From conventional to unconventional : glycosylation on semi-protected donors and syntheses towards natural products

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**From Conventional to Unconventional: Glycosylation on
Semi-Protected Donors and Syntheses towards Natural
Products**

Báti Gábor

School of Physical and Mathematical Sciences

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Table of Contents

Acknowledgement	2
Abstract	6
List of Abbreviations	7
Preface	9
Chapter I.....	11
Introduction.....	11
1.1 Glycosylation in General.....	11
1.1.1 Typical Mechanism for Glycosylation	11
1.1.2 Anomeric Effect.....	13
1.1.3 Sugar Donors	13
1.1.4 Other Factors Driving the Stereo-Outcome of the Glycosylation.....	15
1.2 Glycosylation on Semi-Protected Sugars	16
1.2.1 Inherent Reactivity-Based Regioselectivity.....	18
1.2.2 Tin-Mediated Glycosylation: Early Studies.....	18
1.2.3 Tin-Mediated Glycosylation: A Reliable Procedure	22
1.2.4 Tin-Mediated Glycosylation: Altering from 1,6-Glycosylation to 1,3-Glycosylation and the Mechanism Behind.....	26
1.2.5 Tin-Mediated Glycosylation: From Equimolar to Catalytic	28
1.2.6 Copper-Mediated Glycosylation	30
1.2.7 Boron-Mediated Glycosylation: Early Studies	32
1.2.8 Boron-Mediated Glycosylation: From Equimolar to Catalytic.....	36
1.2.9 Examples to Sn- and Boron-Assisted Total Syntheses.....	41
Chapter II	44
Study on Boron-Mediated Glycosylation.....	44
2.1 The Concept.....	44
2.2 Discussion	45

2.2.1	Optimization Studies	45
2.2.2	Expanding the Scope of Glycosylation	49
2.2.3	Revealing the Mechanism Behind: LT-NMR Studies	54
2.3	Conclusion	59
2.4	Experimental Section.....	59
2.4.1	General Methods	59
2.4.2	General Methods for Glycosylation	60
2.4.3	Method for Low Temperature NMR Experiments.....	62
2.4.4	Characterization of Saccharides	63
2.4.5	Appendix	80
Chapter III.....		82
One-Pot Glycosylation on Semi-Protected Sugars		82
3.1	Introduction to One-Pot Glycosylation	82
3.2	Discussion	85
3.2.1	Our Concept for One-Pot Oligosaccharide Synthesis	85
3.2.2	Constructing Disaccharides Interchangeably	87
3.2.3	Assembly of a Model Trisaccharide.....	89
3.2.4	One-Pot Attempt Towards Branching Trimannoside Core of Gp120 Glycan	91
3.3	Conclusion	95
3.4	Experimental Section.....	95
3.4.1	General Methods	95
3.4.2	Modified Methods.....	96
3.4.3	General Method for Boron-Mediated Glycosylation with AgOTf/ <i>p</i> -NO ₂ PhSCl.....	97
3.4.4	Characterization of Saccharides	99
3.4.5	Appendix	103
Chapter IV.....		106

Attempts Towards the Total Synthesis of <i>N</i>-Acetylglucosamine-1,6-Anhydro-<i>N</i>-Acetyl-Muramylpentapeptide.....	106
4.1 Biological Relevance of <i>N</i>-Acetylglucosamine-1,6-Anhydro-<i>N</i>-Acetyl-Muramylpentapeptide and its Total Synthesis.....	106
4.2 Discussion	108
4.2.1 Our Conceptualized Synthetic Plan.....	108
4.2.2 Synthesis of the Protected Form of <i>N</i> -Acetylglucosamine-1,6-Anhydro- <i>N</i> -Acetylmuramyl Moiety	109
4.2.3 Synthesis of the Semi-Protected Form of <i>N</i> -Acetylglucosamine-1,6-Anhydro- <i>N</i> -Acetylmuramyl Moiety	111
4.2.4 Divergent Syntheses Towards Lipid II Analogue and <i>N</i> -Acetylglucosamine-1,6-Anhydro- <i>N</i> -Acetyl-Muramylpentapeptide	114
4.2.5 Future Plans Towards <i>N</i> -Acetylglucosamine-1,6-Anhydro- <i>N</i> -Acetyl-Muramylpentapeptide and Lipid II Analogue	116
4.3 Conclusion	117
4.4 Experimental Session.....	118
4.4.1 General Methods	118
4.4.2 Syntheses and Characterization of Compounds.....	118
References.....	125

Abstract

By now, tremendous amount of studies have identified specific interactions of carbohydrate-based structures within a biological system. However, the isolation and syntheses of those intricate structures remained laborious and lengthy. In addition to that, the specific stereo-configuration at each anomeric linkage and the diversity in branching withholds the formulation of a universal procedure for the assembly of glycan chains. Therefore, the need for a facile method is still present.

In chapter I, we aimed to discuss efforts have been already done in the field of regio- and stereoselective glycosylation.

In chapter II, we introduced a widely applicable approach that offers both stereoselective glycosidic bond formation and the unnecessary of protection/deprotection steps for further elongation. Using dialkylboryl triflate as an *in situ* masking reagent, a wide array of glycosyl donors bearing one to three unprotected hydroxyl groups have formed various intersugar connections, while expressing excellent control over regio- and stereoselectivity. To reveal to possible mechanism which assists as well as hampers the stereoselective glycosylation, we have conducted elaborate LT-NMR studies.

In Chapter III, we manifested the practicality of this approach in a one-pot assembly of a model trisaccharide. Gaining inspiration from this achievement, we successfully adapted the procedure to dimannosides, and furthermore attempted to assemble the trimannoside core of gp120 peptidoglycan.

In chapter IV, we conceptualized, and interpreted our steps towards the completion of the divergent total syntheses of intricate peptidoglycan and Lipid II analogues.

List of Abbreviations

Å	Ångstrom
Ac	acetyl
Ar	aryl
Bn	benzyl
brs	broad singlet
Bu	butyl
Bz	benzoyl
calcd	calculated
cat.	catalytic
COSY	Correlation Spectroscopy
DMSO	dimethylsulfoxide
EDG	Electron donating
ESI	Electron Spray Ionization
EWG	Electron withdrawing
Et	ethyl
EtOAc	ethyl acetate
HRMS	High Resolution Mass Spectroscopy
Hz	hertz
LA	Lewis acid
Me	methyl
ACN	acetonitrile
mg	milligram
MHz	megahertz
mol	mole(s)

MS	molecular sieves
m/z	mass to charge ratio
ⁿ Bu	n-butyl
ⁿ Pr	n-propyl
NMR	Nuclear Magnetic Resonance
Nu	nucleophile
ov	overnight
<i>p</i>	para
Ph	phenyl
Piv	pivaloyl
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl
ppm	parts per million
pyr	pyridine
rt	room temperature
refl	reflux
^t Bu	tert-butyl
TBAB	tetra- ⁿ butylammonium bromide
TBAI	tetra- ⁿ butylammonium iodide
TEAB	tetra-ethylammonium bromide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
OTf	trifluoromethanesulfonyl
TOCSY	Total Correlation Spectroscopy

Preface

Carbohydrates are the most abundant biomolecules on Earth. Their family is known to be a primary component of cells alongside proteins, nucleic acids and lipids. Therefore, oligosaccharides and their conjugated derivatives are vastly involved in biological processes, such as metabolic events, intercellular communication and carbohydrate-mediated recognition. Yet, their biosynthesis and structural composition are often deemed to be unexplored. In contrast to the gene-coded polymers - such as DNA, RNA and proteins - the carbohydrate oligomers as well as sophisticated glycans are rather being produced by their enzymes, which are triggered by slight physiological changes in living things. Therefore, the cell produces a copiously diverse mixture of carbohydrates in every fraction of time, challenging chemists and biologists to isolate, identify and relate their structures to their activities. The knowledge we have already gained about their crucial involvement in cellular processes could be utilized in synthetic therapeutics and vaccines, yet their potential is not fully exploited.¹

In 1893, the great-grandfather of carbohydrate chemistry, Emil Fischer made a groundbreaking discovery by activating the hemiacetal function of a glucose unit and replacing it with a molecule of methanol.² The performed acid-catalyzed condensation reaction swiftly became popular and indispensable amongst chemists, thus constituted the foundation of carbohydrate chemistry. Since then, this simple bimolecular transformation has evolved to the stage where stereoselectively assembling disaccharides, oligosaccharides and glycoconjugates are no longer just an admirable miracle of Nature, but could be mimicked in our laboratories. To date, glycosylation reactions are most commonly performed in solution phase. However, this has since been expanded to the adapted technology from solid phase peptide syntheses - the era of automated sugar synthesis is at our doorstep. The latter approach combined with enzymatic machinery, might provide us a powerful approach in oligosaccharide synthesis.¹

Control over regio- and stereoselectivity has been a major challenge in oligosaccharide synthesis. Significant effort has been spent on investigating this common issue, however there is still room to improve the existing procedures. Subtle tuning of the donors' reactivity and stereoelectronics, manipulating sterics and conformations with protecting groups, moreover introducing ancillary groups are known to be essential to assemble complex oligosaccharides.³⁻⁷ Indeed, the stereochemistry at the anomeric position became controllable with excellent methods at our disposal. Moreover, the feasibility of synthesizing long and branching glycans are proven multiple times. However, despite newly emerging bench stable but reactive donors and mild procedures in the last few decades, carbohydrate chemists are still lacking a universally applicable procedure in glycoside synthesis. Thus, oligosaccharide synthesis remains a challenging yet rewarding task that attracts chemists to devise novel methodologies and/or adapt existing methodologies from other fields of chemistry.

Chapter I

Introduction

1.1 Glycosylation in General

1.1.1 Typical Mechanism for Glycosylation

The mechanism for glycosylation is still under debate, however the most agreed mechanism involves either S_N1- or S_N2-type displacement at the anomeric position (Figure 1). In both cases, prior to the nucleophilic attack at C1, the activator promotes the departure of the leaving group (LG), thus forming oxocarbenium ion (**B** and **F**). When the sugar donor is equipped with non-participating protecting group at C2 - mostly OBn, N₃ - the formed oxocarbenium ion is not being stabilized, therefore the nucleophilic attack might occur from either the α face (*cis* glycoside for D-sugars) or from the β face (*trans* glycoside for D-sugars) at the same rate. In fact, in the absence of participating groups at C2 the so-called anomeric effect (discussed below) expresses its driving force towards the thermodynamically favored α product (**D**). However, the kinetically favored β product (**C**) is often being formed, deriving from the right choice of protecting group, solvent, temperature, conformation, leaving groups, activator and driven by steric hindrance.⁸⁻¹¹

1,2-*trans* glycosides can be furnished most commonly by attaching participating group at C2, mostly being NPhth, NHTroc, NHTCA, OAc, OBz and so on.¹²⁻¹⁴ Their anchimeric assistance stabilizes the oxocarbenium ion intramolecularly, forming acyloxonium ion (**G**), existing in a rapid equilibrium with the unstabilized form (**F**) (Figure 1). With **G** being abundant in the mixture, expectedly the only trajectory left for the incoming nucleophile is the top face, affording 1,2-*trans* major product (**H**) on S_N2 manner. The stereoselectivity at the anomeric carbon might be diminished due to the poor nucleophilic nature of the acceptor or

weak anchimeric assistance of the protecting group at C2. In those cases, the glycosylation follows S_N1 pathways through oxocarbenium ion (**F**). The attachment of other type of ancillary groups onto 2-OH function renders intriguing stereo-outcome of the glycosylation. As Boons and co-workers have found, (1*S*)-phenyl-2-(phenylsulfanyl)ethyl playing key role in accessing α -glycosides by forming a quasi-stable β sulfonium ion intermediate (**K**).¹⁵ Therefore the displacement of anomeric sulfonium moiety is leading to the exclusive formation of α -glycosides (**L**) by nature. More recently a unique approach was introduced by Liu and Le Mai Hoang installing 2-cyanobenzyl ether group onto C2 (**M**).¹⁶ This novel type of auxiliary group expresses dual-stereo directing effect depending on the electronic nature of the acceptor.

Figure 1. Strategies accessing *cis*- and *trans*-glycosides.

1.1.2 Anomeric Effect

In cyclohexanes, the textbook example for the energetically favored orientation of a larger substituent is equatorial, due to the presence of substantial steric congestion amongst the axially oriented substituent and the hydrogen at the gamma carbon (1,3-diaxial interaction). On the contrary, in carbohydrate chemistry, there are other factors that should be taken into account in the evaluation of possible reaction outcomes. As Edward and Lemieux described, polar substituents ($X = \text{OR}, \text{SR}, \text{Cl}, \text{Br}$) at the anomeric carbon center prefer to exist in an axial orientation which could be reasoned with the substantial involvement of stereoelectronic effects.¹⁷ In fact, hyperconjugation between the nonbonding orbital (n) of ring oxygen and the antibonding orbital (σ^*) of $\text{C}_{\text{anomeric}}\text{-X}$ is present due to the perfect periplanar orientation of those molecular orbitals, therefore stabilizing α glycoside (Figure 2). When $\sigma^*_{\text{C-X}}$ is in an antiperiplanar orientation with the nonbonding orbital of ring oxygen, such stereoelectronic interaction is simply not great enough to stabilize β product. Additionally, the aligned dipole orientation of ring oxygen and X heteroatom further destabilizes the 1,2-*trans* isomer. Overall, the anomeric effect is rather a sum of complex stereoelectronic and electrostatic effects than a single force, therefore we refrain from dissecting this topic in greater detail.

Figure 2. Anomeric effect.

1.1.3 Sugar Donors

The first reaction on glycosyl halides was performed by Michael,¹⁸ whereas hemiacetals was activated by Fischer,² setting the benchmark for the era of glycosyl donors as a coupling

partners with alcohol acceptors (Figure 3). A generally applicable, controlled glycosylation procedure on glycosyl chloride and bromide is merited to Koenigs and Knorr.¹⁹ Although their very early discovery of Ag₂CO₃-activated glycosylation was found to be rather sluggish at that time, the basis of their transformation was adapted by the new generations of carbohydrate chemists. Within a few decades, the method gradually evolved to a first-choice procedure by introducing heavy metal catalysts.²⁰⁻²³ A slightly less popular, but still noteworthy procedure was also introduced around that time, employing anomeric acetates as donors.²⁴ Critical and impactful work has been dedicated from Lemieux's²⁵ and Fletcher's²⁶⁻²⁷ groups to reveal the intriguing correlation between the stereo-outcome of the glycosylation and the nature of the protecting group attached at C2 position. Fairly, 1,2-*trans* glycosylation could be performed stereoselectively on 2-*O*-acetylated sugar donors, genuinely attributed to attached acetyl group. This groundbreaking finding established the strategy and term for S_N2-type displacement-based 1,2-*trans* glycosylation, the so-called neighboring group participation.

For many decades, carbohydrate chemists were confined to the latter approaches, however driven by the desire for more universal, milder and reliable strategies. As a result of that, significant improvement in anomeric leaving group was achieved by the 1970, early 1980s. Here, we compiled a few of the most paramount representatives of the new-wave glycosyl donors: thioglycosides by Ferrier,²⁸ Nicolaou,²⁹ Garegg³⁰ and others,³¹ orthoesters from Kochetkov,³²⁻³³ *O*-imidates by Sinay³⁴ and from Schmidt and Michel,³⁵ thioimidates and fluorides from Mukaiyama.³⁶⁻³⁷ From this era of carbohydrate chemistry, a tremendous amount of novel donors has emerged, undoubtedly the most prominent became the family of trichloroacetimidates,³⁸⁻³⁹ thioglycosides⁴⁰⁻⁴² and fluorides.⁴³ From the late 1980s until today, we have had access to novel procedures being employed on an astonishing variety of glycosyl donors. Without attempting to be comprehensive, the following glycosyl donors have been introduced till now: carboxylates and carbonates,⁴⁴⁻⁴⁵ thiocyanates,⁴⁶ diazirines,⁴⁷ xanthates,⁴⁸

glycals⁴⁹ and epoxides,⁴⁹ phosphites,⁵⁰⁻⁵¹ sulfoxides,⁵² sulfones,⁵³ selenyl⁵⁴ and alkenyl⁵⁵⁻⁵⁷ glycosides, heteroaryl⁵⁸ and iodo glycosides,⁵⁹ phosphates,⁶⁰ telluryl glycosides,⁶¹ sulfonylcarbamates,⁶² disulfides,⁶³ *O*-imidates⁶⁴⁻⁶⁵ and *S*-imidates,⁶⁶⁻⁶⁷ and lastly a revamped procedure for activating hemiacetals.⁶⁸

Figure 3. Representative examples of glycosyl donors.

1.1.4 Other Factors Driving the Stereo-Outcome of the Glycosylation

The nature of the applied solvent during the glycosylation is certainly not negligible factor. Solvents might drive the stereo-outcome of the transformation by solvating the species present in the mixture. Polar solvents are prone to afford β -, whereas non-polar solvents preferably provide α -glycosides. More prevalently, solvents are capable of participating in the reaction by stabilizing the oxonium ion intermediate (**B**), thus expressing driving force towards one preferential anomer (Figure 4). Specifically ether-type solvents, like diethyl ether, THF⁶⁹ and dioxane,⁶⁹ or even nitroethane⁷⁰ are occupying equatorial position while being attached to the sugar moiety (**C**), therefore leading to glycosylation toward 1,2-*cis* glycoside **E** formation.

On the contrary, 1,2-*trans* glycoside (**F**) can be obtained when the axially coordinated acetonitrile (**D**) is present.⁷¹

Figure 4. Solvent effect.

Promoters might be influential on the stereo-outcome of the glycosylation as well. Generally, the application of milder condition is being accompanied with preferential for 1,2-*cis* glycosylation.⁷²

Kinetically controlled reactions predominantly afford 1,2-*trans* glucosides – or cis-mannosides – at lower temperature.⁷³ Therefore, elevating the temperature might alter the anomeric selectivity, furnishing the thermodynamically more stable 1,2-*cis* glucosides – or *trans*-mannosides.

The application of high pressure technique is likewise influential to the stereoselectivity, showing remarkable enhancement in anomeric selectivity.⁷⁴

1.2 Glycosylation on Semi-Protected Sugars

To date, making disaccharides has become less burdensome, while the assembly of longer oligosaccharide chains remained challenging. The latter task often involves multiple protection-deprotection steps to assure the sole formation of regioselectively desired saccharides, thus lengthening the overall synthetic route.

First and foremost, major challenges of glycosylation on semi-protected sugars need to be addressed. To start, in the presence of multiple hydroxyl functions the reaction must be regioselective and must avoid self-condensation. Secondly, having a quick and easy access to glycosyl donors shortens the required time spent on syntheses. Moreover, as the glycan chain

generally consists of a variety of sugar units, the applied method ought to be universal and easily performed. And last but not least, the transformation should be able to provide the naturally occurring, biologically active stereoisomer of the product of interest. Taking a closer look at Emil Fischer's pioneering transformation, we must realize they did not just synthesize a methyl glucoside for the first time, but did so on unprotected sugar which is an odd transformation even in the history of contemporary carbohydrate chemistry. Despite of the precarious nature of glycosylation reaction on unprotected sugars, significant amount of effort was made on this topic, and the related literature was compiled by Hanessian,⁷⁵ and more recently by Hocek.⁷⁶ Their comprehensive work encompasses glycosylations on anomERICALLY activated, unprotected or minimally protected saccharides. Albeit, from a synthetic point of view, employing a sufficiently decorated glycosyl donor might be necessary for branching glycan assembly. This constitutes the so-called 'open glycosylation', referring to regioselective glycosylation on minimally protected sugars, more specifically activating only one hydroxyl group in the presence of multiple. Throughout this chapter we will discuss efforts that have been made to form saccharides, providing potentially applicable methods in oligosaccharide synthesis (Figure 5).

Figure 5. Timeline of studies conducted on glycosylation with semi-protected sugars.

1.2.1 Inherent Reactivity-Based Regioselectivity

One way to prepare branched oligosaccharides, is exploiting the inherent reactivity differences between hydroxyl functions. This approach might render a significantly shorter pathway to the target product due to the redundant protection/deprotection steps. On the contrary, the outcome is profoundly substrate and protecting group dependent therefore often requires tedious screening. Therefore, due to the dubious nature of this approach the procedure might be futile to provide the desired oligosaccharide product. Based on inherent reactivity differences of OH's, significant effort has been made in Linhardt's laboratory to synthesize naturally occurring Dioscin and other members of Saponin family.⁷⁷⁻⁷⁸ To provide a conceivable explanation for the unexpected anomeric selectivity, they suggest an aiding 2-OH neighboring group participation (Figure 6), in which, the ultimately forming 1,2-anhydrosugar intermediate **3** leaves only the β -face available for the attacking trajectory of the aglycone. Therefore, this approach demands 2-OH undecorated, which requirement found to be a necessary but not always sufficient to furnish 1,2-*trans* disaccharides **4** exclusively.

Figure 6. 2-OH aided glycosylation.

1.2.2 Tin-Mediated Glycosylation: Early Studies

Another possible approach to attain regioselective glycosylation is activating one hydroxyl group over the existing others. Aglycones that bear free vicinal hydroxyl groups are exquisite substrates to undergo nucleophilic enhancement on one distinguished oxygen, whilst the remaining hydroxyl functions stay intact.

