75.4, 79.0, 79.1, 79.3 (×3), 79.9, 80.4, 81.4, 81.5, 81.8, 81.9, 96.8, 97.1, 97.6, 97.8, 126.7, 126.9, 127.0, 127.2, 127.3, 127.5, 127.7 (×2), 128.8, 127.9 (×3), 128.0 (×2), 128.2, 128.3 (×5), 128.4 (×8), 128.5 (×2), 128.5 (×3), 128.7 (×6), 128.8 (×12), 129.2 (×6), 136.0 (×3), 138.1 (×6), 138.3, 138.6, 139.0, 139.1 (×3), 166.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{109}H_{114}O_{22}Na$ 1797.7699, found 1797.7731.

Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (3.6). The title compound was obtained as a colorless syrup from glycosyl donor **3.1** (35 mg, 0.06 mmol) and acceptor **3.5b** (57 mg, 0.04 mmol) in 41% (31 mg, 0.01 mmol, 81% with acceptor recovery, α/β > 25/1). Analytical data for **3.6**: R_f = 0.55 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ +71.1 (c = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.30-3.43 (m, 5H, H-6a"", 6b"", OCH_3), 3.45-3.63 (m, 8H, H-2, 2', 2", 2"', 2"", 6a"', 6b", 6b"'), 3.73-3.95 (m, 6H, H-3', 4', 4", 5', 5", 5"'), 3.95-4.18 (m, 12H, H-3, 3", 3"', 3"", 4, 4"', 5, 5"", 6a', 6a", 6b', 6b"), 4.23 (d, 1H, ^2J = 12.0 Hz, ½ CH_2Ph), 4.28-4.63 (m, 19 H, H-1, 6a, 8½ x CH_2Ph), 4.65-4.95 (m, 10H, H-6b, 4½ x CH_2Ph), 5.00 (d,

1H, ^{2}J = 11.5 Hz, ½ C*H*$_2$Ph), 5.37-5.50 (m, 2H, H-1', 4''''), 5.55-5.68 (m, 3H, H-1'', 1''', 1''''), 6.80-7.55 (m, 74H, aromatic), 7.60-8.15 (m, 4H, aromatic), 8.75 (d, 1H, J = 3.2 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.5, 64.1, 68.6, 68.9, 69.0, 69.2, 69.5, 71.1, 71.2, 71.7, 72.3, 72.9, 73.1 (×2), 73.3, 73.5 (×4), 73.6 (×2), 73.7, 74.2, 74.4, 74.6 (×2), 74.8, 74.9, 75.0, 75.3, 79.2, 79.4, 79.5, 79.7 (×2), 80.4, 81.4, 81.7 (×2), 81.8, 96.5, 97.2, 97.6, 97.7, 97.9, 125.8, 126.8 (×2), 126.9 (×2), 127.0 (×2), 127.1 (×2), 127.2 (×3), 127.4 (×2), 127.5 (×3), 127.6, 127.7 (×7), 127.8 (×4), 127.9 (×4), 128.0 (×6), 128.2 (×3), 128.3 (×11), 128.4 (×16), 128.5 (×5), 128.6, 128.7 (×2), 130.0 (×2), 130.2, 136.9, 138.2 (×2), 138.3, 138.4, 138.5, 138.6, 138.7, 139.1, 139.2 (×4), 148.2, 150.0, 164.2, 166.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{142}H_{145}O_{28}NNa$ 2334.9851, found 2334.9789.

Methyl 3,4-di-*O*-benzyl-2,6-di-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3.8). The title compound was obtained as a colorless syrup from glycosyl donor **3.1** (90 mg, 0.15 mmol) and methyl 3,4-di-*O*-benzyl-α-D-glucopyranoside (**3.7**,[49] 20 mg, 0.05 mmol) in 83% (53 mg, 0.04 mmol, α/β = 22/1). Analytical data for **3.8**: R_f = 0.46 (ethyl acetate/hexane, 3/2, v/v); ^{1}H NMR: δ, 3.22 (1H, dd, $J_{5°,6a°}$ = 3.5 Hz, $J_{6a°,6b°}$ = 11.0 Hz, H-6a°), 3.32 (dd, 1H, $J_{5°,6b°}$ = 2.5 Hz, H-6b°), 3.43 (s, 3H, OCH_3), 3.45-3.71 (m, 6H, H- 2, 2', 6a, 6b, 6a', 6b'), 3.73-3.92 (m, 4H, H-2, 3, 4, 5), 4.06-4.22 (m, 4H, H-3°, 3', 5°, 5'), 4.28 (dd, 2H, ^{2}J = 11.8 Hz, C*H*$_2$Ph), 4.43 (dd, 2H, ^{2}J = 12.0 Hz, C*H*$_2$Ph), 4.53-4.91 (m, 11H, H-1, 5 x C*H*$_2$Ph), 4.92 (dd, 2H, ^{2}J = 11.3 Hz, C*H*$_2$Ph), 4.94 (d, 1H, $J_{1°,2°}$ = 3.6 Hz, H-1°), 5.03 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.39 (dd, 1H, $J_{4',5'}$ = 9.8 Hz, H-4'), 5.45 (dd, 1H, $J_{4°,5°}$ = 9.7 Hz, H-4°), 6.95-7.95 (m, 46H, aromatic), 7.55-7.80 (m, 2H, aromatic), 7.87 (d, 1H, J = 7.8 Hz, aromatic), 8.70 (dd, 1H,

J = 5.4 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.1, 66.1, 68.1, 69.0, 70.7, 71.3, 72.0, 73.1, 73.2, 73.6, 73.7, 75.1, 75.2, 75.3, 75.7, 75.9, 77.4, 77.5, 78.4, 78.7, 79.1, 79.2, 80.0, 81.1, 94.8, 96.3, 97.3, 126.8, 127.0, 127.5 (×3), 127.6, 127.9 (×2), 128.0 (×6), 128.1 (×4), 128.2 (×16), 128.3 (×4), 128.5 (×2), 128.6 (×5), 136.9, 137.0, 137.9, 138.0, 138.3, 138.4 (×2), 138.5, 138.6, 147.8, 147.9, 150.0, 150.1, 163.7, 164.2 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{87}H_{89}O_{18}N$ 1449.6110, found 1449.6103.

Methyl *O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3.9a). The title compound was obtained as a colorless syrup from glycosyl donor **3.1** (26 mg, 0.04 mmol) and acceptor **3.4c** (36 mg, 0.03 mmol) in 87% (47 mg, 0.03 mmol, α/β = 2.4/1). Analytical data for **α-3.9a**: R_f = 0.55 (acetone/toluene, 3/17, v/v); $[\alpha]_D^{25}$ +75.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.31-3.46 (m, 6H, H-2, 2", 6a', OCH_3), 3.48-3.61 (m, 4H, H-2', 6a°, 6b', 6b°), 3.63 (dd, 1H, $J_{2°,3°}$ = 3.7 Hz, H-2°), 3.67-3.97 (m, 10H, H-3", 4', 4", 5, 5', 5", 6a, 6a", 6b, 6b"), 3.98-4.27(m, 5H, H-3, 3', 3°, 4, 5°), 4.31-5.00 (m, 23H, H-1, 11 x C*H*$_2$Ph), 5.30 (d, 1H, $J_{1°,2°}$ = 3.5 Hz, H-1°), 5.41 (dd, 1H, $J_{4°,5°}$ = 9.7 Hz, H-4°), 5.60 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 5.67 (d, 1H, $J_{1",2"}$ = 3.5 Hz, H-1"), 6.90-8.00 (m, 58H, aromatic), 8.65 (d, 1H, *J* = 3.4 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.5, 65.0, 68.9, 69.1, 69.6, 69.7, 71.2, 71.4, 71.5, 72.3, 72.9 (×2), 73.1, 73.5, 73.6, 73.7 (×2), 74.1, 75.0, 75.3 (×2), 77.3, 77.7, 78.2, 79.2, 79.3, 79.9, 80.1 (×2), 81.7 (×2), 81.8, 96.7, 97.0, 97.2, 97.8, 125.7, 126.8 (×2), 127.2 (×2), 127.3, 127.4 (×2), 127.5, 127.6, 127.7 (×8), 127.8 (×2), 127.9 (×7), 128.0 (×4), 128.1, 128.2, 128.3 (×4), 128.4 (×12), 128.5 (×7), 128.6 (×2), 128.7 (×2), 138.1, 138.2, 138.3 (×3), 138.7,

138.8, 139.1 (×2), 139.4, 149.8, 164.0 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{108}H_{113}O_{23}NNa$ 1816.0355, found 1816.0309.

Methyl *O*-(2,3,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3.9b). The title compound was obtained as a colorless syrup from glycosyl donor **3.1** (26 mg, 0.04 mmol) and acceptor **3.4d** (36 mg, 0.03 mmol) in 82% (47 mg, 0.03 mmol, α/β = 3/1). Selected analytical data for α-**3.9b**: R_f = 0.56 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ +50.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.24-3.36 (m, 5H, H-6a', 6b', OCH_3), 3.37-3.71 (m, 12H, H-2, 2', 2", 2°, 4', 5', 5", 6a, 6a", 6a°, 6b", 6b°), 3.72-3.91 (m, 4H, H-3', 4', 5, 6b), 3.93-4.12 (m, 5H, H-3, 3", 3°, 4, 5°), 4.15 (d, 1H, ^2J = 12.1 Hz, ½ CH_2Ph), 4.27-4.73 (m, 21H, H-1, 10 x CH_2Ph), 4.75-4.99 (m, 4H, 2 x CH_2Ph), 5.13 (d, 1H, $J_{1°,2°}$ = 3.4 Hz, H-1°), 5.36 (dd, 1H, $J_{4°,5°}$ = 9.9 Hz, H-4°), 5.44 (d, 1H, $J_{1",2"}$ = 3.5 Hz, H-1"), 5.60 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 6.90-8.00 (m, 63H, aromatic), 8.60 (d, 1H, *J* = 5.7 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.5, 66.0, 68.4, 68.9, 69.1, 69.5, 71.0, 71.2, 71.4, 72.1, 72.8, 72.9 (×2), 73.3, 73.4, 73.6 (×2), 73.7 (×2), 74.2, 75.2, 75.3 (×2), 75.7, 77.9, 79.1, 79.6, 79.8, 80.0 (×2), 81.4, 81.6, 82.3, 97.0, 97.2, 97.3, 97.8, 125.4, 126.9 (×3), 127.2 (×3), 127.4 (×3), 127.5 (×2), 127.6 (×2), 127.7, 127.8 (×4), 127.9 (×13), 128.0 (×3), 128.2 (×6), 128.3 (×6), 128.4 (×8), 128.5 (×3), 128.6 (×4), 136.9, 138.1, 138.2 (×3), 138.3 (×2), 138.6 (×2), 138.7, 139.0 (×2), 139.5, 148.0, 150.0, 164.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{115}H_{119}O_{23}NNa$ 1904.8071, found 1904.8123.

Selected analytical data for β-**3.9b**: R_f = 0.40 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ +33.9 (*c* = 1.0, $CHCl_3$); δ, 3.30-3.40 (m, 4H, H-6a', OCH_3), 3.45-3.61 (m, 7H, H-2, 2', 2", 2°, 5', 6a°, 6b'), 3.62-3.87 (m, 7H, H-3°, 4', 4°, 5°, 6a, 6b, 6b°), 3.88-3.95 (m, 3H, H-3', 4, 5), 3.96-4.12 (m, 5H, H-3, 3", 4", 5", 6a"), 4.19-4.27 (m, 2H, H-6b", ½ CH_2Ph), 4.32-4.45 (m, 6H, 3 x CH_2Ph), 4.46-4.64 (m, 8H, H-1, 1°, 3 x CH_2Ph), 4.65-4.81 (m, 6H, 3 x CH_2Ph), 4.83-5.02 (m, 5H, 2½ x CH_2Ph), 5.33 (dd, 1H, $J_{4°,5°}$ = 9.8 Hz, H-4°), 5.46 (d, 1H, $J_{1",2"}$ = 3.3 Hz, H-1"), 5.67 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 6.90-8.00 (m, 63H, aromatic), 8.69 (d, 1H, *J* = 4.8 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.6, 68.3, 68.8, 69.2, 69.9, 70.3, 71.2, 71.3, 72.7 (×2), 73.1, 73.3, 73.4 (×2), 73.5, 73.6 (×2), 74.1, 74.8, 75.1, 75.3, 75.4, 75.7, 77.1, 77.8, 79.5, 79.6, 80.0, 81.3, 81.7, 81.9, 82.3 (×2), 97.1, 97.9 (×2), 103.7, 125.7, 126.8 (×2), 126.9 (×2), 127.0, 127.1, 127.2, 127.5 (×4), 127.6 (×2), 127.7 (×4), 127.8 (×6), 127.9 (×2), 128.0 (×4), 128.1 (×3), 128.3 (×7), 128.4 (×9), 128.5 (×7), 128.6 (×6), 137.0, 138.1 (×2), 138.2 (×2), 138.3 (×2), 138.6 (×2), 138.8, 138.9, 139.0, 139.5, 147.9, 150.0, 164.3 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{115}H_{119}O_{23}NNa$ 1904.8071, found 1904.8100.

Methyl *O*-(2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3.9c). The title compound was obtained as a colorless syrup from glycosyl donor **3.1** (26 mg, 0.04 mmol) and acceptor **3.10** (36 mg, 0.03 mmol) in 43% yield (91% with acceptor **3.10** recovery, 23 mg, 0.01 mmol, α/β = 23/1). Analytical data for α-**3.9c**: R_f = 0.47 (ethyl acetate/hexane, 3/2, v/v); $[\alpha]_D^{23}$ +37.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.32 (dd, 1H, $J_{5',6a'}$ = 3.8 Hz, $J_{6a',6b'}$ = 10.8 Hz,

H-6a'), 3.37-3.45 (m, 4H, H-6b', OCH_3), 3.47 (dd, 1H, $J_{2,3}$ = 8.9 Hz, H-2), 3.52-3.67 (m, 5H, H-2', 2", 2°, 6a", 6b"), 3.74 (dd, 1H, $J_{6a,6b}$ = 10.8 Hz H-6a), 3.85(dd, 1H, $J_{5°,6a°}$ = 3.6 Hz, $J_{6a°,6b°}$ = 9.3 Hz, H-6a°), 3.89-4.00 (m, 2H, H-5, 6b), 4.20-4.27 (m, 10H, H-3, 3', 3", 3°, 4, 4', 5°, 5', 5", 6b°), 4.30 (dd, 2H, ^2J = 11.7 Hz, CH_2Ph), 4.32-4.61 (m, 15H, $J_{1,2}$ = 3.6 Hz, H-1, 7 x CH_2Ph), 4.62-4.71 (m, 2H, CH_2Ph), 4.72-4.86 (m, 4H, 2 x CH_2Ph), 5.00 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 5.24 (d, 1H, $J_{1°,2°}$ = 3.4 Hz, H-1°), 5.38 (m, 2H, H-4", 4°), 5.51 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.58 (d, 1H, $J_{1",2"}$ = 3.6 Hz, H-1"), 6.90- 8.00 (m, 61H, aromatic), 8.60-8.70 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 55.5, 66.0, 68.9 (×2), 69.1, 69.6, 69.8, 71.1, 71.5, 72.1, 72.3, 72.8, 72.9, 73.4, 73.5, 73.6, 73.7 (×2), 74.4, 74.9, 75.3 (×2), 75.5, 77.5, 79.2, 79.4 (×2), 79.6, 79.9, 80.0, 81.2, 81.4, 97.2, 97.3, 97.7, 97.9, 125.5, 126.9, 127.0 (×2), 127.2 (×2), 127.4 (×3), 127.5 (×2), 127.6 (×4), 127.7, 127.8, 127.9 (×11), 128.0 (×7), 128.2 (×5), 128.3 (×6), 128.4 (×6), 128.5 (×3), 128.6 (×3), 128.7 (×3), 136.9, 138.1 (×2), 138.2 (×2), 138.3, 138.4, 138.5, 138.6, 138.7, 139.1, 139.6, 148.0, 148.1, 150.0 (×2), 164.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{114}H_{116}O_{24}N_2Na$ 1919.7816, found 1919.7792.

Methyl 2,3-Di-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3.10). The title compound was obtained as a colorless syrup from glycosyl donor **3.1** (65 mg, 0.11 mmol) and acceptor **3.3c** (67 mg, 0.08 mmol) in 89% yield (94 mg, 0.07 mmol, α/β = 24/1). Analytical data for **3.10**: R_f = 0.66 (ethyl acetate/hexane, 3/2, v/v); $[\alpha]_D^{24}$ +64.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.37 (s, 3H, OCH_3), 3.46-3.61 (m, 4H, H-2, 2', 6a°, 6b°), 3.65 (dd, 1H, $J_{2°,3°}$ = 9.5 Hz, H-2°), 3.75-4.10 (m, 7H, H-3', 5, 5', 6a, 6a', 6b, 6b'), 4.03-4.21 (m,

4H, H-3, 3°, 4, 4'), 4.26 (m, 1H, H-5°), 4.34 (d, 1H, ^2J = 12.2 Hz, ½ CH_2Ph), 4.38-4.83 (m, 14H, H-1, 6½ x CH_2Ph), 4.88 (d, 1H, ^2J = 11.3 Hz, ½ CH_2Ph), 5.03 (d, 1H, ^2J = 11.5 Hz, ½ CH_2Ph), 5.13 (d, 1H, $J_{1°,2°}$ = 3.5 Hz, H-1°), 5.45 (dd, 1H, $J_{4°,5°}$ = 9.8 Hz, H-4°), 5.70 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 6.90-8.10 (m, 41H, aromatic), 8.63 (d, 1H, J = 4.1 Hz, aromatic) ppm; ^{13}C NMR: δ, 55.4, 66.1, 68.6, 68.8, 69.7, 70.0, 71.0, 71.6, 72.0, 72.4, 72.5, 73.3, 73.6, 73.7 (×2), 74.5, 75.2, 75.6, 77.3, 79.5, 79.8, 80.8, 81.6, 82.0, 95.9, 97.7, 97.8, 125.7, 127.1 (×2), 127.2, 127.4 (×2), 127.5 (×3), 127.6, 127.8 (×4), 127.9, 128.0 (×6), 128.1 (×3), 128.2 (×2), 128.3 (×5), 128.4 (×4), 128.6 (×7), 137.5, 138.0, 138.1, 138.3, 138.4, 138.6, 138.8, 139.0, 139.2, 147.6, 149.7, 163.8 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{81}H_{85}O_{18}NNa$ 1382.5664, found 1382.5603.

3.5. References

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CHAPTER 4

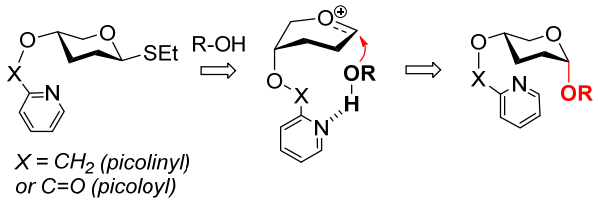
Hydrogen bond-mediated aglycone delivery: leaving group and promoter effect on 1,2-*cis* glucoside synthesis

4.1. Introduction

O-Glycosylation reactions form a new chirality center and uncontrolled reactions commonly provide mixtures of 1,2-*cis* (α) and 1,2-*trans* (β) diastereomers. Obtaining an *O*-glycosidic linkage with complete stereoselectivity requires special care and the last few decades have witnessed a number of new techniques that have been developed to address this challenge in many different ways.[1] Among a plethora of methods developed, a very successful technique involving the participatory assistance of the neighboring acyl substituent has been developed for the synthesis of 1,2-*trans* glycosides.[2-4] On the other hand, although a number of dedicated methodologies have been developed for 1,2-*cis* glycosylation, obtaining complete stereoselectivity in 1,2-*cis* glycoside synthesis still remains a challenge.[5]

Our group has been studying picolinyl and picoloyl substituents both at the neighboring (C-2) and remote positions (C-3, 4, and 6) and, among other interesting findings, introduced *H*-bond mediated aglycone delivery concept. Over the course of this study we acquired a compelling evidence of the nucleophile, the hydroxyl of the glycosyl acceptor, forms hydrogen bond with the picolinyl (or picoloyl) nitrogen and it is delivered at the anomeric center in the syn fashion with respect to the picolinyl (or picoloyl) group to form the new glycosidic bond (Scheme 4.1).

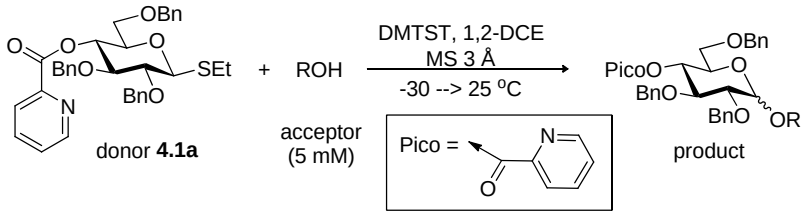
Scheme 4.1. 1,2-*cis* glycosylation *via H*-bond-mediated Aglycone Delivery (HAD) assisted by picolinyl/picoloyl substituents.

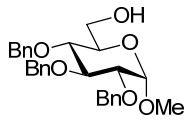
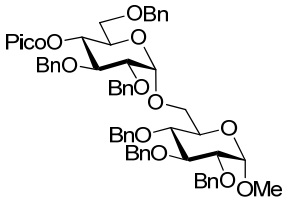
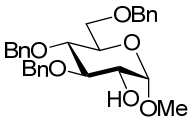
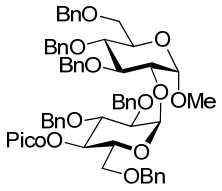
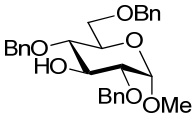
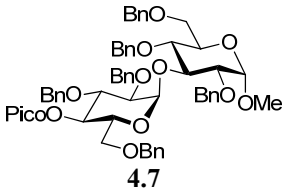
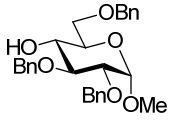
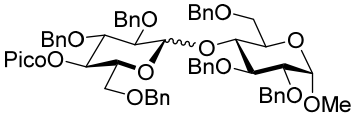


This new mode to control stereoselectivity of glycosylation allowed for the synthesis of both 1,2-*trans*- and 1,2-*cis* glycosidic linkages and has been proven to be applicable to the synthesis of challenging α-glucosides, β-rhamnosides, and β-mannosides with high or even complete selectivity.[6] We also have applied this technique to the synthesis of both linear and branched α-glucans. Although the synthesis of these oligosaccharides was successful, we also encountered some intrinsic problems with this method related to the weakening of the H-bonding with some bulky or sterically hindered acceptors, as well as some loss of reactivity/stereoselectivity in certain cases.

The study detailed herein is solely dedicated to the refinement of the synthesis of one glycosidic linkage, 1,2-*cis*-glucose, which is among the most abundant linkages in nature, yet remains challenging to chemists. Our preliminary results dedicated to this important linkage are summarized in Table 4.1. In particular, the 4-*O*-picoloylated S-ethyl glycosyl donor **4.1a** was found to be very beneficial in this particular application. In most cases, high stereoselectivity was only obtained under high dilution, reaction conditions that became standard for this type of glycosylation. DMTST was found to be the promoter of choice because it does not interfere with the N-atom of the picoloyl group. Both primary **4.2** and secondary glycosyl acceptors **4.4**, **4.6**, and **4.8** with 4-*O*-picoloylated donor **4.1a** gave very high or near complete 1,2-*cis* selectivity.[6] Disaccharides **4.3**, **4.5**, **4.7**, and **4.9** were obtained in high yields of 73-91% and exceptional α-selectivity (Table 4.1).

Table 4.1. Survey of the previous results on the 4-*O*-picolinyl/picoloyl-assisted stereoselective glycosylation.[6]



Entry	*Acceptor*	*Time*	*Product*	*Yield*	*α/β Ratio*
1	 **4.2**	4 h	 **4.3**	73%	>25 / 1
2[a]	 **4.4**	5 h	 **4.5**	93%	>25 / 1
3	 **4.6**	16 h	 **4.7**	81%	>25 / 1
4	 **4.8**	24 h	 **4.9**	81%	21 / 1

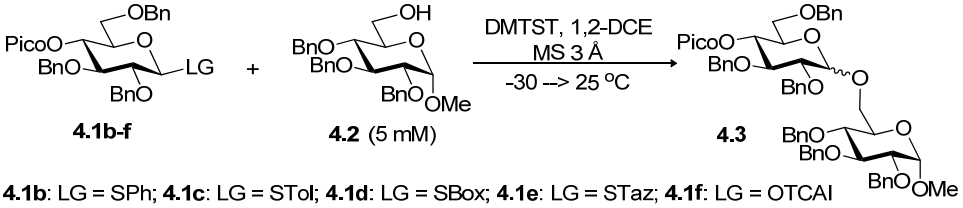
[a] 5 mM of glycosyl acceptor was used

4.2. Results and Discussion

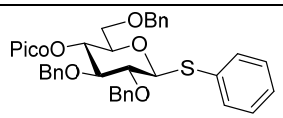
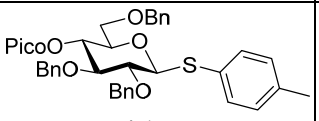
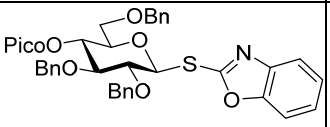
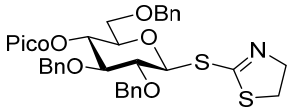
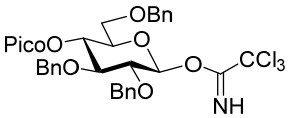
As an extension of this study we have decided to perform further refinement of this methodology for the synthesis of α-gluco linkage in application to other classes of glycosyl donors, activators, systems, etc. to see the applicability of this method for other types of leaving groups for 1,2-*cis* glycosylation. As the first attempt of identifying better

glycosyl donors for HAD, 4-*O*-picoloylated thiophenyl glycoside **4.1b** was coupled with glycosyl acceptor **4.2**[7] to obtain the disaccharide **4.3** under the previously reported standard glycosylation condition.[6] To our surprise, only a moderate stereoselectivity was obtained (α/β = 5.3/1, 85%, entry 1, Table 4.2). A very similar result in terms of the yield and stereoselectivity was obtained in the glycosidation of *p*-tolyl thioglycoside **4.1c** (α/β = 6.7/1, 90%, entry 2).

Table 4.2. Effect of the leaving group and promoters on the stereoselectivity.



4.1b: LG = SPh; **4.1c**: LG = STol; **4.1d**: LG = SBox; **4.1e**: LG = STaz; **4.1f**: LG = OTCAI

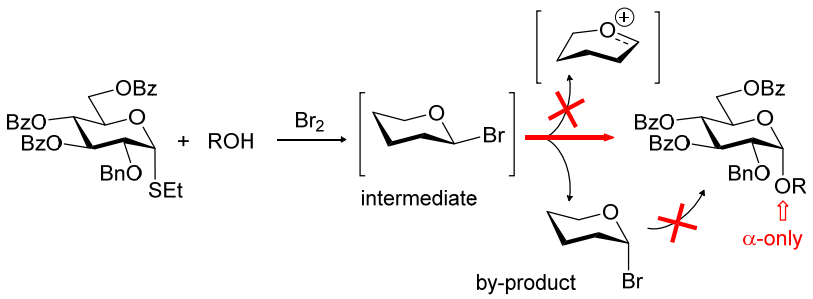
Entry	*Donor*	*Conditions*[a]	*Yield, α/β ratio*
1	 **4.1b**	DMTST (2 equiv.), 2.5 h	**4.3** (85%, 5.3/1)
2	 **4.1c**	DMTST (2 equiv.), 3 h	**4.3** (90%, 6.7/1)
3	 **4.1d**	AgOTf (2 equiv.), 2 h	**4.3** (79%, 1/1.9)
4	**4.1d**	DMTST (2 equiv.), 6 h	**4.3** (80%, 6.1/1)
5	 **4.1e**	AgOTf (2 equiv.), 6 h	**4.3** (86%, 6.3/1)
6	 **4.1f**	TMSOTf (0.5 equiv.), 3 h	**4.3** (44%, 5.9/1)
7	**4.1f**	TfOH (0.5 equiv.), 2 h	**4.3** (92%, 9.7/1)

Having no success with other types of thioglycosides, we decided to study O/S-imidates, another popular class of glycosyl donors.[8-10] When the *S*-benzoxazolyl (SBox) glycosyl donor **4.1d** was first activated with AgOTf, a reverse selectivity was obtained with a slight shift towards the 1,2-*trans* linked **4.3** (α/β = 1/1.9, 79%, entry 3). A higher, yet far from being satisfactory α-selectivity was obtained when SBox donor **4.1d** was activated with DMTST. In this case disaccharide **4.3** was obtained in 80% yield (α/β = 6.1/1, entry 4). A similar outcome was achieved upon AgOTf-promoted activation of S-thiazolinyl (STaz) donor **4.1e** (α/β = 6.3/1, 86%, entry 5). Finally, we tested O-trichloroacetimidate (TCAI) donor **4.1f**. Over the course of this study, we noticed that moderate selectivity and yield of **4.3** obtained in the TMSOTf-promoted activation of TCAI donor **4.1f** (α/β = 5.9/1, 44%, entry 6) could be significantly enhanced by performing the activation in the presence of TfOH instead. In the latter case disaccharide **4.3** was isolated in 92% yields and high α-selectivity (α/β = 9.7/1, entry 7). This was the highest stereoselectivity observed in this series of experiments, but it also indicated that the S-ethyl leaving group used in our original study remains the best for the purpose of HAD.

As a rationale for lower selectivity observed with other leaving groups we propose the following. In case of S-aryl glycosides, the sulfur atom is less nucleophilic than that of their S-ethyl counterparts. Therefore, interaction of the S-aryl glycosides with DMTST is sluggish and as a result, excess DMTST would begin interfering with the picoloyl nitrogen making it unavailable to perform HAD. A similar reduction of selectivity was previously observed even with S-ethyl glycosides if a large excess of DMTST (6 equiv.) was used.[6] In case of O/S-imidates, the basis for the reduced

selectivity is arguably different. It is our assumption that the presence of the additional N-atom of the leaving group, and as a result additional *H*-bond acceptor sites, might be the reason for decreased stereoselectivity recorded with glycosyl imidates. This effect is particularly strong in case of the SBox leaving group, which is activated by the direct pathway *via* the anomeric sulfur.[11,12] This leaves the nitrogen atom of the leaving group available to form the undesirable H-bond with glycosyl acceptor. In turn, this effect is weakened in case of STaz and TCAI, which are activated *via* the remote N-atom.[12-14] A lower selectivity in case of STaz in comparison to that of TCAI could be related due to the complexation of Ag(I) used for the activation of STaz with picoloyl nitrogen making it less effective in conducting efficient HAD.

Scheme 4.2. Bromine-promoted activation of thioglycosides.[15]



Having concluded that the S-ethyl is the best leaving group for reactions *via* HAD, it came to our attention that another approach for α-glucosylation recently introduced by our laboratory was also based on the S-ethyl leaving group.[15] From this study we have demonstrated that ethyl thioglycosides activated with bromine provide exclusive α-stereoselectivity in glucosylations. In case of S-ethyl glycosides equipped with the superdisarming protecting group pattern (2-*O*-benzyl-3,4,6-tri-*O*-benzoyl)[16] these bromine-mediated reactions proceed *via* the highly reactive 1,2-*trans* bromide

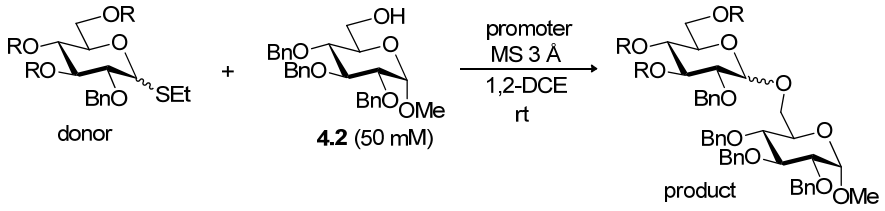
intermediate while 1,2-*cis* bromide remains unreactive (Scheme 4.2). Since the 1,2-*trans* bromide is the only intermediate leading to products, and the displacement is performed in the concerted bimolecular fashion, this reaction gives exclusive α-stereoselectivity.[15]

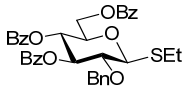
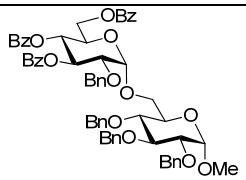
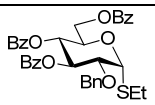
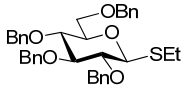
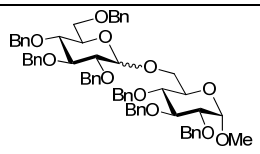
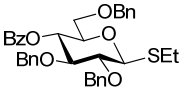
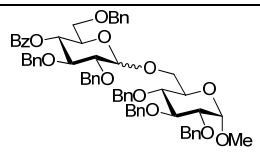
For instance, 2-*O*-benzyl-3,4,6-tri-*O*-benzoyl thioglycoside **β-4.10** was coupled with acceptor **4.2** in the presence of bromine to afford disaccharide **4.11** with exclusive 1,2-*cis* selectivity (entry 1, Table 4.3). The low yield of 28% was due to the fact that **β-4.10** forms predominantly α-bromide (~68%), which is unable to react under these reaction conditions. As a result, β-bromide is formed in ~32%; it gave the disaccharide in 28%, with the remaining 4% accounting for the concomitant isomerization into the α-bromide. We were able to enhance the utility of this reaction by using glycosyl donor **α-4.10**, which, upon reaction with bromine, produced the β-bromide predominantly. As a result, disaccharide **4.11** was obtained in a good yield of 67% and with exclusive α-selectivity (entry 2). The yield could be further improved by using $HgBr_2$ as the co-promoter and in this case disaccharide **4.11** was isolated in 86% yield (entry 3). However, the stereoselectivity dropped unremarkably (α/β = 8.0/1) because mercury(II) salts can readily activate α-bromides (Helferich conditions).[17]

Other more reactive thioglycosides, such as the standard armed thioglycoside donor **4.12**,[18] failed to produce high levels of stereoselectivity. This is because per-*O*-benzylated α-bromide is sufficiently reactive to produce glycosides, and it does so with scrambled selectivity. Thus, coupling of glycosyl donor **4.12** with acceptor **4.2** in the presence of Br_2 produced disaccharide **4.13** in 68% yield and poor selectivity (α/β = 2.4/1, entry 4). The glycosidation of the 4-*O*-benzoylated donor **4.14** with acceptor **4.2**

was even less selective and disaccharide **4.15** was produced in 75% yield and α/β = 1/1.8 (entry 5).

Table 4.3. Bromine-mediated activation of different S-ethyl donors.



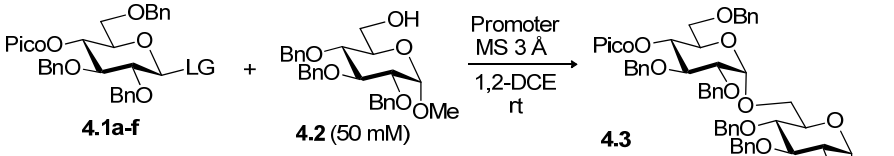
Entry	*Donor*	*Conditions*[a]	*Product*	*Yield, α/β ratio*
1[15]	 **β-4.10**	Br_2, 16 h	 **4.11**	28%, α only
2[15]	 **α-4.10**	Br_2, 16 h	**4.11**	67%, α only
3[15]	**α-4.10**	$Br_2/HgBr_2$, 5 h	**4.11**	86%, 8.0/1
4	 **4.12**	Br_2, 0.25 h	 **4.13**	68%, 2.4/1
5	 **4.14**	Br_2, 16 h	 **4.15**	75%, 1/1.8

[a] Br_2 (1equiv.) or $Br_2/HgBr_2$ (1/1 equiv.) was used

The series of results presented in Table 4.3 clearly demonstrated that bromine-mediated activation of thioglycosides offers a promising method for the synthesis of α-glucosides. However, notable limitations including modest yields and high substrate specificity (only works for superdisarmed α-thioglycoside) limit the application of this very highly stereoselective method. Having also encountered some limitations of the

HAD approach, we wondered whether combining these two promising techniques would allow us to develop a more flexible and a well-rounded methodology for α-glycosylation. With this idea in mind, a test glycosylation reaction of 4-picoloylated thioglycoside donor **4.1a** with glycosyl acceptor **4.2** in the presence of Br_2 produced disaccharide **4.3** in 77% yield and complete α-selectivity (entry 1, Table 4.4). The use of $HgBr_2$ as an additive further enhanced the yield to 83% and the stereoselectivity still remained complete (entry 2). Both reactions were performed under normal dilution (50 mM of **4.3**), conditions which DMTST-promoted activation of **4.1a** gave very low selectivity (entry 3).[6] In our opinion this is because the H-bonded acceptor is in competition with the free acceptor in

Table 4.4. Effect of the leaving group on Br_2 activation.



4.1a: LG = SEt; **4.1b**: LG = SPh; **4.1c**: LG = STol;
4.1d: LG = SBox; **4.1e**: LG = STaz; **4.1f**: LG = OTCAI

Entry	*Donor*	*Conditions*	*Yield, α/β ratio*
1	**4.1a**	Br_2, 4.5 h	77%, α only
2	**4.1a**	$Br_2/HgBr_2$, 2 h	83%, α only
3	**4.1a**	DMTST, 4 h	85%, 2.8/1
4	**4.1b**	Br_2, 5.5 h	72%, α only
5	**4.1b**	$Br_2/HgBr_2$, 3 h	79%, α only
6	**4.1c**	Br_2, 16 h	70%, α only
7	**4.1c**	$Br_2/HgBr_2$, 16 h	86%, α only
8	**4.1d**	Br_2, 16 h	71%, α only
9	**4.1e**	Br_2, 16 h	87%, α only
10	**4.1f**	Br_2, 0.5 h	89%, 18/1

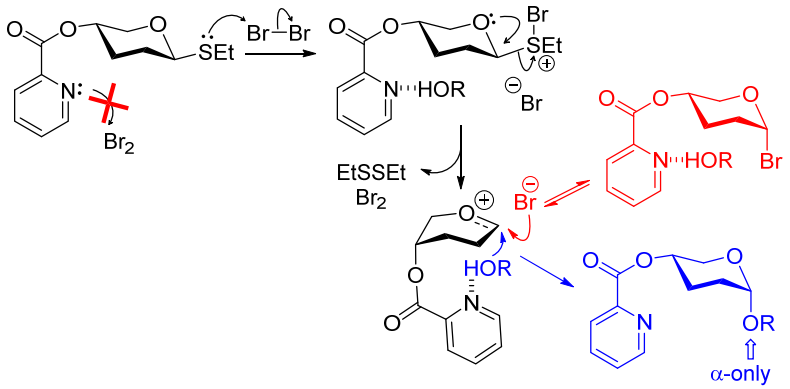
solution. This issue was addressed by using high dilution conditions, mandatory for most reactions using HAD.[6] The result with bromine-promoted activation indicates that HAD

reactions can now be successfully conducted under normal dilution conditions. Encouraged by this intriguing finding, we decided to reinvestigate other glycosyl donors **4.1b-f**, which were found less compatible with HAD due to lower selectivity (*vide supra*). To our delight, both thioglycoside (**4.1b** and **4.1c**) and thioimidate (**4.1d** and **4.1e**) glycosyl donors produced disaccharide **4.3** in high yields of 72-87% and complete 1,2-*cis* selectivity in each case (entries 4-9, Table 4.4). The highly reactive trichloroacetimidate donor **4.1f** also gave high α-selectivity upon activation with Br_2, although the stereoselectivity was slightly lower (α/β = 18/1, entry 10) than that obtained with more stable donors (*vide supra*). The high α-selectivity obtained from all 4-*O*-picoloylated glycosyl donors **4.1a-f** indicates that, unlike previously tested promoter systems, bromine-promoted glycosylations are less sensitive to the nature of the leaving group. These results also indicate that bromine may serve as a convenient and inexpensive promoter for a variety of glycosylation reactions. Some of the leaving groups tested here have never been previously activated with bromine.