Adapted from their previous work,⁷⁹ Matsui and co-workers were able to activate only the targeted hydroxyl functions by using tributylstannyloxide, and eventually assemble a branching trimannoside in a 2-step procedure (Figure 7).⁸⁰ First, they condensed the free mannoside **5** with the stannyl reagent, then applied Koenigs-Knorr glycosylation, serving the orthoester trimannoside **7**. This was a result of the unexpected reversal from mannosyl chloride donor to the orthoester form, followed by the subsequent attack of the stannylene acetal on the electrophilic carbon. This intermediate was further transformed into the desired trimannoside **8** by the treatment of HgBr₂ at high temperature. Although the overall yield was low, the procedure was efficient enough to provide the core structure of several oligosaccharides on an entirely novel manner.

Figure 7. Assembly of trimannoside by Matsui.

Matsui's work has demonstrated the efficient activation of the equatorial oxygen atom at 3rd position over the less reactive 4th. Similarly, Veyrières and co-workers exploited the advantageous feature of stannylene acetal protection strategy in the synthesis of a diglucosylated galactoside **12** (Figure 8).⁸¹ In addition, the Lewis acidic activator, SnCl₄ was able to prompt the reaction not only on brominated glucosides **10**, but also on the pentaacetate derivative **11** as well, ultimately expanding the donor scope. Interestingly, when the stannylene acetal **9** was replaced by the parent diol, the reaction failed to give the trisaccharide. This unexpected phenomenon might create certainty in the nucleophilic enhancement effect of the

Figure 8. Trisaccharide assembly by Veyrières.

stannylene acetal principally. With the working procedure in hand, they devised to synthesize the more challenging α -form of the latter trisaccharide by switching the electrophile to β -chloro glucoside **13**, hoping to drive the stereochemical outcome via S_N2 -type displacement. However, the obtained compound was rather the previously described dioxolane connected product **14**. Replacing HMPA solvent with DCE, acceptor **9** has been glycosylated on both 3rd and 4th positions, thus giving rise to the dioxolane connected **14** di- and trisaccharide **16**. Conversion from orthoester **14** to the desired α -(1 $\rightarrow$ 3) disaccharide **15** has failed despite attempting it with various Lewis and Brønsted acids. Therefore, they switched from C-2 acetyl protection - attributed to the formation of orthoester - to C-2 benzyl group (**17**), eventually omitting the side reaction. Indeed, with the addition of lithium halide they were able to perform galactosidation on 3,4-stannylene galactoside, exclusively on the third position (**18**) in dipolar aprotic solvent. The obtained α selectivity was being reasoned knowing, that halide ion is prone to exchange with the α -configured chlorine on the sugar, altering it to β . The reversal of the configuration at the anomeric position - driven by S_N2 -type displacement of the sugar acceptor - is expected to result in the formation of α configured connection. In the absence of an

Figure 9. Failed and successful attempts to assemble disaccharide **18** by Veyrières.

ancillary group at C2, the expected and experienced results are well aligned, showing high selectivity towards α product (Figure 9). On regioselectivity-wise, 1 $\rightarrow$ 3 disaccharides were obtained as a sole product, showing extreme unreactivity of axial 4-hydroxyl function in 4C_1 conformation.⁸²⁻⁸³ Furthermore, the reactivity difference of OH functions in 3,4-vicinal diol is so apparent, that the parent galactoside gave similar result as the stannylene compound in glycosylation.⁸¹

Although acylation,⁷⁹ allylation,⁸⁴ alkylation,⁸⁵ and benzylation^{84, 86-87} of the equatorial hydroxyl group on stannylene sugar derivatives are found to be greatly beneficial and widely used even nowadays, their application in glycosylation have been scarcely explored due to the previously described ambiguous results. More than a decade of silence after Veyrières's work, Martin-Lomas's group shown interest in this type of glycosylation on 1,6-anhydro galactopyranose (Figure 10).⁸⁸ In their study, they planned to examine the potential of stannylene acetals in glycosylation, by comparing it to the parent free triol **19**. By nature, the nucleophilicity in stannylene acetal **19** is expected to be enhanced on the equatorial 4-OH, while the axial 3-OH should remain intact. Albeit, due to a minor nucleophilic enhancement

Figure 10. Martin-Lomas's approach towards disaccharide **22** and comparison with conventional method.

on 3-OH function the regioselectively undesired disaccharide **21** happened to form in a small quantity besides the mixture of α -(1 $\rightarrow$ 4) **23** and β -(1 $\rightarrow$ 4) **22**. To prove the requisition for stannylene acetal being installed on the sugar acceptor, they have repeated the glycosylation under conventional halide-ion catalyzed condition on triol **19**. Interestingly, only the unexpected α -(1 $\rightarrow$ 4) **23** product was isolated. Albeit the conventional method provides the

regioselectively desired (1→4) disaccharide as well, the high conversion rate, therefore an enhanced nucleophilicity under tributyltin oxide condition has proved the method being useful. On the contrary, when free 6-OH was present, the glycosylation on stannylene lactoside **24** has happened exclusively on 6-OH (**25** and **26**) showing the superior reactivity of a primary alcohol over the stannylene acetal derivative (Figure 11).

Figure 11. Superiority of 6-OH over stannylated oxygens by Martin-Lomas.

Similarly, altered regioselectivity was observed by Hasegawa in the sialylation of unprotected galactopyranoside **27**, for they have not provided any explanation (Figure 12).⁸⁹ Under the previously described dibutyltin oxide condition, the expected α -Neu5Ac-(2→3)-Gal disaccharide was not observed. Instead, the mixture of α - and β -Neu5Ac-(2→6)-Gal (**30** and **29**) was formed together with a substantial amount of 2,3-dehydro donor **31**.

Figure 12. Sialylation by Hasegawa.

1.2.3 Tin-Mediated Glycosylation: A Reliable Procedure

Over time, carbohydrate chemists accessed various methods to construct saccharides, however still being greatly confined to 1,2-*trans* linkages. This is usually done by the aiding participation of neighboring group at C2 position in glucose, galactose and glucosamine series, whereas 1,2-*trans* glycosylation could be performed by relying on the anomeric effect in

mannose and rhamnose series. Without installing participating group at C2, the stereochemical outcome of the glycosylation was ambiguous, thus giving rise to a mixture of stereoisomers. Therefore, a long-standing desire for 1,2-*cis* glycosides is still present. To furnish both 1,2-*cis* and 1,2-*trans* disaccharides (**37**, **38**, **39**, **40**, **41**, **42**), Garegg and co-workers were able to activate armed donor **32** with TBAI, and disarmed thioglycosides (**33**, **34**, **35**, **36**) with thiophilic promoter dimethyl(methylthio)sulfonium triflate (DMTST) (Figure 13).⁹⁰ As a further improvement, the scope of 1→6 glycosylation on stannyl galactosides and glucosides were additionally expanded by varying the acceptors as well as the activating methods.

Figure 13. Garegg's study on stannylene glycosides and galactosides accessing 1,6-glycosides.

By that time the scope of stannylated glycosyl acceptors almost covered the family of naturally abundant sugars, and the regioselectivity could be altered in few cases. However,

only the construction of 1,2-*trans* linkages were amenable through neighboring group participation (except for few examples), otherwise the stereochemical outcome might be dubious. In accordance with the latter observation, the syntheses of 1,2-*cis* linkages between sugar units challenged many chemists. The inherently nonstereospecific nature of non-aiding sugars has been clearly acknowledged, but could be surpassed if the aglycone displaces the leaving group at C1 purely in S_N2 manner, thus excluding the involvement of oxocarbenium ion during the course of reaction. Answering the urgent call for the stereoselective synthesis of these type of connections, Hódosi and Kovač provided an excellent method to exploit the nucleophilicity of 1,2-*cis*-*O*-stannylene acetals **A** and **D**.⁹¹ Their approach simply employed tin-masked activated hemiacetal, which was subsequently reacted with triflyl sugar **B** under basic condition, ultimately provided *cis*-glycosidic linkages **C** and **E** (Figure 14). The

Figure 14. Conceptualized glycosylation between stannylene acetals and sugar triflates by Hódosi.

procedure is utterly benefitting from the bimolecular nature of the triflyl displacement on the electrophilic donor, lacking the involvement of oxocarbenium ion and therefore inherently providing the most challenging 1,2-*cis* mannosides and rhamnosides (Figure 15). Triflylation of different OH functions of the donor sugar allowed them to broaden the substrate scope and access β-(1→4) disaccharides, which was rarely a case by then. Except for the unprotected D-

mannose giving rise to the unexpected 6→3 connection (**47**) instead of β-(1→6) **49**. This was being reasoned by having an equilibrium between 1,2-*cis* **F** and 2,3-*cis*-stannylene acetals **G**,

Figure 15. Equilibrium between 1,2-*cis* and 2,3-*cis*-stannylene acetals.

thus activating 3-*O* on the sugar acceptor (Figure 15). By changing the solvent system, the yield could be increased to 59 % for the desired β-(1→6) glycoside **47**. Further improvement could be achieved when 3-*O*-benzylated mannoside was employed, due to the omitted isomerization from **F** to **G**.

Figure 16. Scope of glycosylation with sugar triflate moieties.

Kaji and Harita managed to suppress the generation of intersugar orthoesters when pivaloyl group was installed at 2-OH instead of commonly used acetate or benzoyl functions.

They have also found Ag(I) silica alumina promoter superior over other silver salts or TBAB (Figure 17).⁹² Slightly modifying the existing method resulted in improved yields, together with high β preference employing per-*O*-pivaloylglucopyranosyl bromide **52** and per-*O*-pivaloylglucoronyl bromide **53**. On the other hand, stannylene acceptors remained confined mainly to 1 $\rightarrow$ 6 and 1 $\rightarrow$ 3 connections reasoning the fact, that 6-*O*-stannylated sugars are existing in equilibria with 3,4-*O*-stannylene acetal species, whereby 6-*O* is predominantly more reactive. In the absence of 6-*O* or in its protected form, 3-*O*-glycosides were being formed as such (**56**).

Figure 17. 1,6- and 1,3-glycosylation by Kaji.

1.2.4 Tin-Mediated Glycosylation: Altering from 1,6-Glycosylation to 1,3-Glycosylation and the Mechanism Behind

Overcoming the latter obstacle, a revolutionizing approach was provided from the same group while dissected the reaction mechanism as well.⁹³ As a general observation, glycosyl donors are most likely to form 1,6-*O*-glycosides, whilst, acylating and alkylating reagent are prone to give 3-*O*-substituted sugar predominantly. This was being reasoned by suggesting an

existing equilibrium between 6-*O*-stannyl **A** and the thermodynamically more stable 3,4-*O*-stannyl **C** species (Figure 18). While the stronger electrophiles (acyl and alkyl bromides) are able to afford smoothly the thermodynamically favored 3-*O*-acyl or 3-*O*-alkyl product, the bulky and lousy sugar derived electrophiles **D** are reacting faster with the more accessible form of the stannylene acetal (**B**), giving rise to 1,6-*O*-glycosides **E**.

As they have found, the addition of TBAF shifts the regioselectivity from 1,6 to 1,3 in the glucosidation of galactose, yielding 42 %. Conceivably a pentacoordinated 3,4-*O*-stannyl acetal **G** was being formed by the attack of fluoride ion, thereafter isomerized to 3-alkoxide **H** providing a more reactive key intermediate, thus arriving at β -(1 $\rightarrow$ 3) disaccharides **I** (Figure 18). Since the transformation failed to provide β -(1 $\rightarrow$ 4), the involvement of 4-alkoxide species is negligible. It is worth mentioning that simply reacting bromosugar donor with free sugar acceptor lacking stannylene acetal group failed to furnish the disaccharide. This happened to be a clear evidence for the activation effect of stannylene protection strategy.

Figure 18. Mechanistic rationale for the altered preference in glycosylation.

1.2.5 Tin-Mediated Glycosylation: From Equimolar to Catalytic

Taking stannylene acetal glycosylation to the next level, Muramatsu and Yoshimatsu reduced the need of organotin reagent from equimolar to catalytic amount, while achieving excellent regioselectivity on 3-*O* and high yields for disaccharide formation (Figure 19).⁹⁴ They came to

Figure 19. The scope of regioselective glycosylation by Muramatsu.

the realization, that the reactivity difference between primary 6-OH and secondary alcohols permits to lower the reagent loading to catalytic amount. Interestingly, in the absence of the catalyst no disaccharide formation was observed, whilst the addition of base found to be necessary to obtain high yields. With the optimized condition in hand (Ph_2SnCl_2 10 mol%, Ag_2O and DMPBY weak, bulky base), they coupled a wide range of bromosugars with various acceptors. Pleasingly, in all reported cases, the applied catalytic system was able to differentiate between primary and secondary alcohols, unexpectedly favoring the latter one.

Moreover, only monoglycosylation was observed on 2,3-*cis*-diol moieties, preferably happening at the equatorial position. Reasoning the fact, that coordination of metal ion increases the acidity of an alcohol, the formed stannylene complex can be easily deprotonated by even a weak base from the more accessible site, ultimately giving rise to β -(1 $\rightarrow$ 3) disaccharides and completely omitting the formation of β -(1 $\rightarrow$ 2) disaccharides. Additionally, the authors suggested a concerted mechanism for the deprotonation of 3-*O* and the electrophilic attack on it, therefore the $\text{S}_{\text{N}}2$ -type displacement may occur preserving the orientation around the electrophilic center. Although the authors did not dissect the reason for the preferential generation of β -(1 $\rightarrow$ 3) over β -(1 $\rightarrow$ 6) disaccharides, we may suggest the conceivable formation of a more reactive pentacoordinated stannylene acetal complex, which was isomerized to 3-alkoxide likewise in Kaji's previous work.⁹³

The history of stannylene acetal activated glycosylation stretches along more than 3 decades, and within that period constructing β -(1 $\rightarrow$ 3) and β -(1 $\rightarrow$ 6) connections became amenable on mildly decorated monosaccharide units. The universality of this method is proven by its wide array of donors and aglycones. Moreover, its compatibility with diverse leaving groups at C1 as well as with the related activation methods implies being a prospective methodology for complex glycan synthesis. However, we should address every conceivable drawback of this procedure, particularly being inapt to provide α -products, the inability to form

1→2, and the limited access to 1→4 connections, and last but not least the environmentally harmful nature of the applied tin reagents.

1.2.6 Copper-Mediated Glycosylation

Taking the latter disadvantages into consideration, the utility of stannylene acetal-mediated glycosylation is greatly downsized by now. Therefore, a widely applicable and environmentally less toxic method for regio-, and stereoselective glycosylation is still in high demand. Answering this urgent call, Osborn and co-workers addressed this by making a step towards an eco-friendly regioselective glycosylation by replacing tin reagent with copper chloride (Figure 20).⁹⁵ Seemingly, the presence of base and copper salt is sufficient enough to activate the bromo leaving group, in addition, silver triflate activator rather halted the transformation than promoted. The basis of the transformation is adapted from previous stannylene acetal methods, whereby the complexation of 2,3-diol might enhance the nucleophilicity of 3-*O* while overriding the nucleophilic nature of 2-*O*. Indeed, the copper chelation on 4,6-benzylidene protected glucose **74** and galactose derivatives did favor the α-1,3-glycoside **76** formation over 1,2-glycosylation (**77**). The best selectivity was obtained in the galactosidation of glucoside, providing a modest bias. Surprisingly, β-(1→3) connection has never been observed, although participating acetate function was installed at donor 2-*O* position. To the best of our knowledge, this chemistry has not been applied in further studies, which might be reasoned with the reported narrow substrate scope and incomplete regioselectivity.

Figure 20. Copper-activated glycosylation by Osborn.

As a further development, Wei and co-workers successfully transplanted the copper-mediated activation from Osborn's group (Figure 21).⁹⁶ They did so with a twist, by complexing the donor moiety instead of the aglycone. They have presented an efficient way to prepare several β -disaccharides from glycosyl dithiocarbamates **78** (DTCs), alongside with the efficient *in-situ* one-pot formation of the donor moiety.⁹⁷

Figure 21. Copper-mediated glycosylation on glycosyl dithiocarbamates.

Dissecting the mechanism revealed, the coordinated copper presumably promoted the intermolecular addition of the C2 hydroxyl group onto the thiocarbonyl function, giving rise to bicyclic, fused orthodithiocarbamate. Such intermediate might exist in *trans*-fused **B** and the favored *cis*-fused **C** forms, thus the dominating *cis* bicycle is being attacked from β -face. The exposure of incoming nucleophile from the preferred trajectory serves β product **D** predominantly (Figure 22). Further evidence for the necessity of free C2 hydroxyl was shown when glycosylation was performed on 2-*O* protected sugar. In that case, the copper coordination did not take place, therefore none of the intermediates were preferred, thus leading to a mixture of anomers (1:2 α : β).

Figure 22. Mechanistic rationale for copper-mediated glycosylation on glycosyl dithiocarbamates.

1.2.7 Boron-Mediated Glycosylation: Early Studies

Earlier in time, Aoyama and Oshima became interested in transplanting their phenylboronic acid-mediated alkylation to glycosylation.⁹⁸ They have found a sterically hindered phenylboronic acid selectively activates the equatorial OH on the model fucoside, driving the reaction to β -(1 $\rightarrow$ 3) glycosylation.⁹⁹ At first, tetravalent boron precursor **80** has to be prepared, then upon the treatment of Ag_2CO_3 the activated trivalent boron **81** is forming through B-C bond cleavage (Figure 23). The latter species is prone to undergo alcohol/sugar exchange with vicinal diol **82**, to give the boron acetal form **83**. Finally, the enhanced *O*-nucleophile displaces the leaving group on the bromosugar **84**, giving rise to the disaccharide **85**. Interestingly, glycosylation did not take place when attempted on trivalent boron acetal **86**, thus pinpointing the necessity of tetravalent boronate in the activation of equatorial 3-*O*. Meanwhile the two geminal methyl groups at benzylic position are shielding the benzylic oxygen, therefore completely omitting its participation in the glycosylation. Proving the utility of the concept, regioselective glucosidation happened on fucoside, on 6-trityl glucoside, and on octyl- β -glucoside, although providing lower yield in the latter case. In the case of fully “naked” galactoside and mannoside both, the 6-*O*-monoglycosidated and the 3,6-*O*-diglycosylated sugars were being formed. Their ratio could be finely controlled by the feeding ratio of the donor and acceptor (Figure 25). The observed regioselectivity is in alignment with the anticipated reactivity, with primary alcohol being the ultimate, then amongst the secondary alcohols equatorial OH being the more reactive while the axially oriented OH being completely inactive in this case.

Figure 23. Mechanistic rationale for the boron enhanced glycosylation.

As a further expansion, Aoyama and his group managed to expand the substrate scope with the glucosidation and galactosidation of methyl mannosides, methyl galactosides as well as the thioglycoside counterparts. On the contrary, mannosylation always resulted in the formation of orthoester side product (Figure 24). This is stemming from the acyl function at C2 being axially oriented. Upon forming dioxolanium at the top face, two possible trajectories could be taken into consideration for the incoming sugar acceptor on sugar donor **87**. The acceptor might attack the anomeric center from the congested α -face to form disaccharides or from the more accessible top face on the acyl function, thus giving rise to intersugar orthoesters **88**. As expected, the activated boronate favors the latter less hindered electrophilic center to attack. On the contrary, glucosyl and galactosyl bromides owing an equatorially oriented acyl group at C2 (**89**) are preferably forming β -glycosides **90** over intersugar orthoesters.

Figure 24. Formation of intersugar orthoesters vs. glycosylation.

Another interesting observation has been made on the ambiguous reactivity of different sugar boronate acceptors. As soon as the sugar boronate is being formed, two moieties might present in the mixture alongside with different reactivity. In case of galactosides, the 4,6-boronate form owes a distinguished primary (6-*O*) reactive site, while in the 3,4-boronate form the equatorial (3-*O*) is expected to act as a nucleophile as well, due to the boronate coordination. Seemingly those sites are possessing different reactivity varying the incoming acceptor, specifically glucosidation prefers the primary OH, while galactosidation favors 3rd equatorial hydroxyl group. On the contrary, glucosidation and galactosidation of mannoside acceptor is occurring on the same manner, favoring equatorial 3-*O* (2,3-boronate) over 6-*O* (4,6-boronate).¹⁰⁰

Figure 25. Substrate scope of Aoyama's procedure.

Aoyama's procedure certainly provided an environmentally friendly and hitherto unexplored phenylboronic acid-activated glycosylation procedure, thus introducing a new era of open-glycosylation. However, the highly demanded 1→4 and 1→2 glycosylations remained accessible only by applying traditional multiple steps methods. Less than a decade later, Kaji and co-workers provided limited access to both, by revamping the existing method.¹⁰¹ They were relating to the well-known diol-boronic acid recognition in carbohydrate chemistry and devised to exploit the phenomena as an *in situ* masking method. Conceptually, they were switching from the previously established activation strategy (activating either 3-*O* or 6-*O*) to rather deactivating one of them. Indeed, the dominant 6-*O* glycosylation managed to be suppressed, giving rise to 3-*O* galactosides, and to 2-*O* glucosides. The observed ratio of 1→3 and 1→2 glycosides might be reasoned with taking the configuration of OH at the 4th position into account. An equatorial 4-OH shields 3-*O* in glucopyranosides, therefore favoring glucosidation at 2-*O* position. Conversely, the axial orientation at the same carbon has no shielding effect on the 3-*O*, thus giving rise to 3-*O* galactosides. Interestingly, fucosidation of glucose happens exclusively at 2-*O*, while rhamnosidation occurs at 4-*O* position which was rarely a case in the previous studies (Figure 26).

Donor	Boronic Acid / Activation Method	3-O or 4-O Product (P1)	2-O Product (P2)	Total Yield / P1:P2
104	108 Ag(I) silica-alumina	110	115	78 % / 92:8
105	109 Ag(I) silica-alumina	111	116	78 % / 94:6
106	109 NIS / TMSOTf	112	117	73 % / 81:19
104	109 Ag(I) silica-alumina	113	118	43 % / 14:86
107	109 NIS / TMSOTf	114	119	74 % / 0:100
107	109 NIS / TMSOTf	114	119	89 % / 100:0

Figure 26. Kaji's substrate scope on boron-mediated glycosylation.

1.2.8 Boron-Mediated Glycosylation: From Equimolar to Catalytic

A year later, Taylor and co-workers refined Kaji's latter procedure with introducing a new type of diarylboronic acid catalyst **121**.¹⁰² Conversely to Kaji's previous studies, the aim of their work was rather activating one of the oxygen over the other, then masking it, ultimately achieving substantial increment in the yields for disaccharides, in parallel completely omitting the formation of orthoester side product. Mechanistically, the ethanolamine coordinated

borinic acid catalyst acts as a precatalyst, and upon coordinating to *cis*-diol domain in **120**, the complex liberates the ethanolamine ligand. Subsequently the activated diol-borinic acid adduct **120a** undergoes preferentially S_N2-type displacement with **10**, and predominantly provides the anticipated regioisomer **123**. The executed NMR studies were indeed consistent with the proposed mechanism, eventually ascertained first order kinetics with respect to the donor, acceptor and the catalyst. Another indirect evidence for the bimolecular kinetics is the observed formation of intersugar orthoester **122** when peracetylated β -chloro glucoside **13** is used (Figure 27).

Figure 27. Orthoester vs. glycosylation in Taylor's work.

This observation is suggesting the involvement of S_N2-type displacement rather than the intermediacy of oxocarbenium ion, the latter favoring S_N1-type manner. Gratifyingly the optimized reaction condition provided mostly β -(1 $\rightarrow$ 3) connection with high yields, and found to be robust enough to operate even under the exposure of water. While the range of donor and acceptors is ample, the activation method is mostly confined to Koenigs-Knorr type, thus involving bromosugars or chlorosugars as donors. As they revealed, armed donors require chloro leaving group instead of bromo, rendering higher regiocontrol. Although their preparation requires relatively harsh condition (BCl₃, HBr, HCl), therefore the potential donors ought to be equipped with acid-stable protecting groups. Albeit the procedure genuinely provides an alternative way for open glycosylation, the necessary 6-OH protection must be

taken into account, thus leaving the long-standing need for preferential glycosylation on 3-OH over 6-OH unsatisfied (Figure 28).

Figure 28. Taylor's scope on borinic acid-mediated glycosylation.

Taking this methodology to the next step, Taylor's group attempted to perform regio- and stereoselective glycosylation on 2-deoxy sugars, employing the same catalyst system and reaction condition.¹⁰³ The main limiting factor on the stereoselectivity is presumably the absence of aiding C2 function, making this transformation extremely challenging. Indeed, their first results did not meet with their expectation, giving rise to a mixture of anomeric isomers favoring β -anomer (1.6:1). Seemingly the anomeric selectivity looks unsubstantial, however having in mind that high α -selectivity (1:9) was obtained under uncatalyzed reaction condition, the slight shift to the opposite anomer is clearly attributed to the presence of borinic acid catalyst. On the contrary, the absence of borinic acid had detrimental effect on the disaccharide

yields. Based on this, we can confirm the necessity of catalyst for both regioselectivity and yields.

Keeping that in mind, Taylor's group attempted to troubleshoot the bottleneck of the procedure, by switching from peracetylated chloro sugar donors to *in situ* generated glycosyl methanesulfonates (mesylates).¹⁰⁴ The established method allowed them to perform borinic acid **136** catalyzed regio- and stereoselective glycosylation on armed, nonparticipating donors. Additionally, this powerful method requires only mild PMP base (1,2,2,6,6-Pentamethylpiperidine) while completely omitting the addition of activating reagent, due to reactive but stable nature of glycosyl mesylates. Similarly to their previous studies, the absence of catalyst favors the formation of α product, while the employment of catalyst reverses the stereochemical outcome. Thus, repeatedly underlying the substantial involvement of borinic acid catalyst in the anomeric selectivity. After an extensive screening of base, borinic acid, and catalyst loading they were able to acquire disaccharide with high β selectivity (10:1) despite not having any aiding group positioned at C2. The scope of this transformation was further extended to glucofuranoside donors as well as acceptors with having an intrinsic bias for the secondary α -(1 $\rightarrow$ 5) connection over α -(1 $\rightarrow$ 6) (Figure 30). To disclose the detailed mechanism, extended NMR study had been conducted shedding light on the apparent reversal of anomeric selectivity, assisted by the borinic acid catalyst. At first, they verified the *in situ* formation of glycosyl mesylates. Furthermore, they revealed the existence of a subtle equilibria between the β - and α -mesylates, displaying an evident favor for α . Knowing that, they found that under uncatalyzed condition the major, but less reactive α -mesylate **134A** interchanges with **120**'s OH-function at slow rate, giving rise to the minor β -glycoside **130** (Figure 29). Meanwhile, the parent α -mesylate **134A** anomerizes into the more reactive, but minor β -mesylate form **134B**, produces the major α -glycoside **135** at high rate. On the contrary, under catalyzed condition the presence of more nucleophilic tetracoordinated boronic ester acceptor **120a** accelerates the

interconversion of naturally less reactive α -mesylate **134A** into the β -glycoside **130**. Since the α -glycoside **135** arises predominantly from the uncatalyzed pathway, its low ratio under catalyzed pathway refers to the ultimate preference of borinic ester reacting with α -mesylate.

Uncatalysed pathway

Catalysed pathway

Figure 29. Mechanism under uncatalyzed vs. catalyzed conditions.

Figure 30. Scope of Taylor's glycosylation with borinic acid **136**.

1.2.9 Examples to Sn- and Boron-Assisted Total Syntheses

Proving the applicability and universality of stannylene acetal glycosylation, Nicolaou and co-workers applied this strategy in natural product syntheses.¹⁰⁵ They have assembled

Figure 31. Nicolaou's work.

successfully the FG ring system of Everninomicin 13,384-1 (**153**) while simultaneously constructing 1 β ,1' α mannoside-type disaccharides (Figure 31). Additionally, the excess addition of a glycosyl fluoride provided a series of trisaccharide products with three completely controlled stereogenic centers (**147**). It is noteworthy, that they were able to transplant conventional glycosylation methods to stannylene acetal chemistry, such as TMSOTf-activated glycosyl trichloroacetimidate and fluoride donors.

Figure 32. Stannylene acetal application in total synthesis by O'Doherty's.

Besides Nicolaou, O'Doherty's group also exploited the benefits of stannylene acetal masking strategy in Pd-catalyzed glycosylation serving the key intermediate for the valuable Cleistrioside and Cleistetroside natural products.¹⁰⁶ They addressed major contribution of the dibutyltin acetal in the regioselectivity, comparing the stannylene acetal-mediated glycosylation to conventional methods. Gratifyingly, they could reverse the formation of **157** product to the desired **156** by applying stannylene protection (Figure 32).

Figure 33. Comparative work on Sn- and boron-mediated glycosylation by O'Doherty.

As an utilization of Taylor's chemistry, Doherty's group accessed the family of Mezzettiasides by making use of Pd catalysis,¹⁰⁷ likewise to their previous work mentioned

above.¹⁰⁶ Comparing Sn/Pd-mediated glycosylation to B/Pd-mediated glycosylation shows superiority of the latter procedure, in both yield and selectivity (Figure 33). Besides this work, Taylor's procedure was further exploited in the syntheses of other natural products.¹⁰⁸⁻¹⁰⁹

Chapter II

Study on Boron-Mediated Glycosylation

2.1 The Concept

Compiling the finite library of stereoselective open-glycosylation the following limiting factors should be addressed hampering its sleek performance: usage of environmentally noxious reagents; involvement of the notorious S_N1 displacement accompanied with ambiguous anomeric selectivity; inactive 4-OH to build 1→4 connection; the need for C2 participating group to furnish β and the limited access to α anomers. From the synthetic point of view, the most concerning amongst the above-mentioned factors might be the finite access to diverse intersugar connections, being eminently pronounced in sugar oligomers and glycans.

Capitalizing knowledge on the literature of boronic and borinic acid-supported stereoselective glycosylation being performed on mildly ornamented saccharides, we devised to deliver a solution to the aforementioned challenges. Our mission was to design a strategy, constituting a temporal group being able to bind to the free hydroxyl group(s) of the donor, additionally owing stereo directing effect on the outcome of the glycosylation, and finally being easily removed upon working up. We have planned it so that the interference between the naked donor and the activated form of itself could be eliminated, therefore no self-condensed disaccharide should be observed. Eventually the procedure ought to deliver the anticipated glycosidic bond formation between the donor and the acceptor.

Analogous to Toshima's works have been performed on 1,2-anhydrosugars¹¹⁰⁻¹¹², we set out to investigate the boron-mediated renowned intramolecular aglycon delivery (IAD) approach, rather than activating the equatorial OH over the axial, as previously described. We

initially conceptualized, the applied dialkyl boron triflate reagent **2** would bind to the pendant free 2-OH onto the sugar donor **1**¹¹³ (Figure 1). Subsequently, the liberation of activated leaving group forms the stabilized oxocarbenium ion, which is being attacked by the acceptor. We proposed to influence the trajectory of the incoming nucleophile by fine-tuning the steric bulk of the alkyl boronic reagent. Smaller alkyl groups such as dimethyl **2** is expected to form tetravalent boron intermediate **3** with the acceptor, thus being ready to drive the acceptor from the bottom face, giving rise to 1,2-*cis* product **4**. Whereas bulkier alkyl groups on **5**, such as di-*n*-butyl and 9-BBN are predicted to occupy the bottom face, therefore leaving the top face as the only accessible attacking trajectory, giving rise to 1,2-*trans* anomer **7**. This hitherto unexplored approach would allow us to access both α - and β - glycosides on nonparticipating, armed sugars.

Figure 1. IAD-like Glycosylation vs. Spatial Occupancy Driven Glycosylation.

2.2 Discussion

2.2.1 Optimization Studies

Commencing the optimization studies on glycosylation with 2-OH donor we have found the choice and the adding sequence of the reagents (activator, dialkyl boron triflate, acceptor) are rather crucial to the robust operation (Table 1). At first, we set the activator DMTSF and acceptor MeOH, and began to investigate the choice of boron reagent on sugar

donor. In the absence of boron reagent, the reaction provided 40 % yield for the desired glycoside in favor for the α anomer, together with complex mixture of unidentified products. In entry 2, we examined whether the masking reagent could provide the nucleophile by using diethylmethoxyborane, however it resulted in diminished yield. Interestingly, when the mixture was treated with Et₂BOTf as well, the yield increased and the reaction provided α anomer exclusively together with the hemiacetal form of the donor (entry 3). Since no self-condensed product or complex mixture were being observed, we may suggest that Et₂BOMe is able to provide methoxy anion while Et₂BOTf acts as a masking reagent. Starting the sequence of addition with the coupling partner followed by the Et₂BOTf gave no observable product, but providing hemiacetal – possibly arising from the aqueous workup procedure, showing us full activation of the donor but no glycoside formation – (entry 4). Switching the adding order of the masking reagent and the alcohol gratifyingly served glucoside in decent yield with slight anomeric β preference (entry 5). From the first few results we have observed an improvement in anomeric selectivity from α only to an almost 1:1 anomeric mixture upon the addition of boron reagents. Thus, this observation and the encouraging increment in yield prompted us to fix the sequence of addition for the subsequent entries. In entry 6, we attempted to force the reaction towards the product at ambient temperature, resulting in a dark brown complicated mixture and diminished yield. Next, we proceeded to explore whether the boron reagent influences or reverses the anomeric selectivity. Switching from diethyl, to bulkier dibutyl, dicyclohexyl and 9-BBN boron triflates the stereoselectivity at C1 seemed to be driven towards β -glycoside, albeit moderately. Performing the reaction in acetonitrile (entry 10) halted it, while changing the solvent to toluene (entry 11) exhibited no effect on the yield, however abating the marginal β preference. With this knowledge in mind, we proceeded to further improve the anomeric selectivity with the established procedure: 3 equiv of TTBP was mixed with 1 equiv of donor, followed by the addition of 1.1 eq. of dialkyl boron triflate

Entry ^a	Reagent 1	T	Reagent 2	Solvent	Yield (%) ^b	α/β ^c
1	-	-20 °C	MeOH	DCM	40	2.3/1
2	-	-20 °C	Et ₂ BOMe	DCM	<5	2/1
3	Et ₂ BOTf	-20 °C	Et ₂ BOMe ^d	DCM	20	α only
4	MeOH	-20 °C	Et ₂ BOTf ^e	DCM	-	-
5	Et ₂ BOTf	-20 °C	MeOH	DCM	51	1/1.1
6	Et ₂ BOTf	+20 °C	MeOH	DCM	25	2.2/1
7	9-(BBN)OTf	-20 °C	MeOH	DCM	59	1/1.4
8	Bu ₂ BOTf	-20 °C	MeOH	DCM	60	1/1.5
9	Cy ₂ BOTf	-20 °C	MeOH	DCM	63	1/2.1
10	Bu ₂ BOTf	-20 °C	MeOH	ACN	-	-
11	Bu ₂ BOTf	-20 °C	MeOH	Toluene	59	1/1.1

^a Unless otherwise specified, all reactions were carried out with 1 eq. of **1**, 1.1 eq. of boron reagent, 3 eq. of TTBP, 1.2 eq. of MeOH and 3 eq. of DMTSF in 2 mL of solvent for 12 hs. ^b isolated yield. ^c determined by ¹H-NMR integration. ^d 7 eq. was added. ^e 2.2 eq. was added.

Table 1. Optimizing the masking effect of the boron reagent.

at -20 °C, activated with thiophilic promotor, and lastly the mixture was treated with alcohol acceptor (Table 2). Next, we investigated the steric bulk and nucleophilicity (entries 1-4) of the acceptor. We have found, that increased nucleophilicity (from MeOH to *i*PrOH) follows a trend, as more nucleophilic reagent (on a basis of pK_a values) provides better β selectivities. However, *n*BuOH is somewhat clashes with this trend, since its pK_a value is smaller than for *i*PrOH, but still providing better β selectivity. We believe the reason behind, is that *n*BuOH is relatively good nucleophile (pK_a 16.1) which couples with its small size, thus gives faster reaction, therefore even better β selectivity than *i*PrOH. Unfortunately, bulkier boron reagent (butyl, cyclohexyl, 9-BBN) did not bring further improvement in stereoselectivity. Screening the solvent (entries 5-8) revealed the synergistic effect of the solvent with the steric bulk and boron reagent, however the results are not showing an obvious trend between solvent polarity, selectivity and yield. Having seen that DCM gave the best yield together with modest stereoselectivity, we decided to set DCM as a solvent, butanol as acceptor and investigate the choice of promoter together with the temperature. Gratifyingly, lowering the temperature increased

the yield for glycoside dramatically, providing sole β product (entry 9). We managed to further improve the yield while maintaining excellent anomeric selectivity by applying commonly used activating methods (entries 10-12). Lastly, we examined whether the choice of boron reagent influences the outcome of the reaction. Repeating entries 10-12 with the alkyl boron triflates at our disposal did not abate the excellent 1,2-*trans* selectivity. Notably, the adding sequence of acceptor and activator is switchable without diminishing yield or abating anomeric selectivity (entries 10-12). These results ensured us that the established methodology is compatible with various promoters, while providing excellent yield and β selectivity, therefore owing high potential in disaccharide, possibly in oligosaccharide and branched glycan synthesis.

Entry ^a	Reagent 1	T ₁	Reagent 2	T ₂	Solvent	Yield (%) ^b	α/β ^c
1	MeOH	-20 °C	DMTSF	-20 °C	DCM	8 , 60	1/1.5
2	EtOH	-20 °C	DMTSF	-20 °C	DCM	9a , 62	1/1.8
3	<i>i</i> PrOH	-20 °C	DMTSF	-20 °C	DCM	9b , 59	1/2.5
4	BuOH	-20 °C	DMTSF	-20 °C	DCM	24 , 68	1/4.1
5	BuOH	-20 °C	DMTSF	-20 °C	DMF	24 , 30	β
6	BuOH	-20 °C	DMTSF	-20 °C	CH ₃ CH ₂ NO ₂	24 , 50	1/2
7	BuOH	-20 °C	DMTSF	-20 °C	Toluene	24 , 40	1/6
8	BuOH	-20 °C	DMTSF	-20 °C	ACN	24 , trace	1/5
9	BuOH	-40 °C	DMTSF	-40 °C	DCM	24 , 73	β
10 ^d	BuOH	-40 °C	NIS/TMSOTf	-40 °C	DCM	24 , 89	β
11 ^e	<i>p</i> -NO ₂ PhSCl	-60 °C	BuOH	-78 °C	DCM	24 , 85	β
12 ^f	Ph ₂ SO/Tf ₂ O	-60 °C	BuOH	-78 °C	DCM	24 , 86	β

^a Unless otherwise specified, all reactions were carried out with 1 eq. of **1**, 1.1 eq. of boron reagent, 1.2 eq. of ROH and 3 eq. of DMTSF in 2 mL of solvent for 12 hs. ^b Isolated yield. ^c Determined by ¹H-NMR integration.

^d 1.2 eq. of NIS and 0.2 eq. of TMSOTf were added. ^e 3 eq. of AgOTf and 1.2 eq. of *p*-NO₂PhSCl were added.

^f 1.3 eq. of Ph₂SO and 1.5 eq. of Tf₂O were added. n.d. not detected.

Table 2. Optimization of anomeric selectivity.

In order to dissect the mechanism, we set a few control reactions on fully protected donor **10**¹¹⁴ (Figure 2). Firstly, a typical glycosylation was carried out, affording good yield for **11** and β anomeric preference. The addition of boron reagent prior the activation step diminished the yield dramatically. Premixing butanol acceptor and boron reagent afforded BuO-BBu₂, which

was subsequently added to the activation step, did not provide the glycoside **11**, affording only hydrolyzed donor **12**¹¹⁵. Repeating **A** on unprotected sugar donor has found to give complex mixture, as expected. To conclude, we have observed inhibited glycosylation when boron had no free hydroxyl to react, therefore we have found the order of adding reagents crucial. Thus, we set the sequence as, introduction of the equimolar amount of boron reagent to the donor, followed by the thiophilic activator, then lastly the addition of acceptor.

Figure 2. Study on control experiments.

2.2.2 Expanding the Scope of Glycosylation

With the working procedure in hand, we proceeded to explore its scope on glycosyl donors bearing one free hydroxyl group at different positions (2nd, 3rd, 4th and 6th). Gratifyingly, the method shows high level of disregard on the free hydroxyl position, allowing us to achieve excellent yields and strong β selectivity with 2-OH and 3-OH glycosyl donors (**1**, **13**,¹¹⁶ **15**,¹¹⁷ **16**¹¹⁸ Figure 3). On the contrary, adjacent acetyl group to the unprotected OH abated the anomeric selectivity for **14** and **17**. This unexpected result could not be explained thoroughly at the early stage of our work, therefore extensive ^{11}B -NMR study had to be conducted to examine this phenomenon. In case of perbenzylated 4-OH **19**¹¹⁹, the anomeric effect affected the outcome, however still giving β isomer of **31** as the prominent. This slight change could be

easily surmounted with the aid of directing 2-*O*-benzoyl group (**20**)¹²⁰. Interestingly, glycosyl donor **18** being forced to exist in ¹C₄ conformation underwent intramolecular displacement at

Unless otherwise specified, all reactions were carried out with 1 eq. of donor, 1.1 eq. of Bu₂BOTf, 1.3 eq. of Ph₂SO, 3 eq. of TTBP, 1.5 eq. of Tf₂O, 1.2 eq. of BuOH in 2 mL of solvent for 12 hs. Yields are determined by isolation of product.^a Determined by ¹H-NMR integration.

Figure 3. Scope of glycosylation on unprotected donors.

6-*O* position, forming 1,6-anhydroglucoside **30A**. In case of 6-OH, the activated donor **21** has formed similar anhydro product **30B**, as it was expected. Similarly to 4-OH, glycosylation on perbenzylated donor **22**¹¹⁹ provided anomeric mixture of **33**. We identified the presence of primary 6-OH as a key contributor for the diminished selectivity. However, with the introduction of benzoyl group at 2-OH in **23**¹²¹ we were able to mitigate the effect, arriving at sole β product **34**.