A low temperature (-40 °C) NMR monitoring of the reaction of glycosyl donor **4.1a** with Br_2 showed direct and rapid formation of α-bromide. However, we cannot yet exclude the possibility of the partial formation of β-bromide at the beginning of the reaction, in the highly benzylated system, which very rapidly equilibrates into a more thermodynamically stable α-bromide. Therefore, the β-bromide intermediate would be a very insignificant intermediate en route to glycoylation products. This type of bromide is reactive under these reaction conditions, as seen from experiments with perbenzylated and 4-benzoyl thioglycosides **4.12** and **4.14**, respectively (Table 4.3). In case of 4-picoloylated glycosyl donor, bromide leaving group departs and the HAD kicks in to

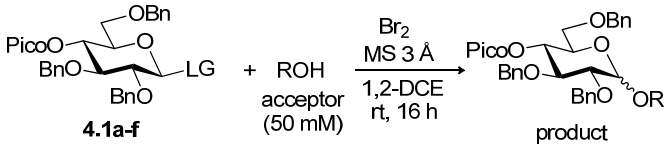
deliver the nucleophile from the bottom face (Scheme 4.3). Minimal formation of other electrophilic species in bromine-promoted HAD maybe the key for success of this method unlike in case with DMTST wherein excess promoter may interfere with the hydrogen bond acceptor.

Scheme 4.3. Cooperative use of bromine-promoted activation and HAD.

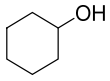
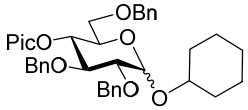
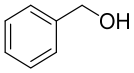
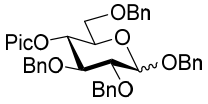
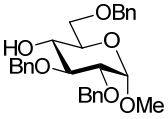
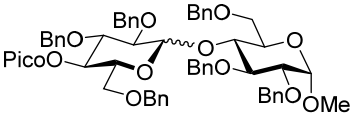
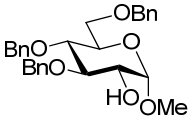
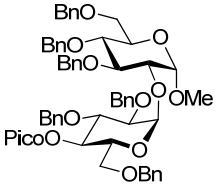
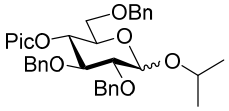


Since all 4-O-picoloylated glycosides gave high 1,2-*cis* selectivity upon coupling with primary acceptor **4.2** in the presence of Br_2, we attempted to expand the approach to different acceptors. Although a vast majority of reactions proceeded with high selectivites and yields (Table 4.5), we noticed some unusual trends. For instance, glycosyl donor **4.1a** was practically ineffective when reacted with secondary glycosyl acceptors, even in the presence of $HgBr_2$. Interestingly, S-phenyl donor **4.1b** could be efficiently coupled both with primary and secondary glycosyl acceptors. Most reactions produced high yields and very high 1,2-*cis* selectivity (entries 4-7). Meanwhile, coupling of glycosyl donors **4.1c-f** provided comparable results and consistently high α-selectivities (entries 8-11).

Table 4.5. Probing the scope and limitations of Br_2-promoted HAD.



4.1a: LG = SEt; **4.1b**: LG = SPh; **4.1c**: LG = STol;
4.1d: LG = SBox; **4.1e**: LG = STaz; **4.1f**: LG = OTCAI

Entry	*Donor*	*Acceptor*	*Product (yield, α/β ratio)*
1	**4.1a**	 **4.16**	 **4.17** (49%, 21/1)
2	**4.1a**	 **4.18**	 **4.19** (51%, 17.1/1)
3	**4.1a**	 **4.8**	 **4.9** (<10%)
4	**4.1b**	**4.8**	**4.9** (60%, α only)
5	**4.1b**	 **4.4**	 **4.5** (72%, α only)
6	**4.1b**	**4.18**	**4.19** (60%, 18.2/1)
7	**4.1b**	 **4.20**	 **4.21** (47%, 13/1)
8	**4.1c**	**4.16**	**4.17** (68%, 19.3/1)
9	**4.1d**	**4.4**	**4.5** (43%, α only)
10	**4.1e**	**4.4**	**4.5** (58%, α only)
11	**4.1f**	**4.4**	**4.5** (78%, >21/1)[a]

[a] reaction was completed in 2.5 h

4.3. Conclusions

We have expanded the HAD concept to different 4-*O*-picoloylated glycosyl donors with widely used leaving groups including SPh, STol and S/O-imidates to study the compatibility of the aforementioned method with various leaving groups and promoter systems. Having investigated a variety of promoter systems we determined the superior properties of Br_2 as promoter for HAD. Very high selectivities and acceptable yields have been recorded in most cases with all classes of glycosyl donors at room temperature. All bromine-promoted reactions have been performed under regular dilution (50 mM concentration of the acceptor) unlike other promoter systems that would mainly work under the high dilution conditions (5 mM). In our opinion, the bromine-promoted HAD enhances the utility of the two previously developed techniques, HAD[6] and bromine-assisted glycosidation of thioglycosides,[15] by complementing each other. The utility of this method that allows to reduce the amount of the reaction solvent by ten-fold should not be underestimated, particularly in cases of the large-scale or industrial preparations of α-glucosides.

4.4. Experimental Section

4.4.1. General Remarks

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 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. AgOTf was co-evaporated with toluene (3 x 10 mL) and dried *in vacuo* for 2-3 h directly prior to application. Optical rotations were measured at 'Jasco P-1020' polarimeter. Unless noted otherwise, ^{1}H NMR spectra were recorded in $CDCl_3$ at 300, 500 or 600 MHz, ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 or 125 MHz.

4.4.2. Synthesis of Glycosyl Donors

Ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (4.1a). The title compound was synthesized according to the reported procedure and the analytical data for **4.1b** was essentially the same as reported previously.[6]

Phenyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (4.1b). To a solution of phenyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[19] (0.50 g, 0.92 mmol) in CH_2Cl_2 (10 mL) picolinic acid (0.23 g, 1.84 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.38 g, 1.84 mmol), and 4-dimethylaminopyridine (23 mg, 0.19 mmol) were added at rt. The reaction mixture was stirred 30 min under argon and the solid was filtered off. The filtrate was diluted with CH_2Cl_2 (100 mL) and washed with brine solution (2x10 mL), 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 give the title compound as a white solid in 94% yield (0.56 g, 0.87 mmol). Analytical data for **4.1b**: R_f = 0.44 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ -38.7 (*c* = 1.0, $CHCl_3$); ^{1}H

NMR: δ, 3.62 (dd, 1H, $J_{2,3}$ = 8.8 Hz, H-2), 3.64-3.70 (m, 2H, H- 6a, 6b), 3.89 (m, 1H, H-5), 3.94 (dd, 1H, $J_{3,4}$ = 8.9 Hz, H-3), 4.48 (s, 2H, CH_2Ph), 4.73 (dd, 2H, ^2J = 11.2 Hz, CH_2Ph), 4.76 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 4.81 (dd, 2H, ^2J =10.3 Hz, CH_2Ph), 5.40 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 7.00-8.00 (m, 23H, aromatic), 8.72 (d, 1H, J = 3.1 Hz, aromatic) ppm; ^{13}C NMR: δ, 69.7, 72.3, 73.6, 75.7 (×2), 77.5, 80.8, 84.0, 87.6, 125.7, 127.2, 127.6, 127.7, 127.8 (×2), 128.1 (×3), 128.3 (×5), 128.5 (×2), 128.6 (×2), 129.1 (×2), 132.1 (×2), 133.6, 137.1, 138.0 (×2), 138.1, 147.6, 150.0, 164.3 ppm. HR FAB MS $[M+H]^+$ calcd for $C_{39}H_{38}NO_6S$ 648.2420, found 648.2437.

Tolyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (4.1c). To a solution of tolyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[20] (0.50 g, 0.90 mmol) in CH_2Cl_2 (10 mL) picolinic acid (0.22 g, 1.80 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.37 g, 1.80 mmol), and 4-dimethylaminopyridine (22 mg, 0.18 mmol) were added at rt. The reaction mixture was stirred for 30 min under argon and the solid was filtered off. The filtrate was diluted with CH_2Cl_2 (100 mL) and washed with brine solution (2x10 mL), 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 give the title compound as a white solid in 96% yield (0.57 g, 0.86 mmol). Analytical data for **4.1c**: R_f = 0.44 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]_D^{25}$ -38.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 2.30 (s, 3H, CH_3), 3.59 (dd, 1H, $J_{2,3}$ = 8.9 Hz, H-2), 3.85 (m, 1H, H- 5), 3.93 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 4.47 (s, 2H, CH_2Ph), 4.69 (d, 1H, $J_{1,2}$ =9.8 Hz, H-1), 4.71 (dd, 2H, ^2J = 11.1 Hz, CH_2Ph), 4.81 (dd, 2H, ^2J =10.4 Hz, CH_2Ph), 5.38 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 6.90-8.15 (m, 22H, aromatic), 8.12 (d, 1H, J = 3.9 Hz, aromatic) ppm; ^{13}C

NMR: δ, 21.2, 69.6, 72.2, 73.5, 75.6 (×2), 77.4, 80.7, 83.9, 87.7, 125.6, 127.1, 127.4, 127.6, 127.7 (×2), 127.9 (×2), 128.2 (×5), 128.5 (×2), 128.7 (×2), 129.4, 129.8 (×2), 132.8 (×2), 137.0, 137.9 (×2), 138.0, 138.1, 147.5, 149.9, 164.2 ppm. HR FAB MS $[M+H]^+$ calcd for $C_{40}H_{40}NO_6S$ 662.2576, found 662.2539.

Benzoxazolyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (4.1d). The solution of **4.1a** (0.50 g, 0.83 mmol) and activated molecular sieves 3Å (0.42 g) in CH_2Cl_2 (12.6 mL) was stirred under an atmosphere of argon for 1 h. Freshly prepared solution of Br_2 in CH_2Cl_2 (8.0 mL, 1/165, v/v) was then added and the reaction mixture was kept for 10 min at rt. After that, CH_2Cl_2 was evaporated off under reduced pressure at rt and dried under high vacuum for 3 h. Crude residue was then treated with KSBox (0.47 mmol) in dry acetone (10.0 mL) under an atmosphere of argon for 2 h at rt. Upon completion, the mixture was diluted with toluene, the solid was filtered-off and the residue was washed with toluene. The combined filtrate (90 mL) was washed with 1% aq. NaOH (15 mL) and water (3x10 mL), the organic layer was separated, dried with $MgSO_4$, and concentrated in *vacuo*. The residue was purified by silica gel (ethyl acetate/ hexane gradient elution) to give the title compound as pale yellow syrup in 82% yield (0.47 g, 0.68 mmol). Analytical data for **4.1d**: R_f = 0.42 (ethyl acetate/hexane, 3/2, v/v); $[\alpha]_D^{23}$ +42.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.75- 3.87 (m, 2H, H- 6a, 6b), 4.02 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 4.12- 4.23 (m, 2H, H- 3,5), 4.55 (dd, 2H, , ^2J = 11.9 Hz, CH_2Ph), 4.90 (dd, 2H, ^2J = 11.2 Hz, CH_2Ph), 4.98 (dd, 2H, ^2J = 10.6 Hz, CH_2Ph), 5.65 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.68 (dd, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 7.15- 7.98 (m, 21H, aromatic), 8.12 (d, 1H, *J* = 7.8 Hz, aromatic), 8.87 (d, 1H, *J* = 4.6 Hz, aromatic) ppm; ^{13}C NMR: δ, 69.1,

71.9, 75.6, 75.7, 75.9, 78.3, 80.6, 84.0, 84.9, 110.3, 119.2, 124.5, 124.6, 125.7, 127.2, 127.5, 127.8, 127.9 (×2), 128.2 (×3), 128.3 (×2), 128.4 (×2), 128.5 (×2), 128.6 (×2), 137.1, 137.5, 137.9 (×2), 142.0, 147.6, 150.1, 152.0, 161.5, 164.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{40}H_{36}O_7N_2SNa$ 711.2141, found 711.2164.

2-Thiazolinyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (4.1e). The solution of **4.1a** (0.50 g, 0.83 mmol) and activated molecular sieves 3 Å (0.42 g) in CH_2Cl_2 (12.6 mL) was stirred under an atmosphere of argon for 1 h. Freshly prepared solution of Br_2 in CH_2Cl_2 (8.0 mL, 1/165, v/v) was then added and the reaction mixture was kept for 5 min at rt. After that, CH_2Cl_2 was evaporated off under reduced pressure at rt and dried in the high vacuum for 3 h. Crude residue was then treated with NaSTaz (0.35 g, 2.5 mmol) in dry acetonitrile (10.0 mL) under an atmosphere of argon for 3½ h at rt. Upon completion, the solvent was evaporated under high *vacuo,* the residue was diluted with CH_2Cl_2 and, the solid was filtered-off. The residue was washed with CH_2Cl_2. The combined filtrate (90 mL) was washed with 1% aq. NaOH (15 mL) and water (3x10 mL), the organic layer was separated, dried with $MgSO_4$, and concentrated in *vacuo*. The residue was purified by silica gel (ethyl acetate/ hexane gradient elution) to give the title compound as a colorless syrup in 84% yield (0.46 g, 0.70 mmol). Analytical data for **4.1e**: R_f = 0.45 (acetone/toluene, 1/4, v/v); $[\alpha]_D^{23}$ +42.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.32 (t, 2H, *J* = 8.1 Hz, SCH_2), 3.58- 3.68 (m, 2H, H- 6a, 6b), 3.71 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2), 3.94 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 3.95 (m, 1H, H-5), 4.03- 4.28 (m, 2H, NCH_2), 4.46 (s, 2H, C*H*$_2$Ph), 4.71 (dd, 2H, ^2J = 11.3 Hz, C*H*$_2$Ph), 4.78 (dd, 2H, ^2J = 10.2 Hz, C*H*$_2$Ph), 5.34 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 5.43 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 6.95- 8.00

(m, 18H, aromatic), 8.70 (d, 1H, J = 4.7 Hz, aromatic) ppm; ^{13}C NMR: δ, 35.2, 64.3, 69.2, 72.0, 73.5, 75.6, 75.8, 77.8, 80.7, 83.9, 84.8, 125.7, 127.2, 127.5, 127.7, 127.9 (×2), 128.1 (×2), 128.2 (×23), 128.3 (×4), 128.6 (×2), 129.2, 129.9, 137.1, 137.6, 137.9, 138.0, 147.6, 150.0, 164.1 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{36}H_{36}O_6N_2S_2Na$ 679.1912, found 679.1943.

2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-β-D-glucopyranosyl trichloroacetimidate (4.1f). To a stirred solution of **4.1a** (0.5 g, 0.84 mmol) in CH_2Cl_2 (10 mL), water (0.5 mL) and $Hg(CF_3CO_2)_2$ (0.7 g, 1.67 mmol) were added at 0 °C and the resulting mixture was stirred 1 hr at that temperature. Then the reaction mixture was removed from the ice bath and stirred at rt overnight. Thereafter, the reaction mixture was diluted with CH_2Cl_2 (~100 mL) and washed with sat. $NaHCO_3$ (10 mL), and water (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 (ethylacetate/ hexane gradient elution) to afford 2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-D-glucopyranose (**4.22**) as a colorless syrup in 87% yield (0.41 g, 0.74 mmol). Analytical data for **4.22** R_f = 0.38 (acetone/toluene, 3/7, v/v); ^{1}H NMR of **α-4.22**: δ, 3.47-3.63 (m, 3H, H-5, 6a, 6b), 3.82-3.95 (m, 2H, H-3, 5), 4.44 (d, 1H, $J_{1,2}$ =9.7 Hz, H-1), 4.55- 5.03 (m, 6H, 3 CH_2Ph), 5.35 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 7.00-8.80 (m, 19H, aromatic) ppm; ^{1}H NMR of **β-4.22**: δ, 3.68 (dd, 1H, d, 1H, $J_{1,2}$ =3.4 Hz, $J_{2,3}$ = 9.4 Hz H-2), 4.28- 4.51 (m, 4H, H-3, 5, 6a, 6b), 4.55- 5.03 (m, 6H, 3 CH_2Ph), 5.25- 5.44 (m, 2H, H-1, 4), 7.00- 8.80 (m, 19H, aromatic) ppm; Selected ^{13}C NMR data for **4.22**: δ, 68.6, 69.1, 69.5, 72.3, 73.0, 73.3, 73.6, 73.7,

74.9, 75.4, 75.5, 79.1 (×2), 80.0, 81.7, 83.0, 91.5, 97.6 ppm. HR FAB MS $[M+H]^+$ calcd for $C_{33}H_{34}NO_7$ 556.2335, found 556.2317.

To a solution of **4.22** (0.41 g, 0.74 mmol) in CH_2Cl_2 (5 mL) trichloroacetonitrile (0.22 mL, 2.21 mmol), K_2CO_3 (0.20 g, 1.48 mmol) were added at rt. The reaction mixture was stirred overnight under argon and the solid was filtered off. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (acetone/ toluene gradient elution) to give the title compound as a white solid in 64% yield (0.33 g, 0.47 mmol). Analytical data for **4.1f**: R_f = 0.43 (acetone/ toluene, 3/7, v/v); $[\alpha]_D^{25}$ -38.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.57-3.74 (m, 2H, H- 6a, 6b), 3.85 (dd, 1H, $J_{2,3}$ = 8.0 Hz, H-2), 3.93-4.04 (m, 2H, H-3, 5), 4.47 (s, 2H, CH_2Ph), 4.71 (dd, 2H, ^2J = 11.4 Hz, CH_2Ph), 4.84 (dd, 2H, ^2J = 10.8 Hz, CH_2Ph), 5.48 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 5.87 (d, 1H, $J_{1,2}$ =7.9 Hz, H-1), 6.95- 8.05 (m, 17H, aromatic), 8.74 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 68.9, 71.8, 73.5, 74.4, 75.3, 79.2, 81.0, 81.7, 91.0, 98.3, 127.2, 127.6 (×2), 127.9 (×2), 128.1 (×2), 128.2 (×2), 128.3 (×4), 128.6 (×2), 128.7, 129.2, 137.2, 138.0 (×2), 138.1, 147.5, 149.9, 161.3, 164.1 ppm. HR FAB MS $[M+Na]^+$ calcd for $C_{35}H_{33}O_7N_2Cl_3Na$ 721.1251, found 721.1289.

4.4.3. Synthesis of oligosaccharides

General procedure for glycosylation in the presence of DMTST. A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $ClCH_2CH_2Cl$ (26 mL, 5 mM) was stirred under argon for 1 h. The mixture was then cooled to -30 °C and DMTST (0.26 mmol) was added. The resulting mixture was allowed to warm to rt over a period of 1 h and stirreed at rt for the

time specified in Schemes. Upon completion, Et_3N (0.3 mL) was added and the resulting mixture was stirred for 30 min. The mixture was diluted with CH_2Cl_2 (10 mL), the solid was filtered off, and the residue was washed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 20% aq. $NaHCO_3$ (10 mL) and water (3 x 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). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^1H NMR spectra.

General procedure for glycosylation in the presence of AgOTf. A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $ClCH_2CH_2Cl$ (26 mL, 5 mM) was stirred under argon for 1 h. The mixture was then cooled to -30 °C and AgOTf (0.26 mmol) was added. The resulting mixture was allowed to warm to rt over a period of 1 h and stirreed at rt for the time specified in Schemes. Upon completion, Et_3N (0.3 mL) was added and the resulting mixture was stirred for 30 min. The mixture was diluted with CH_2Cl_2 (10 mL), the solid was filtered off, and the residue was washed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 20% aq. $NaHCO_3$ (10 mL) and water (3 x 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). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^1H NMR spectra.

General procedure for glycosylation in the presence of TMSOTf (or TfOH). A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $ClCH_2CH_2Cl$ (26 mL, 5 mM) was stirred under argon for 1 h. The mixture was then cooled to -30 °C and TMSOTf (or TfOH, 0.07 mmol) was added. The resulting mixture was allowed to warm to rt over a period of 1 h and stirreed at rt for the time specified in Schemes. Upon completion, Et_3N (0.3 mL) was added and the resulting mixture was stirred for 30 min. The mixture was diluted with CH_2Cl_2 (10 mL), the solid was filtered off, and the residue was washed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 20% aq. $NaHCO_3$ (10 mL) and water (3 x 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). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^1H NMR spectra.

General procedure for glycosylation in the presence of Br_2. A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in $ClCH_2CH_2Cl$ (26 mL, 5 mM) was stirred under argon for 1 h. Then Br_2 (0.14 mmol) was added and the resulting mixture was stirreed at rt for 2- 24 hrs as specified in Tables. Upon completion, mixture was diluted with CH_2Cl_2 (10 mL), the solid was filtered off, and the residue was washed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 20% aq. $NaHCO_3$ (10 mL) and water (3 x 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). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

General procedure for glycosylation in the presence of Br_2/ $HgBr_2$. A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in $ClCH_2CH_2Cl$ (26 mL, 5 mM) was stirred under argon for 1 h. Then Br_2 (0.14 mmol) was added and stirreed at rt for 15 minuites. Thereafter, mercury (II) bromide ($HgBr_2$, 0.14 mmol) was added and the resulting mixture was stirred for the time specified in Schemes. Upon completion, mixture was diluted with CH_2Cl_2 (10 mL), the solid was filtered off, and the residue was washed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 20% aq. $NaHCO_3$ (10 mL) and water (3 x 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). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (4.3). The title compound was obtained as a white solid from 4-*O*-picoloylated glycosyl donors and acceptor **4.2** in yields and

stereoselectivity as listed in tables. Analytical data for **4.3** was in accordance with that reported previously.[6]

Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (4.5). The title compound was obtained as a white solid from 4-*O*-picoloylated glycosyl donors and acceptor **4.4** in yields and stereoselectivity as listed in tables. Analytical data for **4.5** was in accordance with that reported previously.[6]

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (4.9). The title compound was obtained as a white solid from 4-*O*-picoloylated glycosyl donors and acceptor **4.8** in yields and stereoselectivity as listed in table (5 mM). Analytical data for **4.9** was in accordance with that reported previously.[6]

Cyclohexyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranoside (4.17). The title compound was obtained from Br_2 activation method as colorless syrup from 4-*O*-picoloylated glycosyl donors and cyclohexanol, **4.16** (50 mM), in yields and stereoselectivity as listed in Table 4.5. Analytical data for **4.17**: R_f = 0.58 (acetone/ toluene, 1/4, v/v); ^{1}H NMR: δ, 1.05-2.10 (m, 10H, OC_6H_{10}), 3.50-3.62 (m, 3H, H- 6a, 6b, OCH), 3.65 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.19 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 4.23 (m, 1H, H-5), 4.46 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.72 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.84 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 4.96 (d, 1H, $J_{1,2}$ =3.7 Hz, H-1), 5.42 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-

4), 6.95- 8.15 (m, 18H, aromatic), 8.74 (m, 1H, J = 3.9 Hz, aromatic) ppm; ^{13}C NMR: δ, 24.4, 24.7, 25.8, 31.7, 33.7, 68.7, 69.1, 72.4, 73.4, 73.7, 75.5, 76.2, 79.5, 80.0, 95.3, 125.9, 127.2, 127.4, 127.5, 127.9 (×2), 128.0 (×2), 128.1, 128.3 (×6),), 128.6 (×2), 137.3, 138.1, 138.4, 138.8, 147.8, 149.9, 164.2 ppm. HR FAB MS $[M+H]^+$ calcd for $C_{39}H_{44}O_7N$ 638.3118, found 638.3097.

Benzyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranoside (4.19). The title compound was obtained from Br_2 activation method as colorless syrup from 4-*O*-picoloylated glycosyl donors and benzyl alcohol, **4.18** (50 mM), in yields and stereoselectivity as listed in Table 4.5. Analytical data for **4.19**: R_f = 0.55 (acetone/ toluene, 1/4, v/v); ^{1}H NMR: δ, 3.48-3.55 (m, 2H, H- 6a, 6b), 3.64 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.14 (m, 1H, H-5), 4.21(dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 4.45 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.50- 4.77 (m, 5H, 2 ½ CH_2Ph), 4.80- 4.90 (m, 2H, H- 1, ½ CH_2Ph), 5.42 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 7.05- 8.10 (m, 23H, aromatic), 8.72 (d, 1H, J = 4.1 Hz, aromatic) ppm; ^{13}C NMR: δ, 68.9, 69.0, 69.4, 72.1, 73.4, 73.7, 75.6, 79.5, 79.9, 95.7, 125.8, 127.1, 127.5, 127.6, 128.0 (×3), 128.1 (×2), 128.2 (×3), 128.3 (×4), 128.6 (×4), 128.8 (×2), 137.1, 137.2, 138.0, 138.2, 138.6, 147.8, 149.9, 164.2 ppm. HR FAB MS $[M+H]^+$ calcd for $C_{40}H_{40}O_7N$ 646.2805, found 646.2841.

Isopropyl 2,3,6-Tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranoside (4.21). The title compound was obtained from Br_2 activation method as colorless syrup from 4-*O*-picoloylated glycosyl donor **4.1b** and isopropanol, **4.20** in 47% yield (α/β = 13/1). Analytical data for **4.21:** R_f = 0.57 (acetone/ toluene, 1/4, v/v); ^{1}H NMR: δ, 1.17 (m, 6H,

2 CH_3), 3.43-3.52 (m, 2H, H- 6a, 6b), 3.58 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.85 (m, 1H, OC*H*$(CH_3)_2$), 4.38 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.66 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.70 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 4.80 (d, 1H, $J_{1,2}$ =3.8 Hz, H-1), 5.37 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 6.90- 8.10 (m, 18H, aromatic), 8.68 (d, 1H, J = 3.5 Hz, aromatic) ppm; ^{13}C NMR: δ, 21.5, 23.5, 68.7, 69.0, 70.0, 72.3, 73.5, 73.7, 75.6, 79.6, 79.9, 95.4, 125.9, 127.1, 127.4, 127.5, 127.9 (×2), 128.0 (×2), 128.1, 128.3 (×4), 128.4 (×2), 128.7 (×3), 129.9, 137.3, 138.0, 138.4, 138.7, 149.9 ppm. HR FAB MS $[M+H]^+$ calcd for $C_{36}H_{40}O_7N$ 598.2805, found 598.2837.

4. 5. References

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CHAPTER 5

Development of picolinyl-based glycosyl donors with switchable stereoselectivity

5.1. Introduction

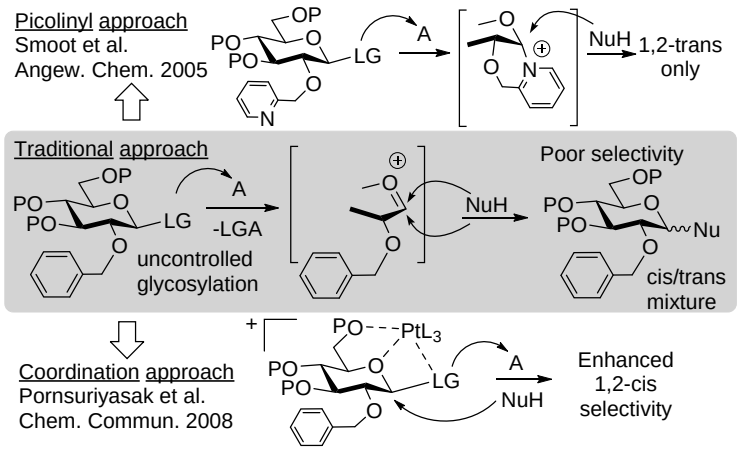
Current knowledge about the key roles of carbohydrates is still limited. However, thanks to the explosive growth of the field of glycobiology in recent years, we know that carbohydrates are involved in a broad range of vital biological processes.[1] Carbohydrates are also involved in many harmful processes and the fact that many of these processes are directly associated with pathogenesis of many if not all diseases has been particularly stimulating for major scientific efforts in the field of modern glycosciences.[2-4] It is already appreciated that a chemical or enzymatic synthesis[5] could lead to natural glycostructures for studying their composition,[6] conformation,[7] interaction with other molecules,[8] and determining their roles.[9] Also, only the synthetic approach can provide unnatural mimetics that are often of interest due to their therapeutic and diagnostic potential.[10] However, even with significant progress, the stereocontrolled chemical synthesis of complex carbohydrates remains difficult.

Complex carbohydrates consist of monomeric sugar units (e.g. glucose), which are connected *via* O-glycosidic linkages into elaborate oligosaccharide networks. A glycosylation reaction, a promoter/activator (A)-assisted monomolecular nucleophilic displacement of a leaving group (LG) of the glycosyl donor with a hydroxyl moiety of the glycosyl acceptor (NuH, Scheme 5.1) forms a new O-glycosidic linkage. Other reactive functional groups on both the donor and acceptor are temporarily masked with protecting groups (P) for the ease of the reaction control. Upon the leaving group departure, the flattened oxacarbenium ion is formed that often leads to anomeric mixtures.[11] Therefore, particular care has to be taken with regards to the stereoselectivity

of glycosylation. This requirement represents a major challenge in comparison to that of the synthesis of other natural biopolymers, peptides and nucleosides.

The aim of stereocontrolling of the glycosylation has been approached in a variety of ways and the anchimeric assistance effect of a neighboring acyl-type participating group has been widely used to obtain 1,2-*trans* glycosides.[12] Recently our group has expanded methods available for 1,2-*trans* glycosylation by developing neighboring 2-*O*-picolinyl (pyridylmethyl) participating group.[13,14] Thus, it has been demonstrated that the picolinyl-assisted glycosylation proceeds *via* the formal six-membered intermediate resulting in the formation of 1,2-*trans* glycosides with complete stereocontrol (Scheme 5. 1). The outcome of these reactions differs drastically from the effect of other ether-type substituents (benzyl) that are unable to provide anchimeric assistance and is typically limited to steric effect.

Scheme 5.1. Traditional method and recent enhancements.



Our group has also expanded methods available for 1,2-*cis* glycosylation, the topic that remains one of the challenges of modern glycosciences.[15] For instance, we demonstrated that metal coordination can have a noteworthy effect offering a significant

5-fold enhancement in 1,2-*cis* stereoselectivity in comparison to that obtained with conventional non-complexed counterparts.[16] Specifically engineered building blocks were designed to ensure that platinum(IV) complexation would hinder the top (*trans*) face of the sugar ring, hence helping to direct the nucleophilic attack to the opposite (*cis*) face (Scheme 5.1).

5.2. Results and Discussion

The main goal of this Chapter is the development of a novel method for stereocontrolled glycosylation. The study proposed herein is based on and is expected to complement other studies in this field that have been reported by our research group: picolinyl-assisted synthesis and the formation of transition metal complex intermediates en route to products of glycosylation.[14,16] A major driving force for developing of the study presented herein is to investigate whether the coordination chemistry tools can help to solve the long-standing challenge of stereoselective glycoside synthesis by means of metal complexation of carbohydrate ligands of enhanced affinity. It should be noted that the role of metal complexation in chemical glycosylation is practically unexplored because common oxygen-containing carbohydrates typically form unstable flexidentate complexes.[17,18] It was our expectation that targeted coordination can be achieved by the introduction of N-Lewis base substituents. Among other possibilities, the picolinyl group would be suitable for providing nitrogen atoms for subsequent complexation. This would allow us to obtain metal complexes with enhanced stability, which is the key to their ability to survive during the entire glycosylation process, hence providing the desired effects that may include enhanced stereocontrol.

As aforementioned, previous studies in our laboratory have clearly shown that 2-*O*-picolinyl protecting group can be used to provide complete 1,2-*trans* stereoselectivity of glycosylation. This is achieved *via* N-participation at the anomeric center. We conceptualize that if the nitrogen atom of the picolinyl moiety were temporarily blocked by coordination to the metal center, it would become unavailable to provide the anchimeric assistance in glycosylation and hence the stereoselectivity could be "switched". The anticipated significance of this approach would be the use of a single glycosyl donor for the synthesis of either 1,2-*cis* or 1,2-*trans* linkage on demand, a trait that is rather uncommon in glycosylation.

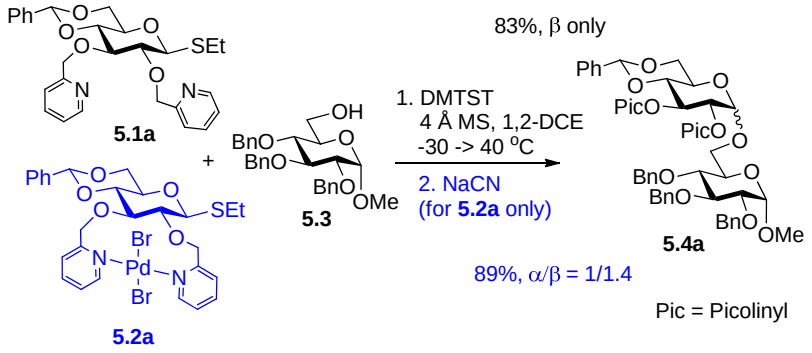
We assumed that the complexation of two picolinyl groups in the same molecule will open the oxacarbenium ion for the nucleophilic attack leading to the enhanced 1,2-*cis* selectivity. With the purpose of verifying the concept of switchable stereoselectivity, we obtained a range of building blocks bearing 2,3-di-*O*-picolinyl protection. In an unrelated study, we already refined methods for synthesizing building blocks equipped with remote picolinyl protecting groups.[19] This allowed for a straightforward synthesis of ethylthio glycosyl donor **5.1a** equipped with picolinyl groups at C-2 and C-3. We then attempted to obtain a Pd(II) complex of **5.1a**. The precedent of this type of complexation exists as our group has developed a number of concepts for temporary deactivation of sugar building blocks using $PdBr_2$ along with specifically developed series of leaving groups.[20,21]

Palladium metal complexes in general are promising candidates for these studies because their complexes with sugars form readily, are relatively stable and the complexation modes can be detected by spectral or crystallographic techniques. Indeed,

reaction of **5.1a** with $PdBr_2$ afforded the complex **5.2a** and, the structure of the latter was verified by X-ray crystallography (*vide infra*, refer to Figure 5.1), ultimately confirming that Pd (II) forms a bidentate *trans*-square planar complex with the two picolinyl groups.

Preliminary glycosidations of donors **5.1a** and **5.2a** with acceptor **5.3** have been performed in the presence of dimethyl(thiomethyl) sulfonium triflate (DMTST)[22] as a promoter of choice that does not interfere with picolinyl protecting groups.[14] Glycosidation of non-complexed donor **5.1a** gave the anticipated 1,2-*trans* stereoselectivity due to the participation of the 2-*O*-picolinyl group. Thus, disaccharide **5.4a** was obtained in 83% yield in complete β-selectivity (Scheme 5.2). A very different outcome was obtained with palladium(II) complex **5.2a** that showed a shift toward 1,2-*cis* selectivity: disaccharide **5.4a** was obtained in 89% yield as a mixture of diastereomers (α/β = 1/1.4, Scheme 5.2).

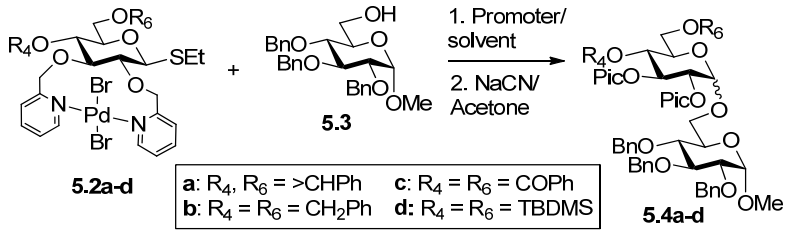
Scheme 5.2. Comparative glycosidation of donors 5.1a *vs.* 5.2a.



This set of results clearly proves the concept that the complexed picolinyl moiety is unable to provide participation at the anomeric center. In our opinion, this result also demands to search for conditions to enhance 1,2-*cis* stereoselectivity. Therefore, we envisaged further enhancements to emerge from studying common modes to enhance

stereoselectivity including protecting groups, reaction solvents, promoters, and leaving groups.[23] This search began with screening the protecting groups at C-4 and C-6 of the donor. While, for simplicity, the preliminary study was conducted with 4,6-*O*-benzylidene protected glycosyl donor **5.2a**, we wanted to study other protecting groups as well.

Table 5.1. Investigation of protecting groups, solvents, and promoters.



Entry	*Donor*	*Promoter (2 equiv.)*	*Solvent,* time*	*Temperature (°C)*	*Yield*	*Product*	*α/β ratio*
1	**5.2a**	DMTST	1,2-DCE, 24 h	-30 → 40	89%	**5.4a**	1/1.4
2	**5.2b**	DMTST	1,2-DCE, 6 h	-30 → 40	91%	**5.4b**	1/1.5
3	**5.2c**	DMTST	1,2-DCE, 6 h	-30 → 40	53%	**5.4c**	1/1.7
4	**5.2d**	DMTST	1,2-DCE, 7 h	-30 → rt	83%	**5.4d**	1/1.9
5	**5.2a**	DMTST	Toluene, 16 h	-5 → 40	85%	**5.4a**	1/1.6
6	**5.2a**	DMTST	Tol/Dxn, 16 h	-5 → 40	71%	**5.4a**	1.6/1
7	**5.2b**	DMTST	Tol/Dxn, 8 h	-5 → 40	84%	**5.4b**	1/1.2
8	**5.2a**	IDCP	Tol/Dxn, 48 h	-5 → 40	<5%	**5.4a**	n/a
9	**5.2b**	IDCP	Tol/Dxn, 8 h	-5 → 40	81%	**5.4b**	1.8/1
10	**5.2a**	NIS/TfOH	Tol/Dxn, 16 h	-5 → 40	76%	**5.4a**	1.9/1
11	**5.2b**	NIS/TfOH	Tol/Dxn, 16 h	-5 → 40	65%	**5.4b**	1/2.0

* - 1,2-DCE – 1,2-dichloroethane; Tol/Dxn - Toluene/1,4-Dioxane (1/3, v/v).

For this purpose we synthesized 4,6-di-*O*-benzyl and 4,6-di-*O*-benzoyl donors **5.2b** and **5.2c**, respectively. In addition, to investigate the effect of β-face shielding by

steric hindrance, particularly those at the C-6 position,[24-26] we synthesized glycosyl donor **5.2d** equipped with bulky O-*tert*-butyldimethylsilyl (TBDMS) groups. The result of this comparative study is summarized in Table 5.1 (entries 1-4). Unfortunately, the effect of the remote protecting group was very minor and although the respective disaccharides **5.4a-d** were isolated in 53-91% yield, stereoselectivity of glycosylations remained rather poor (α/β = 1/1.0-1.9).

The stereodirecting effect of different reaction solvents is often used to obtain enhanced stereoselectivity. As a rule of thumb, nitrile-type solvents are used to obtain equatorial and ether-type solvents to obtain axial glycosides.[27] In most part, this approach is limited to only marginal effect on stereoselectivity (although examples of significant enhancements are also known).[23] To explore the possible effect of reaction solvent, we decided to study the effect of toluene neat or in combination with 1,4-dioxane, the solvent mixture that was found the best amongst other ethereal solvents.[28] It should be noted that Pd-complexed thioglycosides **5.2a** and **5.2b** showed very poor solubility in other ethereal solvents such as diethyl ether and THF, either neat or in combination with 1,2-dichloroethane or toluene. Selected results of the solvent screening study for enhancing the 1,2-*cis* selectivity of Pd-complexed 2,3-di-picolinyl donors are summarized in the Table 5.1 (entries 5-7). A slight improvement of stereoselectivity was noted with both donors **5.2a** and **5.2b** using toluene-dioxane solvent mixture; therefore, we used this solvent system to perform the screening of various promoters.

The presence of the reactive picolinyl nitrogen atom limits the application of many common electrophilic promoters used for the activation of thioglycosides: iodonium(di-γ-collidine)perchlorate (IDCP), MeOTf, iodine, *N*-iodosuccinimide (NIS)

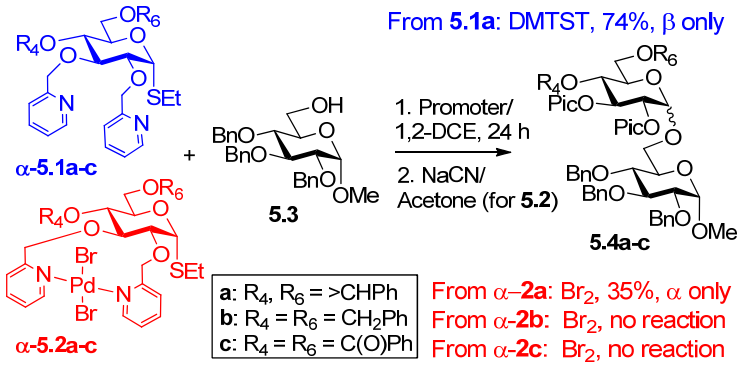
along with additives such as TfOH. That is because glycosyl donors turn into unreactive N^+E^- salts under practically all of these activation conditions.[14] However, we deemed that these promoters should be suitable for the activation of the precomplexed donors since the nucleophilic picolinyl nitrogen in these compounds is already blocked by metal coordination. This study will help us to establish the promoter stereoselectivity relationship and to understand the reactivity of metal coordinated building blocks in general. Thereby we have tested glycosidation of complexed donor **5.2a** in the presence of IDCP as the promoter in toluene/1,4-dioxane (1/3, v/v). This coupling only gave a trace amount of **5.4a** even after 48 h (entry 8), which was attributed to the disarming effect of 4,6-*O*-benzylidene group.[29] Indeed, similar coupling of the armed donor **5.2b** in the presence of IDCP in toluene/dioxane (1/3, v/v) was much more rapid, and the corresponding disaccharide **5.4b** was obtained in 81% yield in 8 h. However, no enhancement of stereoselectivity was detected (α/β = 1.8/1, entry 9). Expectedly a similar reaction in 1,2-dichloromethane gave even lower α-selectivity (the result is not shown). Glycosylations of **5.2a** and **5.2b** in the presence of NIS/ TfOH were uneventful and smoothly produced the respective disaccharides in good yields, but marginal selectivity (**5.4a**, α/β = 1.9/1, entry 10; **5.4b**, α/β = 1/2.0, entry 11).

In order to investigate possible leaving group involvement, we committed to a systematic study. However, the outcome of this study was somewhat disappointing. Although more reactive leaving groups such as O/S-imidates [30-32] that have already been tested and showed compatibility with 2-*O*-picolinyl derivatives and activation thereof,[14] we could not generate and purify the Pd complexes. In all cases, 2,3-di-picolinyl O/S-imidates gave inseparable mixtures of metal-sugar complexes, most likely due to the

presence of the additional N-atom in the leaving group. On the other hand, S-tolyl glycosides were too stable to undergo glycosylation at suitable reaction rates.

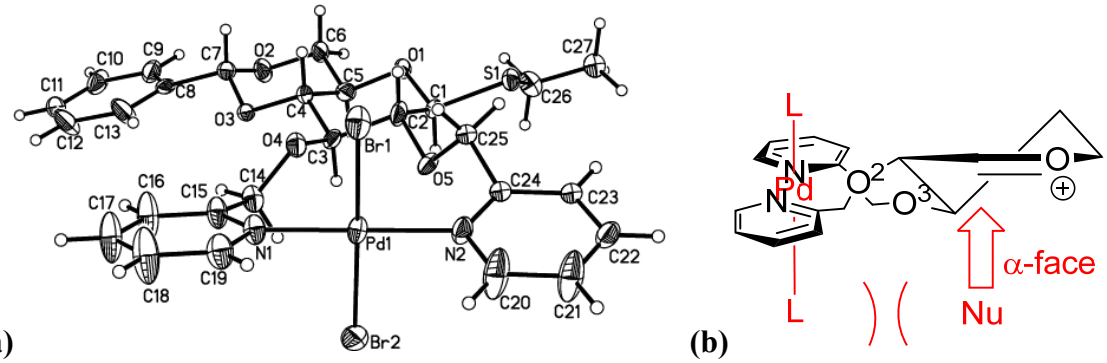
Overall, all traditional modes to enhance stereoselectivity did not give us the desired enhancement. As the last resort, we wanted to see whether Br_2-mediated glycosidation of 1,2-*cis* thioglycoside, a method recently developed in our laboratory, would help to achieve higher 1,2-*cis* stereoselectivity. The rationale for the enhanced stereoselectivity is that these reactions were found to proceed *via* a very reactive 1,2-*trans* bromide intermediate.[33] We anticipated that this approach would be advantageous herein, but the success of this reaction is truly dependent on our ability to generate a stable β-bromide and control its isomerization into its α-counterpart that would remain inert under these reaction conditions. Previously, this was accomplished with α-thioglycoside of the superdisarmed series, equipped with remote acyl substituents. With applying this approach to our system in mind, we have synthesized the 2,3-di-picolinyl-α-thioglycosides **α-5.1a-c**. Expectedly, glycosidation of these donors was completely β-stereoselective in the presence of DMTST. For instance, glycosidation of **α-5.1a** in the presence of DMTST (2 equiv.) gave disaccharide **5.4a** in 74% with exclusive β-stereoselectivity (Scheme 5.3).

Scheme 5. 3. Bromine-assisted glycosidation of complexed α-thioglycoside donors.



We then obtained Pd-complexed donors **α-5.2a-c** and to our delight the coupling of **α-5.2a** with **5.3** using Br_2 as the promoter gave disaccharide **5.4a** in 35% yield with complete 1,2-*cis* selectivity and α-bromide of the donor was isolated as the major byproduct. It should be emphasized that the stereoselectivity of this reaction was complete, and the poor yield reflect the accumulation of the α-bromide that is totally unreactive under these conditions. The rapid competing anomerization of reactive β-bromide into its stable α-counterpart is the reason that donors **α-5.2b** and **α-5.2c** failed to produce any of the anticipated disaccharides.

Figure 5.1. X-Ray crystal structure of 5.2a (a) and a possible reason why traditional modes to enhance α-selectivity fail (b).



5.3. Conclusions and Outlook

As a result of the extended screening of common conditions to enhance stereoselectivity we only managed to achieve very marginal variation of the reaction selectivities and yields. A very modest effect of toluene-dioxane, a known powerful 1,2-*cis*-directing solvent system should be particularly emphasized. It is possible that the *trans*-ligand square planar metal complex obtained from $PdBr_2$ hinders the access to the

α-face of the ring (Figure 5.1b). Some indication of this can be deducted from the X-ray crystal structure of **5.2a** (Figure 5.1a).

Certainly, bromine-mediated glycosylation helps to obtain enhanced stereoselectivity in these reactions because as proven by our prior mechanistic work the anomeric displacement of β-bromide follows the concerted bimolecular pathway. It is quite possible that the *trans*-ligand orientation is disadvantageous in general because the nucleophilic attack would be parallel in respect to the electron rich ligands. It is also possible that 2,3-dipicolinyl complexation restrains the conformational mobility of the ring, withdraws electron density from the carbohydrate, and may disfavor the bottom face of the oxacarbenium ion towards the nucleophilic attack. It is already appreciated that glycosyl donors in unusual conformations may have very unusual implications on the stereoselectivity and reactivity profile.[34] Further studies of the metal-assisted switching of anomeric stereoselectivity are currently underway in our laboratory.

5.4. Experimental Section

5.4.1. General Remarks

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 $ClCH_2CH_2Cl$ (1,2-DCE) and toluene 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 and dioxane were used as 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. AgOTf was co-evaporated with toluene (3 x 10 mL) and dried *in vacuo* for 2-3 h directly prior to application. Optical rotations were measured at 'Jasco P-1020' polarimeter. Unless noted otherwise, ^{1}H NMR spectra were recorded in $CDCl_3$ at 300, 500 or 600 MHz, ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 or 125 MHz.

5.4.2. Synthesis of Glycosyl Donors

Ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside (5.1a). To a solution of ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside[35] (1.0 g, 3.2 mmol) in DMF (10 mL) NaH (60% in mineral oil, 0.77 g, 19.2 mmol) and picolinyl bromide hydrobromide (3.2 g, 12.8 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h, quenched with ice-water (~10 mL, 30 min) and then extracted with ethyl acetate /diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~150 mL) was washed with cold water (3 × 30 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound as a white amorphous solid in 86% yield (1.3 g, 2.8 mmol). Analytical data for **1a**: R_f = 0.37 (ethyl acetate/hexane, 7/3, v/v); $[\alpha]_D^{20}$ -39.1 (c = 1.0, $CHCl_3$); ^{1}H-NMR: δ, 1.25 (t, 3H, J = 7.4 Hz, SCH_2CH_3), 2.71 (m, 2H, SCH_2CH_3), 3.45 (m, 1H, H-5), 3.52 (dd, 1H, $J_{2,3}$ = 8.3 Hz, H-2), 3.65-3.78 (m, 2H, H-4, 6a), 3.84 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.31 (dd, 1H, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 10.4 Hz, H-6b), 4.55 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.80- 5.08 (m, 4H, 2 CH_2Ph), 5.50 (s, 1H, >C*H*Ph), 6.90-7.65 (m, 11H, aromatic), 8.35-

8.55 (m, 2H, aromatic) ppm; ^{13}C-NMR: δ, 15.2, 25.1, 68.8, 70.2, 75.7, 76.5, 81.4, 82.0, 83.4, 85.7, 101.3, 121.6, 121.8, 122.3, 122.4, 126.1 (×2), 128.3 (×2), 129.1, 136.6(×2), 137.2, 148.8, 148.9, 158.2, 158.6 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{27}H_{31}N_2O_5S$ 495.1954, found 495.1982.

Ethyl 4,6-di-*O*-benzyl-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside (5.1b) To a stirring mixture of **5.1a** (0.50 g, 1.00 mmol) in CH_2Cl_2 (10 mL), water (150 μL) and trifluoroacetic acid (TFA)/CH_2Cl_2 (1/9, v/v, 1.0 mL) were added at rt. The reaction mixture was stirred for 3 h, neutralized with Et_3N (3 mL) and then diluted with dichloromethane (200 mL) and washed with cold water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and cold water (20 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (methanol - dichloromethane gradient elution) to afford ethyl 2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside as a white amorphous solid in 89% yield (0.36 g, 0.89 mmol). Analytical data: R_f = 0.52 (methanol/dichloromethane, 1/9, v/v); $[\alpha]_D^{19}$ -110.7 (*c* = 1.0, $CHCl_3$); ^{1}H-NMR: δ, 1.24 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.70 (m, 2H, SCH_2CH_3), 3.33-3.48 (m, 2H, H-2, 5), 3.58 (dd, 1H, $J_{3,4}$ = 8.6 Hz, H-3), 3.67 (dd, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 3.79 (dd, 1H, $J_{5,6a}$ = 5.6 Hz, $J_{6a,6b}$ = 11.7 Hz, H-6a), 3.95 (dd, 1H, $J_{5,6b}$ = 3.7 Hz, H-6b), 4.49 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.78- 5.09 (m, 4H, 2 CH_2Ph), 6.95-7.80 (m, 6H, aromatic), 8.40- 8.60 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 15.1, 24.9, 63.1, 71.2, 74.1, 76.0, 80.0, 81.8, 84.8, 89.5, 121.8, 122.0, 122.5, 122.9, 136.7, 137.4, 148.6, 149.0, 158.1, 158.2 ppm; HR FAB MS $[M+Na]^+$ calcd for $C_{20}H_{26}N_2O_5SNa$ 429.1460, found 429.1425.

To a solution of ethyl 2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside (0.36 g, 0.89 mmol) in DMF (5.0 mL), NaH (60% in mineral oil, 0.21 g, 5.3 mmol) and benzyl bromide (0.21 mL, 1.8 mmol) were added at rt. The reaction mixture was stirred for 2 h, then quenched with ice water (15 mL, 30 min) and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 30 mL). The combined organic extract (~90 mL) was washed with cold water (3 × 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give ethyl 4,6-di-*O*-benzyl-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside as a white amorphous solid in 83% yield (0.43 g, 0.74 mmol). Analytical data for **5.1b**: R_f = 0.49 (methanol/dichloromethane, 1/9, v/v); $[\alpha]_D^{20}$ +6.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.30 (t, 3H, *J* = 7.5 Hz, SCH_2CH_3), 2.76 (m, 2H, SCH_2CH_3), 3.51 (m, 1H, H-5), 3.54 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.63-3.84 (m, 4H, H-3, 4, 6a, 6b), 4.49 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.59 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.67 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 4.97 (dd, 2H, ^2J = 12.5 Hz, CH_2Ph), 5.51 (s, 2H, CH_2Ph), 7.00-7.70 (m, 16H, aromatic), 8.49 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 15.3, 25.0, 69.2, 73.6, 75.2, 76.1, 76.3, 78.0, 79.3, 82.3, 85.0, 87.1, 121.5, 121.9, 122.4 (×2), 127.8, 127.9 (×3), 128.3 (×2), 128.5 (×4), 136.7 (×2), 138.1, 138.4, 149.0, 149.1, 158.3, 158.6 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{34}H_{39}N_2O_5S$ 587.2580, found 587.2597.

Ethyl 4,6-di-*O*- benzylidene -2,3- di-*O*- picolinyl-1-thio-α-D-glucopyranoside (α-5.1a)

To a solution of ethyl 4,6-*O*-benzylidene-1-thio-α-D-glucopyranoside[35] (1.0 g, 3.2 mmol) in DMF (10 mL) NaH (60% in mineral oil, 0.77 g, 19.2 mmol) and picolinyl bromide hydrobromide (3.2 g, 12.8 mmol) were added at 0 °C. The reaction mixture was stirred

for 1.5 h, quenched with ice-water (~10 mL, 30 min) and then extracted with ethyl acetate /diethyl ether (1/1, v/v, 3 × 50 mL). The combined organic extract (~150 mL) was washed with cold water (3 × 30 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound as a white amorphous solid in 89% yield (1.4 g, 2.9 mmol). Analytical data for Analytical data for **α-5.1a**: R_f = 0.40 (methanol/dichloromethane, 1/19, v/v); $[\alpha]_D^{19}$ +157.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.23 (t, 3H, *J* = 7.5 Hz, SCH_2CH_3), 2.52 (m, SCH_2CH_3), 3.60- 3.80 (m, 2H, H-4, 5), 3.88- 4.02 (m, 2H, H-2. 3), 4.17- 4.35 (m, 2H, H-6a, 6b), 4.80 (dd, 2H, ^2J = 13.2 Hz, CH_2Ph), 4.96 (dd, 2H, ^2J = 13.9 Hz, CH_2Ph), 5.51 (s, 1H, >C*H*Ph), 5.56 (d, 1H, $J_{1,2}$ = 4.7 Hz, H-1), 6.90- 7.70 (m, 11H, aromatic), 8.47 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 14.9, 23.9, 62.9, 68.9, 73.2, 75.8, 79.5, 79.8, 81.8, 83.7, 101.5, 121.5, 121.8, 122.2, 122.5, 126.2 (×2), 128.3 (×2), 129.0, 136.5, 136.8, 137.3, 148.8, 148.9, 158.1, 159.1 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{27}H_{31}N_2O_5S$ 495.1954, found 495.1994.

Ethyl 4,6-tri-*O*-benzyl-2,3-di-*O*-picolinyl-1-thio-α-D-glucopyranoside (α-5.1b) To a stirred solution of **α-5.1a** (0.50 g, 1.00 mmol) in CH_2Cl_2 (10 mL), water (150 μL) and trifluoroacetic acid (TFA)/CH_2Cl_2 (1/9, v/v, 1.0 mL) were added at rt. The reaction mixture was stirred for 3 h, then neutralized with Et_3N (3 mL) and then diluted with dichloromethane (200 mL) and washed with cold water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and cold water (20 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography

on silica gel (methanol - dichloromethane gradient elution) to afford ethyl 2,3-di-*O*-picolinyl-1-thio-α-D-glucopyranoside as a white amorphous solid in 87% yield (0.35 g, 0.87 mmol). Analytical data: R_f = 0.46 (methanol/ dichloromethane, 1/9, v/v); $[\alpha]_D^{19}$ +57.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.27 (t, 3H, *J* = 7.5 Hz, SCH_2CH_3), 2.57 (m, 2H, SCH_2CH_3), 3.68-3.98 (m, 5H, H-2, 3, 4, 6a, 6b), 4.10 (m, 1H, H-5), 4.85 (dd, 2H, ^2J = 13.3 Hz, CH_2Ph), 5.01 (dd, 2H, ^2J = 14.9 Hz, CH_2Ph), 5.58 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1), 7.05-7.35 (m, 3H, aromatic), 7.50-7.40 (m, 3H, aromatic), 8.55 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 14.8, 23.7, 62.9, 71.0, 72.0, 72.8, 73.8, 79.7, 82.7, 84.9, 121.6, 121.7, 122.7, 123.0, 136.9, 137.4, 148.6, 149.1, 158.3, 158.5 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{20}H_{27}N_2O_5S$ 407.1641, found 407.1627.

To a solution of ethyl 2,3-di-*O*-picolinyl-1-thio-α-D-glucopyranoside (0.35 g, 0.87 mmol) in DMF (5.0 mL), NaH (60% in mineral oil, 0.21 g, 5.3 mmol) and benzyl bromide (0.21 mL, 1.8 mmol) were added at rt. The reaction mixture was stirred for 2 h, then quenched with ice water (15 mL, 30 min) and extracted with ethyl acetate/ diethyl ether (1/1, v/v, 3 × 30 mL). The combined organic extract (~90 mL) was washed with cold water (3 × 10 mL). The organic phase was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to give the title compound as a white amorphous solid in 88% yield (0.45 g, 0.77 mmol). Analytical data for **α-5.1b**: R_f = 0.53 (methanol/dichloromethane, 1/9, v/v); $[\alpha]_D^{20}$ +146.0 (*c* = 1.0, $CHCl_3$); NMR: δ, 1.27 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3), 2.56 (m, 2H, SCH_2CH_3), 3.66 (dd, 1H, $J_{5,6a}$ = 1.7 Hz, $J_{6a,6b}$ = 10.6 Hz, H-6a), 3.68-3.78 (m, 1H, H- 4), 3.80 (dd, 1H, $J_{5,6b}$ = 3.6 Hz, H-6b), 3.88- 4.03 (m, 2H, H- 2,3), 4.22 (m, 1H, H-5), 4.56 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.66 (dd, 2H, ^2J

= 11.9 Hz, C*H*$_2$Ph), 4.79 (dd, 2H, ^2J = 13.3 Hz, C*H*$_2$Ph), 5.02 (dd, 2H, ^2J = 13.0 Hz, C*H*$_2$Ph), 5.60 (d, 1H, $J_{1,2}$ = 4.2 Hz, H-1), 6.95-7.65 (m, 16H, aromatic), 8.40- 8.60 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 14.9, 23.8, 68.6, 70.6, 72.8, 73.6, 75.1, 76.2, 77.6, 80.0, 82.8, 83.1, 121.5, 121.7, 122.3, 122.5, 127.8 (×2), 128.1 (×4), 128.4 (×2), 128.5 (×2), 136.6, 136.8, 138.0, 138.3, 148.9, 149.1, 158.2, 159.0 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{34}H_{39}N_2O_5S$ 587.2580, found 587.2579.

Ethyl 4,6-di-*O*-benzoyl-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside (5.1c). To a solution of ethyl 2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside (0.36 g, 0.89 mmol) in CH_2Cl_2 (10 mL), benzoic acid (0.19 g, 1.52 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.31 g, 1.52 mmol), and 4-dimethylaminopyridine (25 mg, 0.20 mmol) were added at rt. The reaction mixture was stirred for 3 h under argon, the solid was filtered off and rinsed successively with CH_2Cl_2. The combined filtrate (~100 mL) was washed with brine (2 x 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 give the title compound as a white amorphous solid in 83% yield (0.46 g, 0.74 mmol). Analytical data for **5.1c**: R_f = 0.57 (methanol/dichloromethane, 1/9, v/v); $[\alpha]_D^{20}$ +13.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 1.26 (t, 3H, *J* = 7.5 Hz, SCH_2CH_3), 2.73 (m, 2H, SCH_2CH_3), 3.73 (dd, 1H, $J_{2,3}$ = 9.1 Hz, H-2), 3.95 (m, 1H, H-5), 4.09 (dd, 1H, $J_{3,4}$ = 8.9 Hz, H-3), 4.40 (dd, 1H, $J_{5,6a}$ = 5.7 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.55 (dd, 1H, $J_{5,6b}$ = 2.9 Hz, H-6b), 4.67 (d, 1H, $J_{1,2}$ =9.7 Hz, H-1), 4.98 (dd, 2H, ^2J =13.6 Hz, C*H*$_2$Ph), 5.09 (dd, 2H, ^2J = 12.8 Hz, C*H*$_2$Ph), 5.49 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 6.80-7.60 (m, 12H, aromatic), 7.75-8.70 (m, 4H, aromatic) ppm; ^{13}C NMR: δ, 15.2, 25.1, 63.8, 71.2, 74.9, 75.2, 75.9, 81.9, 84.7, 85.0, 122.1, 122.2, 122.7, 122.9, 128.4, 128.5 (× 3), 129.2, 129.8 (×

2), 130.1 (× 2), 130.4, 133.2, 133.4, 137.7, 137.8, 147.3, 147.9, 157.4, 165.4, 166.3, 170.8 ppm; HR FAB MS $[M+Na]^+$ calcd for $C_{34}H_{34}N_2O_7SNa$ 637.1984, found 637.1992.

Ethyl 4,6-di-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside (5.1d). 2,6-Lutidine (0.57 mL, 4.9 mmol) was added to a solution. of ethyl 2,3-di-*O*-picolinyl-1-thio-α-D-glucopyranoside (0.50 g, 1.2 mmol) in anhydrous THF (10 mL) and the resulting mixture was stirred under argon for 10 min at rt. After that, the mixture was cooled to -78 ^oC, TBDMSOTf (0.71 mL, 3.1 mmol) was added. The resulting reaction mixture was stirred for 2 hr at -78 ^oC and the volatiles were evaporated *in vacuo*. The residue was diluted with CH_2Cl_2 (~150 mL) and washed with 20% aq. $NaHCO_3$ (30 mL) and water (3 x 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 - hexane gradient elution) to afford the title compound in 87% yield (0.68 g, 1.1 mmol) as a white amorphous solid. Analytical data for **5.1d**: R_f = 0.69 (methanol/dichloromethane, 1/9, v/v); $[\alpha]_D^{20}$ +39.6 (*c* = 1.0, $CHCl_3$); ^1H NMR: δ, -0.12-.06 (4s, 12H, $SiCH_3$), 0.75-0.95 (2s, 18H, $SiC(CH_3)_3$), 1.25 (t, 3H, *J* = 7.5 Hz, SCH_2CH_3), 2.70 (m, 2H, SCH_2CH_3), 3.22 (m, 1H, H-5), 3.45 (dd, 1H, $J_{2,3}$ = 8.8 Hz, H-2), 3.53 (dd, 1H, $J_{3,4}$ = 8.6 Hz, H-3), 3.66 (dd, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 3.71 (dd, 1H, $J_{5,6a}$ = 5.0 Hz, $J_{6a,6b}$ = 11.3 Hz, H-6a), 3.85 (dd, 1H, $J_{5,6b}$ = 1.9 Hz, H-6b), 4.48 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1), 4.84 (dd, 2H, ^2J = 12.5 Hz, CH_2Ph), 4.93 (dd, 2H, ^2J = 13.4 Hz, CH_2Ph), 6.90-7.70 (m, 6H, aromatic), 8.30- 8.45 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, -5.2, -4.9, -4.7, -3.9, 15.2, 18.2, 18.6, 24.6, 26.1(×6), 62.6, 70.5, 75.9, 76.1, 81.5, 83.0, 84.4, 87.1, 120.9,

121.6, 122.0, 122.3, 136.5, 136.6, 148.8, 148.9, 158.3, 158.9 ppm; HR FAB MS $[M+H]^+$ calcd for $C_{32}H_{55}N_2O_5SSi_2$ 635.3370, found 635.3397.

[$PdBr_2$][5.1a] (5.2a). A mixture of ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside **(5.1a,** 200 mg, 0.41 mmol) and freshly activated molecular sieves (4 Å, 400 mg) in CH_2Cl_2 (5.0 mL) was stirred under argon for 1 h. Then $PdBr_2$ (161.4 mg, 0.60 mmol) was added at rt and the resulting mixture was srirred for 18 h. The solid was filtered off and the residue was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (methanol- dichloromethane gradient elution) to afford the title compound in 94% yield (290 mg, 0.38 mmol) as a bright orange amorphous solid. Analytical data for **5.2a**: R_f = 0.71 (methanol/dichloromethane, 1/19, v/v); $[\alpha]_D^{20}$ -49.4 (*c* = 1.0, $CHCl_3$); ^{1}H-NMR: δ, 1.19 (t, 3H, *J* = 7.5 Hz, SCH_2CH_3), 2.64 (m, 2H, SCH_2CH_3), 3.42 (m, 1H, H-5), 3.62-3.86 (m, 3H, H-2, 4, 6a), 4.11 (dd, 1H, $J_{3,4}$ = 8.9 Hz, H-3), 4.23 (dd, 1H, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 10.4 Hz, H-6b), 4.56 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 5.33 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 5.48 (s, 1H, >C*H*Ph), 5.53 (dd, 2H, ^2J = 9.1 Hz, CH_2Ph), 6.85-7.80 (m, 11H, aromatic), 8.90- 9.10 (m, 2H, aromatic) ppm; ^{13}C-NMR: δ, 15.2, 25.1, 68.8, 70.0, 75.1, 76.2, 81.1, 82.6, 82.7, 85.8, 101.2, 124.4, 124.7, 126.0 (×2), 126.6, 127.3, 128.5 (×2), 129.2, 137.3, 138.9, 139.0, 154.6, 154.8, 157.6, 158.1 ppm; HR FAB MS $[M-Br]^+$ calcd for $C_{27}H_{30}BrN_2O_5SPd$ 681.0091, found 681.0094.

[$PdBr_2$][5.1b] (5.2b). A mixture of ethyl 4,6-di-*O*-benzyl-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside **(5.1b,** 200 mg, 0.34 mmol) and freshly activated molecular sieves (4 Å, 400 mg) in CH_2Cl_2 (5.0 mL) was stirred under argon for 1 h. Then $PdBr_2$ (134 mg, 0.5

mmol) was added at rt and the resulting mixture was srirred for 18 h. The solid was filtered off and the residue was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (methanol- dichloromethane gradient elution) to afford the title compound in 89% yield (259 mg, 0.30 mmol) as a bright orange amorphous solid. Analytical data for **5.2b**: R_f = 0.67 (methanol/dichloromethane, 1/19, v/v); $[\alpha]_D^{20}$ -26.2 (*c* = 1.0, $CHCl_3$); ^{1}H-NMR: δ, 1.29 (t, 3H, *J* = 7.5 Hz, SCH_2CH_3), 2.76 (m, 2H, SCH_2CH_3), 3.52 (m, 1H, H-5), 3.63-3.75 (m, 3H, H-2, 6a, 6b), 3.84 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 3.92 (dd, 1H, $J_{3,4}$ = 9.1, H-3), 4.54 (dd, 2H, ^2J = 9.6 Hz, CH_2Ph), 4.55 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1), 4.75 (dd, 2H, ^2J = 11.8 Hz, CH_2Ph), 5.45 (dd, 2H, ^2J = 10.3 Hz, CH_2Ph), 5.59 (dd, 2H, ^2J = 9.3 Hz, CH_2Ph), 6.50-7.80 (m, 16H, aromatic), 9.05- 9.25 (m, 2H, aromatic) ppm; ^{13}C-NMR: δ, 15.3, 25.1, 69.1, 73.7, 74.5, 76.5, 79.4, 80.1, 81.0, 85.4, 85.9, 89.8, 124.3, 124.5, 126.9, 127.1 (×2), 127.5, 127.8(×2), 127.9 (×2), 128.5, 128.6(×2), 128.8 (×3), 138.3, 138.4, 138.8, 138.9, 158.1, 158.5 ppm; HR FAB MS $[M-Br]^+$ calcd for $C_{34}H_{38}BrN_2O_5SPd$ 773.0720, found 773.0719.

5. 4. 3 Synthesis of Oligosaccharides

General procedure for glycosylation in the presence of DMTST. A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in solvent specified in Tables (2.6 mL, 50 mM) was stirred under argon for 1 h. The mixture was then cooled to the specified temperature and DMTST (0.26 mmol) was added. The resulting mixture was allowed to warm to rt over a period of 1 h and stirreed at rt for the time specified in Schemes. Upon completion, Et_3N (0.3 mL) was added and the resulting mixture was stirred for 30 min. The mixture was

diluted with CH_2Cl_2 (10 mL), the solid was filtered off, and the residue was washed sucessively with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 20% aq. $NaHCO_3$ (10 mL) and water (2 x 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- toluene gradient elution). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^1H NMR spectra.

General procedure for glycosylation in the presence of IDCP. A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in solvent specified in Tables (2.6 mL, 50 mM) was stirred under argon for 1 h. The mixture was cooled to the specified temperature, IDCP (0.26 mmol) was added, and the reaction mixture was allowed to warm to rt and stirred until the completion (see tables). The resulting mixture was diluted with CH_2Cl_2 (~10 mL), the solid was filtered off and the residue was washed with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 10% aq. $Na_2S_2O_3$ (10 mL) and water (2 x 10 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (acetone- toluene gradient elution). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^1H NMR spectra.

General procedure for glycosylation in the presence of NIS/ TfOH. A mixture of a glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated

molecular sieves (4 Å, 200 mg) in solvent specified in Tables (2.6 mL, 50 mM) was stirred under argon for 1 h. The mixture was cooled to the specified temperature, NIS (0.26 mmol) and TfOH (0.026 mmol) were added, and the reaction mixture was allowed to warm to rt and stirred until the completion (see tables). The resulting mixture was diluted with CH_2Cl_2 (~10 mL), the solid was filtered off and the residue was washed with CH_2Cl_2. The combined filtrate (~30 mL) was washed with 10% aq. $Na_2S_2O_3$ (10 mL) and water (2 x 10 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (acetone-toluene gradient elution). Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-β-D-glucopyranosyl)-α-D-glucopyranoside (β-5.4a)

The title compound was obtained as a white amorphous solid from glycosyl donor **5.1a** and acceptor **5.3** in 83% (α/β> 1/25). Analytical data for **β–5.4a**: R_f = 0.43 (acetone/hexane, 2/3, v/v); $[\alpha]_D^{20}$ +1.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: δ, 3.32 (s, 3H, OCH_3), 3.40 (m, 1H, H-5'), 3.48-3.53 (m, 2H, H-2, 4), 3.62 (dd, 1H, $J_{2',3'}$ = 8.1 Hz, H-2'), 3.68-3.89 (m, 5H, H-3', 4', 5, 6a, 6a'), 3.95 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.12 (dd, 1H, $J_{6a,6b}$ = 9.8 Hz, H-6b), 4.32 (dd, 1H, $J_{5,6b'}$ = 4.9 Hz, $J_{6a',6b'}$ = 10.4 Hz, H-6b'), 4.46 (d, 1H, ^2J = 10.9 Hz, ½ CH_2Ph), 5.52 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 5.58 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.60-4.69 (m, 2H, CH_2Ph), 4.72-4.82 (m, 2H, CH_2Ph), 4.87-5.15 (m, 5H, 2½ CH_2Ph), 5.53 (s, 1H, >C*H*Ph), 6.95-7.60 (m, 26H, aromatic), 8.44 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 55.5, 66.3, 68.9 (× 2), 69.8, 73.7, 75.0, 75.9, 77.4, 77.6, 77.9, 79.9, 81.3, 82.2 (×

2), 82.4, 98.4, 101.5, 104.1, 122.5, 126.3 (× 4), 127.8, 127.9 (× 6), 128.2 (× 3), 128.4 (× 2), 128.5 (× 7), 128.6 (× 2), 128.7 (× 3), 129.2, 137.3, 138.4, 138.5, 140.0 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{53}H_{56}N_2O_{11}Na$ 919.3782, found 919.3756.

[Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-α-D-glucopyranosyl)-α-D-glucopyranoside] $PdBr_2$ ([α-5.4a] $PdBr_2$)

The title compound was obtained as a white amorphous solid from glycosyl donor **α-5.2a** and acceptor **5.3** in 35% (α/β > 25/1) upon activation with bromine. Analytical data for **[α-5.4a] $PdBr_2$**: R_f = 0.41 (acetone/hexane, 2/3, v/v); $[\alpha]_D^{20}$ -31.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR: 3.30 (s, 3H, OCH_3), 3.47 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.54 (dd, 1H, $J_{4,5}$ = 9.2 Hz, H-4), 3.69-3.91 (m, 5H, H-4', 5, 6a', 6b, 6b'), 3.92-4.01 (m, 2H, H-3, 5'), 4.08 (dd, 1H, $J_{2',3'}$ = 9.4 Hz, H-2'), 4.28 (dd, 1H, $J_{5,6a}$ = 4.7 Hz, $J_{6a,6b}$ = 10.1 Hz, H-6a), 4.45 (dd, 1H, $J_{3',4'}$ = 9.2 Hz, H-3'), 4.58-4.79 (m, 6H, H-1, 2 ½ CH_2Ph), 4.93 (d, 1H, ^2J = 10.4 Hz, ½ CH_2Ph), 4.13 (dd, 2H, ^2J = 10.2 Hz, CH_2Ph), 5.37 (dd, 1H, $J_{1',2'}$ = 3.7 Hz, H-1'), 5.41(dd, 2H, ^2J = 10.4 Hz, CH_2Ph), 5.56 (s, 1H, >C*H*Ph), 7.10-7.70 (m, 26H, aromatic), 9.25 (m, 2H, aromatic) ppm; ^{13}C NMR: δ, 55.7, 62.4, 65.7, 69.4, 71.0, 72.6, 73.3, 75.3, 75.9, 76.2, 77.8, 78.1, 79.8, 80.2, 82.2, 83.2, 97.2, 98.0, 101.7, 124.2, 124.3, 126.3 (× 3), 126.6, 127.9 (× 2), 128.0 (× 2), 128.3 (× 3), 128.6 (× 6), 128.7 (× 4), 129.3, 137.7, 138.1, 138.5, 138.6, 138.8, 138.9, 155.8, 155.9, 157.8, 158.7 ppm; HR-FAB MS $[M-Br]^+$ calcd for $C_{53}H_{56}BrN_2O_{11}Pd$ 1083.2099, found 1083.2093.