Unless otherwise specified, all reactions were carried out with 1 eq. of donor, 2.1 eq. of Bu₂BOTf, 1.3 eq. of Ph₂SO, 3 eq. of TTBP, 1.5 eq. of Tf₂O, 1.2 eq. of BuOH in 2 mL of solvent for 12 hs. Yields are determined by isolation of product. ^a Determined by ¹H-NMR integration. ^b 3.1 eq. of Bu₂BOTf was used.

Figure 4. Scope of glycosylation on donors bearing multiple free hydroxyl function.

Glycosylation on diols have been carried out as well (Figure 4). Donors **35**,¹²² **36**¹²³ bearing free OH at 2 and 3 positions found to be greatly aiding the formation of sole β **47**, albeit primary 6-OH (**41**)¹²⁴ immensely abated the anomeric selectivity for **53**. Similarly to prior studies, benzoyl ester function at C2 (**42**)¹²⁵ preserved the stereo selectivity for **54**. The same procedure was applied on triols providing good yields while in case of 2,4,6-OH (**45**)¹²⁶

exceptional anomeric selectivity was achieved (**57**), despite carrying primary OH at 6th position. In the rest of the cases (**43**,¹²⁷ **44**,¹²⁸ **46**) good yields and β preference were observed (**55**, **56**, **58**). Due to a low solubility issue carrying out glycosylation on 2,3,4,6-OH donor did not proceed.

The successful results encouraged us to expand the substrate survey to disaccharides, taking another step towards oligosaccharide synthesis. Firstly, we have considered to investigate one of the most abundant intersugar connection, the 1 $\rightarrow$ 6 glycosidic bond formed in our case with acceptor **62**¹²⁸ and **63**¹²⁹ (Figure 5). To our delight, glucosylation with free 2-OH (**1**) glucose derivative provided good yields and sole β products **64**, **65**. Glycosylation with the epimer of glucose donor, such as 2-OH mannoside **59**¹³⁰ also afforded high yield and the anticipated α product **66**. Gratifyingly, allosidation with **60** exclusively furnished β -glycoside **67**, which was rather surprising, when compared to literature data.¹¹⁴ This prompted us to assume that the boron reagent might express its significant role by hindering the α -face through bonding to the axial 3-OH, thus forcing to form β configured glycosidic bond. The boron reagent binding to free OH at 3rd position of donor **15** somehow govern the anomeric selectivity towards β **68** as well. These results are rather intriguing, as substantial steric crowding at the bottom face could not be involved, therefore we assume other factors were associated with the boron effect. Glucose bearing free 4-OH **19** and its C4 galactoside epimer **61**¹³¹ have shown comparable anomeric selectivity to their perbenzylated forms, implying the successfully expressed masking but no remote control effect. To our gratitude, the application of bulkier boron reagent resulted in pure β configuration for **69**. Diol glucose **35** provided **71** glucoside diastereoselectively as well. As a further powerful proof on our concept we have demonstrated the feasibility of constructing $\beta(1\rightarrow2)$ with acceptor **74**,¹³² $\beta(1\rightarrow3)$ with **73**,¹³³ and $\beta(1\rightarrow4)$ with **72**¹³⁴ glycosidic bonds (Figure 6).

Unless otherwise specified, all reactions were carried out with 1 eq. of donor, 1.1 eq. of Bu₂BOTf, 1.3 eq. of Ph₂SO, 3 eq. of TTBP, 1.5 eq. of Tf₂O, 1.2 eq. of acceptor in 2 mL of solvent for 12 hs. Yields are determined by isolation of product. ^aDetermined by ¹H-NMR integration. ^b2.1 eq. of Bu₂BOTf was used. ^c1.1 eq. of Cy₂BOTf was used.

Figure 5. Scope of disaccharides with 1→6 connection.

Unless otherwise specified, all reactions were carried out with 1 eq. of donor, 1.1 eq. of Bu₂BOTf, 1.3 eq. of Ph₂SO, 3 eq. of TTBP, 1.5 eq. of Tf₂O, 1.2 eq. of acceptor in 2 mL of solvent for 12 hs. Yields are determined by isolation of product.

Figure 6. Scope of disaccharides with 1→4, 1→3 and 1→2 connections.

2.2.3 Revealing the Mechanism Behind: LT-NMR Studies

In this subchapter we sought to answer the burning question; what is the intriguing role of boron reagent in our glycosylation. To cater the best possible answer, we conducted extended low-temperature NMR (LT-NMR) studies. At first, we examined whether an alcohol connected tetravalent boron is forming, supporting our initial idea, the IAD-type glycosylation. In this manner, we expected to acquire 1,2-*cis* glycoside when less bulky boron is being used, administering the delivery to the oxocarbenium ion. In the second scenario, a tetravalent boron

is also being formed, however a triflate-alcohol interchange on the boron center is not occurring, therefore the IAD-like displacement is not feasible. In this fashion, the stereoconfiguration of the disaccharide is rather influenced by the steric bulkiness of the boron reagent, providing 1,2-*trans* glycosides.

Commencing our LT-NMR studies, 2-OH free donor (**1**) was chosen as the model substrate. We devised to carry out ^{11}B NMR measurements as well to provide the best plausible mechanism. Since $\text{BF}_3\cdot\text{OEt}_2$ has found to be a common standard reference in ^{11}B NMR studies,¹³⁵ we collected spectra for $\text{BF}_3\cdot\text{OEt}_2$, Et_2BOMe and Bu_2BOTf at $-40\text{ }^\circ\text{C}$ (Figure 7).

Figure 7. ^{11}B NMR measurements for standard $\text{BF}_3\cdot\text{OEt}_2$ (A), reagents Et_2BOMe (B) and 1 M DCM solution of Bu_2BOTf (C).

We set the boron peak for $\text{BF}_3\cdot\text{OEt}_2$ as 0 ppm, and observed singlet for Et_2BOMe at 54.8 ppm, and a broad peak at 64.0 ppm for Bu_2BOTf (possibly due to the commercially available dilute DCM solution). The peaks for the masking reagents appeared in the positive region, clarifying the utility of the common method, since trivalent boron centers are known to be shifted to the positive region. Upon coordinating to the donor, we expect it to shift to the negative region, showing clear evidence for the tetravalent boron center. With this knowledge in hand, we began to investigate the spectral influence of the boron coordination with the model substrate (Figure 8). Upon the addition of Bu_2BOTf , the OH peak immediately disappeared, while the adjacent

C-2 proton endured downfield shift from 3.56 ppm to 4.20 ppm (Figure 8, left). The disappearance of alcohol proton shows obvious evidence for the boron replacement, while the exerted deshielding on the adjacent sugar ring proton illustrates the electron withdrawing effect of the boron coordination. Gradual elevation of the temperature shows decomposition at -10 °C, unless otherwise found to be stable enough to carry out complex and time consuming 2D NMR measurements (see Appendix). Gratifyingly, we have observed a new peak at -3 ppm in ^{11}B NMR spectra, clarifying the generation of the tetravalent boron species upon coordination to the sugar donor **1** (Figure 8, right).

Figure 8. 1D-TOCSY NMR measurement of the mixture (**left A**). Addition of boron reagent (**left B**) ^1H NMR measurement of donor **1** (**left C**). ^{11}B NMR measurement of the coordinated boron species (**right A**). Control ^{11}B NMR measurement of donor **1** (**right B**).

Next, we aimed to identify the nature of the tetravalent boron species. When only 0.5 equivolar Bu_2BOTf was introduced, we identified a mixture of coordinated and parent sugar donors in the NMR tube, implying the presence of $\text{RO-BBu}_2\text{-OTf}$ rather, than $\text{RO-BBu}_2\text{-OR}$. This might be due to the stronger affinity of triflate ion to the tetravalent boron center, or to the simple fact that we introduced excess amount of triflate in the form of other reagents (AgOTf , Tf_2O , TMSOTf). Addition of an equivalent amount of BuOH into the mixture did not influence the ^1H spectrum over extended period of time, however extensive introduction of alcohol shows

the presence of boron-masked and intact donors in the mixture. This might be due to the sugar-alcohol interchange being slow enough to observe on the NMR time-scale at -40 °C.

To conclude our findings from the acquired NMR data we suggest dismissing the firstly proposed IAD-like displacement of the leaving group, and supporting the boron exhibited spatial occupancy theory. The latter scenario is indeed supported by Kim's findings, whereby they described the so-called remote electron-withdrawing effect.^{117, 136} According to them, electron-withdrawing groups at 3-*O*, 4-*O* and 6-*O* significantly affected the stereochemical outcome of glucosylation, galactosylation and mannosylation. We identified the electron-withdrawing nature of the *O*-bonded boron, which explains the reason of the observed high β preference, in particular when boron bonded to 3-OH or 4-OH. Being aligned with Kim's theory, we believe that our glycosylation is largely controlled by remote electron-withdrawing effect of the boron reagent, as well as by its spatial occupancy.

During the expansion of substrate scope we found the paradoxical behaviour of 2-OAc (**17**) and 3-OAc (**14**), giving rise to the unexpected anomeric mixture. Instalment of participating groups at 2-OH generally drives the stereoconfiguration towards β , while unprotected, but boron-masked 2-OH exhibits the same effect on the stereochemical outcome. The diminished selectivity prompted us to reveal the source of this anomaly, thus we repeated the extended LT-NMR studies on benzylidene derivative (**14a**) of donor **14** (Figure 9). Upon the addition of boron reagent, we observed the disappearance of OH_{H} at C-2, while H-2 endured downfield shift from 3.56 ppm to 4.30 ppm, similarly to the latter case. Additionally, H-3 has shifted slightly to 5.48 ppm from its original 5.26 ppm position. The substantial change on the ^{11}B NMR spectra (broad peak at -20 ppm) prompted us to suggest an interfering 3-OAc coordination to the boron center, therefore attenuating its participation in the glycosylation. Repeating the NMR study on 3-OH benzylidene derivative (**17a**) of donor **17**, we identified a similar pattern on the acquired spectrum (Figure 9). The OH_{H} peak at C-3 disappeared, while

adjacent H-3 endured downfield shift from 3.83 ppm to 4.50 ppm. Additionally, H-2 has shifted slightly to 4.94 ppm from its original 5.10 ppm position. Again, a substantial change on the ^{11}B NMR spectra (broad peak at -20 ppm) prompted us to suggest an interfering 2-OAc coordination to the boron center.

Figure 9. LT-NMR spectra. 1D-TOCSY NMR measurement of the mixture of **14a** and Bu_2BOTf (top left **A**). 1D-TOCSY NMR measurement of the **14a** (top left **B**). ^{11}B NMR measurement of the mixture (top right **A**). Control ^{11}B NMR measurement of donor **14a** (top right **B**). 1D-TOCSY NMR measurement of the mixture of **17a** and Bu_2BOTf (bottom left **A**). ^1H NMR measurement of the mixture (bottom left **B**). ^1H NMR measurement of the **17a** (bottom left **C**). ^{11}B NMR measurement of the mixture (bottom right **A**). Control ^{11}B NMR measurement of donor **17a** (bottom right **B**).

2.3 Conclusion

Control over regio- and stereoselectivity has been a long-standing challenge in glycoscience, therefore it attracts distinguished attention from the carbohydrate chemists. To tackle the difficulty of stereoselective glycosylation in the presence of one to multiple free hydroxyl group(s), we hereby presented our boron-mediated glycosylation strategy. Our methodology has been tested on a wide array of glycosyl donors and acceptors, accessing 22 glycosylated monosaccharides and 11 disaccharides. To our gratitude, the method further proved its practicality by being compatible with many common activating strategies.

To reveal the mechanism behind the transformation, we have elaborated an extensive NMR study, including 2D ^1H and 1D ^{11}B techniques. From the acquired data we suggested a synergistic effect playing key role in the stereo-outcome of the glycosylation, involving the electron-withdrawing nature of the oxygen bonded boron reagent, as well as its spatial occupancy. Our reasoning behind the excellent as well as the abated anomeric selectivity is strongly supported by recent literature data. Lastly, we are happy to say that this work has been published in 2017.¹³⁷ Therefore, all results and data presented here were reused from the publication material with the approval of the publisher and authors, while strictly adhering the relevant guidelines for research integrity.

Our main mission, to utilize this protocol in a streamlined one-pot synthetic strategy has been devised and began to be executed in the following chapter.

2.4 Experimental Section

2.4.1 General Methods

All reactions were conducted under an atmosphere of nitrogen, unless otherwise indicated. Anhydrous solvents were transferred via oven-dried syringe. Flasks were flame-dried and

cooled under a stream of nitrogen. All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010-0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. Optical rotations were measured in CHCl₃ or CH₂Cl₂ with a 1 cm cell (c given in g/100 mL). High resolution mass spectra (HRMS) were recorded on Q-TOF mass spectrometer. Accurate masses are reported for the molecular ion [M+H]⁺, [M+Na]⁺ or a suitable fragment ion. Unless otherwise specified, NMR spectra were recorded at room temperature on a 400 MHz and 500 MHz NMR spectrometer. The residual solvent signals were taken as the reference (7.26 ppm for ¹H-NMR spectroscopy and 77.23 ppm for ¹³C-NMR spectroscopy). Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane (TMS). Chemical shift (δ) is referred in terms of ppm, coupling constants (*J*) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, br = broad or unresolved.

2.4.2 General Methods for Glycosylation

Method A: Activation with DMTSF

To a magnetically stirred DCM (2 mL) solution of donor (0.1 mmol, 1 eq.) 2,4,6-tri-tert-butylpyrimidine (3 eq.) was added at -20 °C. After which, to the mixture was added dropwise 1 M DCM solution of dibutylboryl trifluoromethanesulfonate (1.2 eq.), then subsequently the temperature was lowered to -40 °C. After reaching the set temperature, the mixture was treated with n-butanol (1.2 eq.), thereafter 5 mins with

dimethyl(methylthio)sulfonium tetrafluoroborate (3 eq.), and stirred for 12 hs. After which the mixture was quenched with triethylamine (50 μ L). The crude product was washed with water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded pure products.

Method B: Activation with NIS/TMSOTf

To a magnetically stirred DCM (2 ml) solution of donor (0.1 mmol, 1 eq.) 2,4,6-tri-tert-butylpyrimidine (3 eq.) was added at -20 °C. After which, to the mixture was added dropwise 1 M DCM solution of dibutylboryl trifluoromethanesulfonate (1.2 eq.), then subsequently the temperature was lowered to -40 °C. After reaching the set temperature, the mixture was treated with n-butanol (1.2 eq.), thereafter 5 mins with N-Iodosuccinimide (1.2 eq.) and trimethylsilyl trifluoromethanesulfonate (0.2 eq.), and stirred for 12 hs. After which the mixture was quenched with triethylamine (50 μ L). The crude product was washed with sat. Na₂S₂O₃, water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded pure products.

Method C: Activation with AgOTf/*p*-NO₂PhSCI

To a magnetically stirred DCM:toluene 1:1 (2 mL) solution of donor (0.1 mmol, 1 eq.), AgOTf (3 eq., co-evaporated with toluene prior the addition) and 2,4,6-tri-tert-butylpyrimidine (3 eq.) were added at -20 °C. After which, to the mixture was added dropwise 1 M DCM solution of dibutylboryl trifluoromethanesulfonate (1.2 eq.), then subsequently the temperature was lowered to -60 °C. After reaching the set temperature, *p*-nitrobenzenesulfonyl chloride (1.1 eq.) was added, thereafter 5 mins the mixture was treated with n-butanol (1.2 eq.) The temperature was decreased to -78 °C and stirred for 12 hs. After which the mixture was quenched with triethylamine (50 μ L) and the inorganic materials were filtered off. The crude product was washed with water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded pure products.

Method D: Activation with Ph₂SO/Tf₂O

To a magnetically stirred DCM (2 mL) solution of donor (0.1 mmol, 1 eq.) 2,4,6-tri-tert-butylpyrimidine (3 eq.), diphenyl sulfoxide (1.3 eq) were added at -20 °C. After which, to the mixture was added dropwise 1 M DCM solution of dibutylboryl trifluoromethanesulfonate (1.2 eq.), then subsequently the temperature was lowered to -60 °C. After reaching the set temperature, the mixture was treated with 1 M DCM solution of trifluoromethanesulfonic anhydride (1.5 eq.), after 5 mins with n-butanol (1.2 eq.) and stirred for 12 hs. After which the mixture was quenched with triethylamine (50 μ L). The crude product was washed with water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded pure products.

2.4.3 Method for Low Temperature NMR Experiments

Donor **1**, **14** or **17** (0.1 mmol) and TTBP (0.3 mmol) were dried under high vacuum, prior dissolving in 0.4 mL of CD₂Cl₂. The mixture was transferred to a quartz 5 mm NMR-tube (<0.01 ppm Boron), thereafter introduced into the NMR spectrometer's (400 MHz) probe. The temperature was set to -40 °C, then the sample was properly tuned, matched locked and shimmed while maintaining -40 °C. After recording ¹H NMR spectrum, the sample was lifted up and 1 M DCM solution of Bu₂BOTf (0.11 mmol) was introduced then promptly lowered into the NMR probe. To ensure homogeneity in the mixture, the sample was lifted up once more and carefully shaken prior recording of the subsequent NMR spectra. To assign boron coordination, multiple ¹H-NMR and ¹¹B-NMR spectra were recorded after 1 min, 5 mins, 10 mins and 30 mins. To assign the observed chemical shifts, 1D-TOCSY selective irradiation and 2D-COSY were performed as well.

NMR spectra were also collected for standards at -40 °C: A) 0.1 mL of BF₃·OEt₂ (0.8 mmol dissolved in 0.4 mL CD₂Cl₂); B) 0.1 mL of Et₂BOMe (0.7 mmol dissolved in 0.4 mL CD₂Cl₂); C) 0.1 mL of 1 M DCM solution of Bu₂BOTf (0.1 mmol diluted with 0.4 mL CD₂Cl₂).

2.4.4 Characterization of Saccharides

Methyl-3,4,6-tri-*O*-benzyl-D-glucopyranoside 8 (Method A)

27 mg (60 % yield) as a white solid.

¹H-NMR (500 MHz, CDCl₃, 1α/1.5β): δ (ppm) 7.37-7.14 (m, 30H, both isomers), 4.92-4.79 (m, 10H, both isomers), 4.64-4.49 (m, 9H, both isomers), 4.18 (d, 1H, *J* = 7.6 Hz), 3.77-3.41 (m, 28H, both isomers), 2.32 (s, 1H), 2.12 (d, 1H, *J* = 7.9 Hz).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 138.8-138.1, 128.7-127.9, 103.8, 99.6, 84.7, 83.5, 77.8, 77.7, 75.5, 75.4, 75.3, 75.2, 75.1, 74.8, 73.7, 73.1, 70.6, 69.0, 68.7, 57.3, 55.4.

HRMS (ESI): *m/z* calcd for C₂₈H₃₃O₆ [M+H]⁺: 465.2277, found: 465.2278.

Ethyl-3,4,6-tri-*O*-benzyl-D-glucopyranoside 9a (Method A)

29 mg (62 % yield) as a white solid.

¹H-NMR (500 MHz, CDCl₃, 1α/1.8β): δ (ppm) 7.38-7.15 (m, 25H, aromatic), 4.95-4.9 (m, 2H, both isomers), 4.85-4.81 (m, 3H, both isomers), 4.64-4.48 (m, 5H, both isomers), 4.25 (d, 1H, *J* = 7.6 Hz), 4.02-3.94 (m, 1H), 3.82-3.45 (m, 13H, both isomers), 2.31 (s, 1H), 2.12 (d, 1H, *J* = 1.8 Hz), 1.27-1.22 (m, 5H, both isomers).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 138.9-138.1, 128.6-127.8, 102.7, 98.3, 84.7, 83.7, 77.8, 77.6, 75.5, 75.4, 75.3, 75.2, 74.8, 73.7, 73.2, 70.7, 67.1, 67.7, 65.5, 63.7, 15.3, 15.2.

HRMS (ESI): *m/z* calcd for C₂₉H₃₅O₆ [M+H]⁺: 479.2434, found: 479.2438.

Isopropyl-3,4,6-tri-*O*-benzyl-D-glucopyranoside 9b (Method A)

28 mg (59 % yield) as a colorless oil.

¹H-NMR (500 MHz, CDCl₃, 1α/2.5β): δ (ppm) 7.38-7.14 (m, 22H, aromatic), 4.99-4.93 (m, 2H, both isomers), 4.84-4.81 (m, 3H, both isomers), 4.64-4.47 (m, 4H, both isomers), 4.31 (d, 1H, *J* = 7.7 Hz), 4.02-3.46 (m, 10H, both isomers), 2.31 (s, 1H), 2.01 (d, 1H, *J* = 2.3 Hz), 1.28-1.17 (m, 10H, both isomers).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.8-138.0, 128.4-127.6, 101.2, 96.8, 84.6, 83.7, 77.6, 76.7, 75.3, 75.1, 75.0, 74.7, 73.5, 73.4, 72.9, 71.9, 70.5, 70.3, 69.1, 68.5, 23.5, 23.3, 22.0, 21.6.

HRMS (ESI): m/z calcd for $\text{C}_{30}\text{H}_{37}\text{O}_6$ $[\text{M}+\text{H}]^+$: 493.2590, found: 493.2598.

Butyl-3,4,6-tri-*O*-benzyl- β -D-glucopyranoside 24 (Method A, B, C, D)

46 mg (86 % yield) as a colorless oil.

$[\alpha]_{\text{D}}^{20} +58.2$ (c 0.1, CHCl_3).

^1H -NMR (500 MHz, CDCl_3): δ (ppm) 7.37-7.16 (m, 15H, aromatic), 4.93 (d, 1H, $J = 11.3$ Hz), 4.83 (d, 1H, $J = 11.2$ Hz), 4.62-4.52 (m, 3H), 4.24 (d, 1H, $J = 7.6$ Hz), 3.94-3.90 (m, 1H), 3.74 (dd, 1H, $J = 1.9$ Hz, $J = 10.8$ Hz), 3.69 (dd, 1H, $J = 4.7$ Hz, $J = 10.8$ Hz), 3.61-3.53 (m, 5H), 2.31 (s, 1H), 1.62-1.60 (m, 2H), 1.40-1.38 (m, 2H), 0.93 (t, 3H, $J = 7.0$ Hz).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.8-127.81, 102.9, 84.7, 77.8, 75.4, 75.3, 75.2, 74.9, 73.7, 70.0, 69.1, 31.8, 19.4, 14.1.

HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{38}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 529.2566, found: 529.2568.

Butyl-3-*O*-benzyl-4,6-*O*-benzylidene- β -D-glucopyranoside 25 (Method D)

34 mg (83 % yield) as a colorless oil.

$[\alpha]_{\text{D}}^{20} -31.6$ (c 0.1, CHCl_3).

^1H -NMR (500 MHz, CDCl_3): δ (ppm) 7.49-7.25 (m, 10H, aromatic), 5.56 (s, 1H), 4.96 (d, 1H, $J = 11.8$ Hz), 4.81 (d, 1H, $J = 11.7$ Hz), 4.39 (d, 1H, $J = 7.7$ Hz), 3.91-3.87 (m, 1H), 3.80 (t, 1H, $J = 10.3$ Hz), 3.72-3.64 (m, 2H), 3.58-3.53 (m, 2H), 3.48-3.41 (m, 1H), 2.38 (s, 1H), 1.64-1.61 (m, 2H), 1.41-1.38 (m, 2H), 0.92 (t, 3H, $J = 7.4$ Hz).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.4-120.5, 103.3, 101.3, 81.4, 80.2, 74.6, 74.4, 70.2, 68.7, 66.4, 31.6, 19.1, 13.8.

HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{31}\text{O}_6$ $[\text{M}+\text{H}]^+$: 415.2121, found: 415.2123.

Butyl-3-*O*-acetyl-4,6-*O*-para-methoxybenzylidene-D-glucopyranoside 26 (Method D)

30 mg (72 % yield) as a white solid.

¹H-NMR (500 MHz, CDCl₃, 1α/4.5β): δ (ppm) 7.38-7.35 (m, 2H, aromatic), 6.87-6.86 (m, 2H, aromatic), 5.44 (s, 1H), 5.31 (t, 1H, *J* = 9.7 Hz), 5.21 (t, 1H, *J* = 9.5 Hz), 4.87 (d, 1H, *J* = 3.8 Hz), 4.43 (d, 1H, *J* = 7.7 Hz), 4.32 (dd, 1H, *J* = 4.9 Hz, *J* = 10.5 Hz), 4.25 (dd, 1H, *J* = 4.9 Hz, *J* = 10.3 Hz), 3.91-3.46 (m, 12H, both isomers), 2.6 (s, 1H), 2.11 (s, 4H, both isomers), 1.65-1.59 (m, 2H, both isomers), 1.43-1.35 (m, 2H, both isomers), 0.92 (m, 3H, both isomers).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 170.8, 161.1, 129.5, 127.5, 113.6, 103.5, 101.4, 99.0, 78.5, 73.5, 73.4, 72.5, 71.8, 70.3, 68.8, 68.6, 66.5, 55.3, 3.6, 31.5, 20.9, 19.1, 13.8.

HRMS (ESI): *m/z* calcd for C₂₀H₂₈O₈Na [M+Na]⁺: 419.1682, found: 419.1692.

Butyl-2,4,6-tri-*O*-benzyl-β-D-glucopyranoside 27 (Method D)

44 mg (88 % yield) as a colorless oil.

[α]_D²⁰ +66.0 (c 0.5, CHCl₃).

¹H-NMR (500 MHz, CDCl₃): δ (ppm) 7.35-7.22 (m, 15H, aromatic), 4.96 (d, 1H, *J* = 11.5 Hz), 4.83 (d, 1H, *J* = 11.1 Hz), 4.67-4.54 (m, 4H), 4.35 (d, 1H, *J* = 7.8 Hz), 3.98-3.93 (m, 1H), 3.76-3.65 (m, 3H), 3.55-3.44 (m, 3H), 3.25 (t, 1H, *J* = 8.1 Hz), 2.43 (s, 1H), 1.66-1.58 (m, 2H), 1.44-1.41 (m, 2H), 0.93 (t, 3H, *J* = 7.4 Hz).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 138.4-127.6, 103.2, 81.2, 76.8, 76.7, 74.8, 74.5, 74.3, 73.4, 69.7, 69.1, 31.8, 19.3, 13.8.

HRMS (ESI): *m/z* calcd for C₃₁H₃₈O₆Na [M+Na]⁺: 529.2566, found: 529.2564.

Butyl-2-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside 28 (Method D)

36 mg (87 % yield) as a colorless oil.

[α]_D²⁰ +9.6 (c 0.1, CHCl₃).

¹H-NMR (500 MHz, CDCl₃): δ (ppm) 7.49-7.25 (m, 10H, aromatic), 5.52 (s, 1H), 4.95 (d, 1H, *J* = 11.4 Hz), 4.72 (d, 1H, *J* = 11.4 Hz), 4.51 (d, 1H, *J* = 7.7 Hz), 4.33 (dd, 1H, *J* = 4.9 Hz, *J* = 10.5 Hz), 3.96-3.91 (m, 1H), 3.85-3.75 (m, 2H), 3.58-3.52 (m, 2H), 3.43-3.42 (m, 1H), 3.34 (t, 1H, *J* = 8.0 Hz), 2.43 (s, 1H), 1.67-1.63 (m, 2H), 1.44-1.42 (m, 2H), 0.94 (t, 3H, *J* = 7.4 Hz).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.2-126.3, 103.8, 101.7, 81.8, 80.4, 74.7, 73.1, 70.2, 68.7, 66.1, 31.8, 19.2, 13.8.

HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{31}\text{O}_6$ $[\text{M}+\text{H}]^+$: 415.2121, found: 415.2120.

Butyl-2-*O*-acetyl-4,6-*O*-*para*-methoxybenzylidene- β -D-glucopyranoside 29 (Method D)

32 mg (81 % yield) as a white solid.

^1H -NMR (500 MHz, CDCl_3 , $1\alpha/6\beta$): δ (ppm) 7.54-7.39 (m, 4H, aromatic), 5.76 (s, 1H), 5.58 (s, 1H), 4.99 (d, 1H, $J = 5.3$ Hz), 4.90 (d, 1H, $J = 3.7$ Hz), 4.83 (dd, 1H, $J = 3.7$ Hz, $J = 9.7$ Hz), 4.74 (dd, 1H, $J = 3.7$ Hz, $J = 9.9$ Hz), 4.33 (dd, 1H, $J = 4.7$ Hz, $J = 10.1$ Hz), 4.23-4.19 (m, 1H), 4.15-4.09 (m, 1H), 3.94-3.68 (m, 3H, both isomers), 3.59 (t, 1H, $J = 9.3$ Hz), 3.43-3.37 (m, 6H, both isomers), 3.05 (d, 1H, $J = 3.3$ Hz), 2.74 (dd, 1H, $J = 6.3$ Hz, $J = 8.2$ Hz), 2.45 (d, 1H, $J = 2.9$ Hz), 2.19 (s, 3H), 2.16 (s, 3H), 1.68-1.62 (m, 2H, both isomers), 1.44-1.33 (m, 2H, both isomers), 0.92 (t, 3H, $J = 7.5$ Hz, both isomers).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 171.0, 160.3, 129.7, 127.7, 113.7, 103.7, 101.6, 99.2, 78.7, 73.7, 73.6, 72.6, 72.0, 70.5, 69.0, 68.8, 66.7, 55.4, 31.8, 31.7, 21.1, 19.2, 13.9.

HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{28}\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$: 419.1682, found: 419.1688.

Butyl-2,3,6-tri-*O*-benzyl- β -D-glucopyranoside 31 (Method D)

42 mg (86 % yield) as a colorless oil.

$[\alpha]_{\text{D}}^{20}$ -78.2 (c 0.5, CHCl_3).

^1H -NMR (500 MHz, CDCl_3): δ (ppm) 7.36-7.24 (m, 15H, aromatic), 4.93 (t, 2H, $J = 10.4$ Hz), 4.74-4.55 (m, 4H), 4.40 (d, 1H, $J = 7.3$ Hz), 3.96-3.92 (m, 1H), 3.77 (dd, 1H, $J = 3.9$ Hz, $J = 10.4$ Hz), 3.70 (dd, 1H, $J = 5.5$ Hz, $J = 10.4$ Hz), 3.59-3.46 (m, 5H), 2.52 (s, 1H), 1.66-1.62 (m, 2H), 1.58-1.43 (m, 2H), 0.93 (t, 3H, $J = 7.4$ Hz).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.6-127.7, 103.7, 84.1, 81.7, 75.3, 74.7, 74.0, 73.6, 71.7, 70.4, 69.8, 31.8, 19.3, 13.8.

HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{38}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 529.2566, found: 529.2561.

Butyl-2,3-di-*O*-benzoyl-6-*O*-benzyl- β -D-glucopyranoside 32 (Method D)

43 mg (85 % yield) as a colorless oil.

$[\alpha]_{\text{D}}^{20} +29.4$ (c 0.5, CHCl₃).

¹H-NMR (500 MHz, CDCl₃): δ (ppm) 7.98-7.94 (m, 4H, aromatic), 7.51-7.25 (m, 11H, aromatic), 5.46-5.38 (m, 2H), 4.67-4.59 (m, 3H), 3.96-3.85 (m, 4H), 3.71-3.67 (m, 1H), 3.52-3.48 (m, 1H), 3.26 (d, 1H, $J = 3.2$ Hz), 1.48-1.47 (m, 2H), 1.24-1.21 (m, 2H), 0.74 (t, 3H, $J = 7.4$ Hz).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 167.2, 165.2, 137.7-127.7, 101.1, 74.6, 73.8, 71.6, 71.2, 70.2, 69.8, 31.4, 18.9, 13.6.

HRMS (ESI): m/z calcd for C₃₁H₃₄O₈Na [M+Na]⁺: 557.2151, found: 557.2170.

1,6-Anhydro-2,3-di-*O*-*tert*-butyldimethylsilyl- β -D-glucopyranose 30A (Method D)

35 mg (91 % yield) as a white solid.

$[\alpha]_{\text{D}}^{20} -30.2$ (c 0.5, CHCl₃).

¹H-NMR (500 MHz, CDCl₃): δ (ppm) 5.25 (s, 1H), 4.49-4.47 (m, 1H), 4.28 (d, 1H, $J = 6.9$ Hz), 3.74-3.71 (m, 2H), 3.47 (d, 1H, $J = 1.6$ Hz), 3.41 (dd, 1H, $J = 1.7$ Hz, $J = 12.3$ Hz), 3.01 (d, 1H, $J = 12.3$ Hz), 0.91-0.90 (m, 18H), 0.10-0.09 (m, 12H).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 101.9, 76.2, 73.6, 71.3, 71.1, 64.7, 25.7, 25.6, 17.9, 17.8, -4.7, -4.8, -4.9, -5.0.

HRMS (ESI): m/z calcd for C₁₈H₃₈O₅Si₂Na [M+Na]⁺: 413.2155, found: 413.2160.

Butyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside 33 (Method D)

14 mg (27 % yield) as a colorless oil.

$[\alpha]_{\text{D}}^{20} +82.1$ (c 0.5, CHCl₃).

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.39-7.28 (m, 15H, aromatic), 5.04-4.79 (m, 4H), 4.72 (d, 1H, $J = 3.6$ Hz), 4.69-4.65 (m, 2H), 4.04 (t, 1H, $J = 9.2$ Hz), 3.79-3.52 (m, 7H), 1.66-1.58 (m, 3H), 1.44-1.40 (m, 2H), 0.95 (t, 3H, $J = 7.4$ Hz).

¹³C-NMR (100 MHz, CDCl₃): δ (ppm) 138.8-127.6, 96.8, 81.9, 80.3, 77.5, 77.2, 75.6, 75.1, 73.2, 70.7, 67.9, 61.9, 31.5, 19.4, 13.8.

HRMS (ESI): m/z calcd for C₃₁H₄₀O₆ [M+H]⁺: 507.2747, found: 507.2755.

Butyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside 33_beta (Method D)

27 mg (54 % yield) as a colorless oil.

[α]_D²⁰+14.5 (c 0.2, CHCl₃).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.35-7.28 (m, 15H, aromatic), 4.97-4.61 (m, 6H), 4.46 (d, 1H, *J* = 7.8 Hz), 3.98-3.87 (m, 2H), 3.74-3.66 (m, 2H), 3.61-3.55 (m, 2H), 3.45-3.38 (m, 2H), 1.68-1.64 (m, 2H), 1.47-1.41 (m, 2H), 0.96 (t, 3H, *J* = 7.4 Hz).

¹³C-NMR (100 MHz, CDCl₃): δ (ppm) 138.5-127.6, 103.7, 84.5, 82.3, 77.7, 77.2, 75.7, 75.1, 74.9, 74.9, 70.1, 62.1, 31.8, 31.6, 29.6, 19.2, 13.8.

HRMS (ESI): m/z calcd for C₃₁H₄₀O₆ [M+H]⁺: 507.2747, found: 507.2752.

Butyl-2,3-di-*O*-benzoyl-4-*O*-benzyl-β-D-glucopyranoside 34 (Method D)

44 mg (83 % yield) as a colorless oil.

[α]_D²⁰+50.2 (c 0.3, CHCl₃).

¹H-NMR (500 MHz, CDCl₃) δ (ppm) 7.96-7.94 (m, 4H, aromatic), 7.69-7.68 (m, 4H, aromatic), 7.67-7.46 (m, 8H, aromatic), 7.40-7.37 (m, 4H, aromatic), 7.21-7.16 (m, 5H, aromatic), 5.75 (t, 1H, *J* = 9.6 Hz), 5.35 (t, 1H, *J* = 7.7 Hz), 4.73 (d, 1H, *J* = 7.9 Hz), 4.62 (s, 2H), 4.01-3.82 (m, 4H), 3.64-3.61 (m, 1H), 3.55-3.52 (m, 1H), 2.01-1.99 (m, 1H), 1.52-1.49 (m, 2H), 1.26-1.23 (m, 2H), 0.76 (t, 3H, *J* = 7.4 Hz).

¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 165.7, 165.3, 145.6, 137.2, 133.1-124.5, 101.2, 76.7, 75.6, 75.4, 75.0, 74.8, 72.2, 70.1, 61.7, 31.4, 29.7, 29.3, 27.0, 22.7, 18.8, 14.1, 13.5.

HRMS (ESI): m/z calcd for C₃₁H₃₅O₈ [M+H]⁺: 535.2332, found: 535.2329.

1,6-Anhydro-2,3-di-*O*-*tert*-butyldimethylsilyl-4-*O*-*para*-methoxybenzyl-β-D-glucopyranose 30B (Method D)

46 mg (91 % yield) as a white solid.

$[\alpha]_D^{20}$ -30.1 (c 0.3, CHCl₃).

¹H-NMR (500 MHz, CDCl₃): δ (ppm) 7.30-7.26 (m, 2H, aromatic), 6.87-6.85 (m, 2H, aromatic), 5.28 (s, 1H), 4.61 (d, 1H, *J* = 12.1 Hz), 4.55-4.52 (m, 2H), 4.01 (d, 1H, *J* = 6.8 Hz), 3.8 (s, 3H), 3.75 (t, 1H, *J* = 1.5 Hz), 3.66 (t, 1H, *J* = 6.4 Hz), 3.47 (d, 1H, *J* = 1.1 Hz), 3.16 (s, 1H), 0.92-0.86 (m, 18H), 0.11-0.06 (m, 12H).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 159.2, 130.3, 129.3, 113.8, 102.3, 77.7, 76.7, 74.3, 72.3, 71.8, 70.7, 64.8, 55.3, 25.8, 25.6, 18.1, 17.7, -4.3, -4.6, -4.7, -4.8.

HRMS (ESI): *m/z* calcd for C₂₆H₄₇O₆Si₂ [M+H]⁺: 511.2911, found: 511.2922.

Butyl-4,6-*O*-benzylidene-β-D-glucopyranoside 47 (Method D)

30 mg (88 % yield) as a white solid.

$[\alpha]_D^{20}$ -79.9 (c 0.9, CHCl₃).

¹H-NMR (500 MHz, CDCl₃): δ (ppm) 7.51-7.25 (m, 5H, aromatic), 5.53 (s, 1H), 4.39 (d, 1H, *J* = 7.8 Hz), 4.34 (dd, 1H, *J* = 4.9 Hz, *J* = 10.5 Hz), 3.93-3.88 (m, 1H), 3.84-3.77 (m, 2H), 3.59-3.52 (m, 4H), 2.76 (s, 1H), 2.56 (s, 1H), 1.64-1.59 (m, 2H), 1.41-1.37 (m, 2H), 0.93 (t, 3H, *J* = 7.4 Hz).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 136.9, 129.3, 128.3, 16.23, 103.1, 101.9, 80.6, 74.6, 73.1, 70.3, 68.7, 66.4, 31.6, 19.1, 13.8.

HRMS (ESI): *m/z* calcd for C₁₇H₂₄O₆Na [M+Na]⁺: 347.1471, found: 347.1471.

Butyl-4,6-di-*O*-benzyl-β-D-glucopyranoside 48 (Method D)

37 mg (86 % yield) as a colorless oil.

$[\alpha]_D^{20}$ +15.4 (c 0.1, CHCl₃).

¹H-NMR (500 MHz, CDCl₃): δ (ppm) 7.38-7.27 (m, 10H, aromatic), 4.84 (d, 1H, *J* = 11.2 Hz), 4.67-4.57 (m, 3H), 4.27 (d, 1H, *J* = 7.8 Hz), 3.97-3.92 (m, 1H), 3.79 (dd, 1H, *J* = 1.8 Hz, *J* =

10.8 Hz), 3.74-3.70 (m, 3H), 3.57-3.48 (m, 3H), 3.42 (t, 1H, $J = 7.9$ Hz), 2.70 (s, 1H), 2.61 (s, 1H), 1.66-1.63 (m, 2H), 1.42-1.40 (m, 2H), 0.96 (t, 3H, $J = 7.4$ Hz).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.2, 138.1, 128.5-127.6, 102.4, 77.6, 75.1, 74.6, 74.1, 73.5, 69.8, 68.9, 31.7, 19.1, 13.8.

HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{32}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 439.2097, found: 439.2096.

Butyl-3,6-di-*O*-benzyl-D-glucopyranoside 49 (Method D)

36 mg (83 % yield) as a colorless oil.

^1H -NMR (500 MHz, CDCl_3 , $1\alpha/10\beta$): δ (ppm) 7.39-7.25 (m, 11H, aromatic), 5.00 (d, 1H, $J = 11.5$ Hz), 4.96 (d, 1H, $J = 11.6$ Hz), 4.86 (d, 1H, $J = 3.9$ Hz), 4.80 (d, 1H, $J = 11.6$ Hz), 4.77 (d, 1H, $J = 4.9$ Hz), 4.62-4.54 (m, 2H, both isomers), 4.26 (d, 1H, $J = 7.7$ Hz), 3.92-3.87 (m, 1H), 3.78-3.68 (m, 2H, both isomers), 3.61 (t, 1H, $J = 9.0$ Hz), 3.57-3.48 (m, 3H, both isomers), 3.42 (t, 1H, $J = 8.9$ Hz), 2.64 (s, 1H), 2.46 (s, 1H), 2.34 (s, 1H), 2.16 (s, 1H), 1.63-1.59 (m, 2H, both isomers), 1.39-0.94 (m, 2H, both isomers), 0.92 (t, 3H, $J = 7.4$ Hz, both isomers).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.6, 127.6, 104.5, 103.4, 102.7, 101.7, 98.4, 83.7, 83.1, 74.9, 74.6, 74.3, 74.2, 73.7, 73.6, 72.7, 71.6, 70.7, 70.4, 70.1, 69.8, 69.7, 68.0, 31.6, 19.1, 13.8.

HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{32}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 439.2097, found: 439.2097.

Butyl-3,4-di-*O*-benzyl-D-glucopyranoside 50 (Method D)

33 mg (79 % yield) as a colorless oil.