5.5. References

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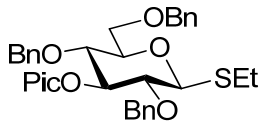
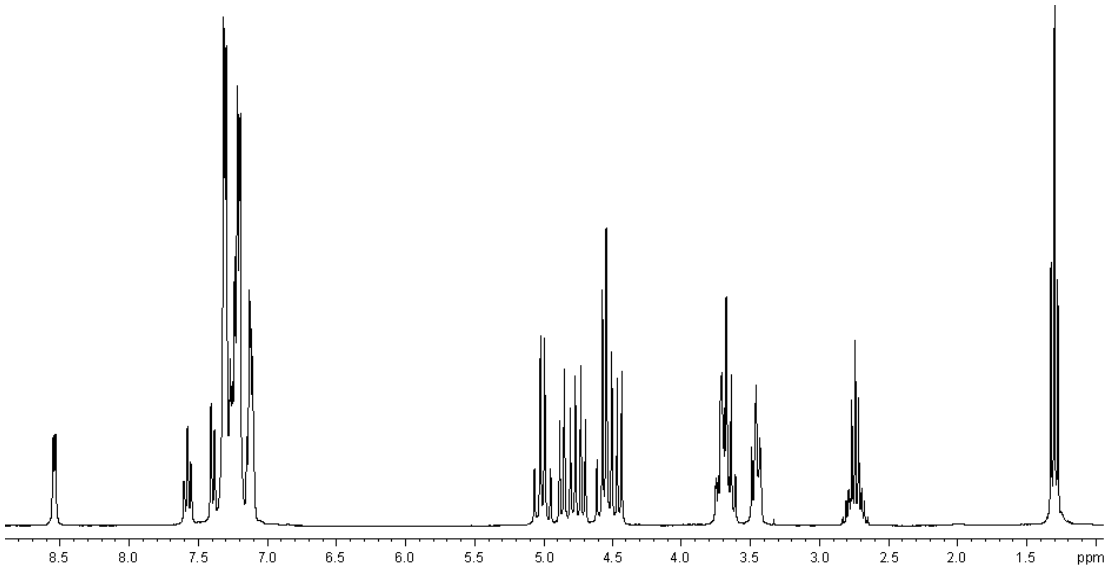
APPENDIX

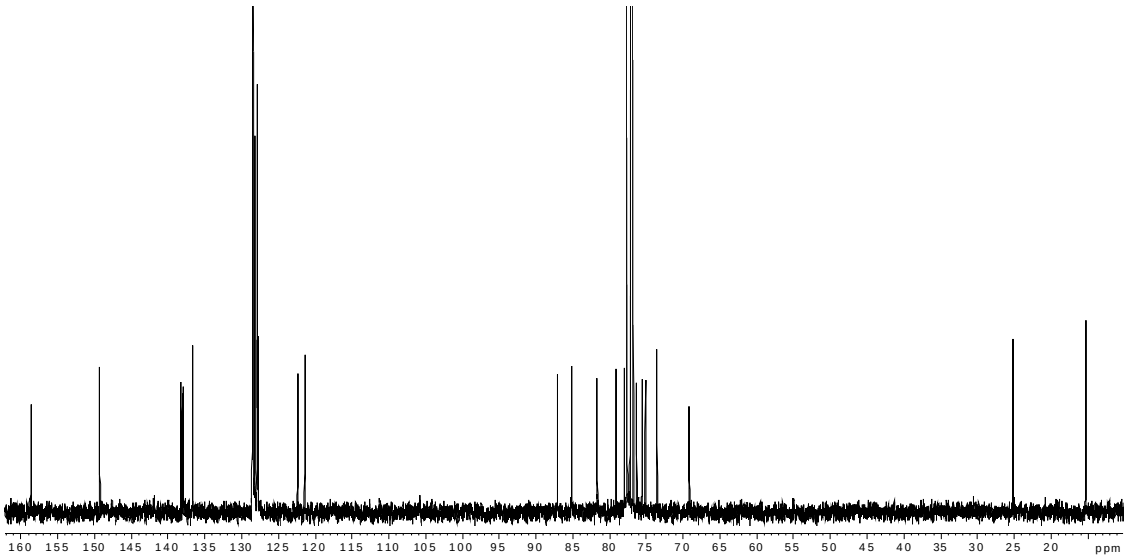


2.1c



$CDCl_3$ 300 MHz

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



$CDCl_3$ 75 MHz

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

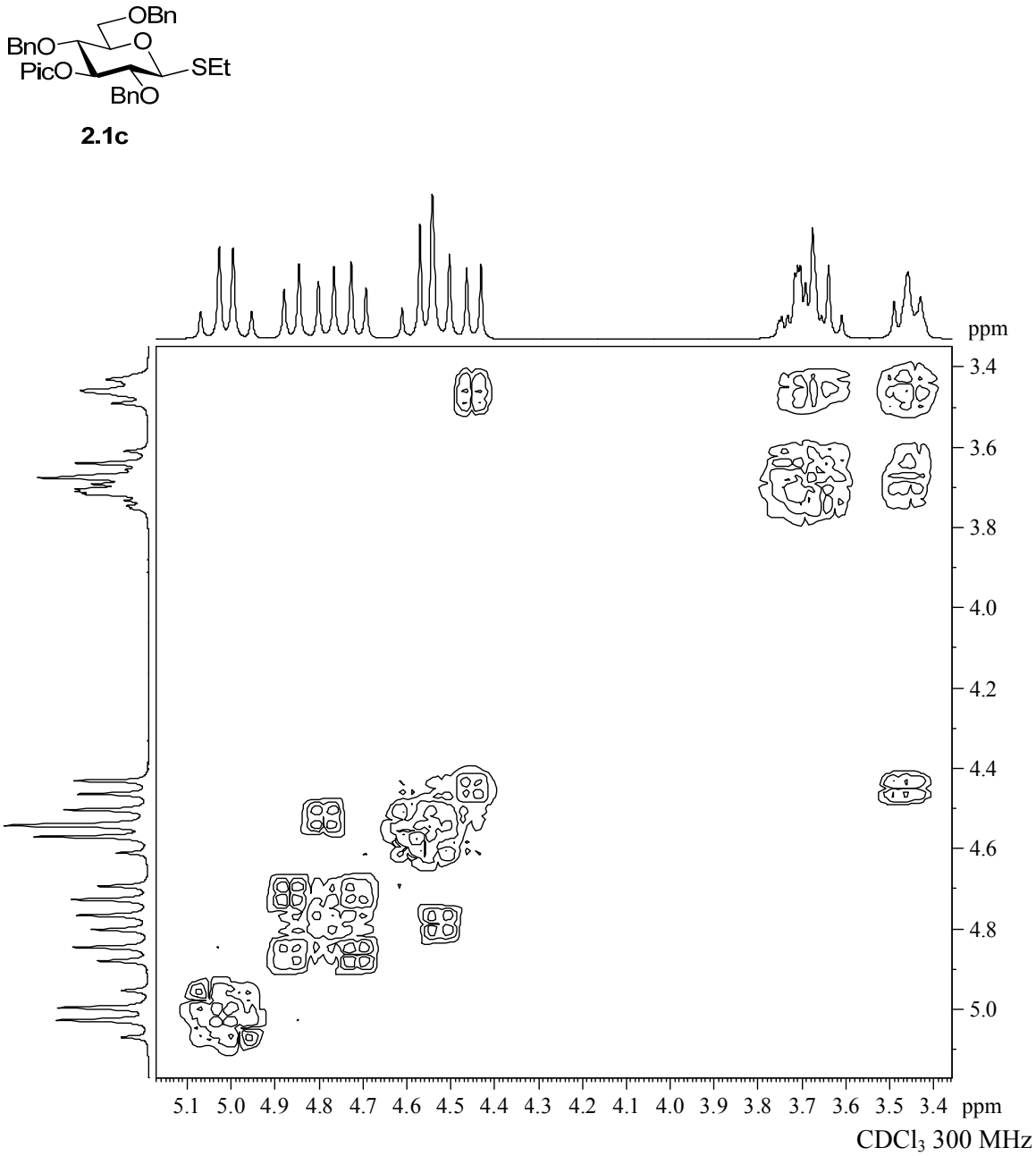
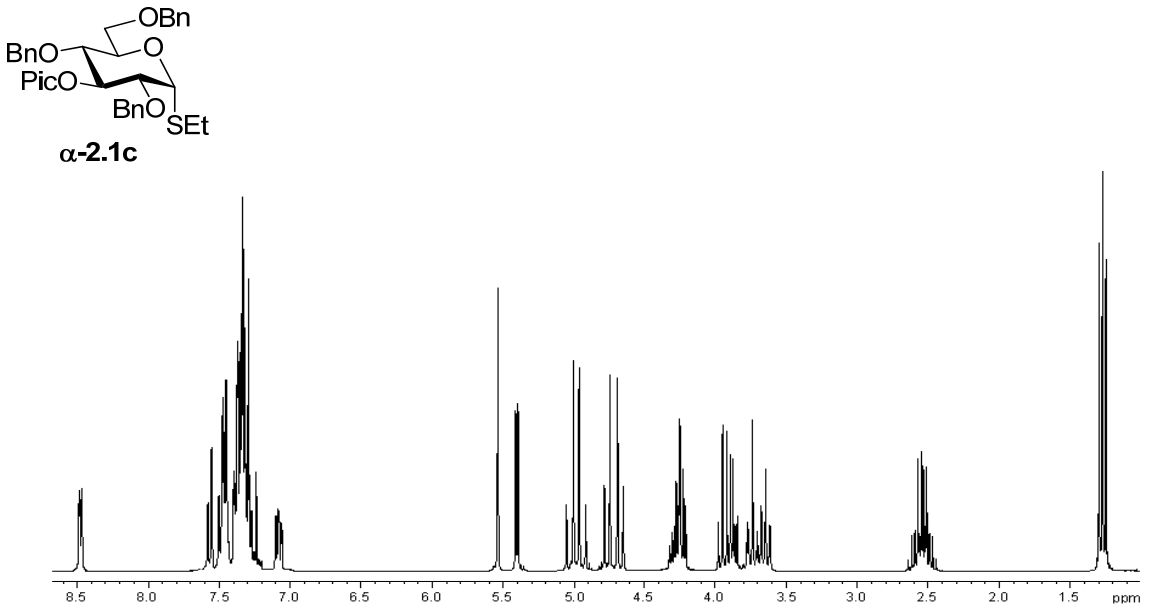
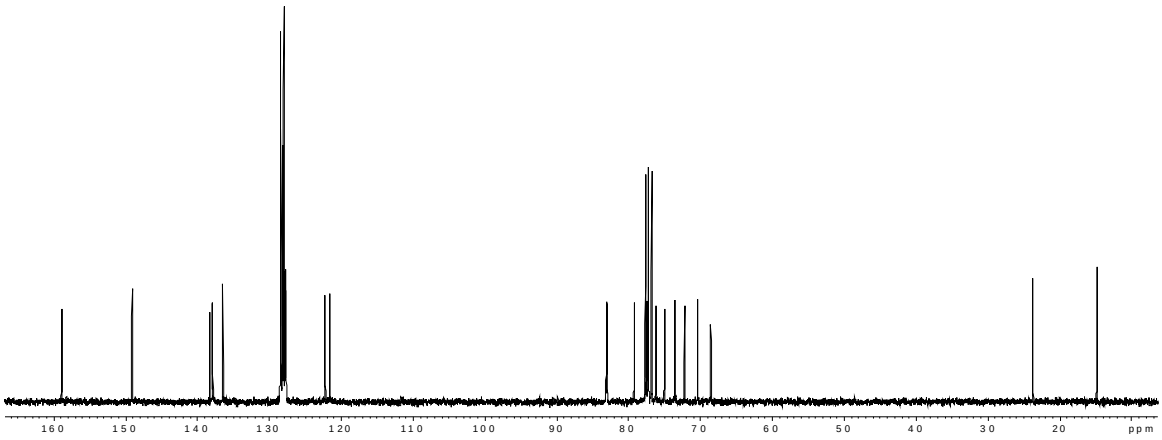


Figure A-3: 2-D NMR COSY spectrum of Ethyl 2,4,6-tri-*O*-benzyl-3-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1c**)



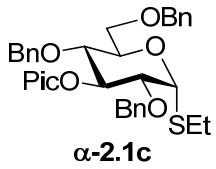
$CDCl_3$ 300 MHz

Figure A-4: ^{1}H NMR spectrum of Ethyl 2,4,6-tri-*O*-benzyl-3-*O*-picolinyl-1-thio-α-D-glucopyranoside (**α-2.1c**)

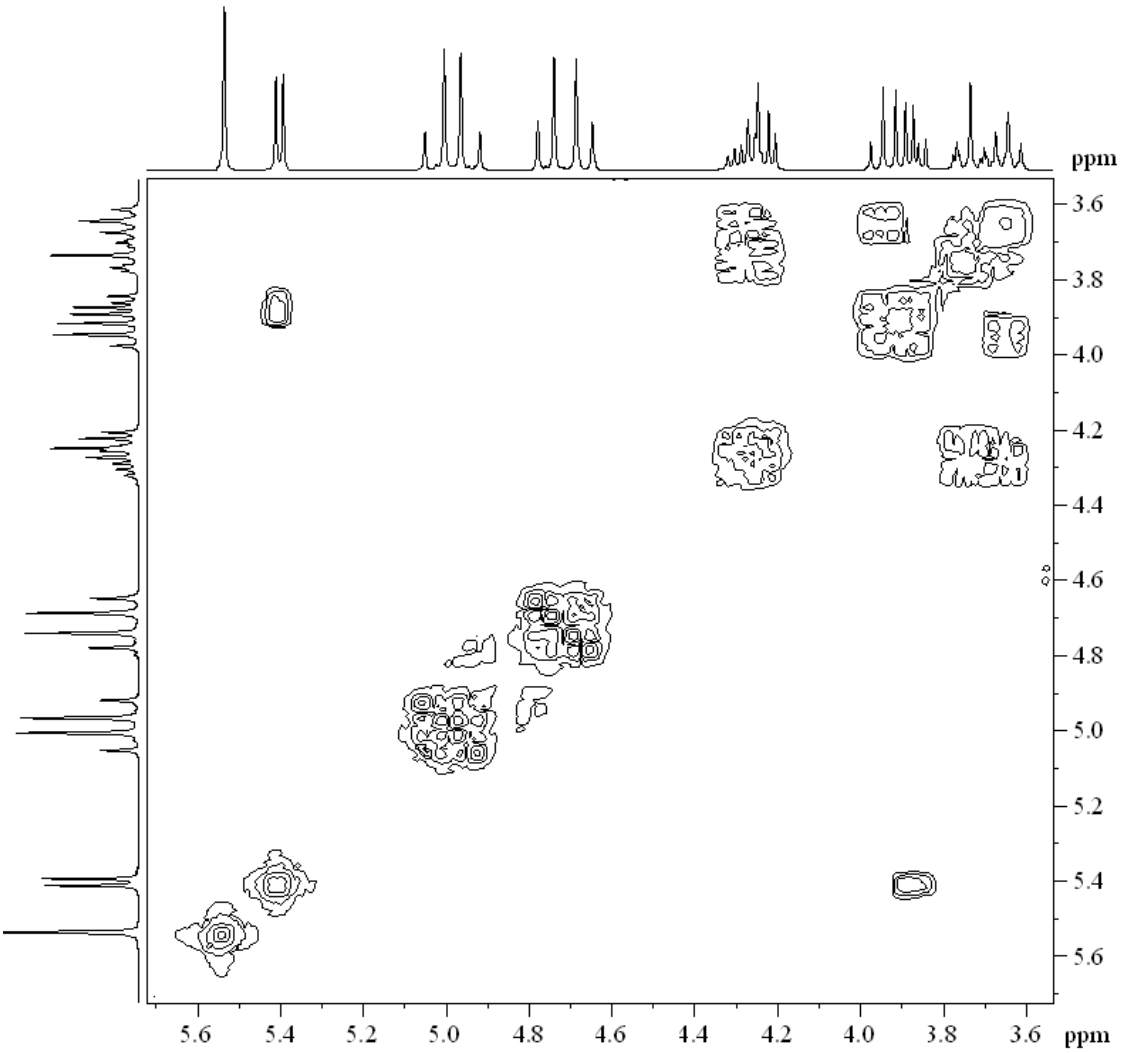


$CDCl_3$ 75 MHz

Figure A-5: ^{13}C NMR spectrum of Ethyl 2,4,6-tri-*O*-benzyl-3-*O*-picolinyl-1-thio-α-D-glucopyranoside (**α-2.1c**)

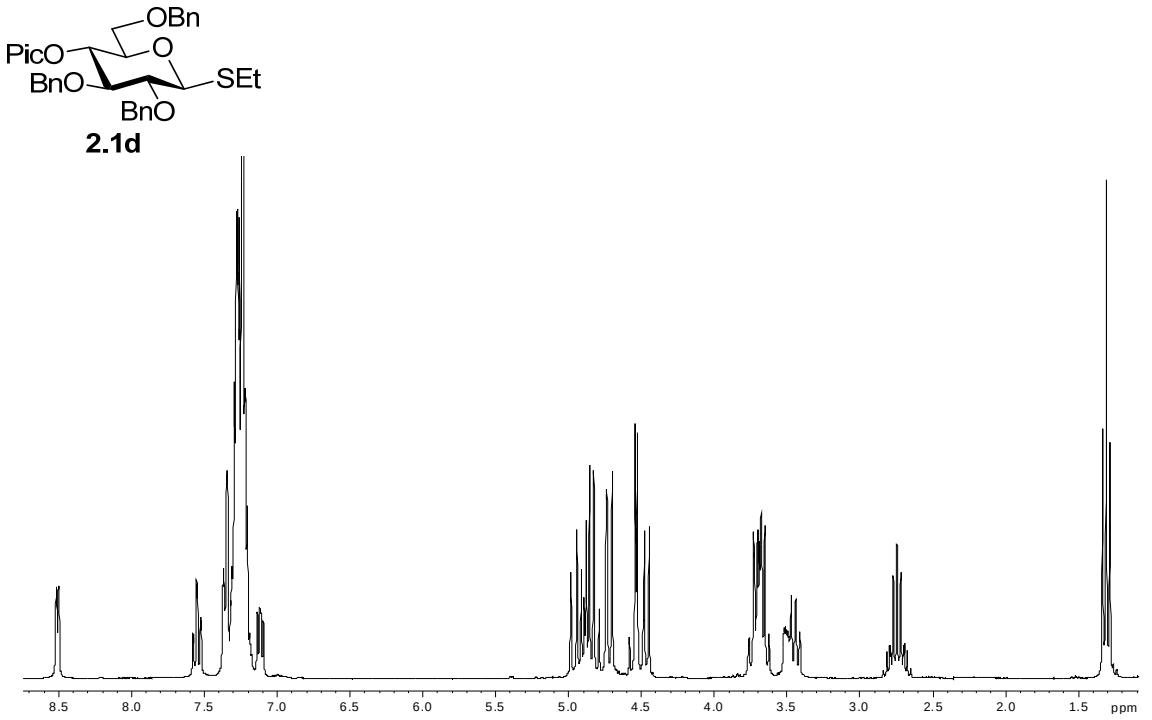


α-2.1c



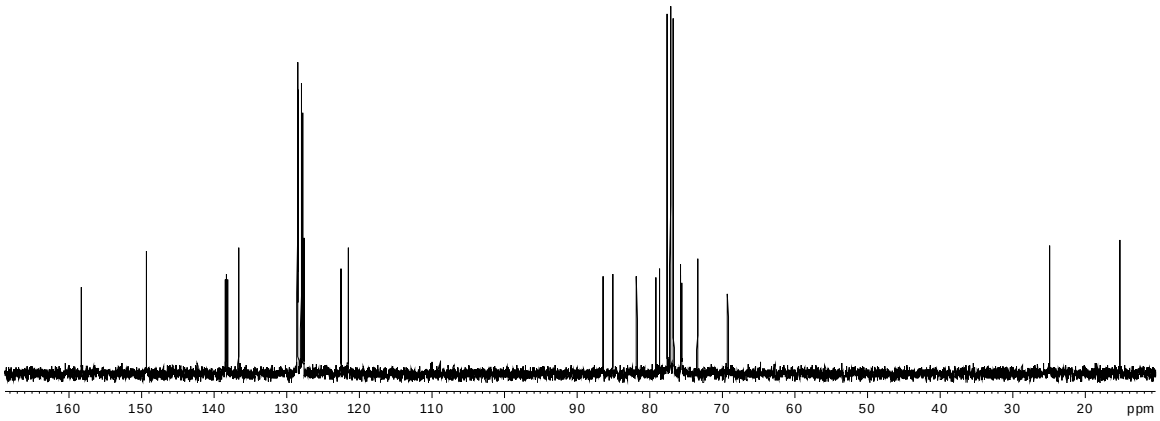
$CDCl_3$ 300 MHz

Figure A-6: 2-D NMR COSY spectrum of Ethyl 2,4,6-tri-*O*-benzyl-3-*O*-picolinyl-1-thio-α-D-glucopyranoside (**α-2.1c**)



$CDCl_3$ 300 MHz

Figure A-7: ^{1}H NMR spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1d**)



$CDCl_3$ 75 MHz

Figure A-8: ^{13}C NMR spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1d**)

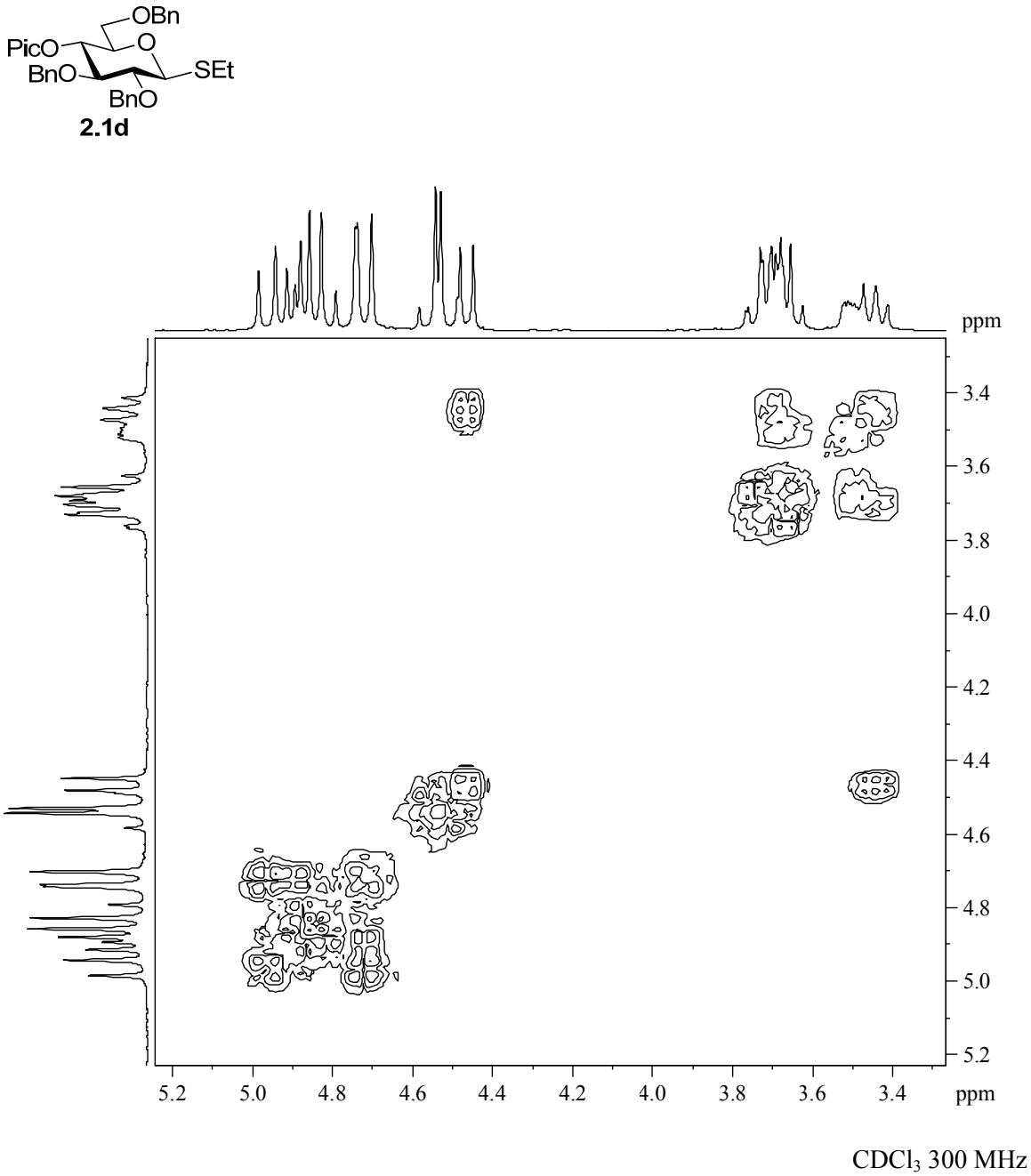


Figure A-9: 2-D NMR COSY spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1d**)

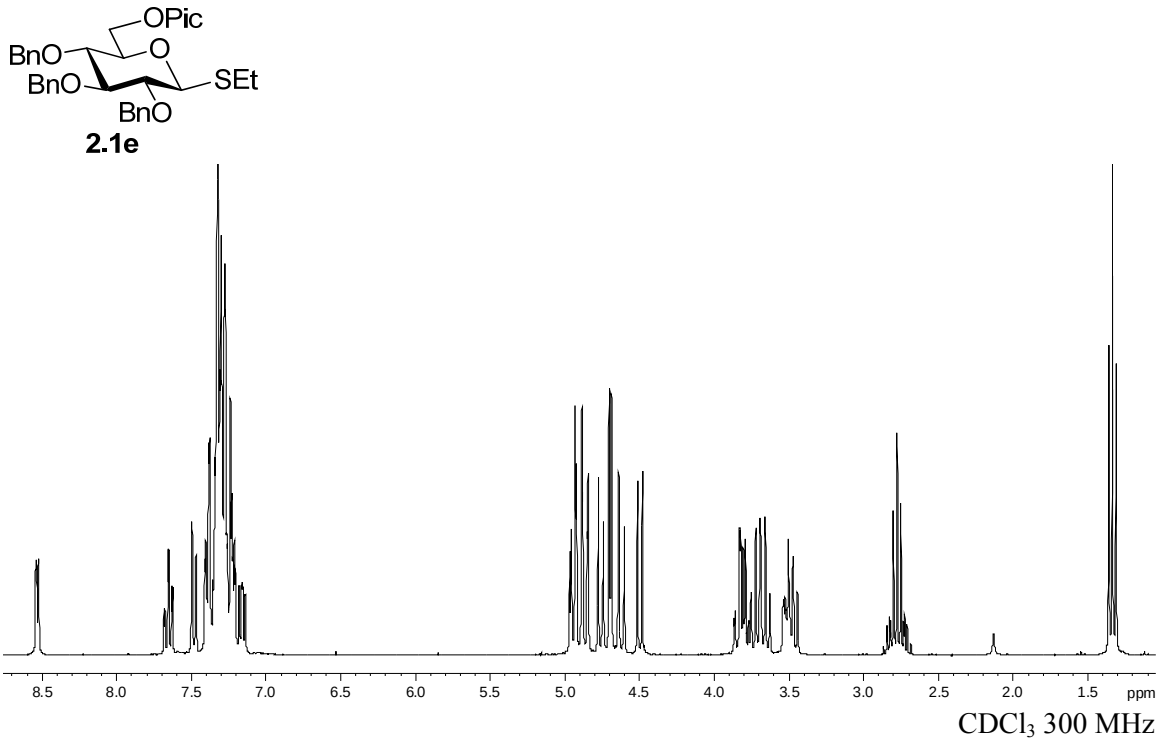


Figure A-10: : ^{1}H NMR spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1e**)

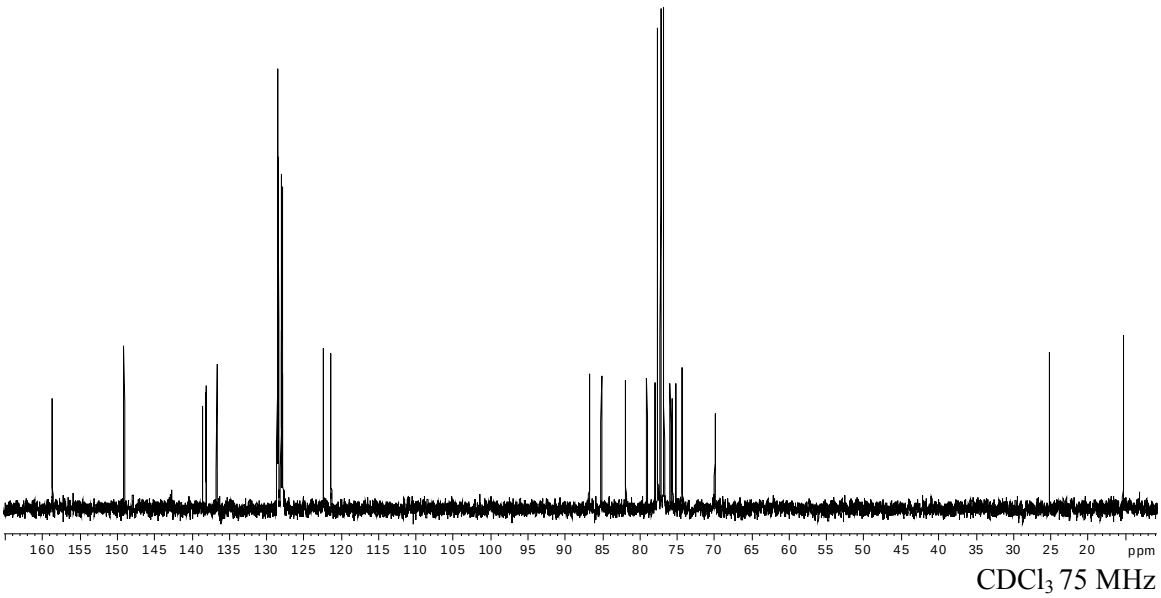


Figure A-11: ^{13}C NMR spectrum of Ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1e**)

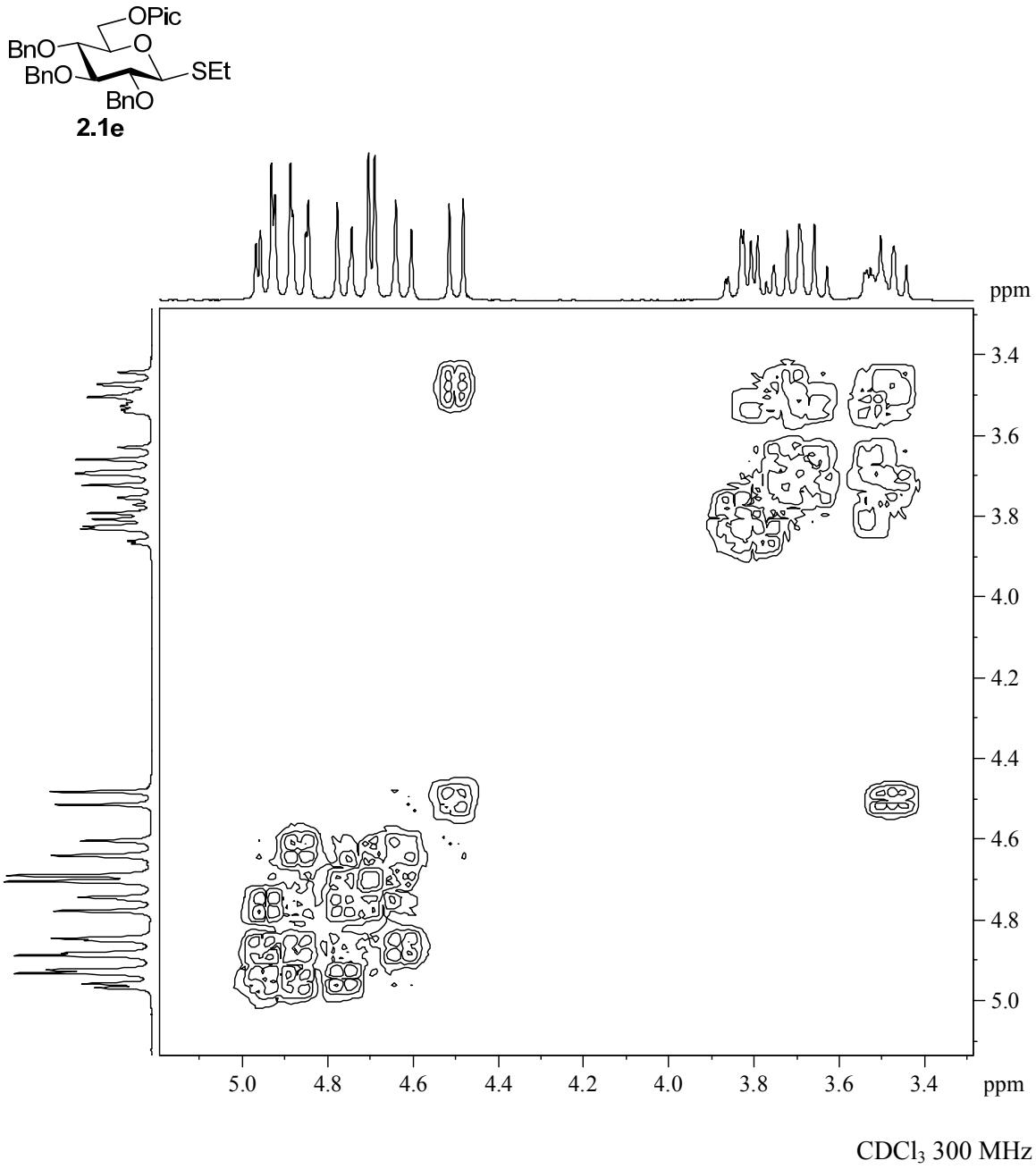
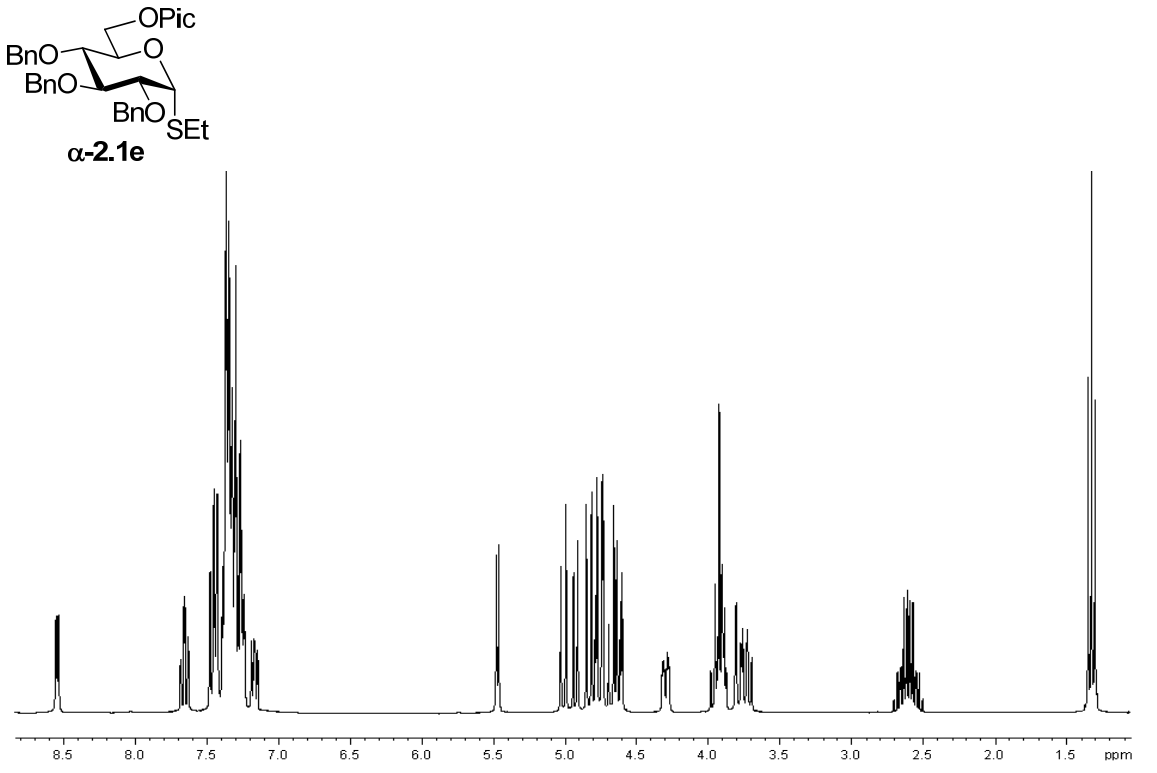
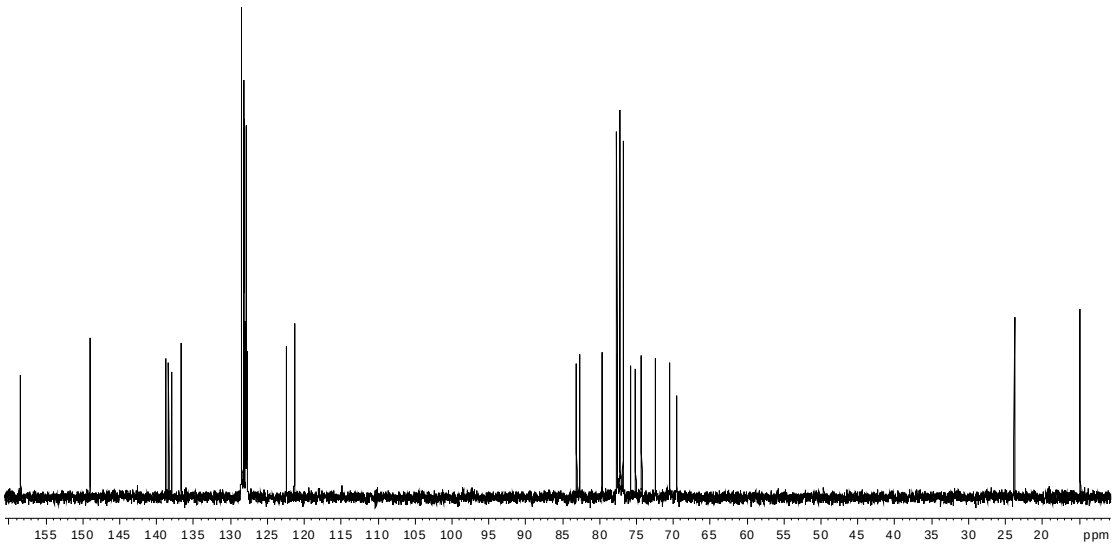


Figure A-12: 2-D NMR COSY spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1e**)



$CDCl_3$ 300 MHz

Figure A-13: ^{1}H NMR spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picolinyl-1-thio-α-D-glucopyranoside **(α-2.1e**)



$CDCl_3$ 75 MHz

Figure A-14: ^{13}C NMR spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picolinyl-1-thio-α-D-glucopyranoside **(α-2.1e**)

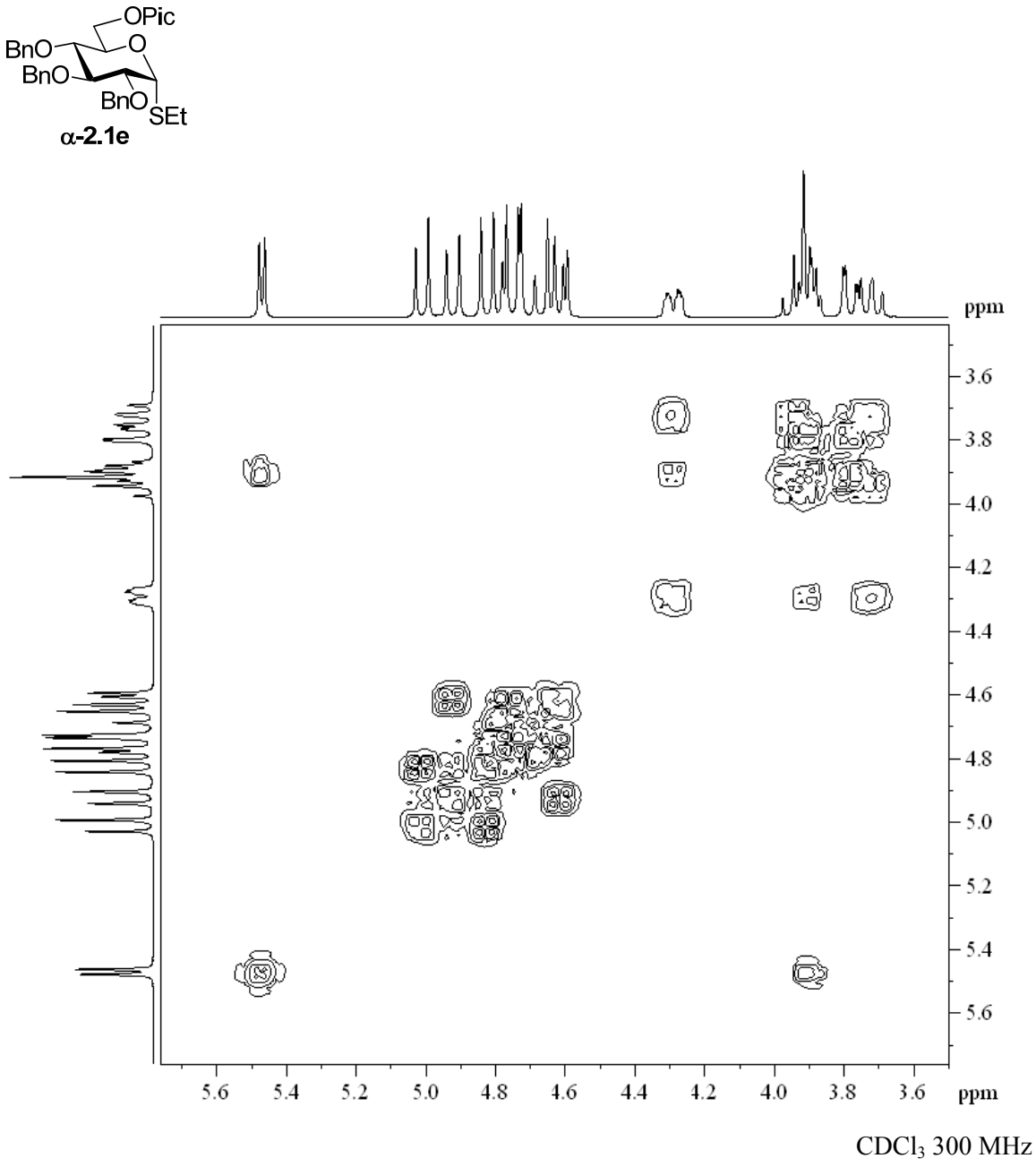
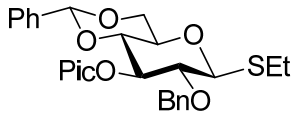
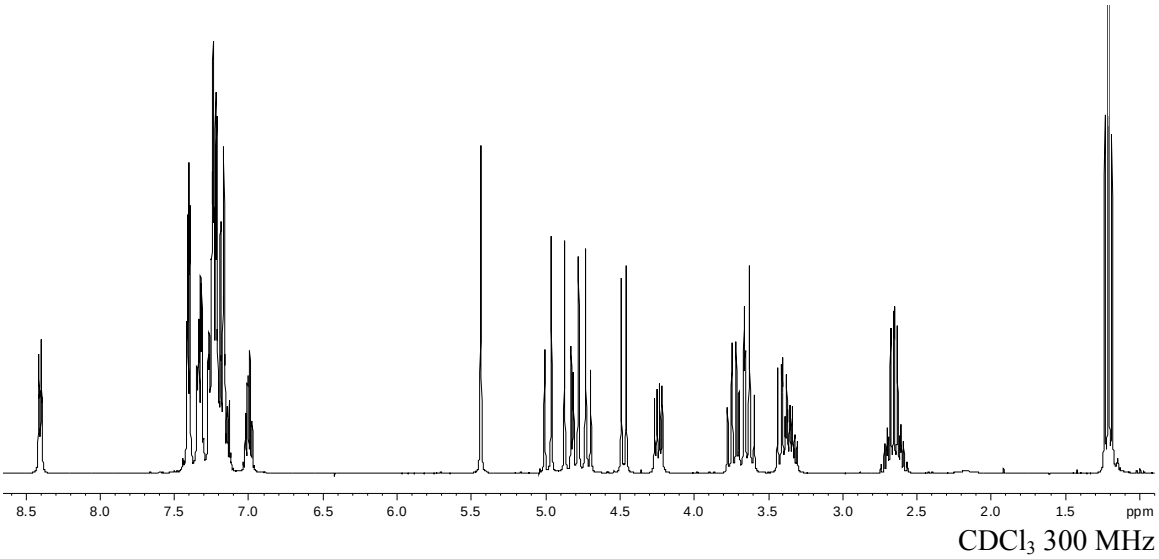