^1H -NMR (500 MHz, CDCl_3 , $1\alpha/1.1\beta$): δ (ppm) 7.39-7.25 (m, 20H, aromatic), 4.97-4.83 (m, 6H, both isomers), 4.65 (d, 2H, $J = 10.9$ Hz, both isomers), 4.29 (d, 1H, $J = 7.7$ Hz), 3.89-3.38 (m, 15H, both isomers), 1.95 (br, 4H, both isomers), 1.61-1.58 (m, 4H, both isomers), 1.41-1.36 (m, 4H, both isomers), 0.93 (t, 6H, $J = 7.4$ Hz, both isomers).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.7-127.7, 102.8, 98.3, 84.3, 83.4, 77.3, 77.2, 75.4, 75.3, 75.1, 74.8, 73.2, 71.1, 70.1, 68.0, 62.1, 61.9, 31.7, 31.5, 29.7, 19.4, 19.2, 13.8.

HRMS (ESI): m/z calcd for $C_{24}H_{32}O_6Na$ $[M+Na]^+$: 439.2097, found: 439.2102.

Butyl-2,6-di-*O*-benzyl-D-glucopyranoside 51 (Method D)

34 mg (84% yield) as a colorless oil.

1H -NMR (500 MHz, $CDCl_3$, $1\alpha/20\beta$): δ (ppm) 7.38-7.28 (m, 10H, aromatic), 4.99 (d, 1H, $J = 11.4$ Hz), 4.79 (d, 1H, $J = 3.5$ Hz), 4.71-4.56 (m, 3H, both isomers), 4.42 (d, 1H, $J = 7.7$ Hz), 3.99-3.93 (m, 1H), 3.80 (dd, 1H, $J = 4.2$ Hz, $J = 10.4$ Hz), 3.80 (dd, 1H, $J = 5.3$ Hz, $J = 10.4$ Hz), 3.58-3.54 (m, 3H, both isomers), 3.52-3.46 (m, 1H), 3.29-3.23 (m, 1H), 2.89 (s, 1H), 2.63 (s, 1H), 1.71-1.59 (m, 2H, both isomers), 1.50-1.39 (m, 2H, both isomers), 0.96 (t, 3H, $J = 7.4$ Hz, both isomers).

^{13}C -NMR (125 MHz, $CDCl_3$): δ (ppm) 138.3, 137.8, 128.5-127.7, 103.3, 96.5, 80.7, 79.3, 76.1, 74.3, 73.9, 73.7, 73.5, 72.8, 72.7, 71.7, 71.1, 70.3, 69.8, 69.7, 67.9, 31.8, 31.5, 19.4, 19.3, 13.8.

HRMS (ESI): m/z calcd for $C_{24}H_{32}O_6Na$ $[M+Na]^+$: 439.2097, found: 439.2096.

Butyl-3,4-di-*O*-benzyl-D-glucopyranoside 52 (Method D)

33 mg (80 % yield) as a colorless oil.

1H -NMR (500 MHz, $CDCl_3$, $1\alpha/2.5\beta$): δ (ppm) 7.41-7.28 (m, 13H, aromatic), 4.94 (d, 1H, $J = 11.4$ Hz), 4.76-4.66 (m, 5H, both isomers), 4.60 (d, 1H, $J = 5.15$ Hz), 4.15 (t, 1H, $J = 9.2$ Hz), 3.89-3.61 (m, 6H, both isomers), 3.48 (t, 1H, $J = 9.15$ Hz), 3.37-3.32 (m, 3H, both isomers), 2.52 (s, 1H), 1.61-1.58 (m, 2H, both isomers), 1.42-1.39 (m, 2H, both isomers), 0.94 (t, 3H, $J = 7.4$ Hz).

^{13}C -NMR (125 MHz, $CDCl_3$): δ (ppm) 138.3, 138.0, 128.5-127.8, 101.3, 96.3, 79.8, 70.6, 79.3, 75.3, 74.6, 73.4, 72.8, 72.1, 71.8, 70.6, 70.3, 67.9, 66.5, 62.1, 31.5, 29.7, 19.4, 13.8.

HRMS (ESI): m/z calcd for $C_{24}H_{32}O_6Na$ $[M+Na]^+$: 439.2097, found: 439.2097.

Butyl-2,3-di-*O*-benzyl-D-glucopyranoside 53 (Method D)

32 mg (78 % yield) as a colorless oil.

¹H-NMR (500 MHz, CDCl₃, 1α/11β): δ (ppm) 7.39-7.28 (m, 11H, aromatic), 5.06 (d, 1H, *J* = 11.5 Hz), 5.01-4.97 (dd, 2H, *J* = 4.1 Hz, *J* = 11.3 Hz), 4.78-4.66 (m, 2H, both isomers), 4.48 (d, 1H, *J* = 7.4 Hz), 3.99-3.41 (m, 8H, both isomers), 3.37-3.33 (m, 1H), 2.39 (s, 1H), 2.13 (s, 1H), 1.69-1.65 (m, 2H, both isomers), 1.48-1.44 (m, 2H, both isomers), 0.96 (t, 3H, *J* = 7.4 Hz, both isomers).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 138.8-117.8, 103.8, 96.8, 83.9, 81.9, 81.3, 80.1, 75.3, 75.2, 74.8, 74.7, 72.8, 70.7, 70.6, 70.5, 70.1, 67.9, 62.7, 62.5, 31.8, 31.5, 19.4, 19.3, 13.8.

HRMS (ESI): *m/z* calcd for C₂₄H₃₂O₆Na [M+Na]⁺: 439.2097, found: 439.2099.

Butyl-2,3-di-*O*-benzoyl-β-D-glucopyranoside 54 (Method D)

35 mg (79 % yield) as a colorless oil.

[α]_D²⁰ +124.3 (c 0.9, CHCl₃).

¹H-NMR (500 MHz, CDCl₃): δ (ppm) 8.01-7.97 (m, 4H, aromatic), 7.55-7.51 (m, 2H, aromatic), 7.41-7.38 (m, 4H, aromatic), 5.45-5.42 (m, 2H), 4.75-4.73 (m, 1H), 4.04-3.89 (m, 4H), 3.63-3.59 (m, 1H), 3.56-3.52 (m, 1H), 3.31 (d, 1H, *J* = 3.3 Hz), 2.23 (br, 1H), 1.69 (s, 1H), 1.54-1.48 (m, 2H), 1.27-1.21 (m, 2H), 0.76 (t, 3H, *J* = 7.4 Hz).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 167.6, 165.3, 133.5, 133.1, 130.1, 129.7, 129.5, 128.8, 128.5, 128.3, 101.2, 75.8, 71.5, 70.1, 70.0, 62.3, 31.4, 18.8, 13.6.

HRMS (ESI): *m/z* calcd for C₂₄H₂₉O₈ [M+H]⁺: 445.1862, found: 445.1870.

Butyl-2-*O*-benzyl-D-glucopyranoside 58 (Method D)

25 mg (79 % yield) as a colorless oil.

¹H-NMR (500 MHz, CDCl₃, 1α/6β): δ (ppm) 7.71-7.28 (m, 7H, aromatic), 4.99 (d, 1H, *J* = 11.4 Hz), 4.77 (d, 1H, *J* = 3.4 Hz), 4.68-4.65 (m, 2H, both isomers), 4.46 (d, 1H, *J* = 7.8 Hz), 3.98-3.90 (m, 2H, both isomers), 3.84-3.81 (m, 1H, both isomers), 3.71-3.66 (m, 1H), 3.59-3.54 (m, 3H, both isomers), 3.40-3.34 (m, 2H, both isomers), 3.24-3.16 (m, 2H, both isomers),

3.8 (br, 2H), 2.2 (br, 1H), 1.68-1.64 (m, 2H, both isomers), 1.46-1.38 (m, 2H, both isomers), 0.96 (t, 3H, $J = 7.4$ Hz, both isomers).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.2, 137.9, 135.2, 134.4, 131.5, 131.5, 130.9, 130.3, 128.5, 128.1, 128.1, 128.0, 103.4, 96.4, 80.8, 79.4, 76.0, 75.0, 74.3, 72.8, 72.7, 70.7, 70.6, 70.5, 70.0, 67.9, 62.5, 62.4, 46.7, 31.8, 31.5, 19.4, 19.2, 13.8.

HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{27}\text{O}_6$ $[\text{M}+\text{H}]^+$: 327.1808, found: 327.1809.

Butyl-3-*O*-benzyl-D-glucopyranoside 57 (Method D)

26 mg (81 % yield) as a colorless oil.

$[\alpha]_{\text{D}}^{20} +16.0$ (c 0.05, CHCl_3).

^1H -NMR (500 MHz, CDCl_3): δ (ppm) 7.40-7.28 (m, 5H, aromatic), 5.05 (d, 1H, $J = 11.7$ Hz), 4.76 (d, 1H, $J = 11.7$ Hz), 4.33 (d, 1H, $J = 7.7$ Hz), 3.95-3.90 (m, 2H), 3.80 (dd, 1H, $J = 5.2$ Hz, $J = 11.8$ Hz), 3.62-3.52 (m, 3H), 3.46-3.40 (m, 2H), 2.35 (br, 2H), 2.1 (br, 1H), 1.66-1.58 (m, 2H), 1.44-1.39 (m, 2H), 0.96 (t, 3H, $J = 7.4$ Hz).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.5, 128.6, 128.0, 102.9, 83.6, 77.3, 77.0, 76.7, 75.1, 74.7, 74.6, 70.3, 70.1, 62.7, 31.7, 19.1, 13.8.

HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{27}\text{O}_6$ $[\text{M}+\text{H}]^+$: 327.1808, found: 327.1808.

Butyl-4-*O*-benzyl-D-glucopyranoside 56 (Method D)

26 mg (80 % yield) as a colorless oil.

^1H -NMR (500 MHz, CDCl_3 , $1\alpha/2.9\beta$): δ (ppm) 7.38-7.28 (m, 7H, aromatic), 4.91-4.86 (m, 1H, both isomers), 4.75-4.73 (m, 1H, both isomers), 4.31 (d, 1H, $J = 7.7$ Hz), 3.92-3.41 (m, 10H, both isomers), 2.86 (s, 1H), 2.74 (s, 1H), 2.1 (br, 1H), 1.65-1.58 (m, 2H, both isomers), 1.42-1.38 (m, 2H, both isomers), 0.95 (t, 3H, $J = 7.4$ Hz, both isomers).

^{13}C -NMR (125 MHz, CDCl_3): δ (ppm) 138.2, 138.1, 128.6, 128.1, 128.0, 102.5, 97.9, 77.2, 77.1, 76.5, 75.3, 75.2, 74.7, 74.1, 72.8, 70.8, 70.0, 68.1, 62.0, 61.9, 31.6, 31.5, 19.4, 19.1, 13.8.

HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{27}\text{O}_6$ $[\text{M}+\text{H}]^+$: 327.1808, found: 327.1799.

Butyl-6-*O*-benzyl- β -D-glucopyranoside 55 (Method D)

26 mg (80 % yield) as a colorless oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3 , $1\alpha/1.7\beta$): δ (ppm) 7.70-7.28 (m, 10H, aromatic), 4.87 (d, 1H, $J = 3.8$ Hz), 4.64-4.57 (m, 3H, both isomers), 4.28 (d, 1H, $J = 7.7$ Hz), 3.91-3.86 (m, 1H), 3.78-3.44 (m, 14H, both isomers), 3.39 (t, 1H, $J = 8.1$ Hz), 3.31-3.12 (m, 2H, both isomers), 2.6 (br, 1H), 1.63-1.59 (m, 3H, both isomers), 1.41-1.36 (m, 4H, both isomers), 0.93 (t, 5H, $J = 7.4$ Hz, both isomers).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ (ppm) 149.9-118.9, 102.5, 98.1, 76.2, 74.7, 74.1, 73.7, 73.6, 73.5, 72.1, 71.8, 71.2, 70.2, 70.1, 69.8, 69.7, 68.1, 46.7, 31.6, 31.4, 19.3, 19.1, 13.8.

HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{27}\text{O}_6$ $[\text{M}+\text{H}]^+$: 327.1808, found: 327.1813.

Methyl-*O*-((3,4,6-tri-*O*-benzyl)- β -D-glucopyranosyl)-(1 $\rightarrow$ 6)-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside 64 (Method D)

34 mg (78 % yield) as a white solid.

$[\alpha]_{\text{D}}^{20} +132.0$ (c 0.1, CHCl_3).

$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ (ppm) 7.36-7.25 (m, 28H, aromatic), 7.17-7.15 (m, 2H, aromatic), 4.98-4.50 (m, 13H), 4.22 (d, 1H, $J = 6.9$ Hz), 4.14 (dd, 1H, $J = 2.1$ Hz, $J = 11.0$ Hz), 3.99 (t, 1H, $J = 9.2$ Hz), 3.82-3.80 (m, 1H), 3.73-3.65 (m, 3H), 3.56-3.45 (m, 6H), 3.37 (s, 3H), 2.49 (s, 1H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ (ppm) 138.7-127.5, 103.5, 98.1, 84.5, 82.0, 79.7, 78.0, 77.5, 77.3, 77.0, 76.7, 75.7, 75.3, 75.1, 75.0, 74.5, 73.4, 69.8, 68.9, 68.7, 55.3.

HRMS (ESI): m/z calcd for $\text{C}_{55}\text{H}_{61}\text{O}_{11}$ $[\text{M}+\text{H}]^+$: 897.4214, found: 897.4215.

Methyl-*O*-((3,4,6-tri-*O*-benzyl)- β -D-glucopyranosyl)-(1 $\rightarrow$ 4)-2,3,6-tri-*O*-benzyl- α -D-glucopyranoside 75 (Method D)

31 mg (69 % yield) as a colorless oil.

$[\alpha]_{\text{D}}^{20} +77.8$ (c 0.1, CHCl_3).

¹H-NMR (500 MHz, CDCl₃): δ (ppm) 7.38-7.15 (m, 30H, aromatic), 5.04-4.43 (m, 14H), 4.00-3.97 (m, 3H), 3.81-3.79 (m, 1H), 3.68 (dd, 1H, *J* = 1.9 Hz, *J* = 11.3 Hz), 3.61 (t, 1H, *J* = 9.3 Hz), 3.52-3.44 (m, 5H), 3.38 (s, 3H), 3.27 (d, 1H, *J* = 2.0 Hz), 3.24-3.21 (m, 1H).

¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 139.3-127.0, 107.6, 103.1, 98.2, 84.5, 80.9, 79.5, 75.6, 75.2, 75.1, 75.0, 74.8, 73.7, 73.5, 73.3, 69.5, 68.8, 68.5, 55.2.

HRMS (ESI): *m/z* calcd for C₅₅H₆₁O₁₁ [M+H]⁺: 897.4214, found: 897.4218.

Methyl-*O*-((3,4,6-tri-*O*-benzyl)-β-D-glucopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 77 (Method D)

30 mg (77 % yield) as a white solid.

[α]_D²⁰ +102.2 (c 0.1, CHCl₃).

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.53-7.19 (m, 25H, aromatic), 5.60 (s, 1H), 4.98-4.78 (m, 6H), 4.61-4.51 (m, 4H), 4.33 (dd, 1H, *J* = 4.7 Hz, *J* = 10.0 Hz), 4.10 (t, 1H, *J* = 9.3 Hz), 3.93-3.87 (m, 1H), 3.81-3.57 (m, 8H), 3.58-2.52 (m, 4H), 2.52 (s, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ (ppm) 138.7-126.1, 104.7, 101.3, 100.1, 84.3, 82.7, 79.8, 77.6, 75.3, 75.1, 75.0, 74.9, 73.5, 69.1, 62.2, 55.4, 29.7.

HRMS (ESI): *m/z* calcd for C₄₈H₅₂O₁₁Na [M+Na]⁺: 827.3407, found: 827.3411.

Methyl-*O*-((3,4,6-tri-*O*-benzyl)-α-D-mannopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 76 (Method D)

30 mg (76 % yield) as a colorless oil.

[α]_D²⁰ +44.8 (c 0.5, CHCl₃).

¹H-NMR (500 MHz, CDCl₃) δ (ppm) 7.47-7.18 (m, 25H), 5.52 (s, 1H), 5.43 (s, 1H), 4.84 (d, 1H, *J* = 11.0 Hz), 4.69-4.61 (m, 5H), 4.52 (t, 2H, *J* = 9.5 Hz), 4.41 (d, 1H, *J* = 12.0 Hz), 4.33-4.25 (m, 2H), 4.16-4.12 (m, 2H), 3.97 (t, 1H, *J* = 9.3 Hz), 3.91-3.89 (m, 1H), 3.87-3.81 (m, 1H), 3.73-3.56 (m, 4H), 3.48-3.45 (m, 1H), 3.39 (s, 3H), 2.34 (s, 1H).

¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 138.8-126.1, 101.5, 99.4, 98.7, 82.6, 79.8, 78.1, 74.9, 74.2, 73.5, 73.3, 71.6, 71.0, 69.0, 68.6, 68.2, 62.9, 55.3, 29.7.

HRMS (ESI): m/z calcd for C₄₈H₅₂O₁₁Na [M+Na]⁺: 827.3407, found: 827.3407.

Methyl-*O*-((4,6-*O*-benzylidene)-β-D-glucopyranosyl)-(1→6)-2,3-di-*O*-tert-butyltrimethylsilyl-4-*O*-benzyl-α-D-glucopyranoside 71 (Method D)

30 mg (81 % yield) as a colorless oil.

[α]_D²⁰+72.6 (c 0.5, CHCl₃).

¹H-NMR (500 MHz, CDCl₃) δ (ppm) 7.51-7.28 (m, 10H, aromatic), 4.93 (d, 1H, *J* = 11.8 Hz), 4.68 (d, 1H, *J* = 3.4 Hz), 4.60 (d, 1H, *J* = 11.9 Hz), 4.37 (d, 1H, *J* = 7.7 Hz), 4.33 (dd, 1H, *J* = 4.9 Hz, *J* = 10.5 Hz), 4.12 (dd, 1H, *J* = 2.0 Hz, *J* = 10.8 Hz), 3.97 (t, 1H, *J* = 8.8 Hz), 3.85-3.75 (m, 4H), 3.69-3.54 (m, 4H), 3.46-3.41 (m, 1H), 3.38 (s, 3H), 3.34 (t, 1H, *J* = 9.8 Hz), 2.70 (s, 1H), 1.87 (br, 1H), 0.95 (s, 18H), 0.14-0.02 (m, 12H).

¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 138.5-126.3, 103.6, 101.9, 100.3, 80.5, 79.6, 74.7, 74.3, 74.2, 74.1, 73.2, 70.0, 69.0, 68.6, 67.9, 66.5, 55.0, 26.3, 26.2, 25.6, 18.4, 18.0, -2.9, -3.2, -4.0, -4.4

HRMS (ESI): m/z calcd for C₃₉H₆₂O₁₁Si₂Na [M+Na]⁺: 785.3728, found: 785.3733.

Methyl-*O*-((3,4,6-tri-*O*-benzyl)-β-D-glucopyranosyl)-(1→6)-2,3-di-*O*-tert-butyltrimethylsilyl-4-*O*-benzyl-α-D-glucopyranoside 65 (Method D)

38 mg (82 % yield) as a colorless oil.

[α]_D²⁰+114.7 (c 0.9, CHCl₃).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.36-7.14 (m, 20H, aromatic), 4.92-4.78 (m, 4H), 4.63 (d, 1H, *J* = 3.4 Hz), 4.57-4.47 (m, 4H), 4.18 (d, 1H, *J* = 8.7 Hz), 4.09 (d, 1H, *J* = 13.3 Hz), 3.92 (t, 1H, *J* = 10.9 Hz), 3.79-3.77 (m, 1H), 3.70-3.50 (m, 7H), 3.42 (br, 1H), 3.33-3.25 (m, 4H), 2.51 (s, 1H), 0.90 (s, 18H), 0.08-0.01 (m, 12H).

¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 138.7-127.0, 103.3, 100.2, 84.5, 79.7, 77.5, 76.7, 75.4, 75.1, 74.6, 74.4, 74.3, 74.2, 73.5, 70.1, 68.9, 68.7, 54.9, 26.5, 26.2, 18.4, 18.0, -2.9, -3.2, -4.0, -4.4.

HRMS (ESI): m/z calcd for C₅₃H₇₇O₁₁Si₂ [M+H]⁺: 945.5004, found: 945.5010.

Methyl-*O*-((3,4,6-tri-*O*-benzyl)- α -D-mannopyranosyl)-(1 $\rightarrow$ 6)-2,3-di-*O*-tert-butyltrimethylsilyl-4-*O*-benzyl- α -D-glucopyranoside 66 (Method D)

36 mg (80 % yield) as a colorless oil.

[α]_D²⁰+104.1 (c 0.9, CHCl₃).

¹H-NMR (500 MHz, CDCl₃) δ (ppm) 7.38-7.19 (m, 20H, aromatic), 4.89-4.86 (m, 2H), 4.77-4.44 (m, 7H), 4.11 (s, 1H), 4.07 (dd, 1H, *J* = 1.7 Hz, *J* = 10.6 Hz), 3.98 (d, 1H, *J* = 2.5 Hz), 3.93 (t, 1H, *J* = 8.8 Hz), 3.85-3.81 (m, 1H), 3.76-3.67 (m, 2H), 3.60 (dd, 1H, *J* = 3.4 Hz, *J* = 9.1 Hz), 3.52 (dd, 1H, *J* = 5.4 Hz, *J* = 10.7 Hz), 3.46 (dd, 1H, *J* = 3.0 Hz, *J* = 9.1 Hz), 3.34-3.27 (m, 5H), 2.42 (s, 1H), 0.92 (s, 18H), 0.11-0.03 (m, 12H).

¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 138.8-127.4, 100.3, 100.0, 81.5, 79.7, 75.6, 75.4, 75.0, 74.6, 74.5, 73.7, 71.6, 70.1, 69.4, 68.5, 68.4, 55.0, 26.6, 26.4, 18.6, 18.2, 0.2, -2.7, -2.9, -3.8, -4.2.

HRMS (ESI): m/z calcd for C₅₃H₇₇O₁₁Si₂ [M+H]⁺: 945.5004, found: 945.5012.

Methyl-*O*-((2,4,6-tri-*O*-benzyl)- β -D-glucopyranosyl)-(1 $\rightarrow$ 6)-2,3-di-*O*-tert-butyltrimethylsilyl-4-*O*-benzyl- α -D-glucopyranoside 68 (Method D)

18 mg (81 % yield) as a colorless oil.

[α]_D²⁰+16.3 (c 0.5, CHCl₃).

¹H-NMR (500 MHz, CDCl₃) δ (ppm) 7.36-7.21 (m, 20H, aromatic), 5.30 (s, 1H), 5.05 (d, 1H, *J* = 11.4 Hz), 4.83-4.51 (m, 8H), 4.28 (d, 1H, *J* = 7.7 Hz), 4.15 (d, 1H, *J* = 10.7 Hz), 3.94 (t, 1H, *J* = 9.1 Hz), 3.82-3.80 (m, 1H), 3.73-3.67 (m, 4H), 3.61-3.56 (m, 2H), 3.47 (t, 1H, *J* = 8.7 Hz), 3.42-3.41 (m, 1H), 3.34-3.30 (m, 4H), 2.39 (s, 1H), 0.90 (s, 18H), 0.11 (s, 12H).

¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 138.6-126.9, 103.2, 100.2, 81.2, 79.7, 74.9, 74.6, 74.5, 74.4, 74.2, 73.4, 69.9, 69.1, 68.6, 58.5, 54.8, 29.7, 26.3, 26.2, 18.5, 18.4, 17.9, -0.1, -3.0, -3.2, -4.0, -4.4.

HRMS (ESI): m/z calcd for C₅₃H₇₇O₁₁Si₂ [M+H]⁺: 945.5004, found: 945.5004.

Methyl-*O*-((2,4,6-tri-*O*-benzyl)-β-*D*-allopyranosyl)-(1→6)-2,3-di-*O*-tert-butyl-*dimethylsilyl*-4-*O*-benzyl-α-*D*-glucopyranoside 67 (Method D)

18 mg (80 % yield) as a colorless oil.

[α]_D²⁰+37.7 (c 0.5, CHCl₃).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.40-7.24 (m, 20H, aromatic), 4.88-4.46 (m, 10H), 4.33 (s, 1H), 4.15 (d, 1H, *J* = 11.3 Hz), 3.97-3.91 (m, 2H), 3.81-3.74 (m, 2H), 3.68-3.61 (m, 3H), 3.50 (dd, 1H, *J* = 3.2 Hz, *J* = 12.2 Hz), 3.40-3.32 (m, 5H), 2.46 (s, 1H), 0.94 (s, 18H), 0.13-0.03 (m, 12H).

¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 138.7-127.0, 100.4, 100.2, 79.5, 77.3, 74.4, 74.2, 73.4, 72.6, 71.9, 71.4, 69.6, 69.3, 68.3, 66.9, 54.5, 26.4, 26.2, 18.4, 17.9, -0.1, -2.9, -3.2, -4.0, -4.4.

HRMS (ESI): m/z calcd for C₅₃H₇₇O₁₁Si₂ [M+H]⁺: 945.5004, found: 945.5005.

Methyl-*O*-((2,3,6-tri-*O*-benzyl)-β-*D*-glucopyranosyl)-(1→6)-2,3-di-*O*-tert-butyl-*dimethylsilyl*-4-*O*-benzyl-α-*D*-glucopyranoside 69 (Method D)

35 mg (79 % yield) as a colorless oil.

[α]_D²⁰+90.9 (c 0.5, CHCl₃).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.41-7.19 (m, 20H), 5.07 (d, 1H, *J* = 11.2 Hz), 4.95 (d, 1H, *J* = 11.4 Hz), 4.83-4.51 (m, 7H), 4.34 (d, 1H, *J* = 7.0 Hz), 4.17 (d, 1H, *J* = 10.1 Hz), 3.95 (d, 1H, *J* = 8.8 Hz), 3.83-3.70 (m, 3H), 3.64-3.59 (m, 3H), 3.53-3.39 (m, 3H), 3.36-3.31 (m, 4H), 2.61 (s, 1H), 0.95-0.93 (m, 18H), 0.14-0.03 (m, 12H).

¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 138.6-126.9, 103.6, 100.2, 84.2, 81.4, 79.5, 77.3, 75.3, 74.7, 74.4, 74.2, 73.9, 73.7, 72.0, 70.1, 69.8, 68.5, 54.8, 26.4, 26.2, 18.4, 17.9, -3.1, -3.2, -4.1, -4.4.

HRMS (ESI): m/z calcd for C₅₃H₇₇O₁₁Si₂ [M+H]⁺: 945.5004, found: 945.5007.

Methyl-*O*-((2,3,6-tri-*O*-benzyl)-β-*D*-galactopyranosyl)-(1→6)-2,3-di-*O*-*tert*-butyldimethyl-silyl-4-*O*-benzyl-α-*D*-glucopyranoside 70 (Method D)

35 mg (77 % yield) as a colorless oil.

¹H-NMR (500 MHz, CDCl₃, 1α/2.5β) δ (ppm) 7.41-7.18 (m, 33H, aromatic), 5.09 (d, 1H, *J* = 3.2 Hz), 5.02 (d, 1H, *J* = 11.1 Hz), 4.83-4.68 (m, 7H, both isomers), 4.59-4.51 (m, 5H, both isomers), 4.28 (d, 1H, *J* = 7.8 Hz), 4.17 (d, 1H, *J* = 9.1 Hz), 4.04 (br, 2H, both isomers), 3.96-3.89 (m, 3H, both isomers), 3.84-3.77 (m, 4H, both isomers), 3.74-3.68 (m, 3H, both isomers), 3.65-3.58 (m, 3H, both isomers), 3.53-3.49 (m, 3H, both isomers), 3.40 (t, 1H, *J* = 9.2 Hz), 3.34-3.29 (m, 6H, both isomers), 2.66 (s, 1H), 2.45 (s, 1H), 0.97-0.92 (m, 29H, both isomers), 0.14-0.03 (m, 20H, both isomers).

¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 138.7-126.9, 103.7, 100.2, 80.7, 79.5, 78.6, 75.2, 74.4, 74.2, 73.6, 74.5, 73.2, 72.3, 69.9, 68.9, 68.6, 66.7, 54.8, 26.4, 26.3, 26.2, 26.1, 18.4, 18.0, 17.9, -2.9, -3.2, -4.0, -4.4.

HRMS (ESI): m/z calcd for C₅₃H₇₇O₁₁Si₂ [M+H]⁺: 945.5004, found: 945.5012.

2.4.5 Appendix

Appendix 1. 2D-COSY of donor **1** after the addition of Bu_2BOTf .

Appendix 2. 2D-COSY of donor **14** after the addition of Bu_2BOTf .

Appendix 3. 2D-COSY of donor **17** after the addition of Bu₂BOTf.

Chapter III

One-Pot Glycosylation on Semi-Protected Sugars

3.1 Introduction to One-Pot Glycosylation

Conducting research in the field of oligosaccharides encompasses copious challenges: the separation of “micro-heterogeneous” variants of a specific core scaffold; discovery of structure related regulatory processes; often laborious syntheses of the target oligosaccharide on regio- and stereoselective manner. Vast amounts of effort have been done to reveal their secrets, albeit the lack of universal procedure accessing oligosaccharides hampers their elaborate understanding.

Traditionally, the oligosaccharide assembly is carried out in a stepwise manner starting from the nonreducing end, and building towards the reducing end, or on the other way around. Having the first disaccharide unit in hand, the anomeric protecting group ought to transform into leaving group serving the new donor, or one of the protected OH ought to be freed furnishing the new acceptor. This tedious and lengthy procedure is being repeated until the required oligosaccharide is obtained. To expedite glycan assembly, one-pot approaches have emerged evading the extensive protection and deprotection manipulation on the growing oligosaccharide chain (Figure 1). The following formidable strategies have been disclosed to acquire biologically relevant oligomers: reactivity, orthogonal activation and preactivated latent leaving group-based one-pot chemical glycosylations. The reactivity-based strategy employs all synthons from one family of sugars, from which the one at the non-reducing end is prerequisite to be the most reactive member. Thus, amongst the competing donors, presumably the more reactive will form glycosides with the acceptors, followed by the second most reactive and so on. Generally, their reactivity could be tuned by decorating donors with electron-donating arming or electron-withdrawing disarming protecting groups, and could be

ranked by their relative reactivity values (RRVs). The second orthogonal activation approach utilizes different leaving groups at the anomeric position, allowing to activate the donors according to the employed activators. The third main strategy is independent from the donors' reactivity; it rather takes advantage of the application of latent leaving groups. After the first coupling the dormant leaving group at the reducing end is being transformed to manifest its leaving ability, thus allowing to grow the oligosaccharide chain. A few excellent example for the reactivity based chemoselective glycosylation was selected, demonstrating the expediency of this strategy (Figure 2). Demchenko's group investigated the selective activation of thioimidoyl glycosides over thioglycosides in one-pot, and found thioglycosides being inactive under the treatment of silver triflate, whereas thioimidoyl group was prone to form glycosides.¹³⁸ In Baasov's procedure fundamentally akin strategy was devised, however exploiting the different leaving ability of thioethers under NIS/TMSOTf activating condition.¹³⁹ Additionally, they made use of the choice of solvent as well as the different reactivity of protected glucosamines attributed to their *N*-protection. Lastly, an essentially distinct approach was provided by Ye and co-workers, applying light activated Umemoto's reagent.¹⁴⁰ Their transformation is clearly photo induced and underwent radical process as the radical scavenger and light-dark experiments undoubtedly confirmed.

Figure 1. Strategies for one-pot oligosaccharide assembly.

Figure 2. Representative examples of one-pot oligosaccharide assembly.

3.2 Discussion

3.2.1 Our Concept for One-Pot Oligosaccharide Synthesis

Our working methodology allowed us to construct diverse glycosidic connections when the sugar acceptors' reducing end were capped with a methoxy function, thus impeding the consecutive glycosylations. Hence, this restriction constrains us to grow the saccharide chain into one direction, away from the reducing end. This could be done since one or more hydroxyl

groups are inherently being present on the saccharide, serving the acceptor moiety in the subsequent glycosylation. Instead, we have envisioned a one-pot streamline procedure rather than a stepwise to grow oligosaccharides, eventually glycans. Applying orthogonal activation methods and leaving groups at C1¹⁴¹⁻¹⁴³ has shown success in the construction of oligosaccharides,^{138, 143-145} but was rather tedious and required vast amounts of synthetic work. To overcome this obstacle, we aimed to apply one single leaving group and activation method in each glycosylation step, allowing us to perform one-pot streamline synthesis.

Having our established method towards disaccharides equipped with leaving group at the reducing end in hand, we envisaged to further exploit its utility by providing an alternative strategy for the laborious glycan syntheses on a one-pot streamline manner, as depicted in Figure 3. Firstly, we intended to source easily accessible sugar donors with at least one existing free OH group, equipped with a thiolate leaving group at the reducing end. Secondly, boron reagent would be added, thereafter upon activation of the donor, the thioglycoside acceptor would be introduced, expectedly resulting in disaccharide formation. As a result of that, the furnished disaccharide is bearing a thiolate leaving group at the reducing end, therefore readily available for further elongation. Theoretically, the concept would operate similarly to a sewing machine. Initially introducing donor and boron reagent into the machinery, then sequentially feeding it with acceptors and the activator, hopefully providing the growing oligosaccharide chain. Additionally, introducing sugar moieties into the oligosaccharide chain with multiple unprotected hydroxyl function would provide exquisite synthons for constructing complex, branching glycans.

Figure 3. Our concept for streamline oligosaccharide/glycan syntheses.

3.2.2 Constructing Disaccharides Interchangeably

Our early studies have shown that our methodology is compatible with various activating conditions. With that knowledge in hand, we aimed to investigate whether any of them are exhibiting preference for the thioether function on the donor, over the thioether

function on the acceptor. To our gratitude, we have found *p*-NO₂PhSCI/AgOTf condition expressing the desired feature. In addition, the reaction afforded one single isomer of the many possible. Thus, the working procedure allowed us to explore the interchangeability of the glycosyl donors and acceptors, providing a helpful tool to build oligosaccharide libraries on a reliable manner. Indeed, from two thioglycosides (**16**,¹⁴⁶ **17**¹⁴⁷) we were able to access all four

Unless otherwise specified, all reactions were carried out with 1 eq. of donor, 1.1 eq. of Bu₂BOTf, 3 eq. of AgOTf, 3 eq. of TTBP, 1.1 eq. of *p*-NO₂PhSCI, 1.2 eq. of acceptor in 2 mL of solvent for 12 hs. Yields are determined by isolation of product. ^a2.1 eq. of Bu₂BOTf was used.

Figure 4. Scope of glycosylation on thioglycoside acceptors.

possible glycosides (**20**, **21**, **22**, **23**) with good yields and exclusive β stereoconfiguration without the need for conventional protecting strategy. Additionally, α -mannosylation was performed on **19** acceptor, providing sole stereoisomer of disaccharide **24** (Figure 4).

3.2.3 Assembly of a Model Trisaccharide

Benefitting from the advantage of this method, we devised to assemble a trisaccharide following two possible routes (Figure 5). Firstly, applying stepwise streamline glycosylation including purification and isolation after each step. We have started from galactoside donor **16**, then connected glucosamine derivative acceptor **17** afforded the isolated disaccharide **21** in high yield. The subsequent glycosylation with mannoside **18** afforded desired trisaccharide **25** in good yield. Followed by that, we were delighted to see that one-pot streamline synthetic route likewise afforded the trisaccharide in reasonably good yield. In this case, the galactoside **16** was masked with boron reagent, then activated with *p*-nitrobenzenesulfonyl chloride/silver triflate protocol, followed by the addition of glucosamine thioglycoside acceptor **17**. After observing full consumption of the donor, fresh silver triflate and activator were added into the mixture, and the second acceptor mannosyl thioglycoside **18** was thereafter introduced. During the course of reaction, no self-condensed side product was being formed, while the observation of hydrolyzed donors in the presence of molecular sieves is stemming from the low reactivity of the acceptors.

Figure 5. Assembly of the model trisaccharide on stepwise and one-pot manners.

3.2.4 One-Pot Attempt Towards Branching Trimannoside Core of Gp120 Glycan

According to World Health Organization (WHO), nearly 38 million people have been reported to carry Human Immunodeficiency Virus (HIV) by 2016, and the numbers are continuously rising. By nature, HIV is a retrovirus targeting the CD4 cells, commonly referred as T-cells. Upon entering into the host cell, the virus induces to transcript its parent RNA into cDNA, thus turning the host cell into a provirus.¹⁴⁸ Eventually, the HIV infection of the CD4 leads to the final stage of HIV, also known as Acquired Immune Deficiency Syndrome (AIDS). It occurs when the infected patient has a CD4 count of less than 200 cells/mm³. At this stage, untreated HIV patients' typical lifespan is about 3 years, succumbing to opportunistic diseases are linked to the dysfunction of their immune system.¹⁴⁹

From a closer look, HIV is known to consist of an RNA which is being encapsulated in a phospholipid envelope. The envelope's surface is being decorated with a surface glycan, called gp120. As studies shown, their presence can be associated with binding and recognition to the T cells.¹⁵⁰ Therefore, this complex structure has attracted distinguished attention from the chemists' and biologists' community, catering the key to impede HIV epidemic.

Significant amount of effort has been made towards gp120 high mannose glycans.¹⁵¹⁻¹⁵⁹ In 2004, Danishefsky and co-workers completed the syntheses of gp120 glycan employing two synthetic strategies: block and layered approach (Figure 6).¹⁵⁷⁻¹⁵⁸ The latter approach distinguished 3 major layers, which were sequentially connected by glycosylation, whereas the block approach divides the nonamannose fragment into 3 blocks - the separately synthesized pentamannose and trimannose moieties. Attaching trimer and pentamer onto the β -linked trimannoside afforded the desired nonamannose. Undoubtedly, the existing procedures are heavily dependent on protecting group employment, therefore we devised to synthesize the branching trimannose core of the gp120 utilizing our one-pot open glycosylation method.

Figure 6. Danishefsky's approaches: Layered and Block.

As shown in our scheme, we set out to perform one-pot open mannosylation on the mannoside branching point, arriving at trimannoside (Figure 7). Applying our boron-masked glycosylation procedure entails the existence of inherently free hydroxyls on the targeted product, which are readily available for further glycosylation. Thus, the protocol is devised to save the deprotection step in the consecutive elongation.

Figure 7. Conceptualized assembly of trimannoside core of gp120.

At first, we have synthesized the benzyl and benzoyl protected glycosyl donor moieties applying literature procedures, aiming to reveal whether arming or disarming affects the yield for glycosylation (Figure 8). Starting from triol **26**, the benzylation provided benzyl-protected

orthoester **27** in high yield.¹⁶⁰ The subsequently attempted thiolation with the addition of thiophenol in DCE as well as in MeNO₂ at reflux temperature, failed to provide thioglycoside **28**.¹⁶¹ Eventually the addition of Lewis acidic HgBr₂ succeeded to afford target product **28**.¹³⁰ Lastly the deacetylation under commonly used Zemplén condition furnished our benzyl protected mannoside donor **29**.¹³⁰ The overall synthesis towards benzylated donor was found to be straightforward and required effortless separation. To obtain benzoyl protected mannoside donor **32**, the starting triol **26** was benzoylated under conventional condition to afford benzoyl protected orthoester **30**.¹⁶² To arrive at the thioglycoside **31**, orthoester was hydrolyzed under acidic condition, then subsequently acetylated, preceding the BF₃-mediated thioglycosylation step. The synthesis was slightly modified from the literature pathway, although the NMR spectrum have shown accordance with published data.¹⁵⁹ In the last step we have found the addition of methanolic solution of HCl acidic enough to remove acetyl group, however mild enough to preserve benzoyl groups on the sugar moiety affording target **32** thioglycoside donor.¹⁶³

Figure 8. Synthetic route towards **29** and **32** mannosyl donors.

With the glycosyl donors **29** and **32** in hand, we devised to validate our methodology on the unprecedented dimannoside formation (Figure 9). Gratifyingly, following our previously established protocol we were able to isolate 1,2-*trans* dimannosides bearing OBz

34¹⁵⁹ and OBn **33**¹⁶⁴ protecting groups (Appendix). Unexpectedly, deactivating benzoyl protection strategy provided higher yield than the activating OBn.

Figure 9. Dimannoside formation with employing boron-mediated strategy.

Nevertheless, with a working method in hand we proceeded to attempt the assembly of the target branching trimannoside. For that, we synthesized known glycosyl acceptor **39** (Figure 10). Starting from diol **35**, regioselective benzylation was performed affording **36** while following literature procedure,¹⁶⁵ then subsequent benzoylation provided fully protected sugar unit **37**.¹⁶⁶ With fully protected donor **37** having synthesized, we proceeded to regioselectively open the ring of 4,6-*O*-benzylidene function, affording **38**.¹⁶⁷ Finally, removal of the 3-*O*-PMB based on akin substrate catered our final glycosyl acceptor **39**.¹⁶⁷ Gratifyingly, its spectral characterization is in accordance with the published NMR data (Appendix).¹⁵²

Figure 10. Synthesis of acceptor **39**.

With all the substrates having synthesized we attempted to assemble core trimannoside **40** applying our methodology (Method B), (Figure 11). Benzoyl protected donor **32** was masked prior activation, then acceptor **39** was added subsequently. However, the glycosylation failed to provide the branching trimannoside as only a complicated mixture of side products was being formed. Therefore, we did not proceed to elaborate more on the construction of branching oligomannosides.

Figure 11. Attempted assembly of the branching trimannoside core of gp120.