Figure A-15: 2-D NMR COSY spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picolinyl-1-thio-α-D-glucopyranoside **(α-2.1e**)

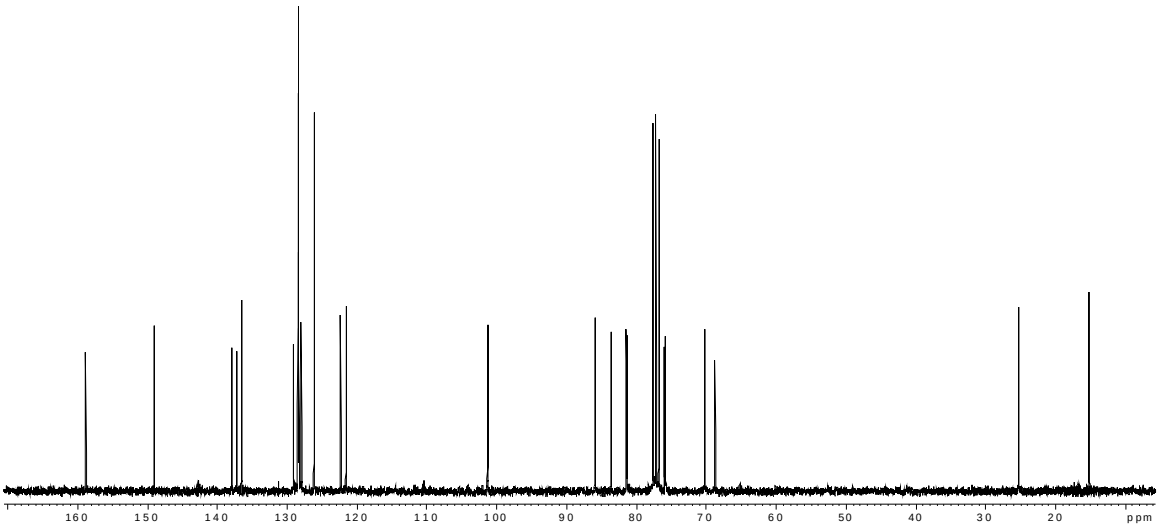


2.1f



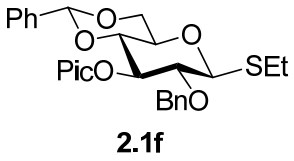
$CDCl_3$ 300 MHz

Figure A-16: ^{1}H NMR spectrum of Ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1f**)

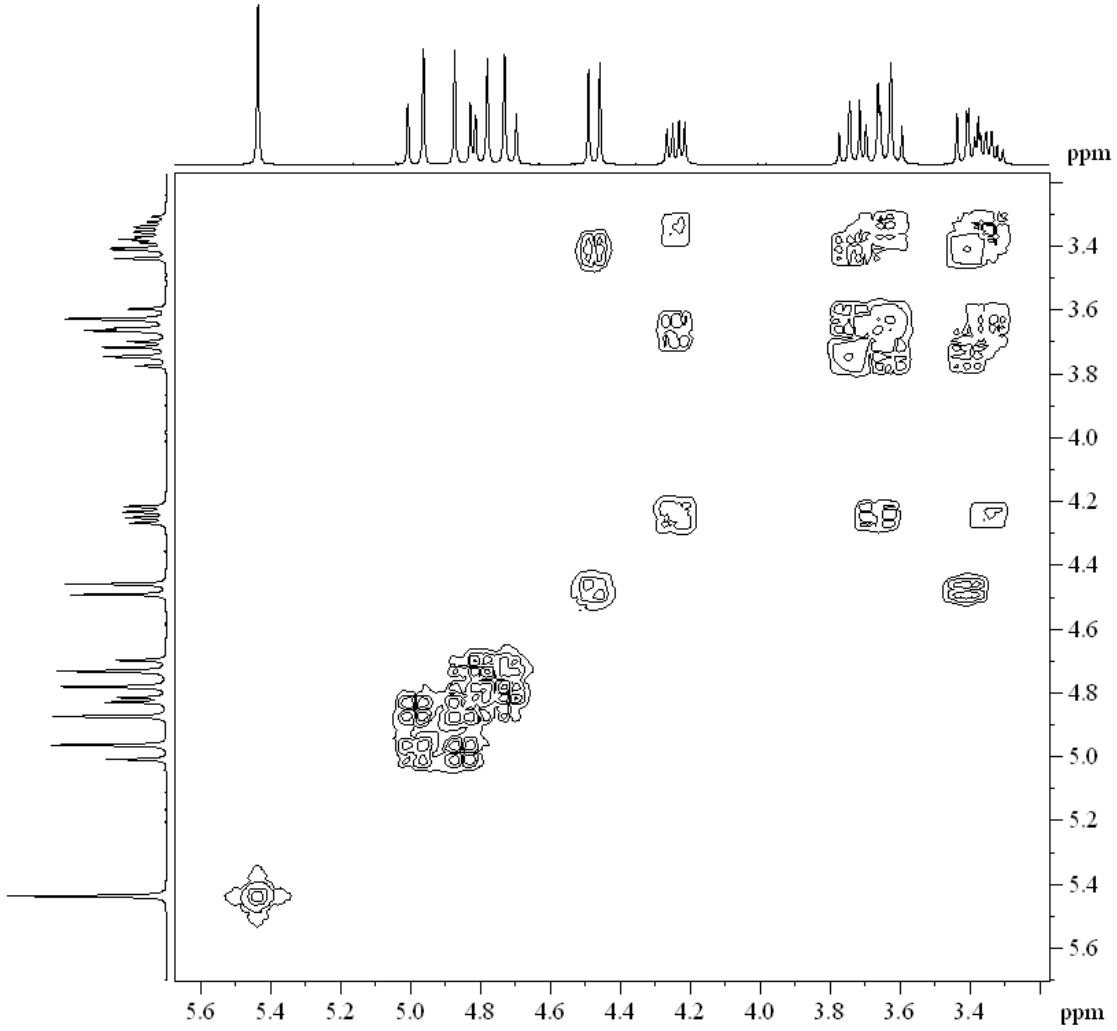


$CDCl_3$ 75 MHz

Figure A-17: ^{13}C NMR spectrum of Ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1f**)

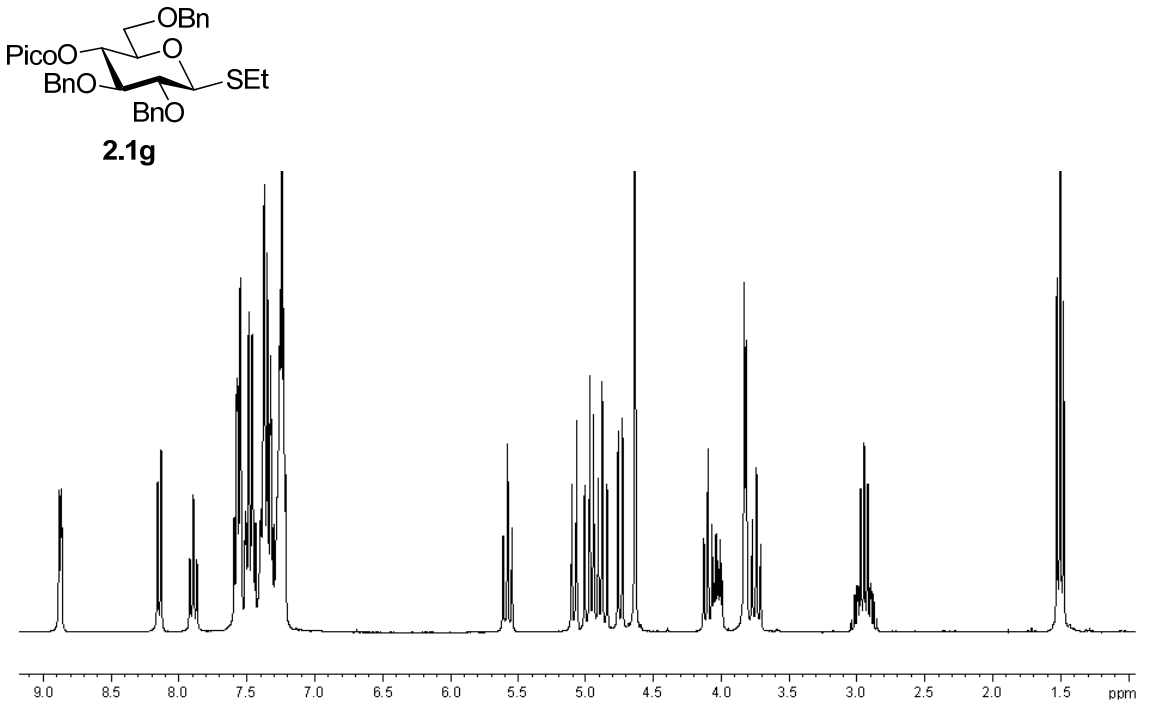


2.1f



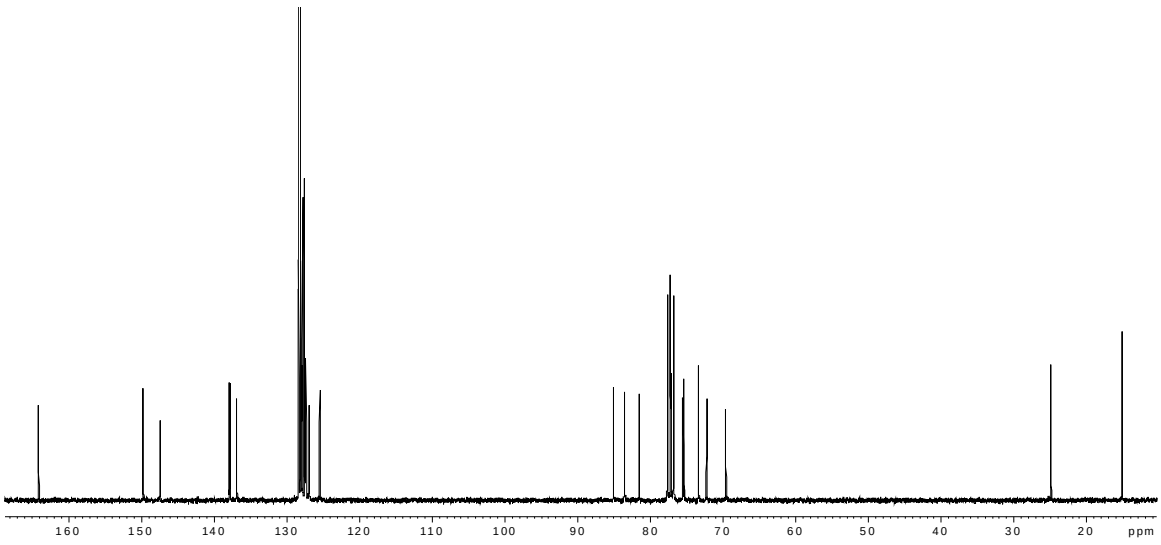
$CDCl_3$ 300 MHz

Figure A-18: 2-D NMR COSY spectrum of Ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-picolinyl-1-thio-β-D-glucopyranoside (**2.1f**)



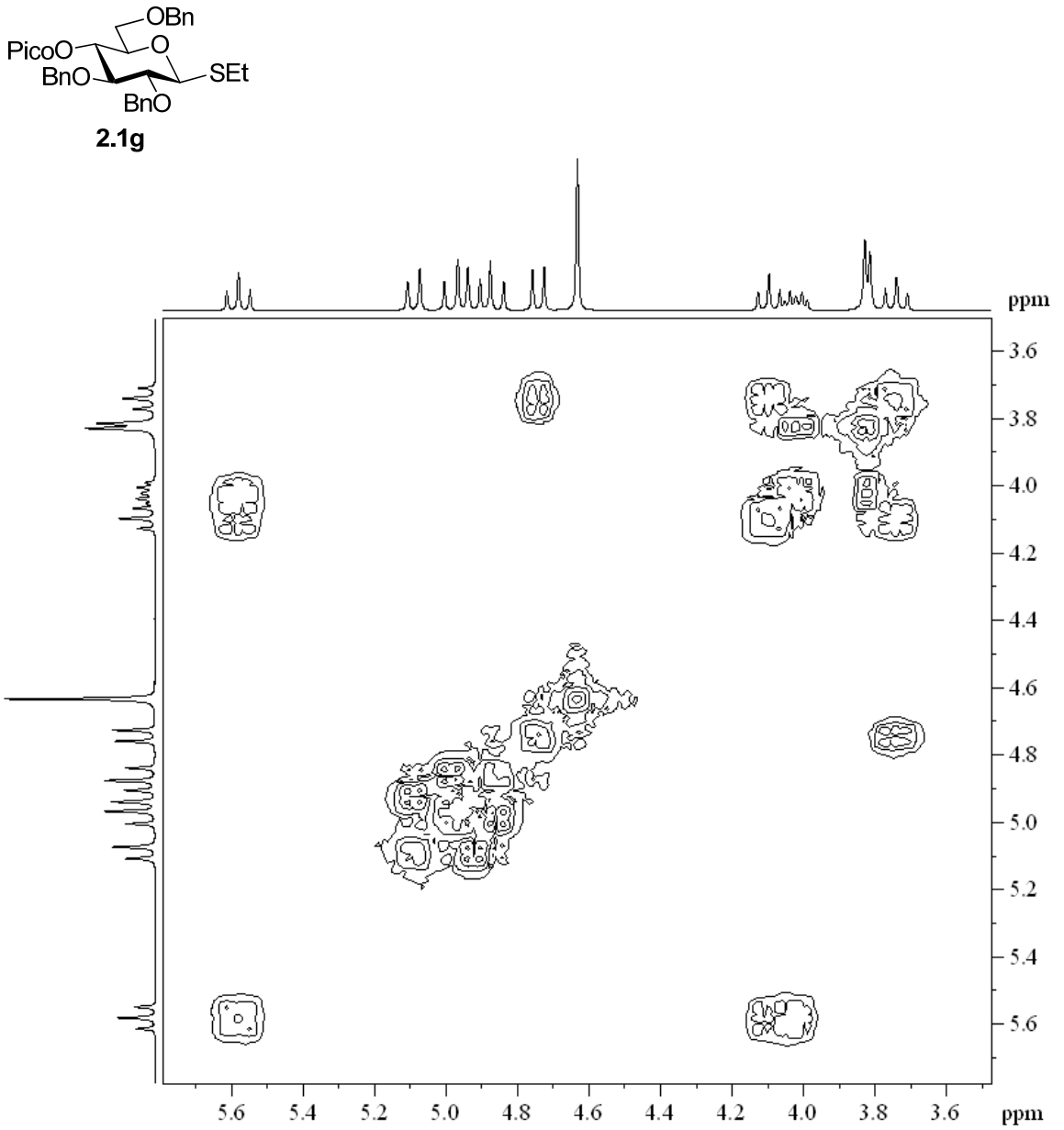
$CDCl_3$ 300 MHz

Figure A-19: ^{1}H NMR spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (**2.1g**)



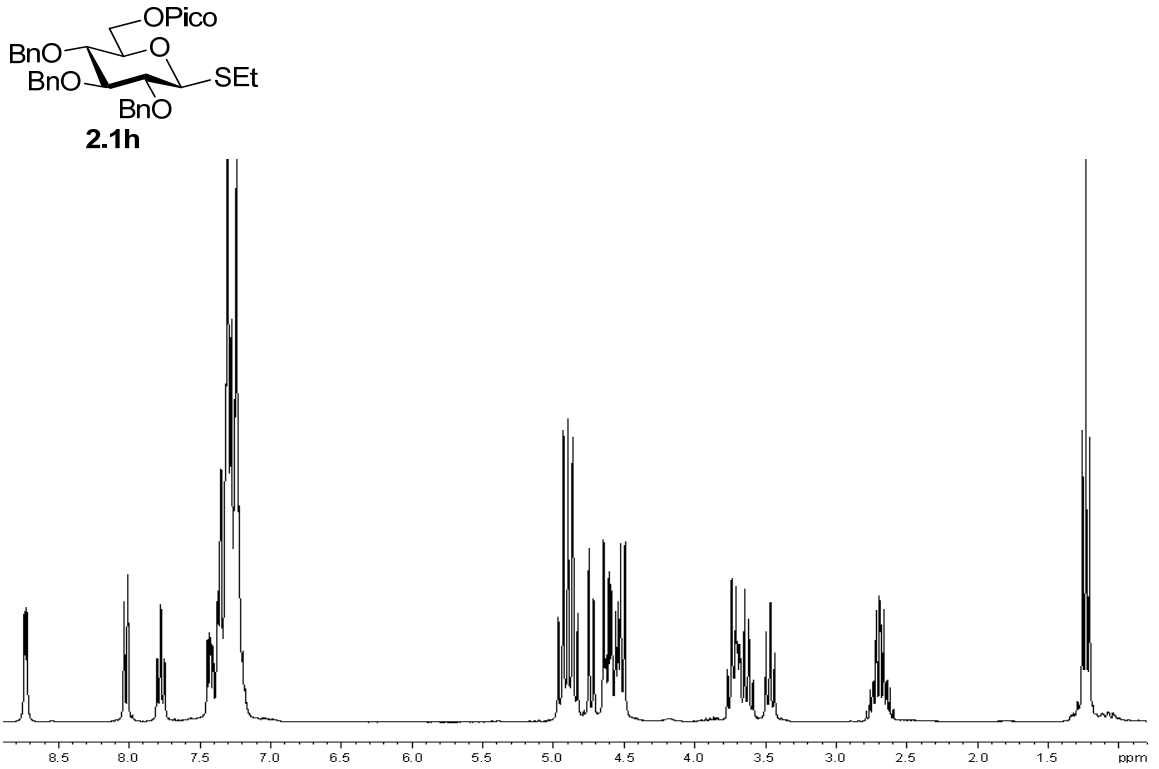
$CDCl_3$ 75 MHz

Figure A-20: ^{13}C NMR spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (**2.1g**)



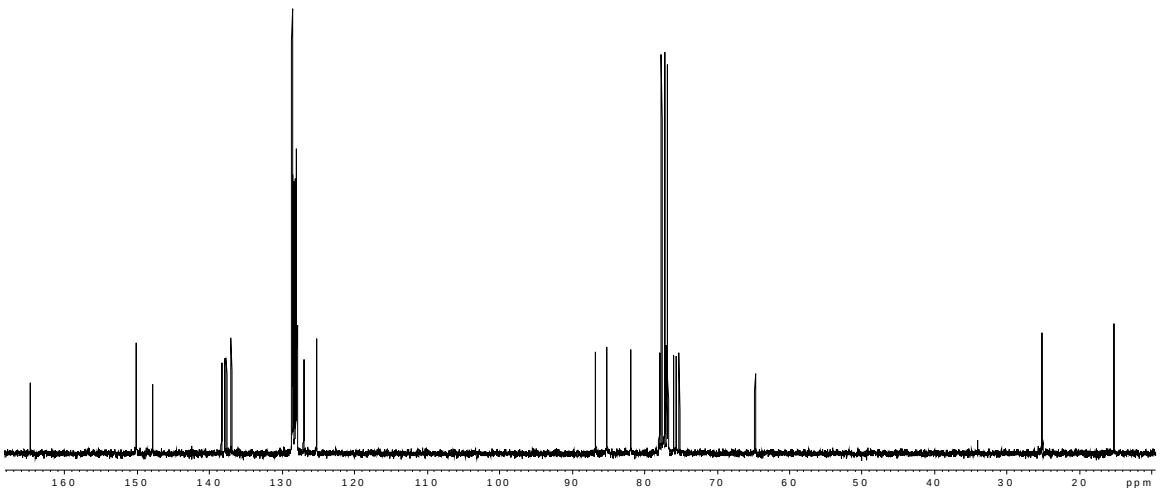
$CDCl_3$ 300 MHz

Figure A-21: 2-D NMR COSY spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-glucopyranoside (**2.1g**)



$CDCl_3$ 300 MHz

Figure A-22: ^{1}H NMR spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-1-thio-β-D-glucopyranoside (**2.1h**)



$CDCl_3$ 75 MHz

Figure A-23: ^{13}C NMR spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-1-thio-β-D-glucopyranoside (**2.1h**)

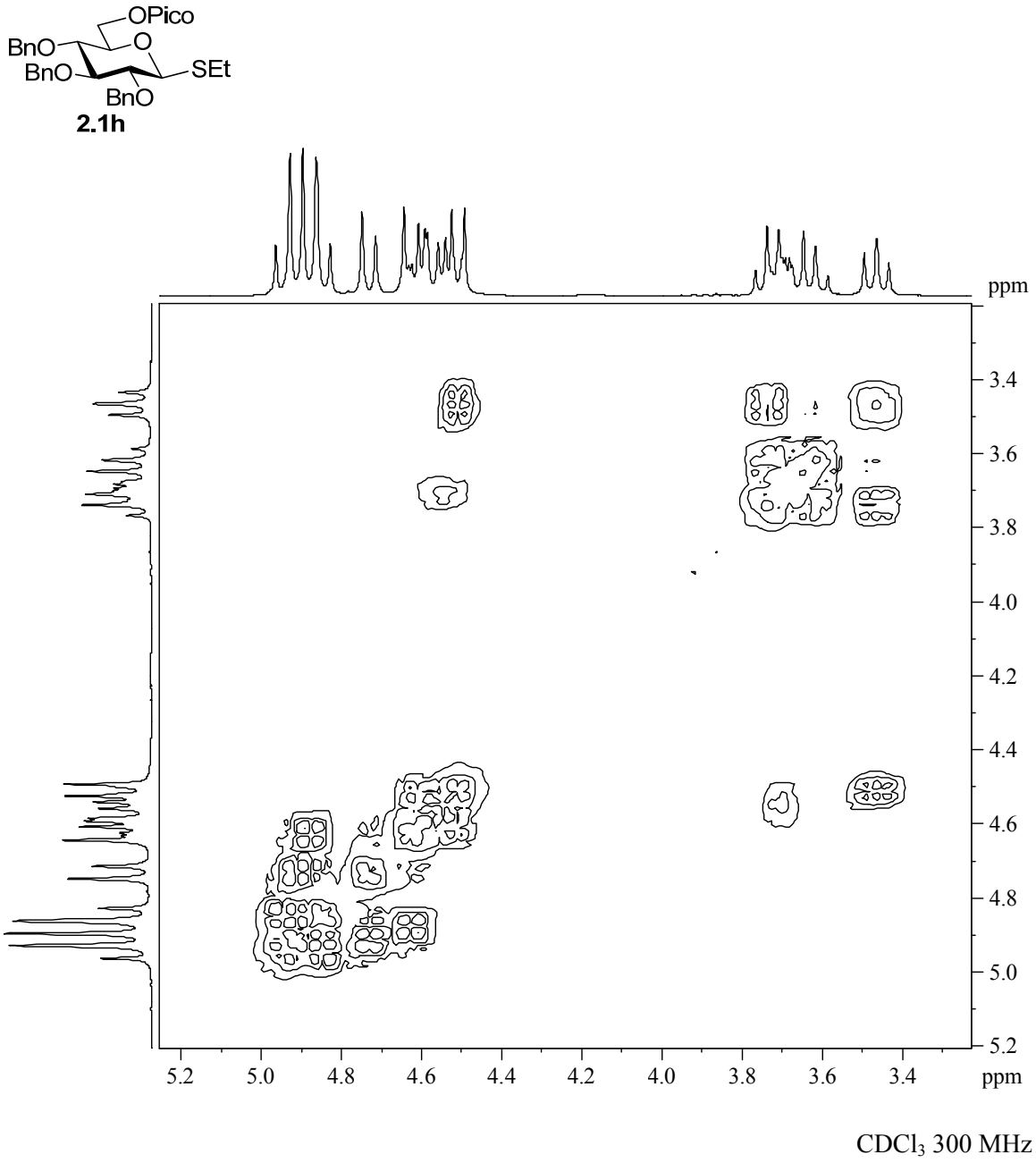


Figure A-24: 2-D NMR COSY spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-1-thio-β-D-glucopyranoside (**2.1h**)

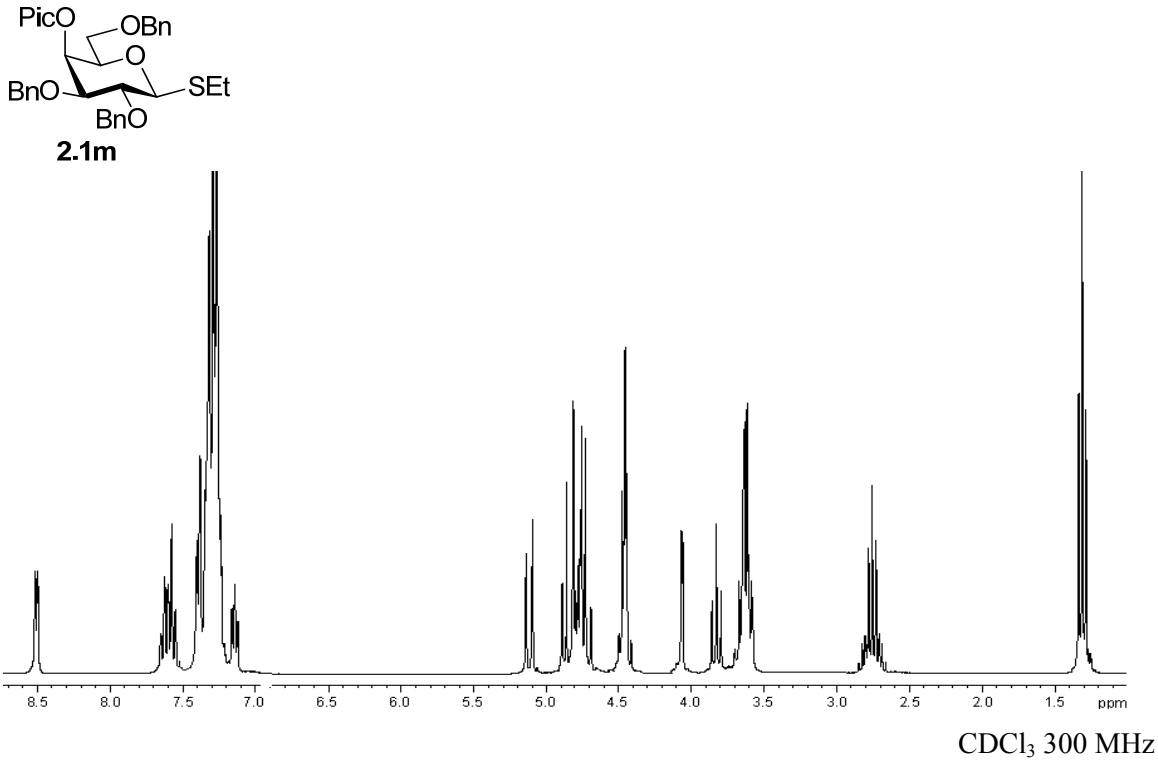


Figure A-25: ^{1}H NMR spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picolinyl-1-thio-β-D-galactopyranoside (**2.1m**)

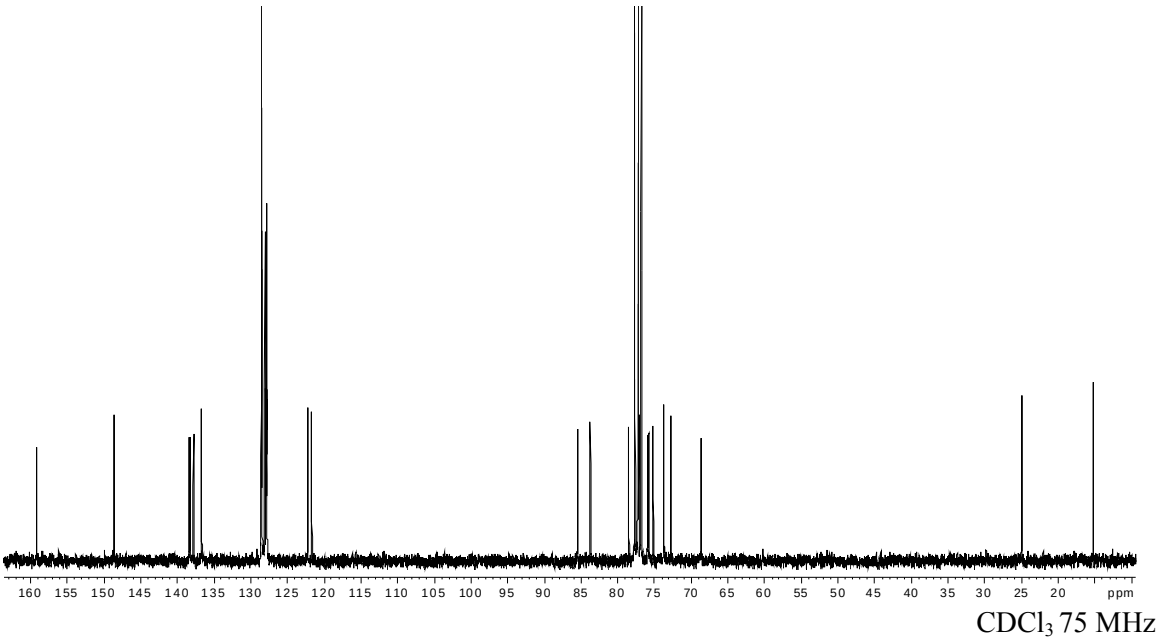


Figure A-26: ^{13}C NMR spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picolinyl-1-thio-β-D-galactopyranoside (**2.1m**)

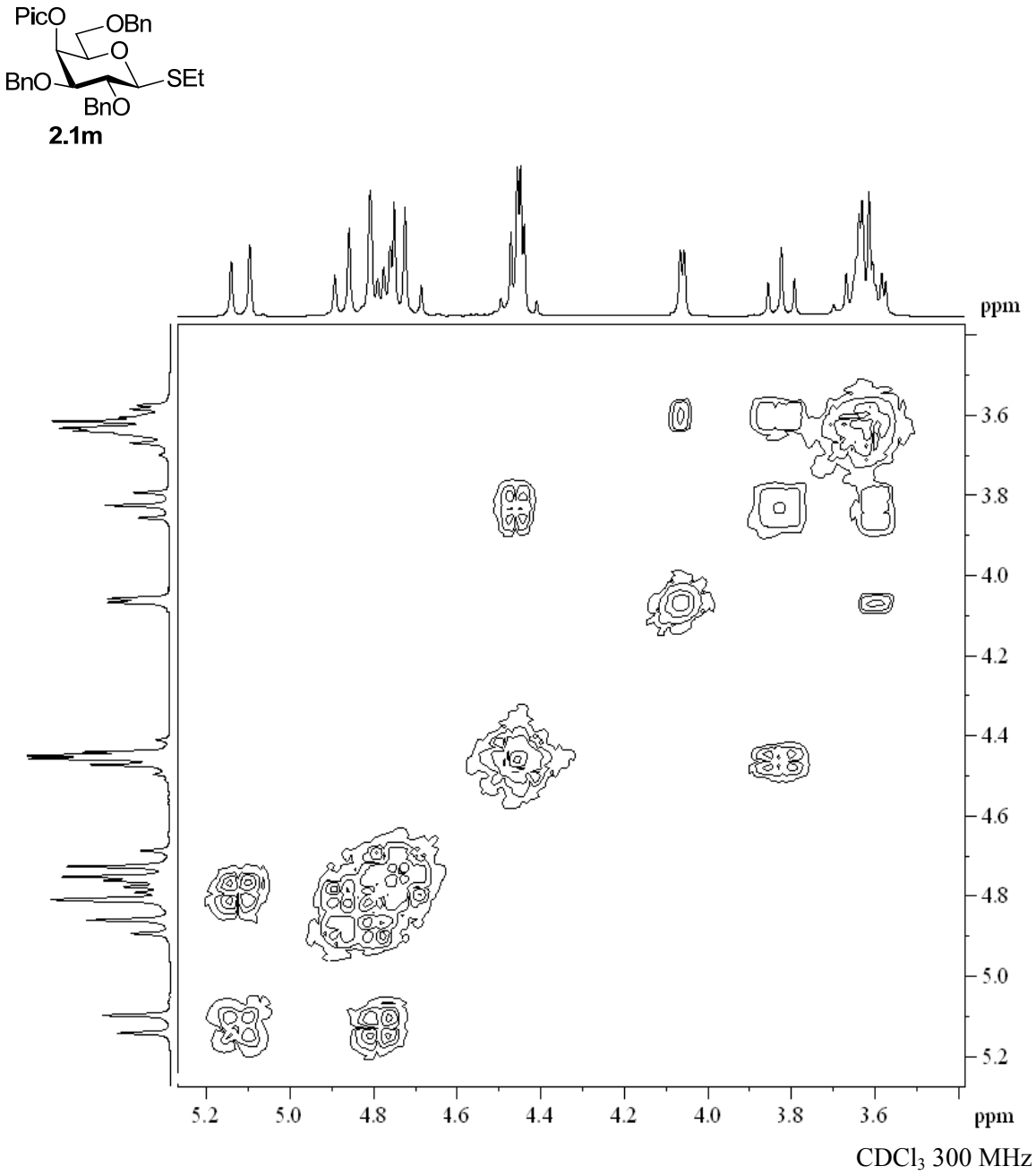


Figure A-27: 2-D NMR COSY spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picolinyl-1-thio-β-D-galactopyranoside (**2.1m**)

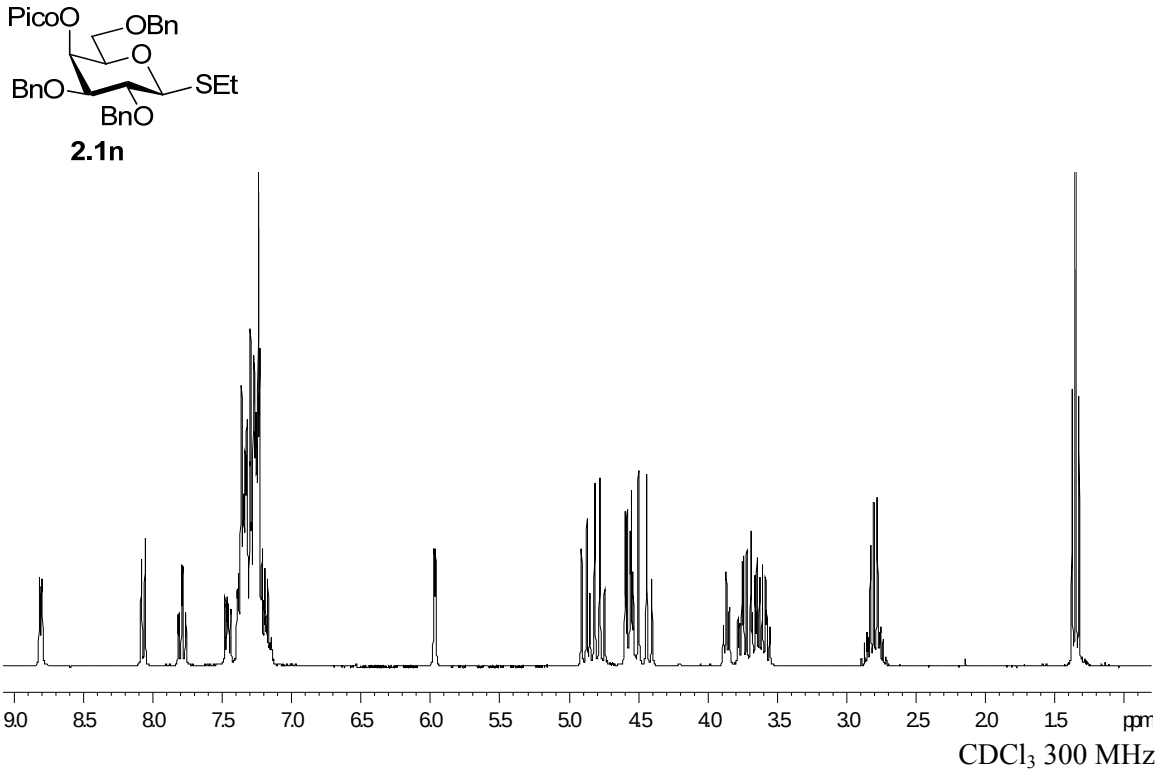


Figure A-28: ^{1}H NMR spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-galactopyranoside (**2.1n**)

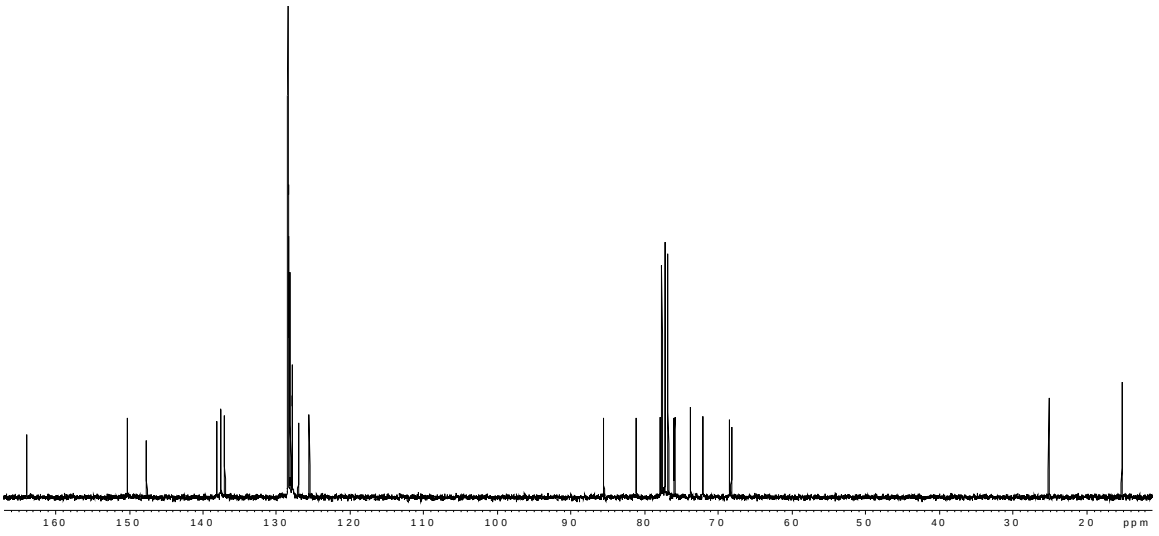


Figure A-29: ^{13}C NMR spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-galactopyranoside (**2.1n**)

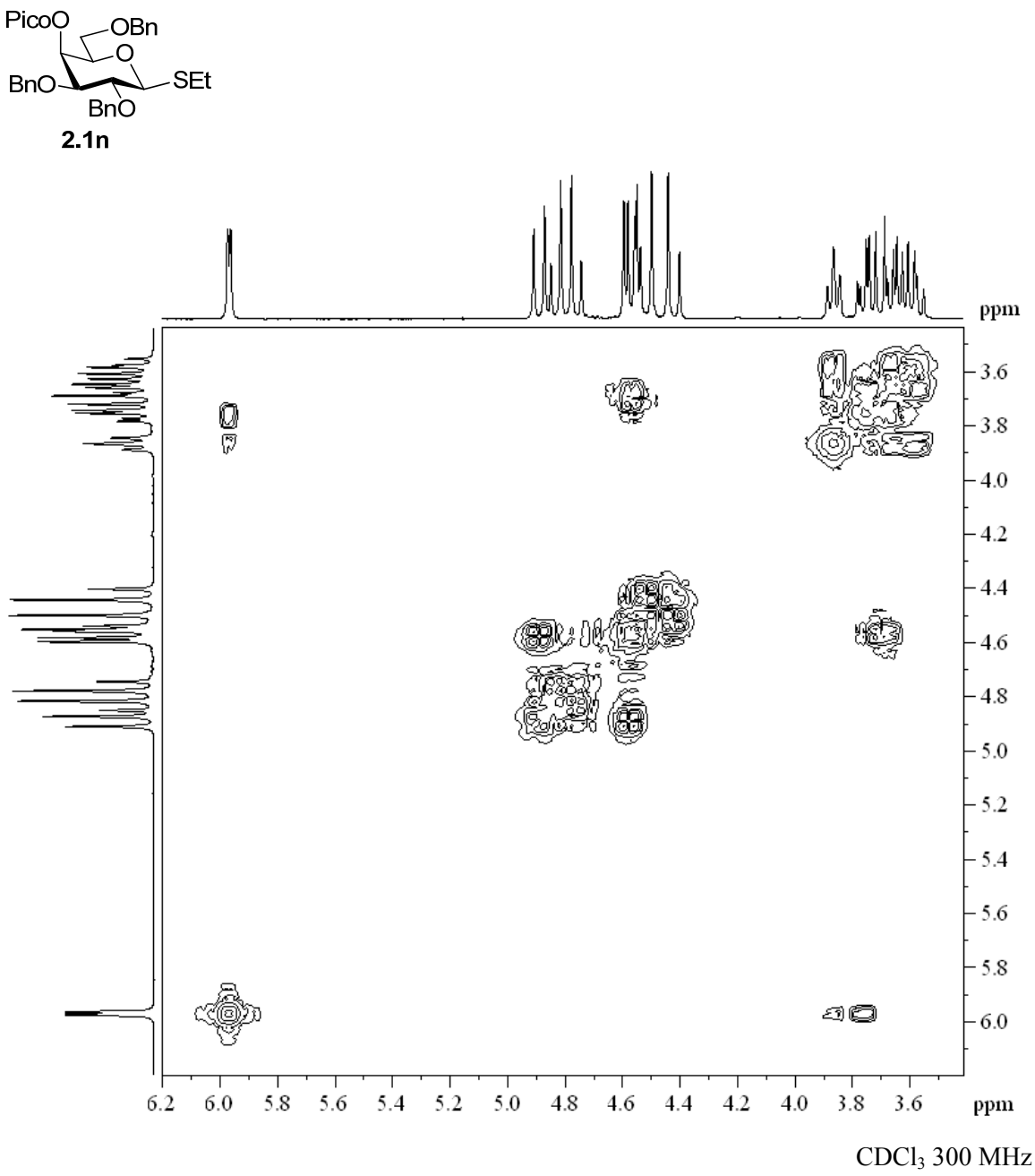
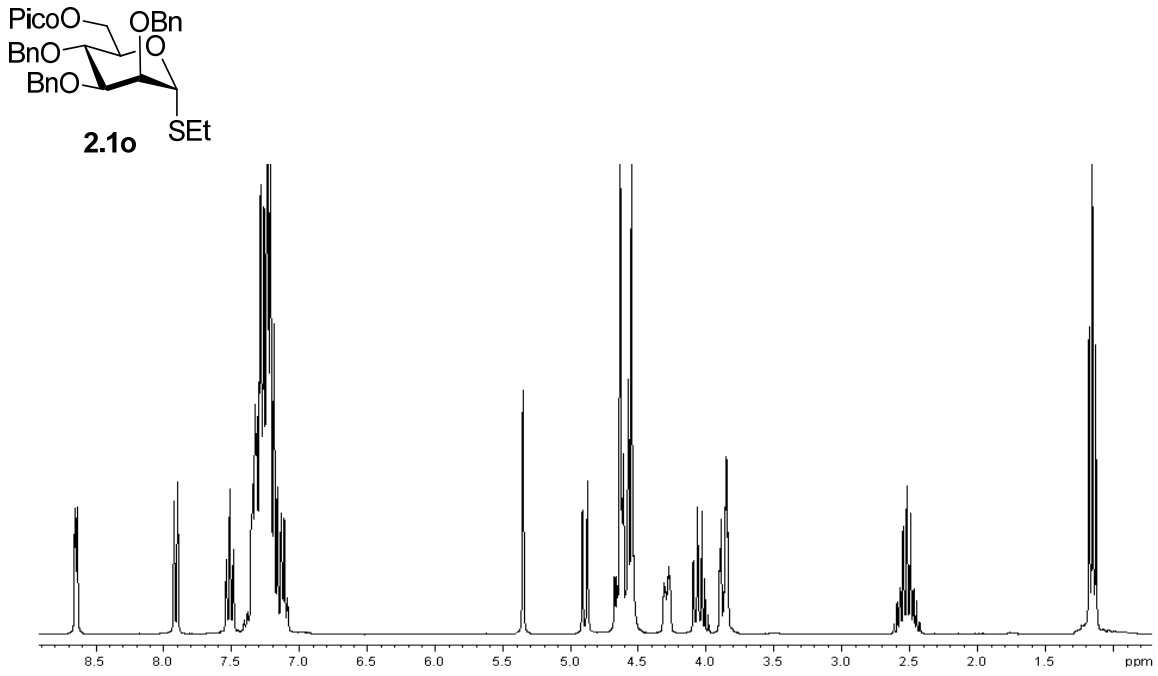
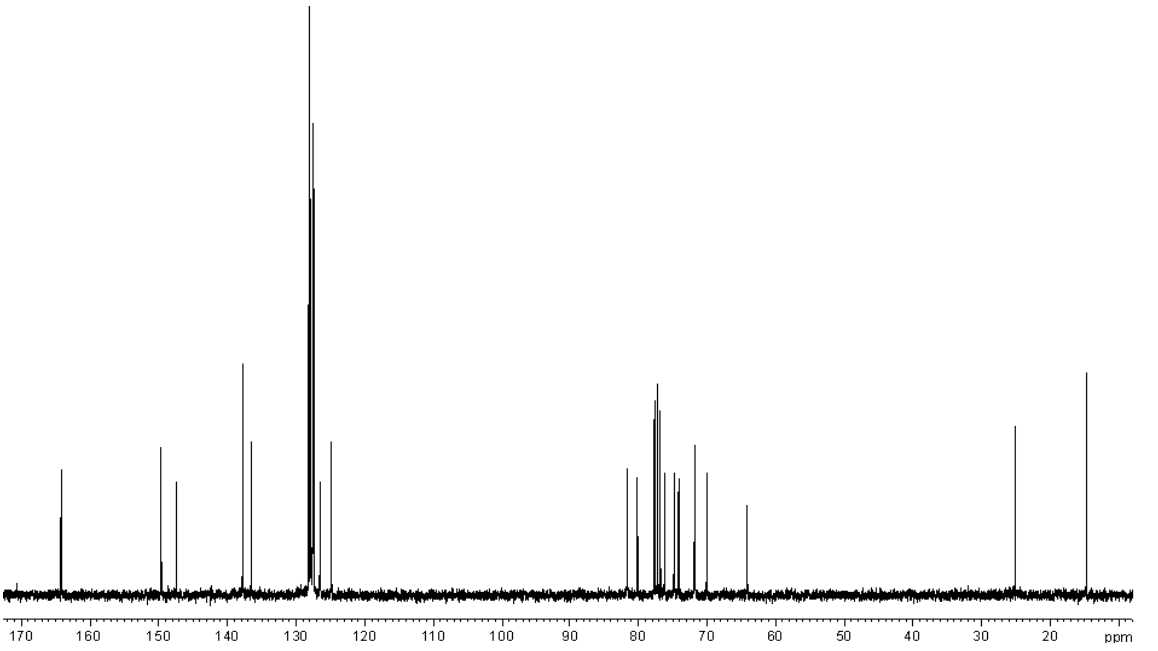


Figure A-30: 2-D NMR COSY spectrum of Ethyl 2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-1-thio-β-D-galactopyranoside (**2.1n**)



$CDCl_3$ 300 MHz

Figure A-31: ^{1}H NMR spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-1-thio-α-D-mannopyranoside (**2.1o**)



$CDCl_3$ 75 MHz

Figure A-32: ^{13}C NMR spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-1-thio-α-D-mannopyranoside (**2.1o**)

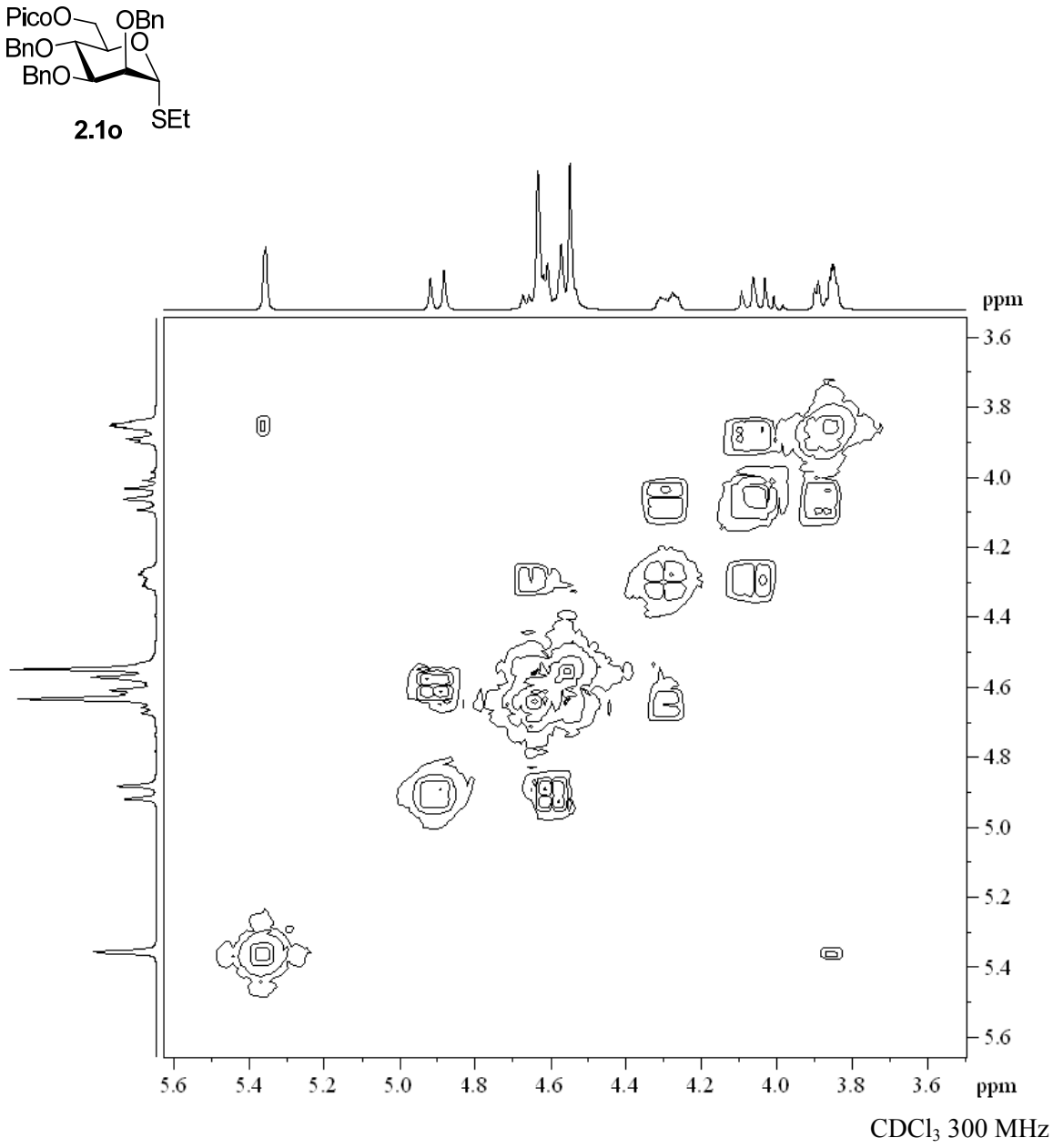


Figure A-33: 2-D NMR COSY spectrum of Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-1-thio-α-D-mannopyranoside (**2.1o**)

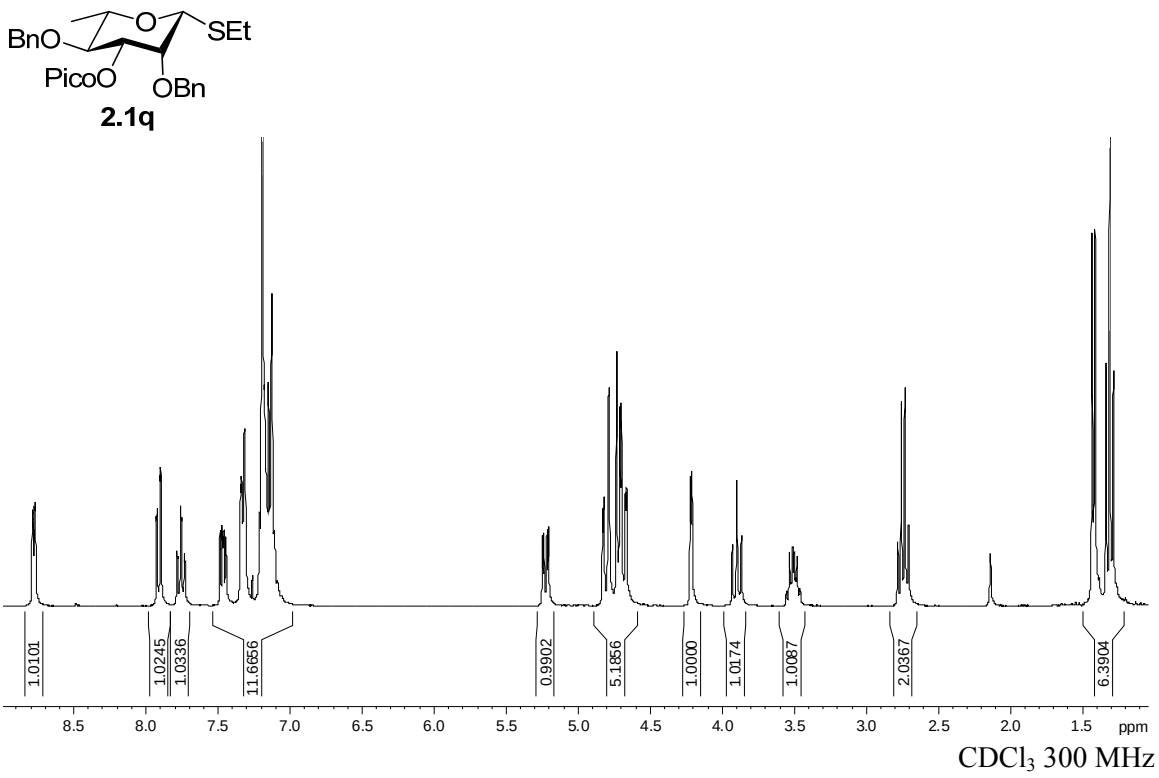


Figure A-34: ^{1}H NMR spectrum of Ethyl 2,4-di-*O*-benzyl-3-*O*-picoloyl-1-thio-β-L-rhamnopyranoside (**2.1q**)

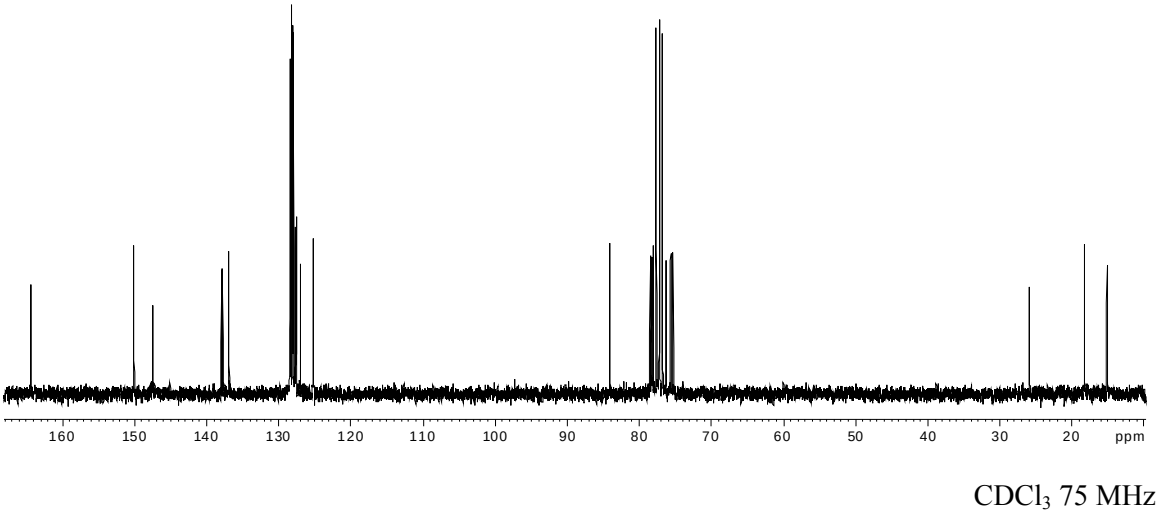


Figure A-35: ^{13}C NMR spectrum of Ethyl 2,4-di-*O*-benzyl-3-*O*-picoloyl-1-thio-β-L-rhamnopyranoside (**2.1q**)

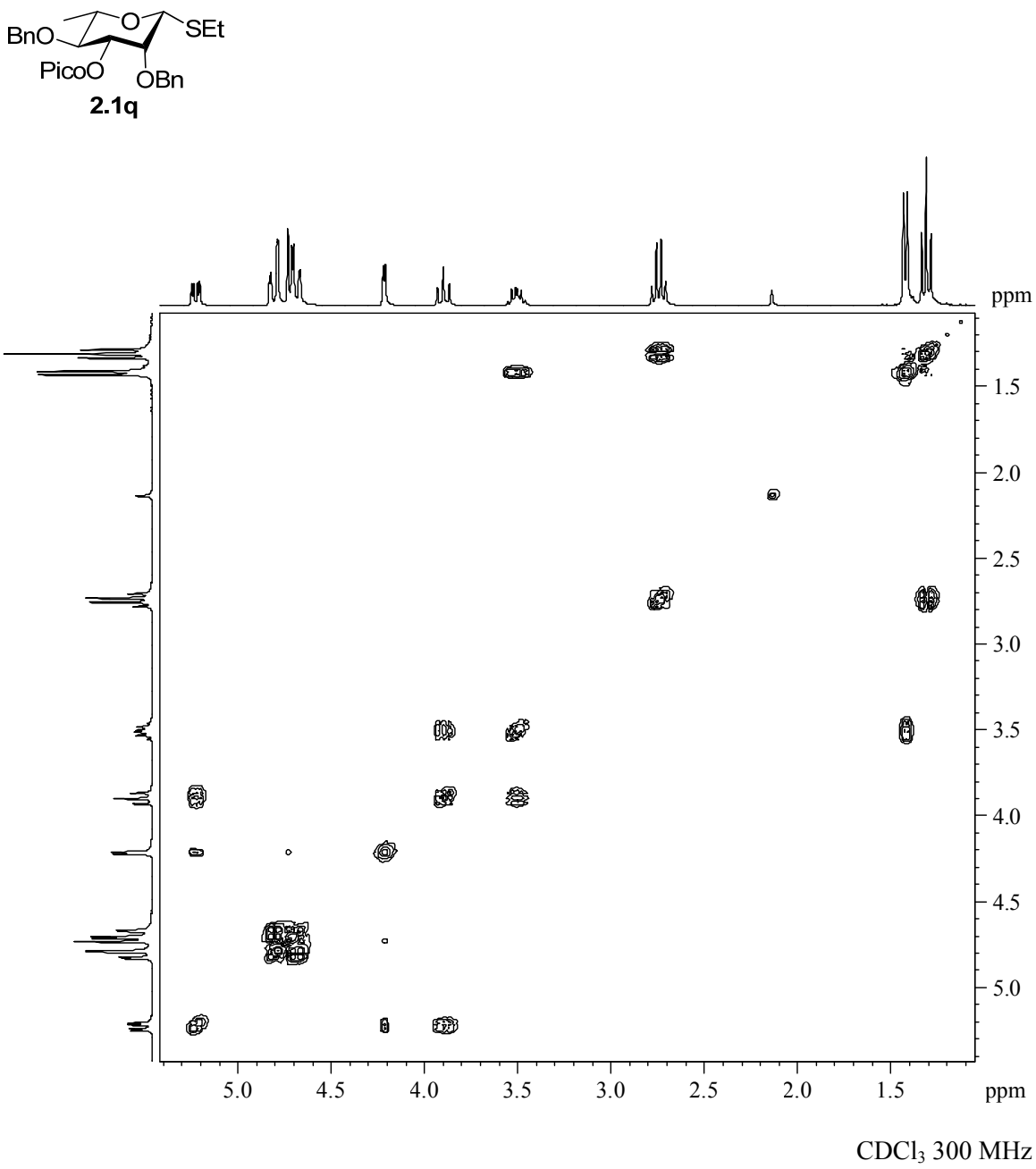


Figure A-36: 2-D NMR COSY spectrum of Ethyl 2,4-di-*O*-benzyl-3-*O*-picoloyl-1-thio-β-L-rhamnopyranoside (**2.1q**)

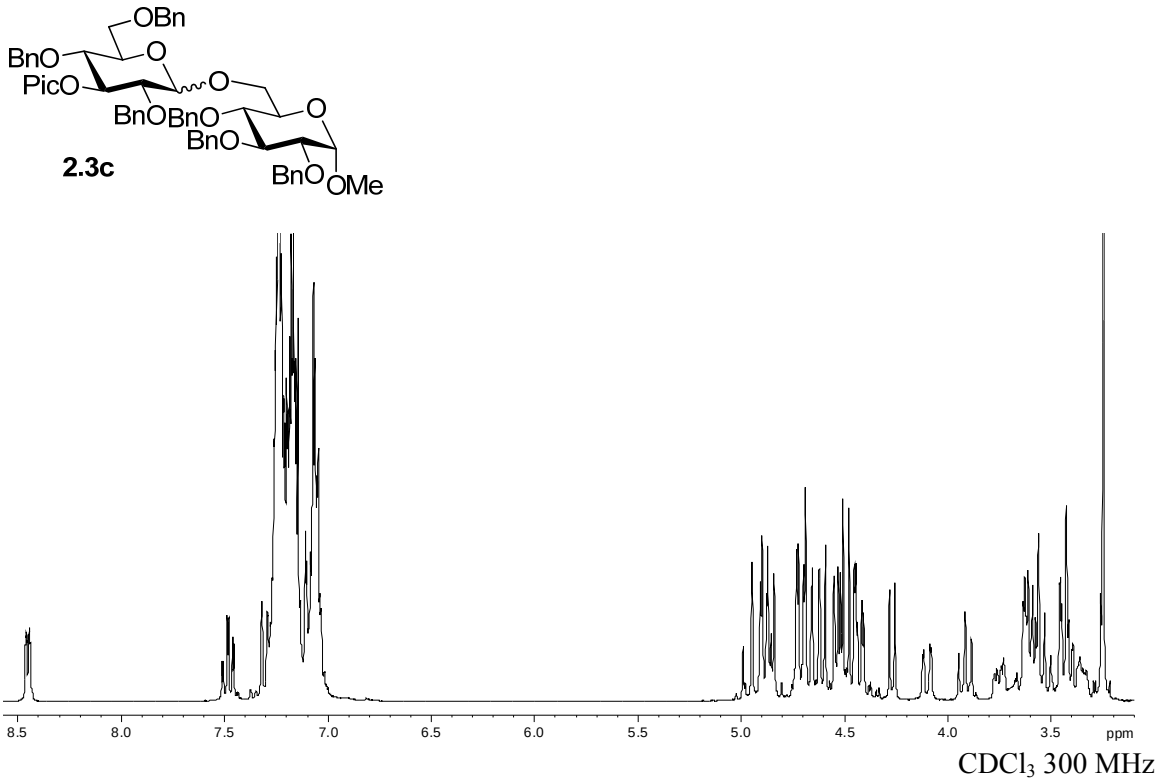


Figure A-37: ^{1}H NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,4,6-tri-*O*-benzyl-3-*O*-picolinyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (**2.3c**)

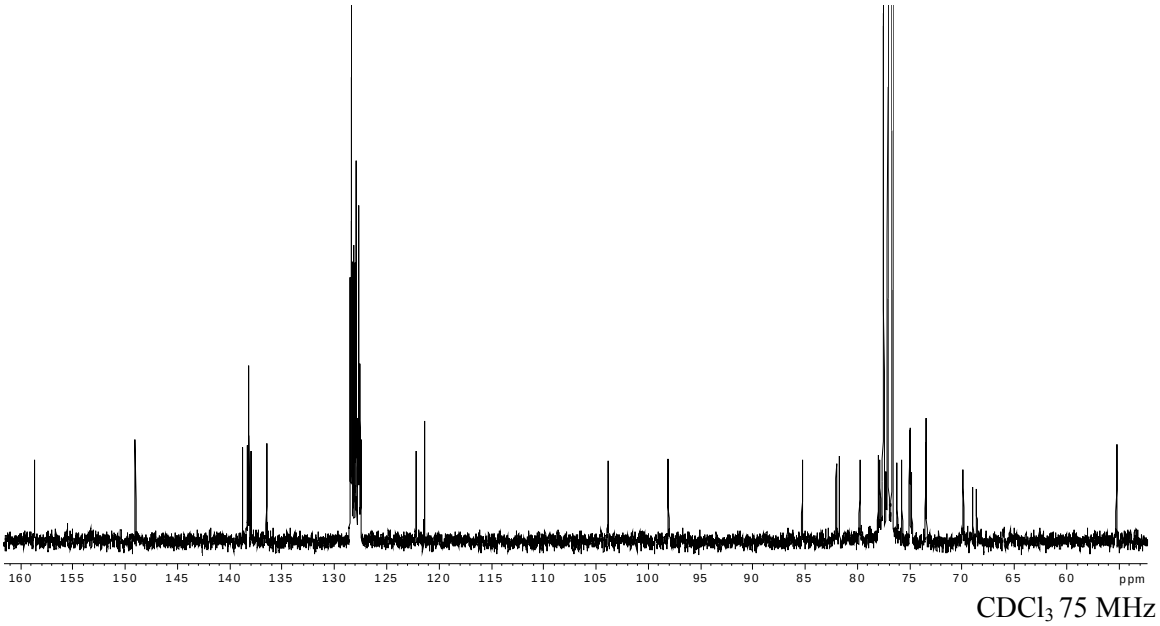


Figure A-38: ^{13}C NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,4,6-tri-*O*-benzyl-3-*O*-picolinyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (**2.3c**)

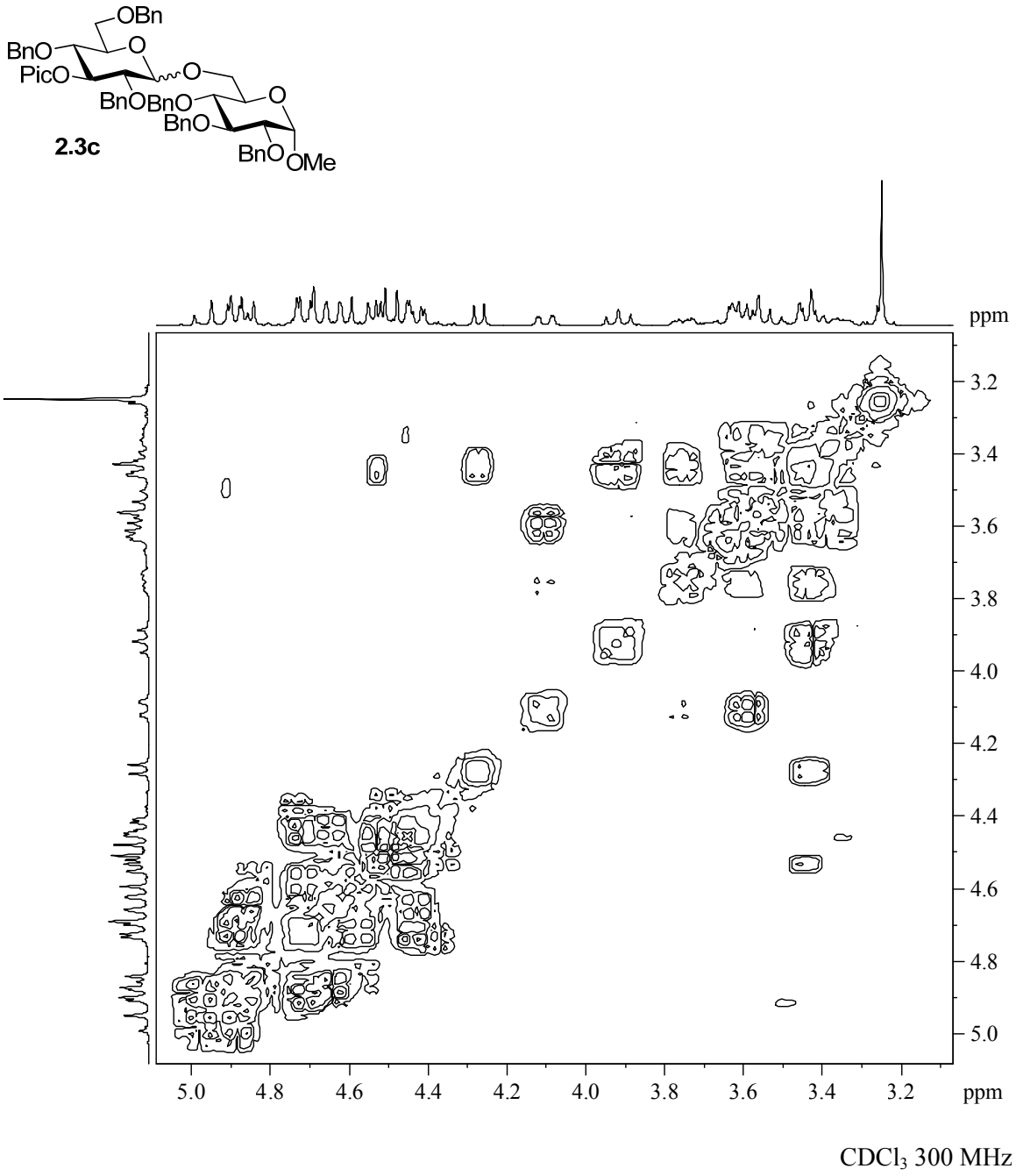
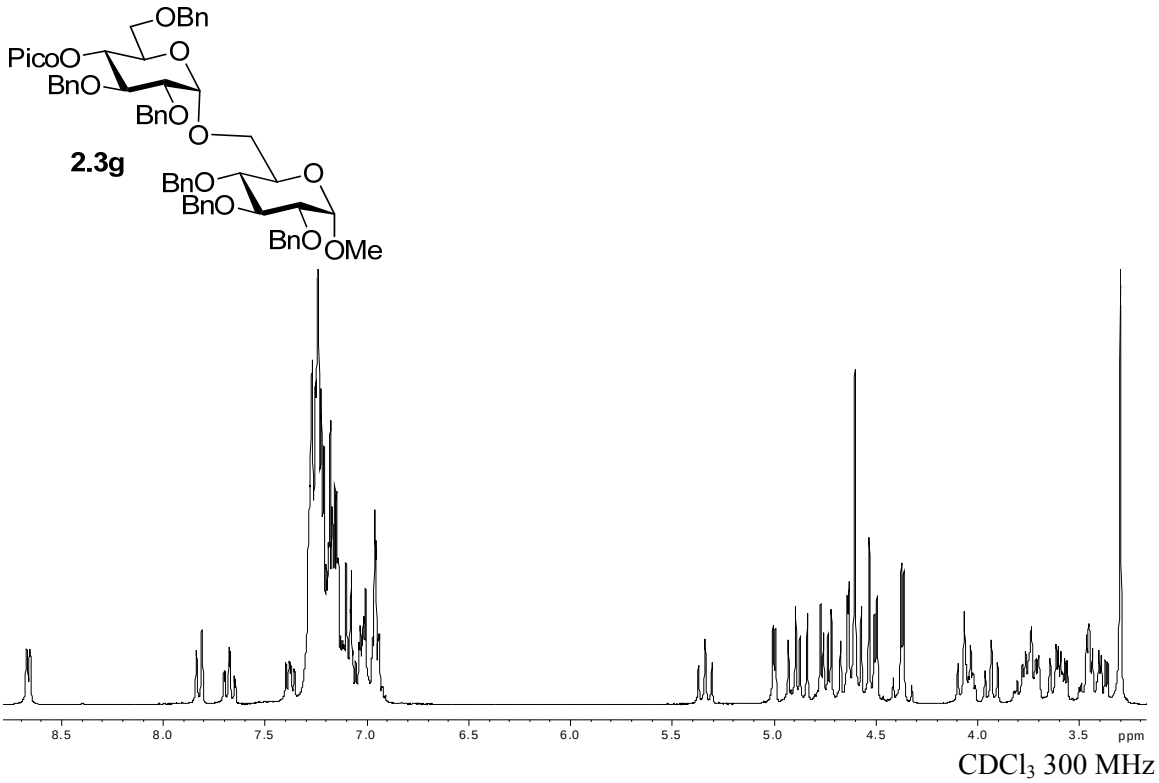
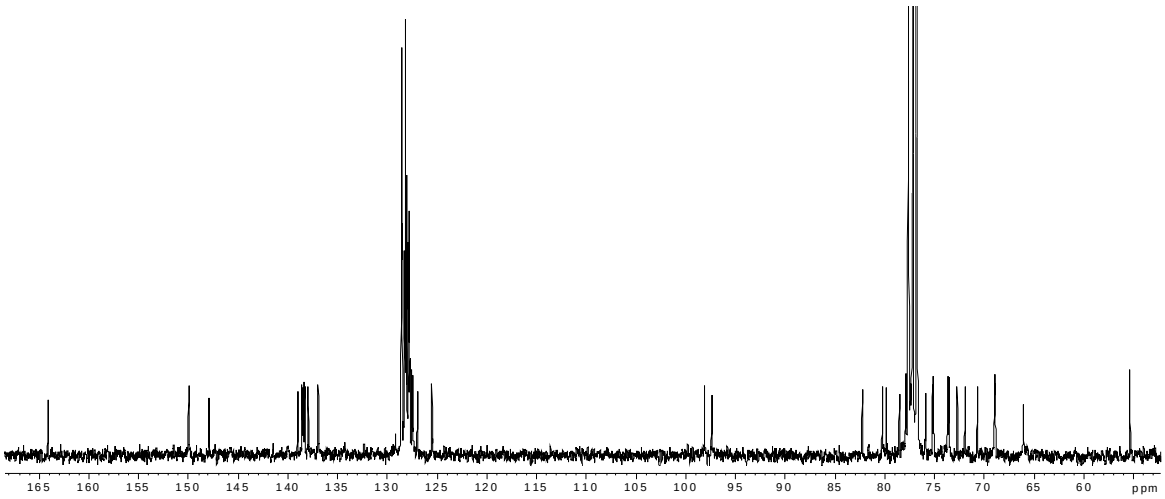


Figure A-39: 2-D NMR COSY spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,4,6-tri-*O*-benzyl-3-*O*-picolinyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (**2.3c**)



$CDCl_3$ 300 MHz

Figure A-40: ^{1}H NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**2.3g**)



$CDCl_3$ 75 MHz

Figure A-41: ^{13}C NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**2.3g**)

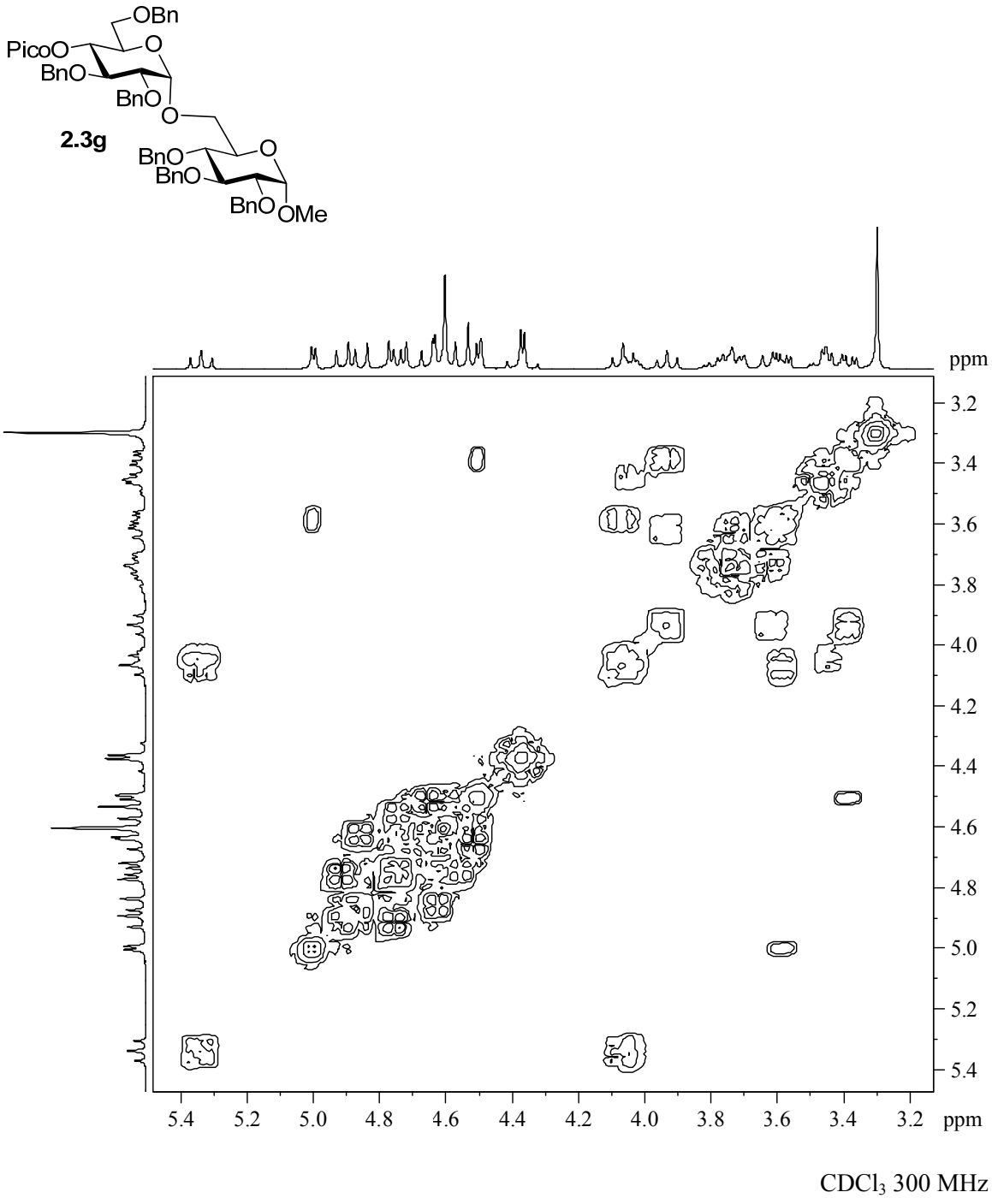


Figure A-42: 2-D NMR COSY spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**2.3g**)

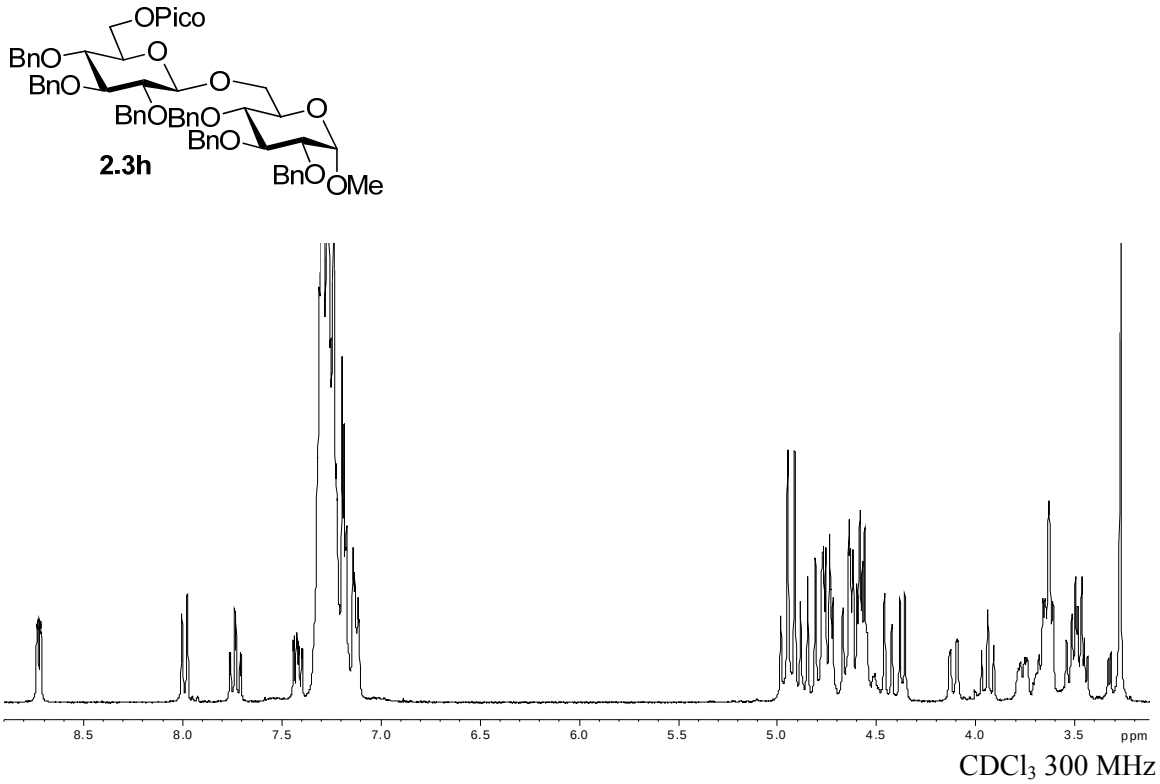


Figure A-43: ^{1}H NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**2.3h**)

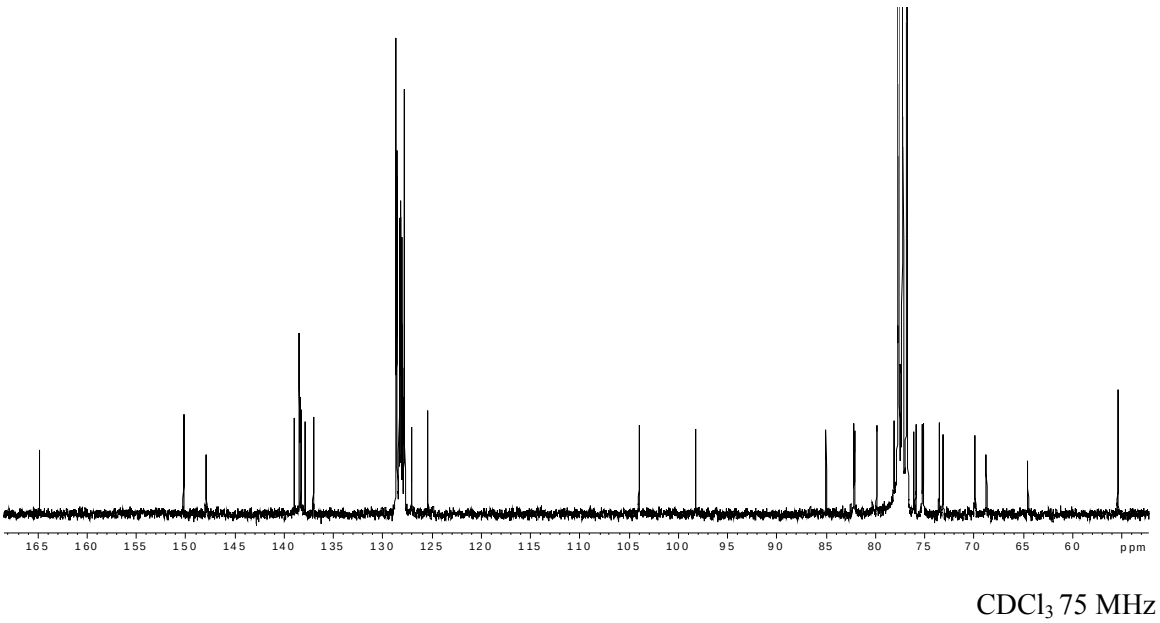


Figure A-44: ^{13}C NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**2.3h**)

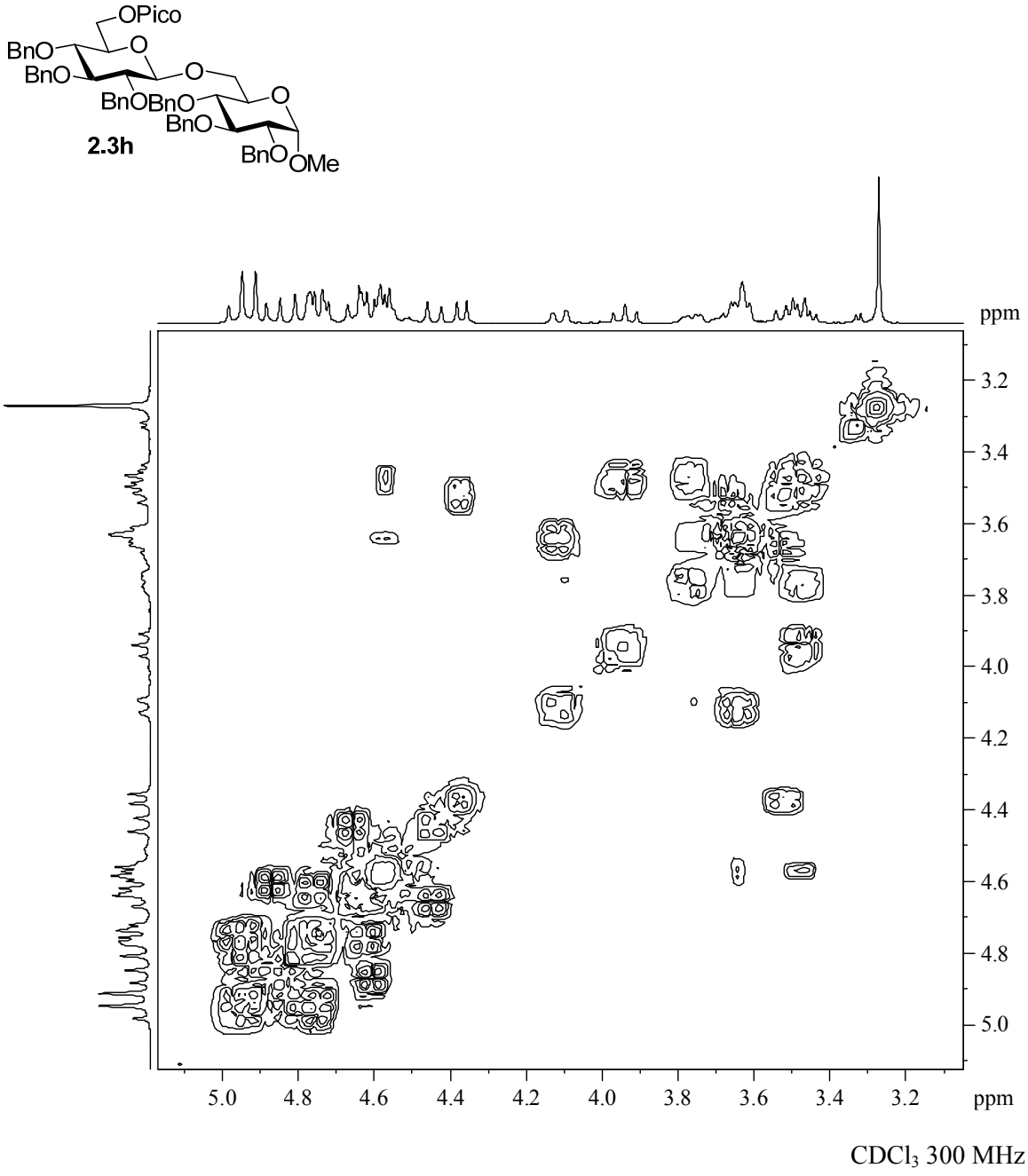


Figure A-45: 2-D NMR COSY spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**2.3h**)

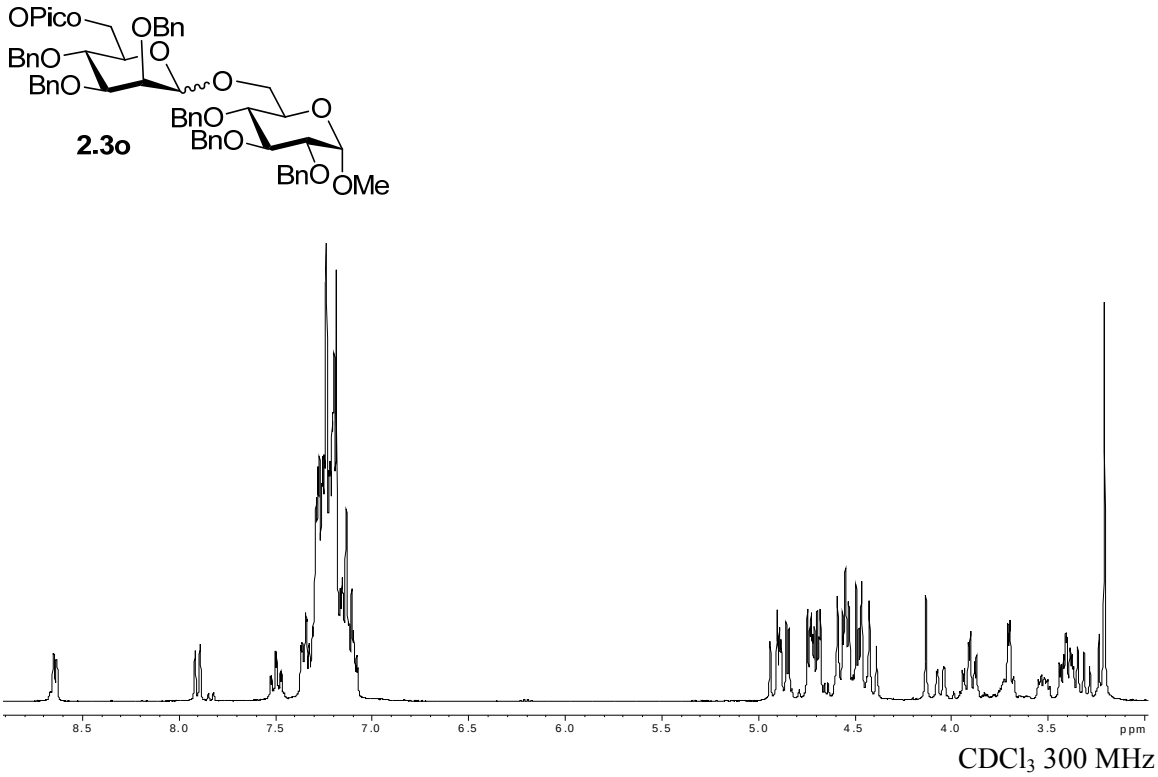


Figure A-46: ^{1}H NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside (**2.3o**)

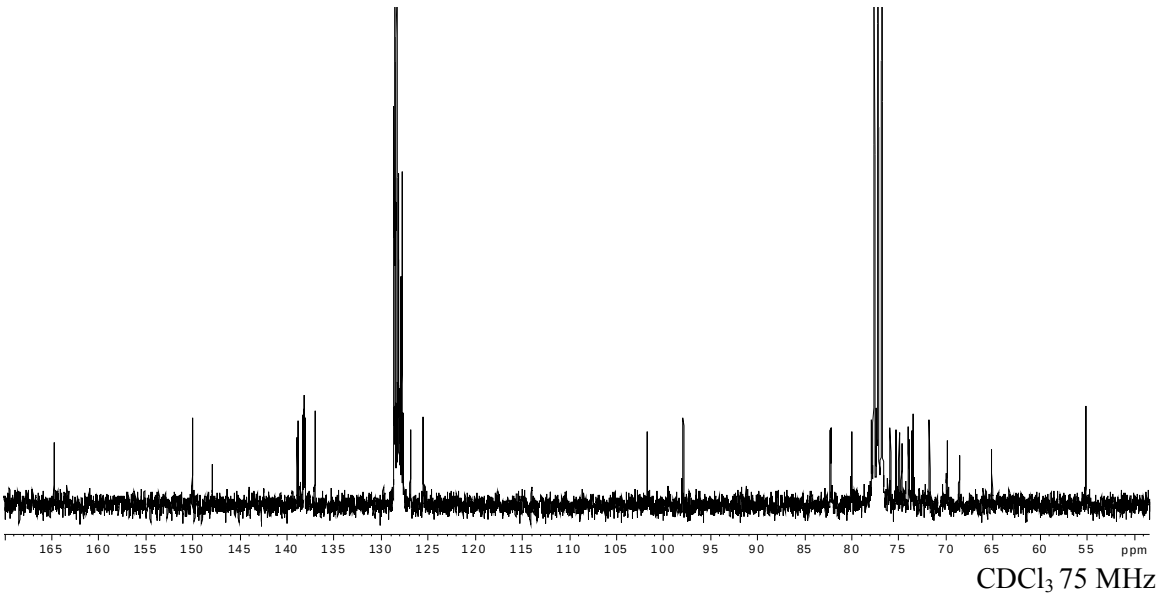


Figure A-47: ^{13}C NMR spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside (**2.3o**)

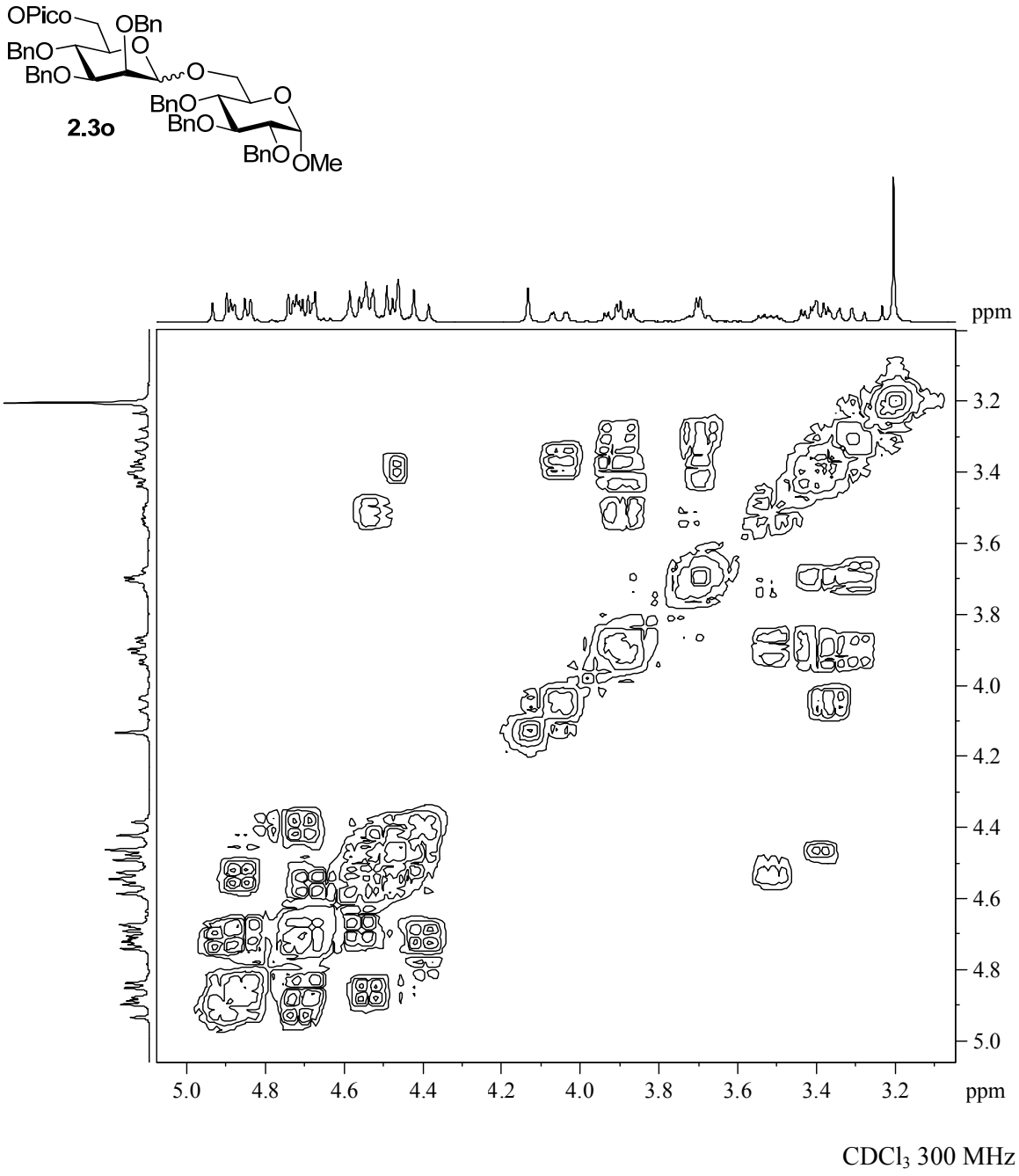
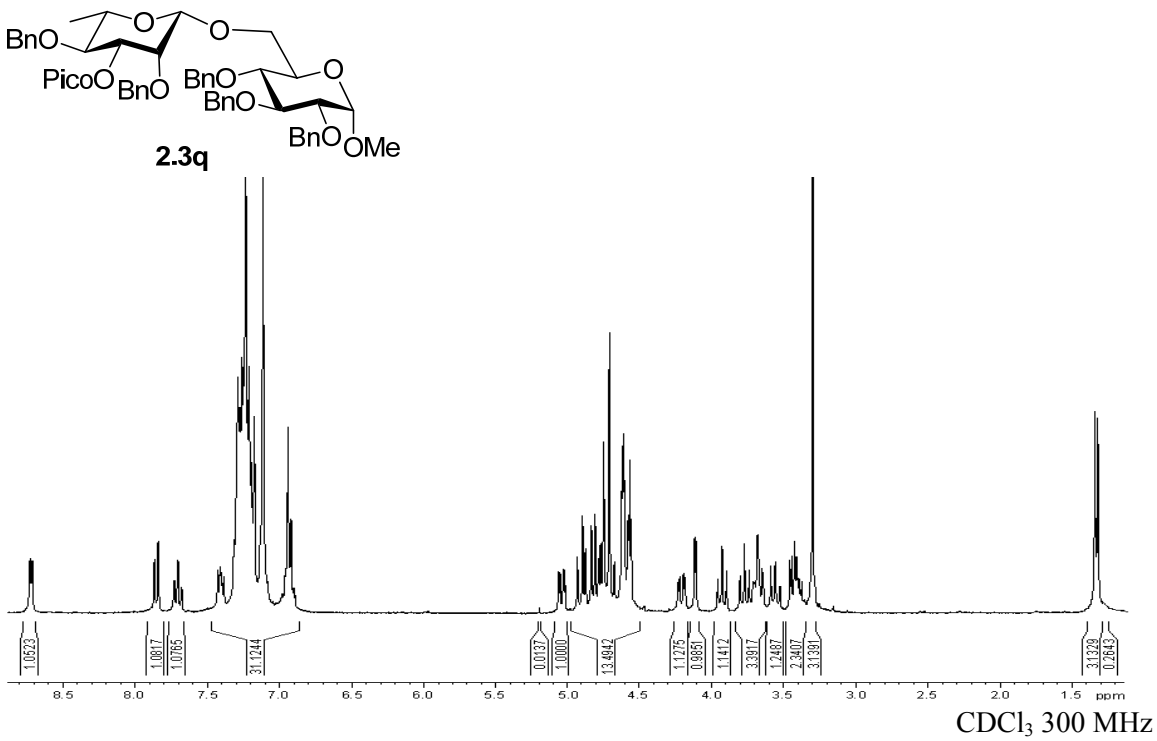
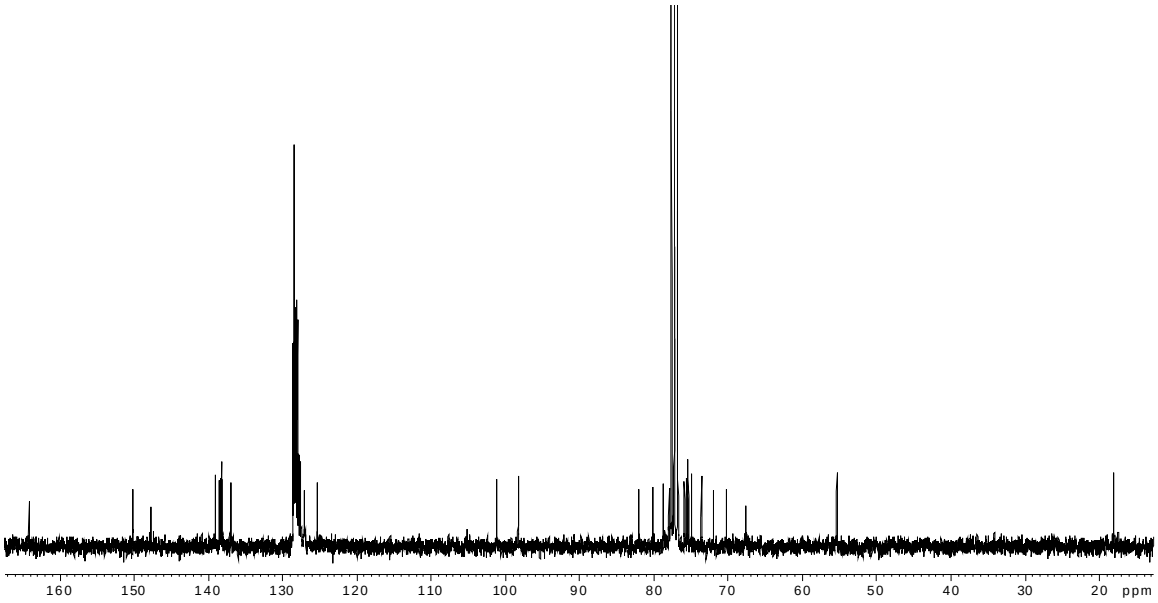


Figure A-48: 2-D NMR COSY spectrum of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-picoloyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside (**2.3o**)



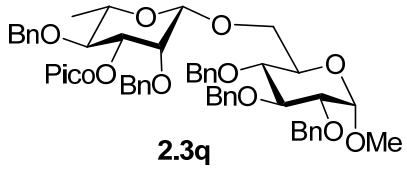
$CDCl_3$ 300 MHz

Figure A-49: ^{1}H NMR spectrum of Methyl 2,3,4-tri-O-benzyl-6-O-(2,4-di-O-benzyl-3-O-picoloyl-β-L-rhamnopyranosyl)-α-D-glucopyranoside (**2.3q**)

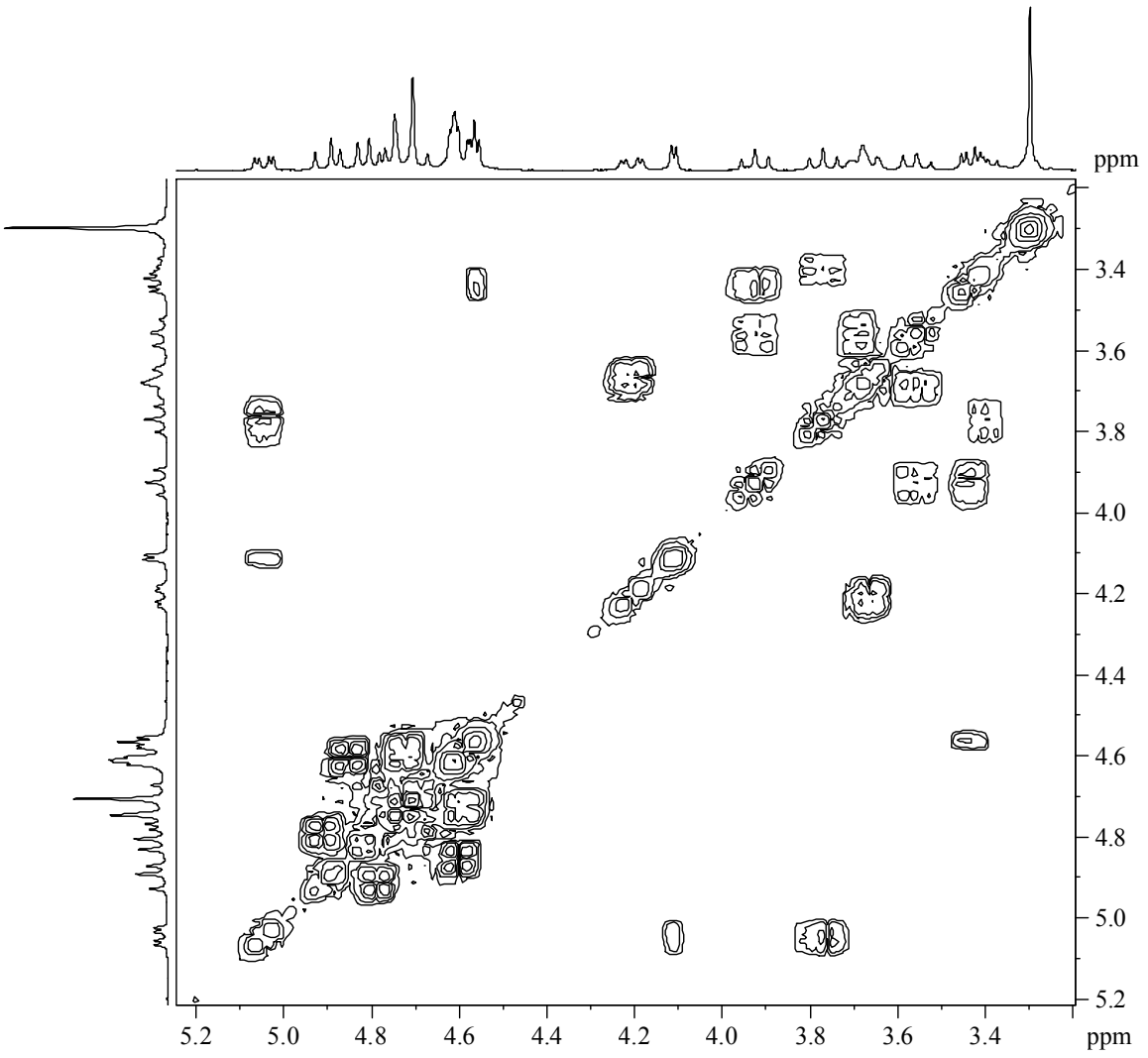


$CDCl_3$ 75 MHz

Figure A-50: ^{13}C NMR spectrum of Methyl 2,3,4-tri-O-benzyl-6-O-(2,4-di-O-benzyl-3-O-picoloyl-β-L-rhamnopyranosyl)-α-D-glucopyranoside (**2.3q**)



2.3q



$CDCl_3$ 300 MHz

Figure A-51: 2-D NMR COSY spectrum of Methyl 2,3,4-tri-O-benzyl-6-O-(2,4-di-O-benzyl-3-O-picoloyl-β-L-rhamnopyranosyl)-α-D-glucopyranoside (**2.3q**)

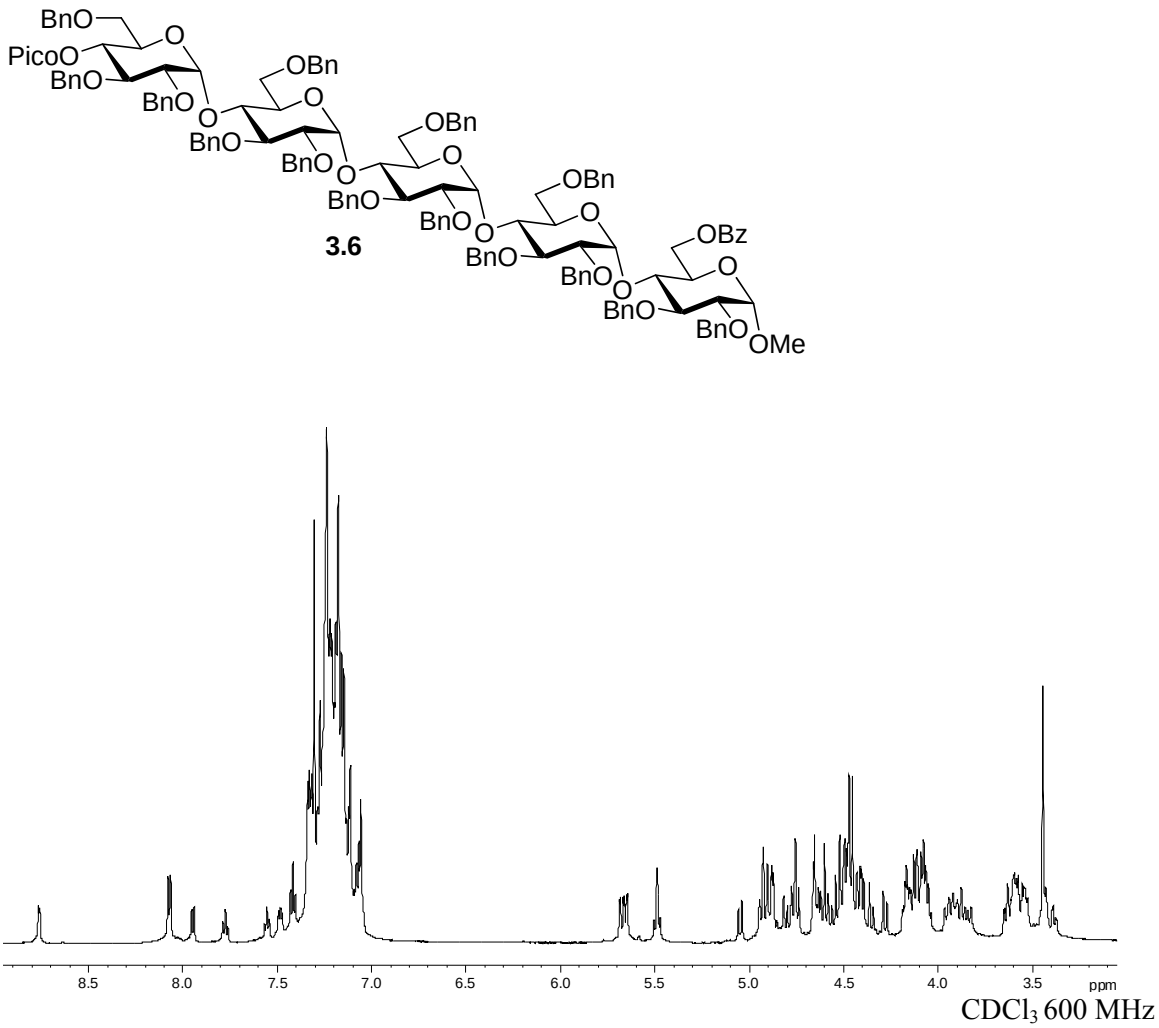
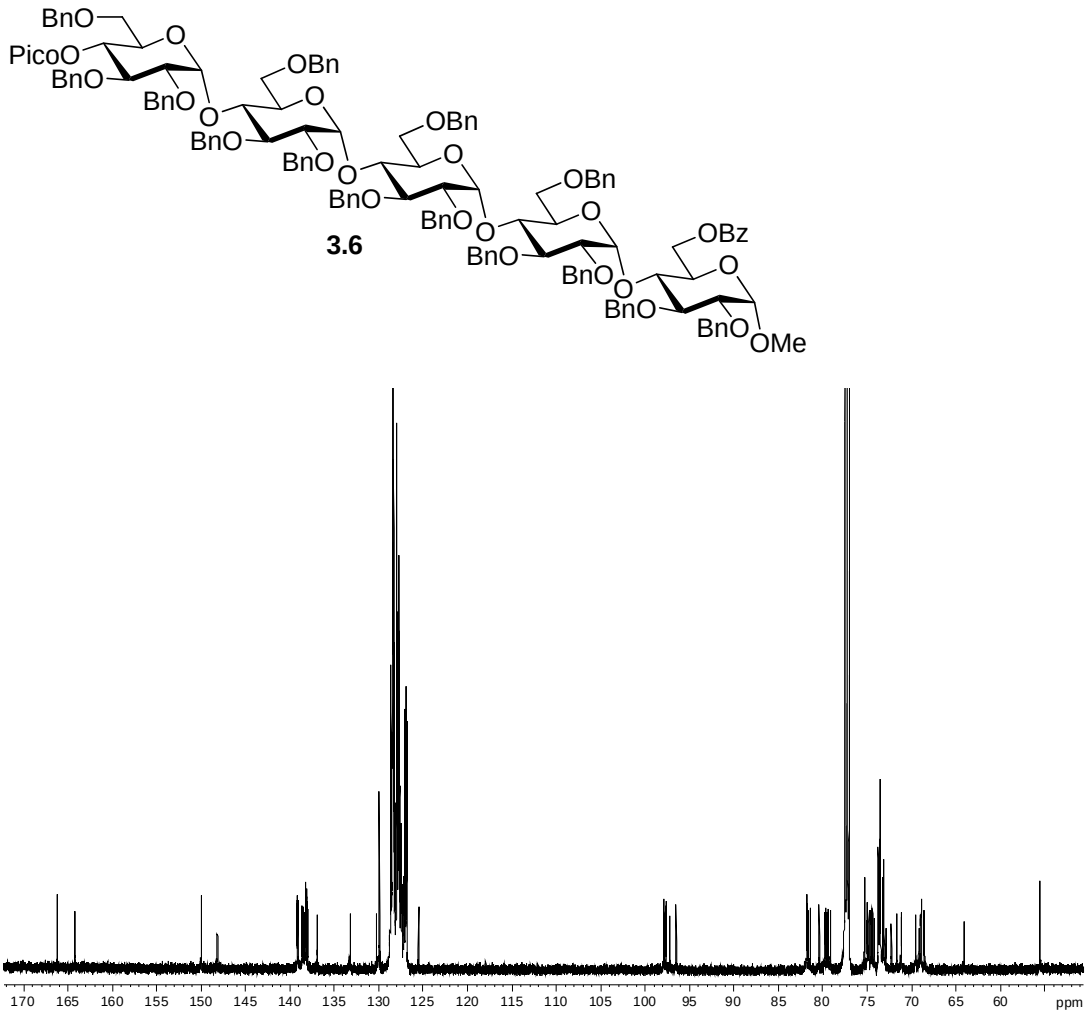
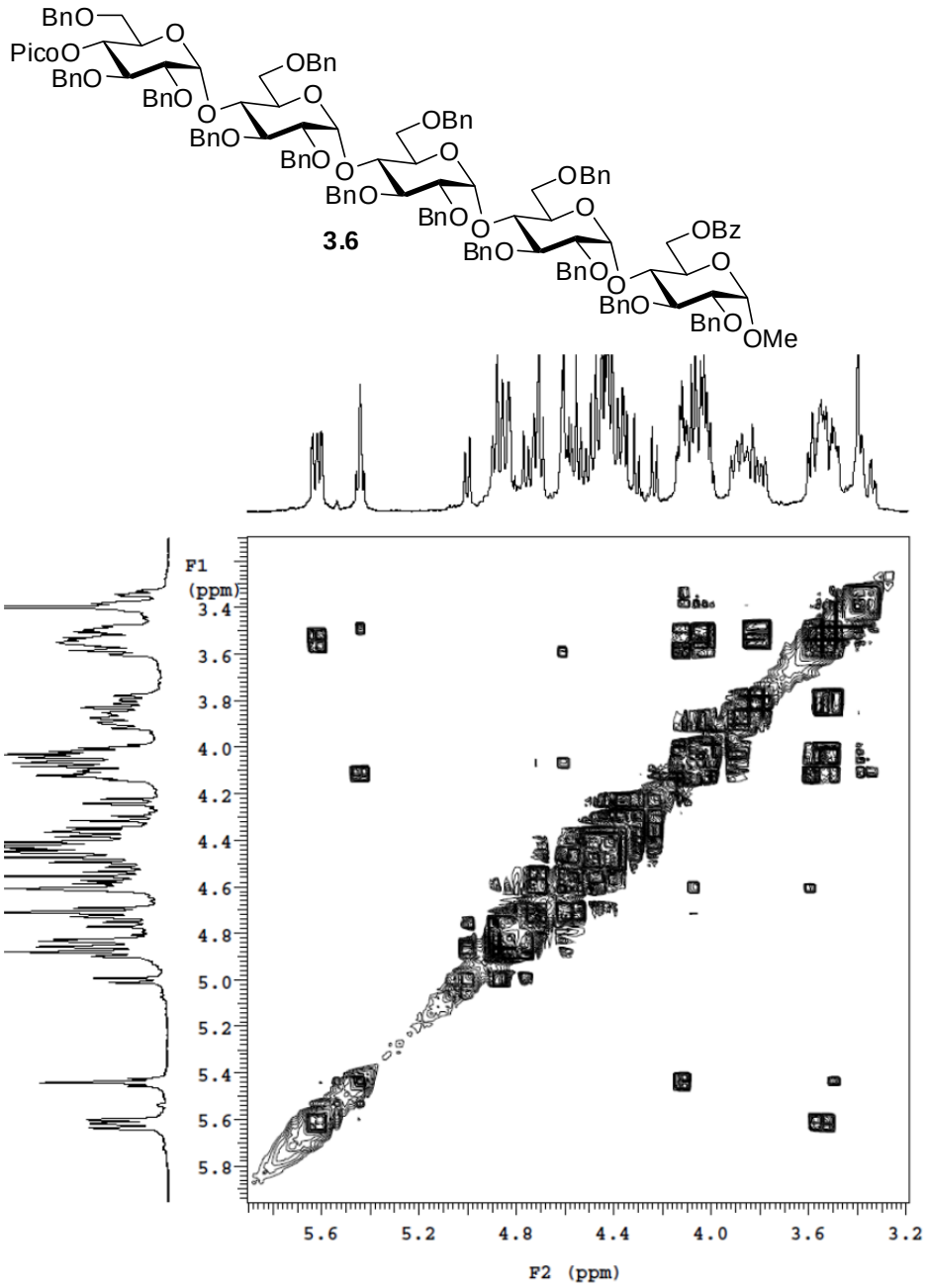


Figure A-52: ^{1}H NMR spectrum of Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (**3.6**)



$CDCl_3$ 150 MHz

Figure A-53: ^{13}C NMR spectrum of Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (**3.6**)



$CDCl_3$ 600 MHz

Figure A-54: 2-D NMR COSY spectrum of Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (**3.6**)

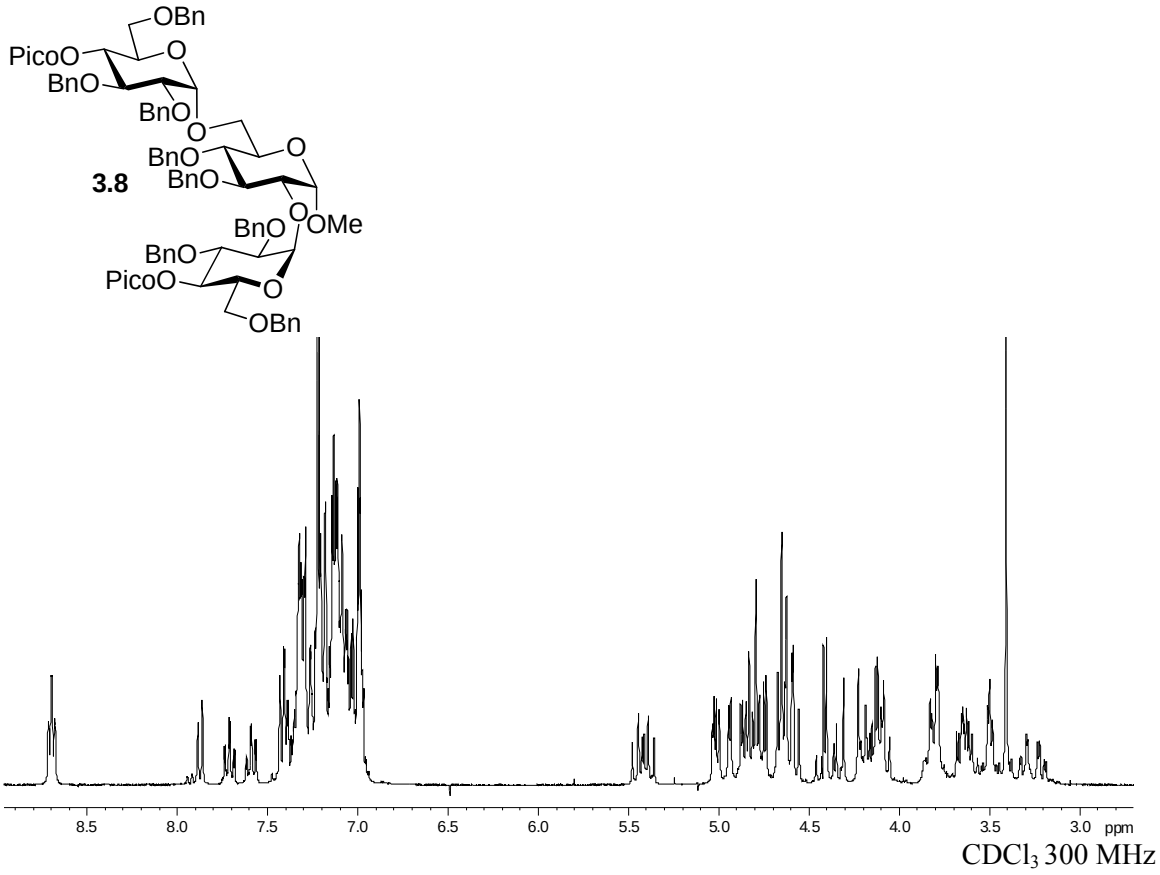


Figure A-55: : ^{1}H NMR spectrum of Methyl 3,4-di-*O*-benzyl-2,6-di-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**3.8**)

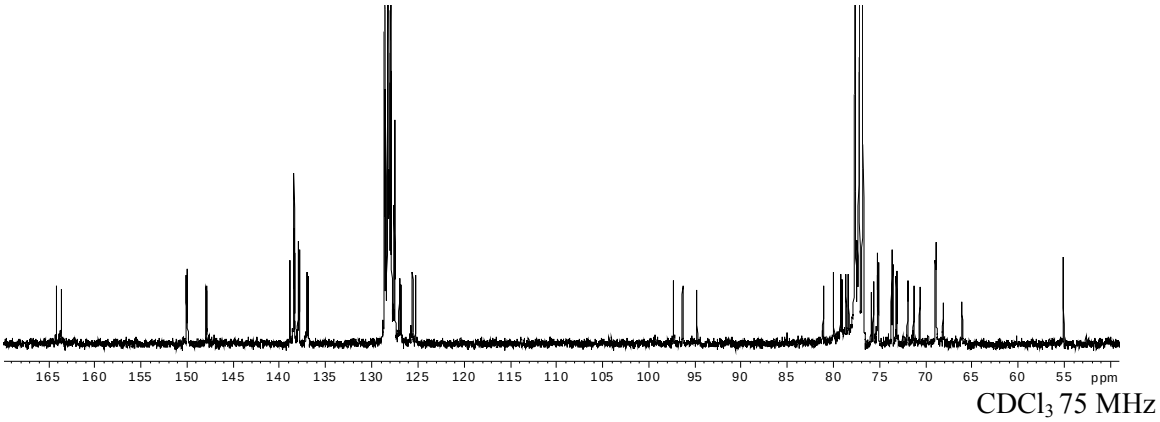


Figure A-56: ^{13}C NMR spectrum of Methyl 3,4-di-*O*-benzyl-2,6-di-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**3.8**)

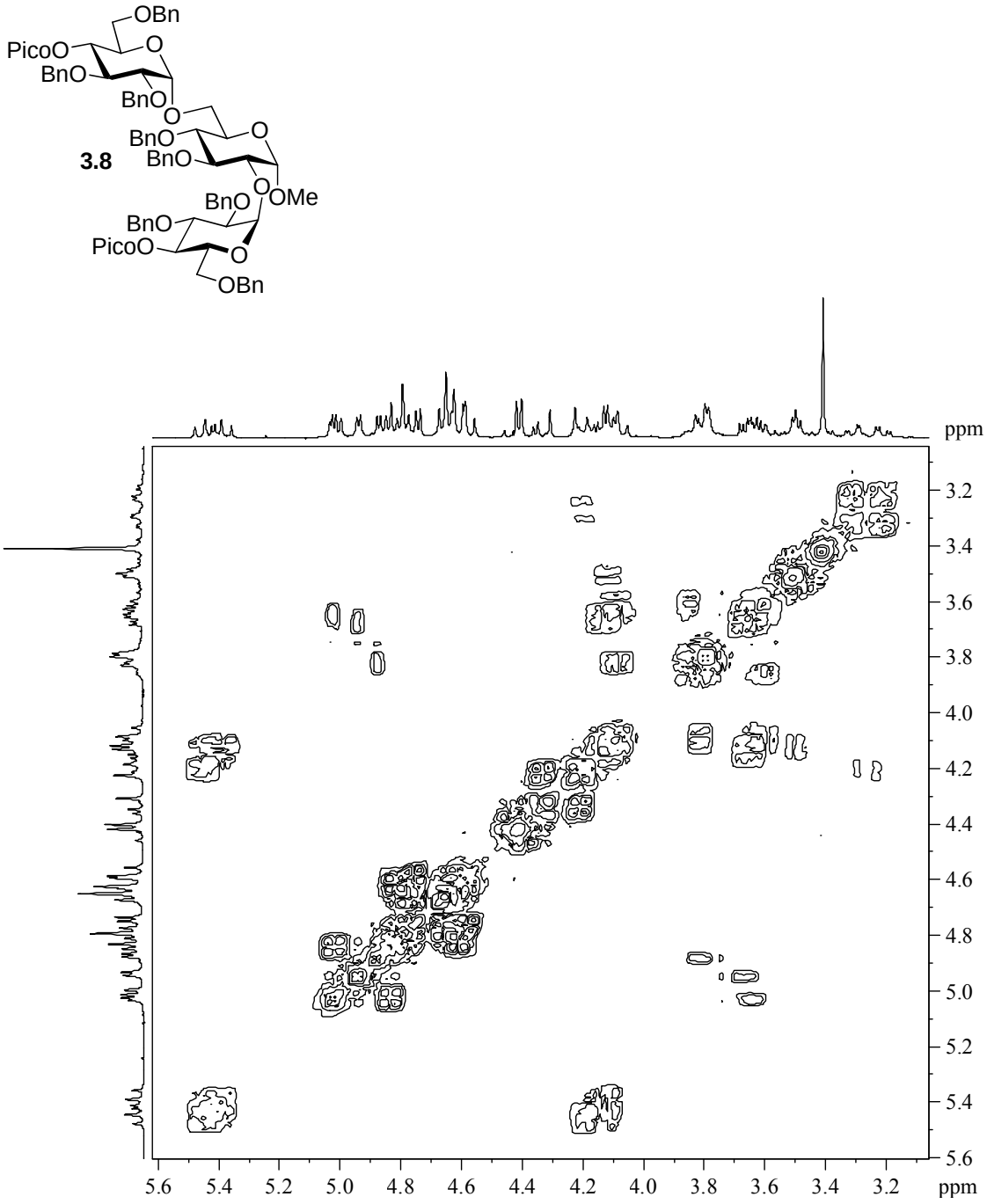
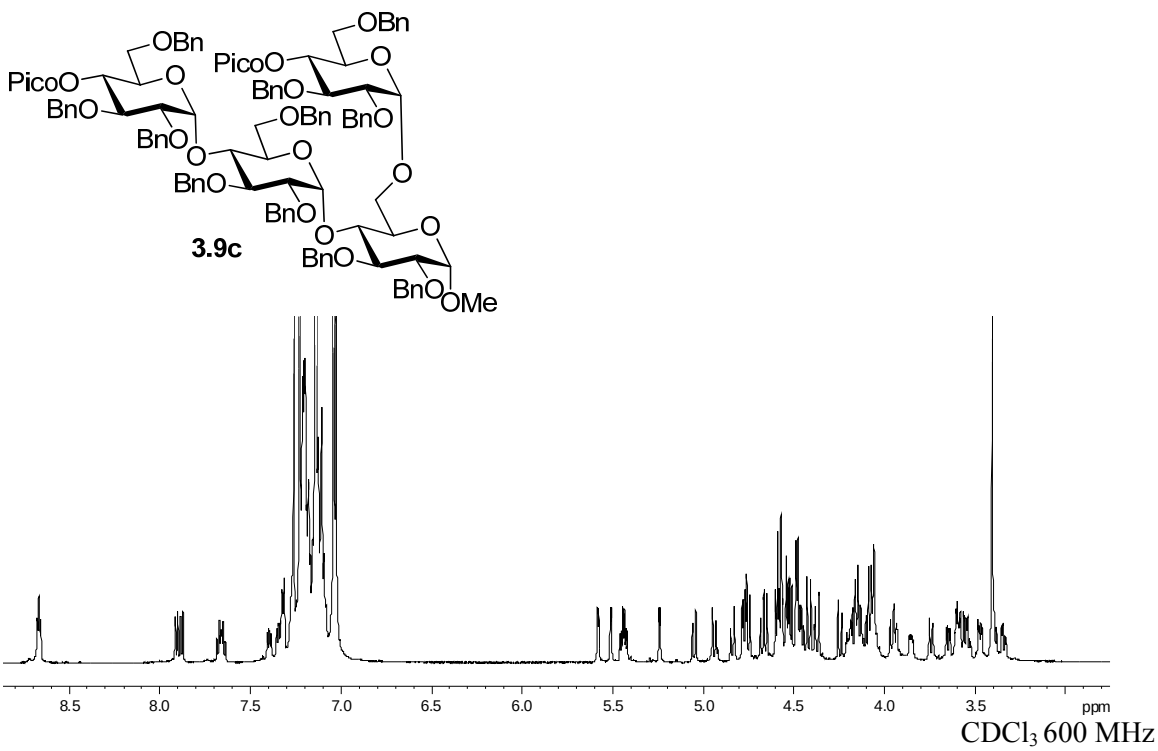
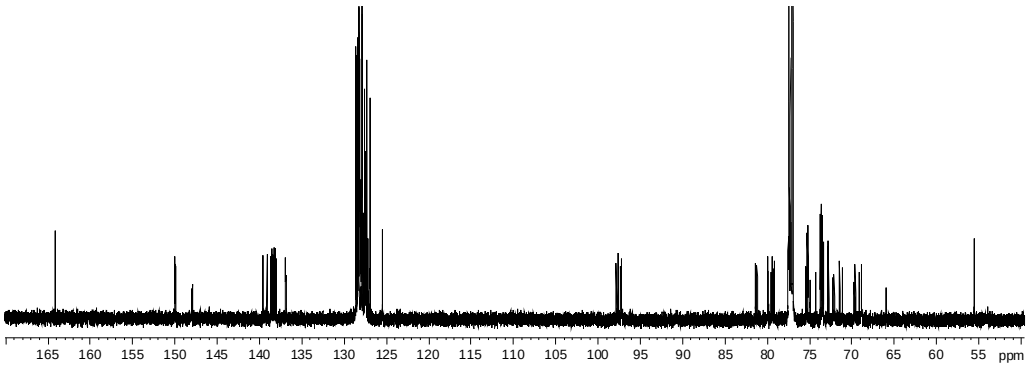


Figure A-57: 2-D NMR COSY spectrum of Methyl 3,4-di-*O*-benzyl-2,6-di-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**3.8**)



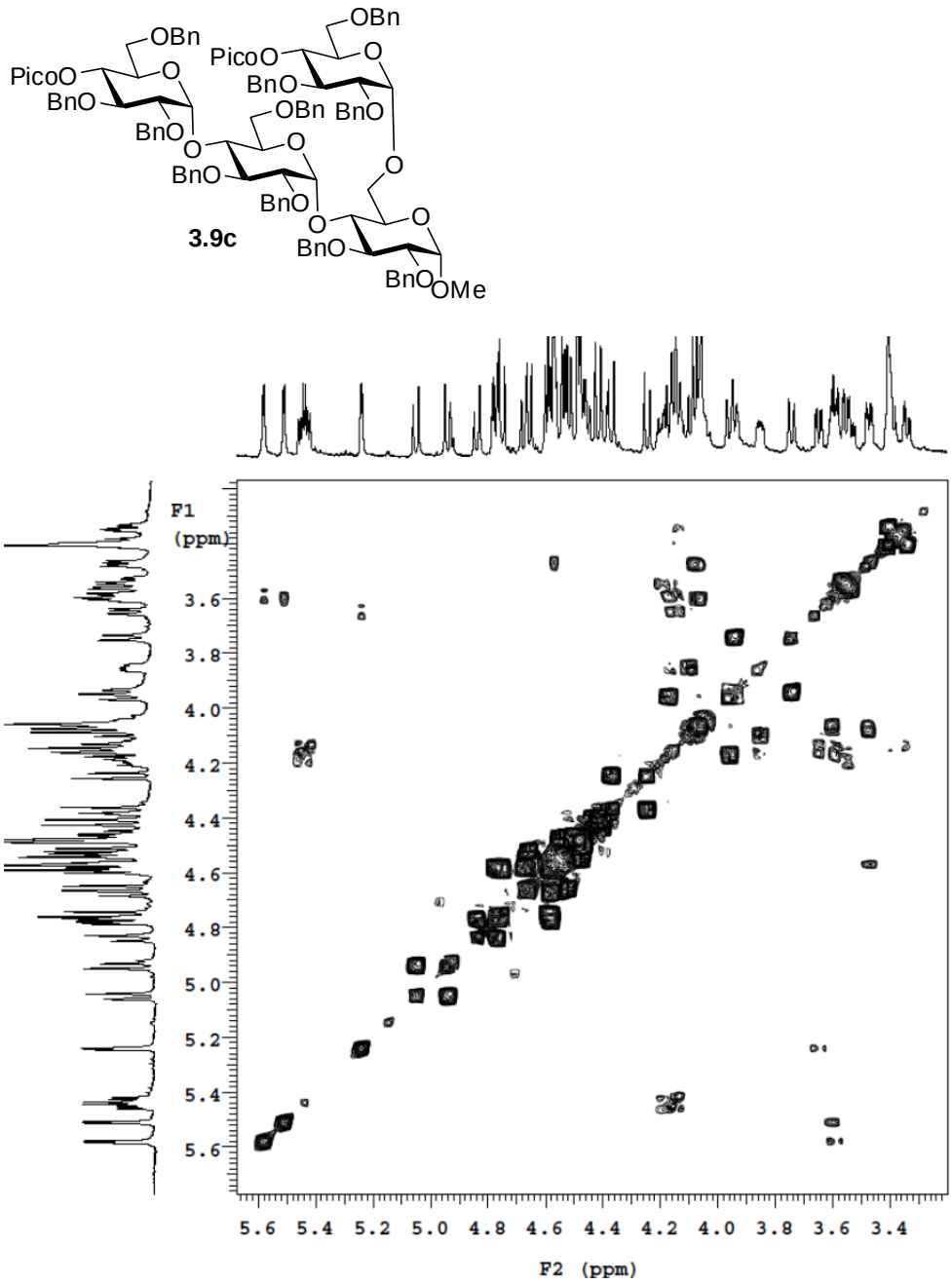
$CDCl_3$ 600 MHz

Figure A-58: : ^{1}H NMR spectrum of Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**3.9c**)



$CDCl_3$ 150 MHz

Figure A-59: ^{13}C NMR spectrum of Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**3.9c**)



$CDCl_3$ 600 MHz

Figure A-60: 2-D NMR COSY spectrum of Methyl *O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-picoloyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**3.9c**)

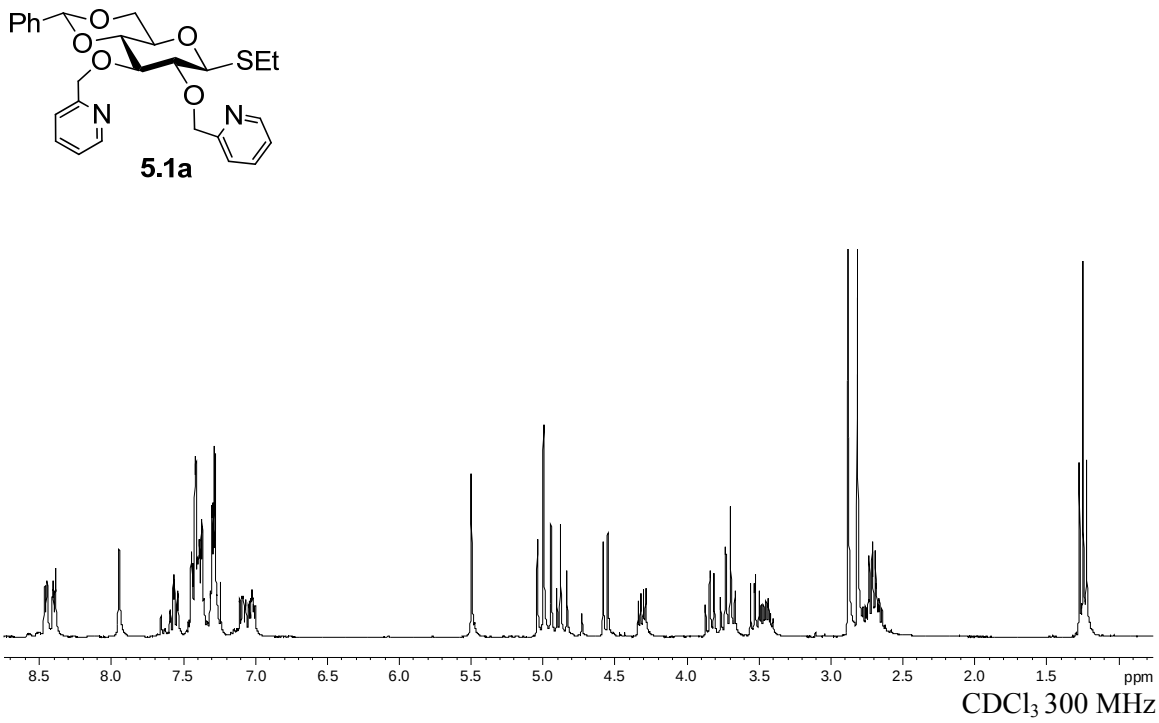


Figure A-61: : ^{1}H NMR spectrum of Ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside (**5.1a**)

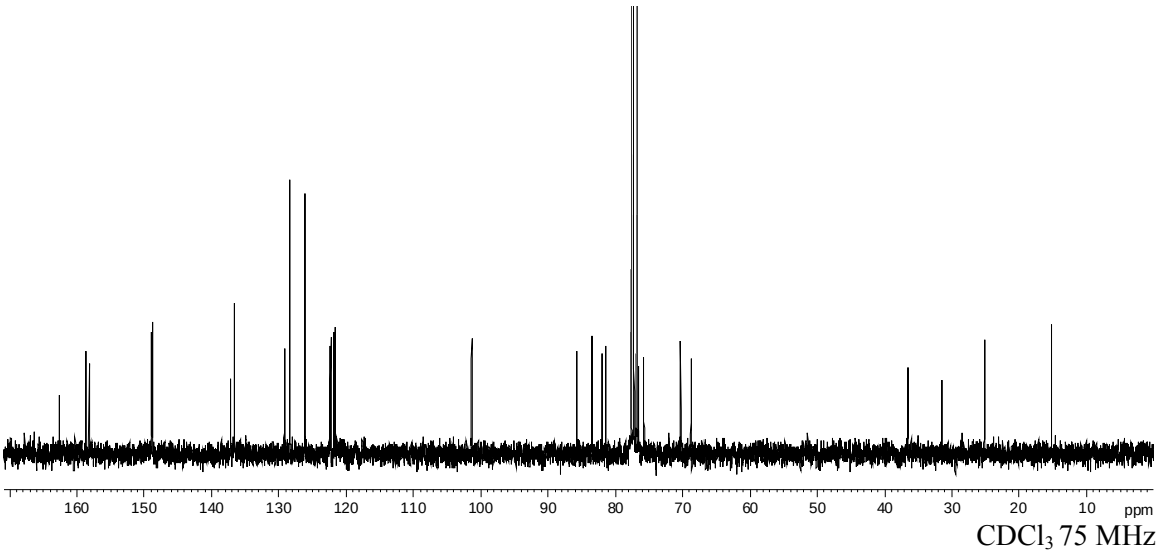


Figure A-62: ^{13}C NMR spectrum of Ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside (**5.1a**)

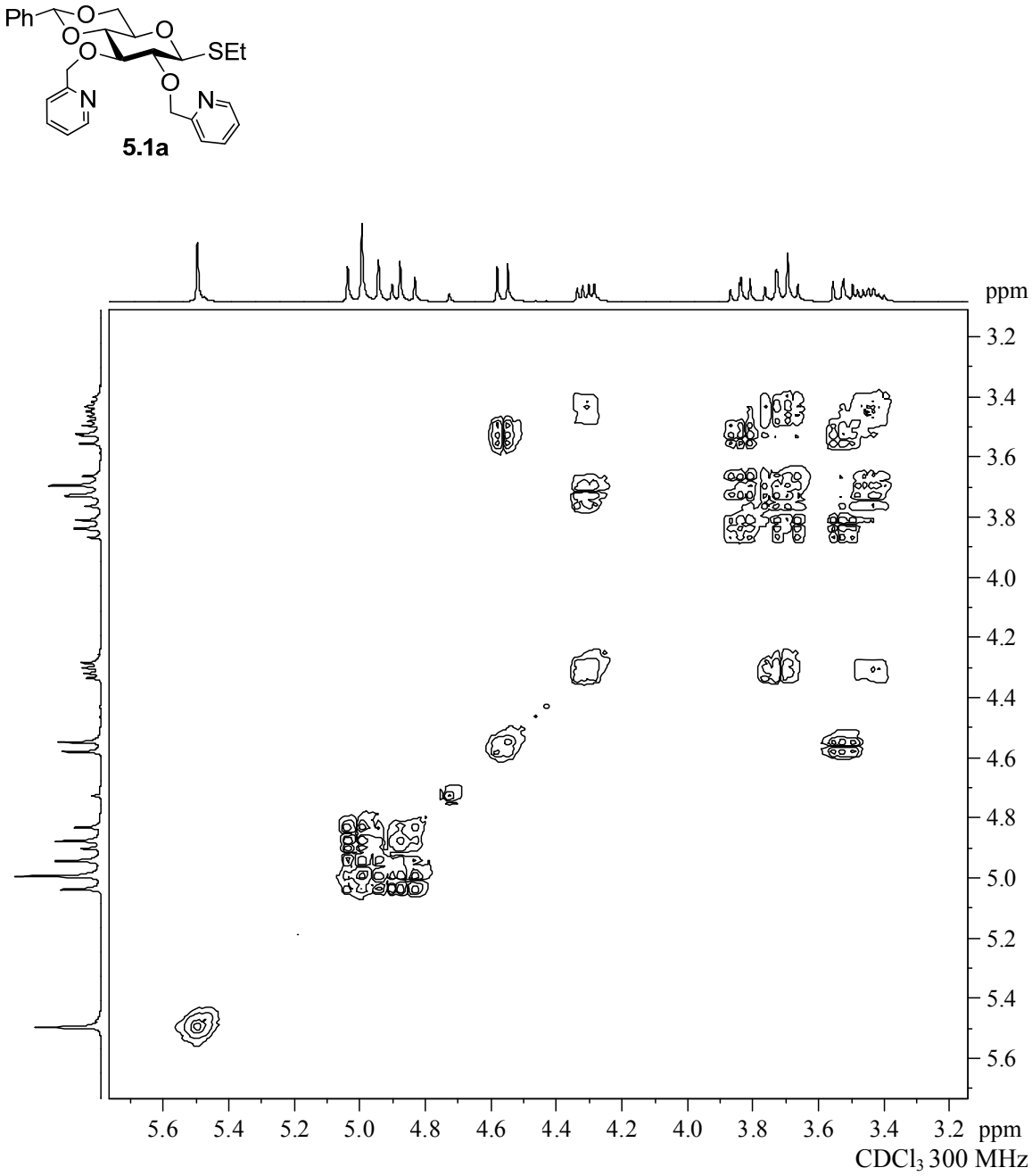
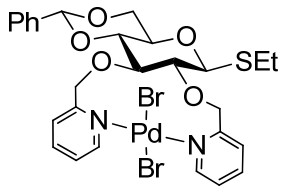
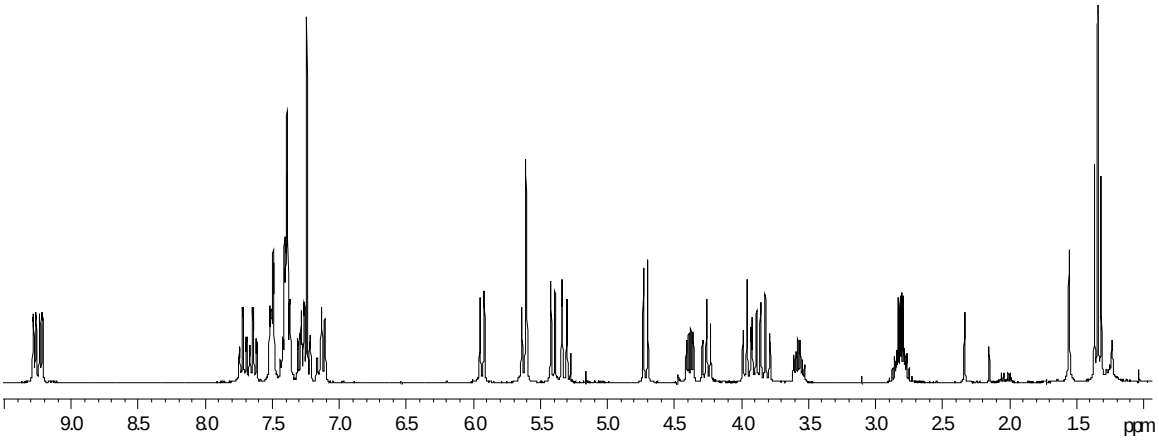


Figure A-63: 2-D NMR COSY spectrum of Ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside (**5.1a**)

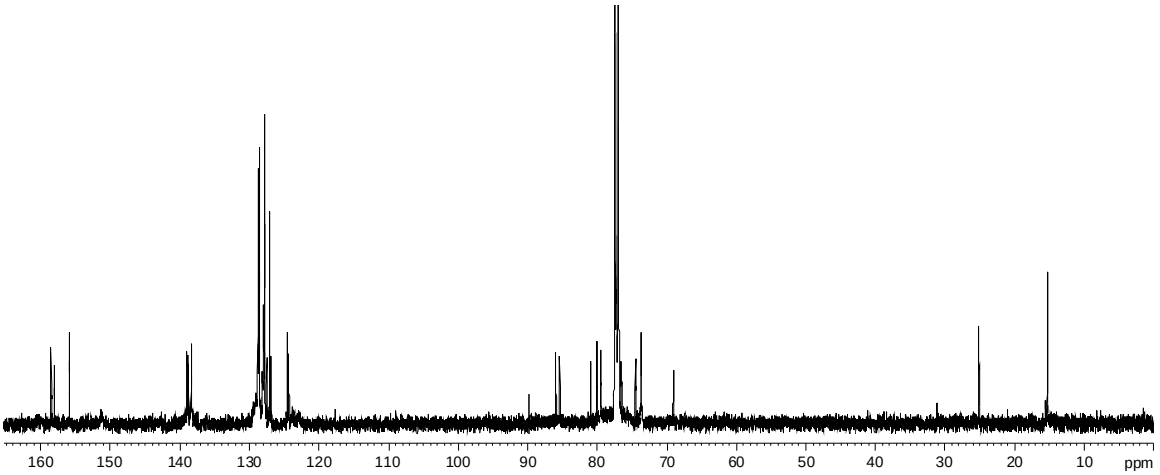


5.2a



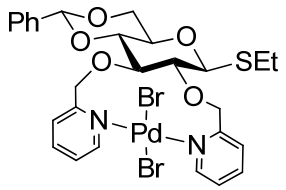
$CDCl_3$ 300 MHz

Figure A-64: : ^{1}H NMR spectrum of [Ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside] $PdBr_2$ (**5.2a**)

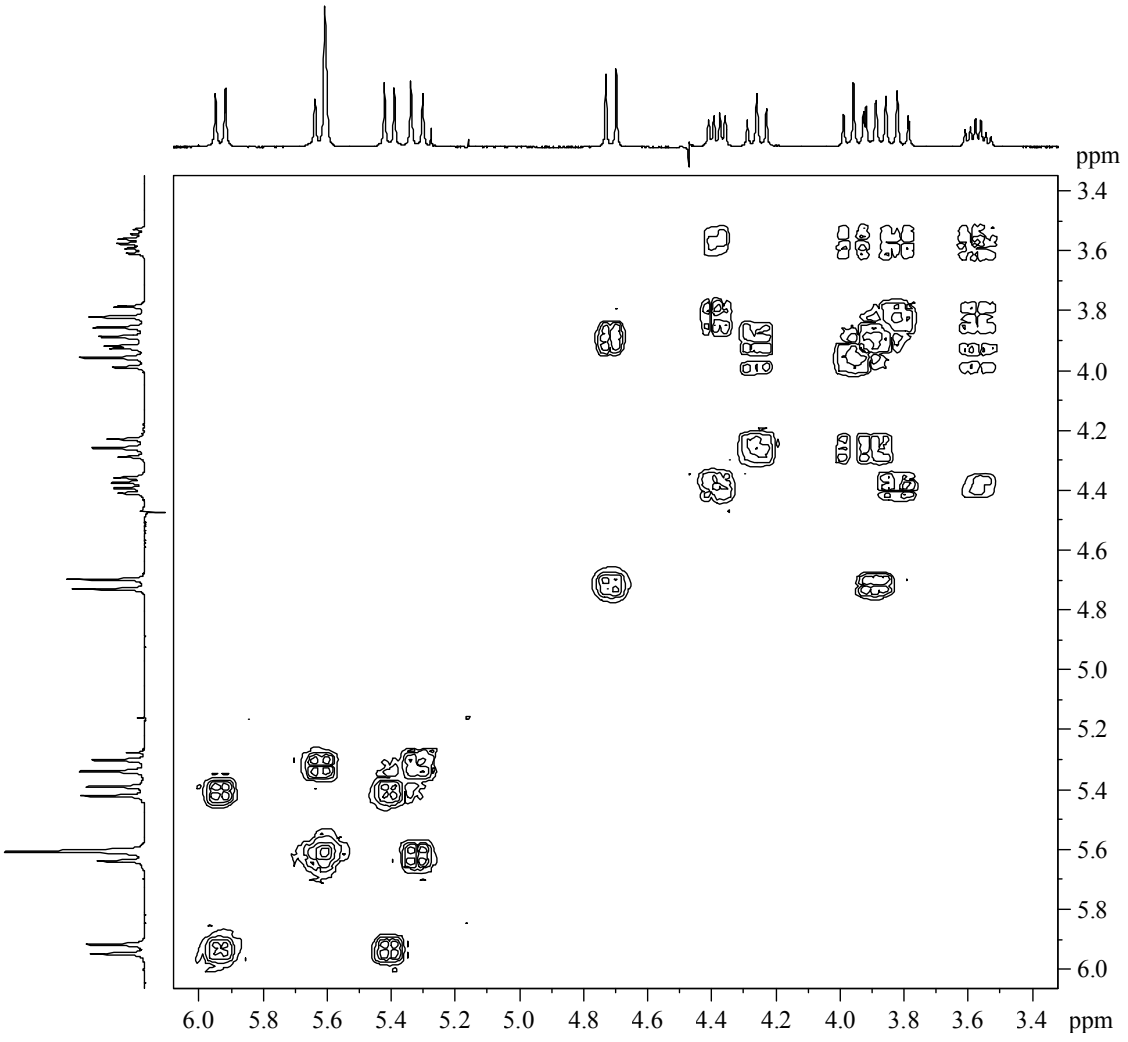


$CDCl_3$ 75 MHz

Figure A-65: ^{13}C NMR spectrum of [Ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside] $PdBr_2$ (**5.2a**)



5.2a



$CDCl_3$ 300 MHz

Figure A-66: 2-D NMR COSY spectrum of [Ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside] $PdBr_2$ (**5.2a**)

Figure A-67: X-Ray crystal structure projection view with 50% thermal ellipsoids of [Ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside] $PdBr_2$ (**5.2a**)

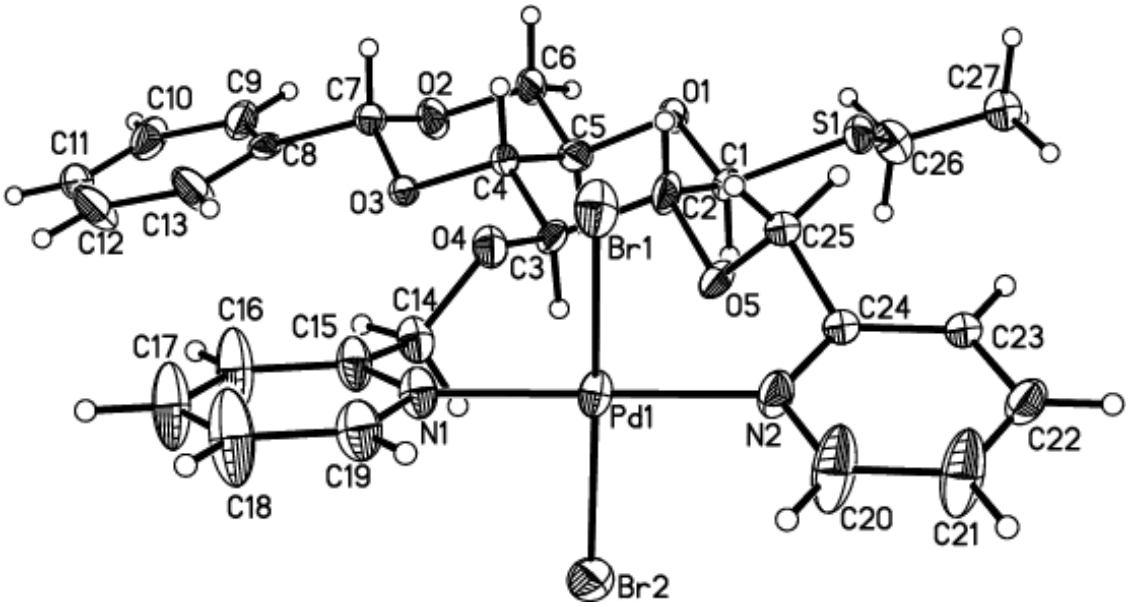


Table 1: Crystal data and structure refinement for [Ethyl 4,6-*O*-benzylidene-2,3-di-*O*-picolinyl-1-thio-β-D-glucopyranoside] $PdBr_2$ (**5.2a**)

Identification code	d13811/lt/x8/dipic-Pd	
Empirical formula	$C_{27}\ H_{30}\ Br_2\ N_2\ O_5\ Pd\ S$	
Formula weight	760.81	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 8.3369(4) Å	α= 90°.
	b = 20.8048(10) Å	β= 112.222(3)°.
	c = 8.5721(4) Å	γ = 90°.

Volume	1376.38(11) $Å^3$
Z	2
Density (calculated)	1.836 Mg/m^3
Absorption coefficient	3.694 mm^{-1}
F(000)	756
Crystal size	0.27 x 0.18 x 0.16 mm^3
Theta range for data collection	1.96 to 27.63°.
Index ranges	$-10 \leq h \leq 10$, $-26 \leq k \leq 27$, $-11 \leq l \leq 11$
Reflections collected	47541
Independent reflections	6314 [R(int) = 0.0420]
Completeness to theta = 27.63°	99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.5947 and 0.4399
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6314 / 22 / 306
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0317, wR2 = 0.0734
R indices (all data)	R1 = 0.0371, wR2 = 0.0757
Absolute structure parameter	0.007(7)
Largest diff. peak and hole	1.205 and -1.018 $e.Å^{-3}$