3.3 Conclusion

To summarize, we have provided a unique approach to assemble disaccharides equipped with leaving group at the reducing end. The retained thioethyl group at the anomeric position allowed us to devise and execute one-pot glycosylation. Successful assembly of a model trisaccharide by two different manners - streamlined stepwise and streamlined one-pot - have exemplified the practicality of this procedure. Additionally, the obtained trisaccharide is inherently bearing free hydroxyl function which is ready to be employed as an acceptor. Being encouraged by these promising results we devised to attempt the synthesis of the branching trimannoside core of gp120 peptidoglycan. Unfortunately, with the synthons having synthesized we were unable to access the target molecule. The syntheses of disaccharides and the assembly of model trisaccharide were disclosed in our recent publication.¹³⁷

3.4 Experimental Section

3.4.1 General Methods

All reactions were conducted under an atmosphere of nitrogen, unless otherwise indicated. Anhydrous solvents were transferred via oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Chromatograms were

visualized by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010-0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. Optical rotations were measured in CHCl₃ or CH₂Cl₂ with a 1 cm cell (c given in g/100 mL). High resolution mass spectra (HRMS) were recorded on Q-TOF mass spectrometer. Accurate masses are reported for the molecular ion [M+H]⁺, [M+Na]⁺ or a suitable fragment ion. Unless otherwise specified, NMR spectra were recorded at room temperature on a 400 MHz and 500 MHz NMR spectrometer. The residual solvent signals were taken as the reference (7.26 ppm for ¹H-NMR spectroscopy and 77.23 ppm for ¹³C-NMR spectroscopy). Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane (TMS). Chemical shift (δ) is referred in terms of ppm, coupling constants (*J*) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, br = broad or unresolved.

3.4.2 Modified Methods

Methods presented in this section are slightly modified from the literature procedures, however the obtained products are known in literature. ¹H and ¹³C NMR spectra are provided in appendix for confirmation

Phenyl-*S*-(3,4,6-tri-*O*-benzoyl)-2-*O*-acetoxy- α -D-mannopyranoside (31)

30 (0.919 mmol, 1 eq.) was dissolved in glacial acetic acid (5 mL) in ice bath and stirred for 10 mins. After 10 mins the temperature was elevated to rt and continued stirring for 3 hs at ambient temperature. Crude mixture was diluted with EtOAc, washed with NaHCO₃, water, brine and dried over Na₂SO₄. Solvent was removed under reduced pressure. Subsequently the

crude product was re-dissolved in the mixture of pyridine:acetic anhydride 1:1 (10 mL), treated with catalytic amount of DMAP and stirred overnight. Crude mixture was diluted with EtOAc and washed with NH₄Cl, water, brine and dried over Na₂SO₄. Purification by flash column chromatography (hexane:EtOAc, 4:1) afforded pure intermediate which was re-dissolved in toluene (10 mL). At 0 °C, thiophenol (2.76 mmol, 3 eq.) and BF₃·OEt₂ (1.84 mmol, 2 eq.) were added into the mixture and stirred overnight while warming up to ambient temperature. Purification by flash column chromatography afforded **31** (328 mg, 57% in 3 steps) as a colorless oil. Recorded NMR data has found to be in accordance with literature data.¹⁵⁹

Ethyl-*S*-2-*O*-benzoyl-4-*O*-benzyl- α -D-mannopyranoside (39**).**

37 (0.0950 mmol, 1 eq.) was dissolved in tetrahydrofuran (2 mL) at 0 °C and treated with 1 M THF solution of borane tetrahydrofuran complex (0.475 mmol, 5 eq.) and 1 M DCM solution of dibutylboron triflate (0.048 mmol, 0.5 eq.). The mixture was stirred at 0 °C for 1 h, then subsequently quenched with 100 μ L of NEt₃ and 2 mL of MeOH. The crude mixture was co-evaporated with MeOH and purified by flash column chromatography, affording **38** (24 mg, 47%). Subsequently **38** (0.0297 mmol, 1 eq.) was dissolved in the mixture of CH₂Cl₂:H₂O 9:1 (2 mL) at 0 °C and treated with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (0.0446 mmol, 1.5 eq.). The mixture was let it to reach ambient temperature and filtered off after 6 hs. The crude product was re-dissolved in EtOAc and washed with NH₄Cl_(aq), water, brine and dried over Na₂SO₄. Purification by flash column chromatography afforded **39** (10 mg, 80%) as a colorless oil. Recorded NMR data has found to be in accordance with literature data.¹⁵² ¹H and ¹³C NMR spectra are provided in Appendix.

3.4.3 General Method for Boron-Mediated Glycosylation with AgOTf/*p*-NO₂PhSCI

Method A: Stepwise manner

To a magnetically stirred DCM:toluene 0.5:1 (1.5 mL) solution of donor (0.1 mmol, 1 eq.), AgOTf (3 eq., co-evaporated with toluene prior the addition) and 2,4,6-tri-*tert*-butylpyrimidine (3 eq.) were added at -20 °C. After which, to the mixture was added dropwise with 1 M DCM solution of dibutylboryl trifluoromethanesulfonate (1.1 eq.), then subsequently the temperature was lowered to -60 °C. After reaching set temperature, *p*-nitrobenzenesulfonyl chloride (1.2 eq.) was added, thereafter 5 mins the mixture was treated with acceptor (1.3 eq.) dissolved in 0.5 mL of DCM. The temperature was elevated to -40 °C and stirred for 12 hs. After which the mixture was quenched with triethylamine (50 µL) and the inorganic materials were filtered. The crude product was washed with water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded pure product.

Method B: One-pot manner

To a magnetically stirred DCM:toluene 0.5:1 (1.5 mL) solution of donor (0.1 mmol, 1 eq.), AgOTf (3 eq., co-evaporated with toluene prior the addition) and 2,4,6-tri-*tert*-butylpyrimidine (3 eq.) were added at -20 °C. After which, to the mixture was added dropwise with 1 M DCM solution of dibutylboryl trifluoromethanesulfonate (1.1 eq.), then subsequently the temperature was lowered to -60 °C. After reaching set temperature, *p*-nitrobenzenesulfonyl chloride (1.2 eq.) was added, thereafter 5 mins the mixture was treated with acceptor (1.2 eq.) dissolved in 0.5 mL of DCM. The temperature was elevated to -40 °C and stirred for 3 hs. Another portion of AgOTf (1.5 eq., co-evaporated with toluene prior the addition) and *p*-nitrobenzenesulfonyl chloride (1.2 eq.) was added at -60 °C, thereafter 5 mins the mixture was treated with the second acceptor (2 eq.) dissolved in 0.5 mL of DCM and stirred for 12 hs. After which the mixture was quenched with triethylamine (50 µL) and the inorganic materials were filtered. The crude product was washed with water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded pure product.

3.4.4 Characterization of Saccharides

Phenyl-*S*-((3,4,6-tri-*O*-benzyl)- α -D-mannopyranosyl)-(1 $\rightarrow$ 4)-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-3-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl- β -D-glucopyranoside 24 (Method A)

41 mg (78 % yield) as a colorless oil.

$[\alpha]_{\text{D}}^{20} +22.5$ (c 1.5, CHCl₃).

¹H-NMR (500 MHz, CDCl₃) δ (ppm) 7.52-7.16 (m, 20H, aromatic), 5.18 (t, 1H, $J = 9.6$ Hz), 5.15-5.13 (m, 2H), 4.84-4.66 (m, 7H), 4.53-4.49 (dd, 2H, $J = 5.3$ Hz, $J = 11.5$ Hz), 3.94-3.90 (m, 2H), 3.86-3.81 (m, 3H), 3.78-3.65 (m, 5H), 3.42-3.39 (m, 1H), 2.11 (s, 3H), 0.93 (s, 9H), 0.06 (s, 6H).

¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 171.1-127.8, 117.9, 101.1, 95.6, 87.3, 80.1, 79.8, 76.4, 75.2, 75.1, 74.7, 74.0, 73.8, 72.5, 72.3, 69.1, 68.7, 62.8, 55.5, 26.2, 26.1, 21.1, 18.6, -4.9.

HRMS (ESI): m/z calcd for C₅₀H₆₂NCl₃SO₁₂SiNa [M+Na]⁺: 1056.2725, found: 1056.2735.

Ethyl-*S*-((2-*O*-benzoyl-4,6-*O*-benzylidene)- β -D-galactopyranosyl)-(1 $\rightarrow$ 3)-2-*O*-benzoyl-4,6-*O*-benzylidene- β -D-galactopyranoside 20 (Method A)

26 mg (68 % yield) as a white solid.

$[\alpha]_{\text{D}}^{20} +18.8$ (c 0.5, CHCl₃).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.01-7.99 (m, 1H, aromatic), 7.82-7.60 (m, 1H, aromatic), 7.58-7.27 (m, 18H, aromatic), 5.68 (t, 1H, $J = 9.7$ Hz), 5.57 (s, 1H), 5.45 (s, 1H), 5.35 (dd, 1H, $J = 8.0$ Hz, $J = 9.8$ Hz), 4.97 (d, 1H, $J = 8.0$ Hz), 4.56 (d, 1H, $J = 9.7$ Hz), 4.44 (d, 1H, $J = 3.1$ Hz), 4.35 (dd, 1H, $J = 1.3$ Hz, $J = 12.3$ Hz), 4.29-4.20 (m, 3H), 4.07-4.00 (m, 2H), 3.70 (td, $J = 3.6$ Hz, $J = 10.8$ Hz), 3.56 (s, 1H), 3.49 (s, 1H), 2.93-2.84 (m, 1H), 2.77-2.68 (m, 1H), 2.57 (d, 1H, $J = 11.1$ Hz), 1.24 (t, 1H, $J = 7.5$ Hz).

¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 166.5, 164.9, 137.7-126.9, 101.4, 100.9, 100.1, 83.1, 77.2, 76.4, 76.3, 75.6, 72.6, 72.1, 70.4, 69.1, 68.8, 68.7, 66.7, 29.7, 22.7, 14.7.

HRMS (ESI): m/z calcd for $C_{42}H_{42}SO_{12}Na$ $[M+Na]^+$: 793.2295, found: 793.2295.

Ethyl-*S*-((2-deoxy-2-phthalimido-6-*O*-benzyl- β -D-glucopyranosyl)-(1 $\rightarrow$ 4)-2-deoxy-2-phthalimido-6-*O*-benzyl- β -D-glucopyranoside 23 (Method A)

28 mg (69 % yield) as a colorless oil.

$[\alpha]_D^{20} +53.2$ (c 0.2, $CHCl_3$).

1H -NMR (400 MHz, $CDCl_3$) δ (ppm) 7.91-7.71 (m, 7H, aromatic), 7.33-7.08 (m, 11H, aromatic), 5.38 (d, 1H, $J = 8.4$ Hz), 5.23 (d, 1H, $J = 10.5$ Hz), 4.53-4.39 (m, 5H), 4.27-4.18 (m, 2H), 4.10 (s, 2H), 3.77-3.70 (m, 4H), 3.58-3.53 (m, 2H), 3.32 (s, 2H), 2.80 (d, 1H, $J = 2.6$ Hz), 2.67-2.55 (m, 2H), 2.43 (d, 1H, $J = 4.4$ Hz), 2.19 (d, 2H, $J = 2.5$ Hz), 1.16 (d, 1H, $J = 7.4$ Hz).

^{13}C -NMR (100 MHz, $CDCl_3$) δ (ppm) 168.1, 167.7, 138.2-123.2, 99.0, 81.7, 80.8, 78.0, 73.7, 73.3, 72.8, 71.3, 71.0, 69.8, 68.4, 56.2, 55.0, 53.8, 31.7, 29.7, 29.3, 23.6, 14.9.

HRMS (ESI): m/z calcd for $C_{44}H_{45}N_2SO_{12}$ $[M+H]^+$: 825.2693, found: 825.2699.

Ethyl-*S*-((2-deoxy-2-phthalimido-6-*O*-benzyl- β -D-glucopyranosyl)-(1 $\rightarrow$ 3)-2-*O*-benzoyl-4,6-*O*-benzylidene- β -D-galactopyranoside 21 (Method A)

27 mg (70 % yield) as a colorless oil.

$[\alpha]_D^{20} -33.5$ (c 0.2, $CHCl_3$).

1H -NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65-7.23 (m, 19H, aromatic), 5.50-5.42 (m, 3H), 4.63 (d, 1H, $J = 11.8$ Hz), 4.53 (d, 1H, $J = 11.7$ Hz), 4.43-4.41 (m, 2H), 4.25 (d, 1H, $J = 12.2$ Hz), 4.16-4.11 (m, 2H), 3.94 (dd, 1H, $J = 3.4$ Hz, $J = 9.7$ Hz), 3.85-3.81 (m, 2H), 3.78-3.74 (m, 1H), 3.70-3.65 (m, 1H), 3.52-3.50 (m, 1H), 3.43 (s, 1H), 2.96 (d, 1H, $J = 2.5$ Hz), 2.81-2.72 (m, 1H), 2.62-2.53 (m, 1H), 2.39 (br, 1H), 1.13 (t, 1H, $J = 7.5$ Hz).

^{13}C -NMR (100 MHz, $CDCl_3$) δ (ppm) 176.9, 167.9, 164.6, 137.8-123.0, 100.9, 99.5, 82.7, 79.8, 76.7, 76.1, 73.9, 73.7, 73.4, 71.8, 70.7, 70.2, 69.1, 68.3, 56.1, 29.5, 22.5, 14.7.

HRMS (ESI): m/z calcd for $C_{43}H_{44}NSO_{12}$ $[M+H]^+$: 798.2584, found: 798.2584.

Ethyl-*S*-((2-*O*-benzoyl-4,6-*O*-benzylidene)- β -D-galactopyranosyl)-(1 $\rightarrow$ 4)-2-deoxy-2-phthalimido-6-*O*-benzyl- β -D-glucopyranoside 22 (Method A)

26 mg, (67 % yield) as a colorless oil.

$[\alpha]_D^{20}$ -25.8 (c 0.2, CHCl₃).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.09-7.28 (m, 19H, aromatic), 5.54 (s, 1H), 5.39 (t, 1H, J = 8.4 Hz), 5.32 (d, 1H, J = 10.5 Hz), 4.68 (d, 1H, J = 8.0 Hz), 4.53-4.46 (m, 2H), 4.32-4.24 (m, 5H), 4.05 (d, 1H, J = 12.2 Hz), 3.87-3.79 (m, 2H), 3.65-3.55 (m, 4H), 2.72-2.56 (m, 3H), 1.20 (t, 1H, J = 7.4 Hz).

¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 168.1, 167.9, 165.7, 138.5-123.3, 101.5, 101.2, 81.3, 81.1, 78.1, 77.2, 75.2, 73.2, 72.6, 71.5, 70.6, 68.5, 68.2, 66.8, 55.3, 24.1, 14.9.

HRMS (ESI): m/z calcd for C₄₃H₄₄NSO₁₂ [M+H]⁺: 798.2584, found: 798.2588.

Phenyl-*S*-((2-*O*-benzoyl-4,6-*O*-benzylidene)- β -D-galactopyranosyl)-(1 $\rightarrow$ 4)-(2-deoxy-2-phthalimido-6-*O*-benzyl- β -D-glucopyranosyl)-(1 $\rightarrow$ 2)-3,4,6-tri-*O*-benzyl)- α -D-mannopyranoside 25 (Method A, B)

19 mg (59 % and 50 % yields) as a colorless oil.

$[\alpha]_D^{20}$ +40.5 (c 0.1, CHCl₃).

¹H-NMR (500 MHz, CDCl₃) δ (ppm) 8.13-6.95 (m, 39H, aromatic), 5.48 (s, 1H), 5.45 (d, 1H, J = 8.5 Hz), 5.35 (s, 1H), 5.08 (dd, 1H, J = 3.6 Hz, J = 10.1 Hz), 4.85-4.26 (m, 13H), 4.14 (t, 1H, J = 9.9 Hz), 4.08-4.00 (m, 4H), 3.93-3.77 (m, 4H), 3.71 (t, 1H, J = 8.9 Hz), 3.64-3.60 (m, 2H), 3.49 (d, 1H, J = 10.8 Hz), 3.28 (s, 1H), 3.11 (dd, 1H, J = 6.7 Hz, J = 10.7 Hz), 2.20 (s, 1H).

¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 169.7, 169.1, 165.0, 138.3-123.0, 101.0, 100.4, 96.8, 84.6, 83.4, 81.2, 78.2, 77.1, 75.7, 74.9, 74.8, 74.2, 73.7, 73.4, 72.9, 72.5, 72.3, 71.5, 71.2, 70.9, 70.3, 69.7, 69.4, 55.9.

HRMS (ESI): m/z calcd for C₇₄H₇₁NSO₁₇Na [M+Na]⁺: 1300.4340, found: 1300.4345.

Phenyl-*S*-((3,4,6-tri-*O*-benzyl)- α -D-mannopyranosyl)-(1 $\rightarrow$ 2)-3,4,6-tri-*O*-benzyl- α -D-mannopyranoside 33 (Method A)

62 mg (50 % yield). Recorded NMR data has found to be in accordance with literature data.¹⁶⁴

¹H and ¹³C NMR spectra are provided in Appendix.

Phenyl-*S*-((3,4,6-tri-*O*-benzoyl)- α -D-mannopyranosyl)-(1 $\rightarrow$ 2)-3,4,6-tri-*O*-benzoyl- α -D-mannopyranoside 34 (Method A)

63 mg (57 % yield). Recorded NMR data has found to be in accordance with literature data.¹⁵⁹

¹H and ¹³C NMR spectra are provided in Appendix.

3.4.5 Appendix

Appendix 1. ¹H NMR data of dimannoside **33**.

Appendix 2. ¹³C NMR data of dimannoside **33**.

Appendix 3. ¹H NMR data of dimannoside **34**.

Appendix 4. ¹³C NMR data of dimannoside **34**.

Appendix 5. ¹H NMR data of acceptor **39**.

Appendix 6. ¹³C NMR data of acceptor **39**.

Chapter IV

Attempts Towards the Total Synthesis of *N*-Acetylglucosamine-1,6-Anhydro-*N*-Acetyl-Muramylpentapeptide

As an extension of our mission, we devised to apply our boron-masked glycosylation method in natural product synthesis. Recently, our group has turned its attention to the syntheses of sugar-based biomolecules, utilizing such methodologies that have been devised, developed and elaborated by ourselves.¹⁶⁸⁻¹⁷¹ Thus, we have chosen the family of peptidoglycans as an adventurous, but rewarding target to synthesize.

4.1 Biological Relevance of *N*-Acetylglucosamine-1,6-Anhydro-*N*-Acetyl-Muramylpentapeptide and its Total Synthesis

In 2017, a seminal work was communicated by Mobashery and co-workers dissecting the functions and substrates of lytic transglycosylases (LTs) found in Gram-negative bacteria.¹⁷² It is well-known that LTs are essential enzymes for the bacterial cell wall, truncating its glycan components into smaller units, such as *N*-Acetylglucosamine-1,6-anhydro-*N*-acetylmuramylpentapeptide.¹⁷³ Mobashery's group confirmed that many of the LTs are able to recognize 1,6-Anhydro-*N*-acetylmuramyl containing peptidoglycans as their own substrate.

Figure 1. Biological relevance of *N*-Acetylglucosamine-1,6-anhydro-*N*-acetyl-muramylpentapeptide.

Moreover, Park and co-workers suggested that cell wall residue *N*-Acetylglucosamine-1,6-anhydro-*N*-acetylmuramylpentapeptide (NAG-AnhNAM peptide) moiety might serve as a feedstock for the continuously growing cell wall, apparently being recycled by the bacterial cell (Figure 1).¹⁷⁴ Alternatively, the anhydro peptidoglycan might diffuse out from the bacteria. Although substantial amount of work has been done in this field, a comprehensive study could not be conducted without having an expeditious access to glycans, including NAG-AnhNAM peptide. To overcome this obstacle, a few synthetic studies have been reported towards the target peptidoglycan and its analogues,¹⁷⁵⁻¹⁷⁹ most recently an elaborative total synthesis within 17 steps (from D-glucal) from Mobashery's group.¹⁸⁰ Compiling the scarcely available literature on this topic (Figure 2), we addressed a few issues hampering the efficient syntheses of muramylpeptides. First and foremost, the notorious protection and deprotection steps of functional groups significantly lengthens the synthetic pathway. The choice of the leaving group and ancillary group on the glucosamine, in conjunction with the employed activator, genuinely affect the realization of the disaccharide moiety, greater than usual. In fact, planning each protecting group attachment and removal should be carefully carried out, ensuring no interference with crucial domains on the structure.

Figure 2. Successful syntheses of *N*-Acetylglucosamine-1,6-anhydro-*N*-acetylmuramyl disaccharides.

4.2 Discussion

4.2.1 Our Conceptualized Synthetic Plan

Taking the essence of the latter procedures, we set out to investigate which is the most facile pathway towards NAG-AnhNAM peptide, preferably taking advantage of our boron-mediated glycosylation strategy.

Retrosynthetically, our synthesis is stemming from commercially available D-glucal **A**, which would form into Cerny epoxide **B** through 3 steps,¹⁸¹⁻¹⁸² providing an excellent substrate for the installment of amino function arriving at **C** (Figure 3).¹⁸² The obtained 1,6-Anhydro moiety would serve as the key intermediate for the syntheses of donor and acceptor moieties. We planned to obtain the acceptor sugar with the attachment of lactate moiety **E**,¹⁷⁸ while the Lewis acid-catalyzed thiolation applying Hanessian's procedure would provide us the glycosyl donor **D** as well.¹⁸³ By employing our boron-masked glycosylation methodology on the latter donor with the acceptor moiety, we hoped to achieve NAG-AnhNAM disaccharide **F**,¹³⁷ while the meticulously chosen aiding group on amine function was expected to furnish 1,2-*trans*-glycoside exceptionally. With the **F** NAG-AnhNAM disaccharide in hand, we set out to

Figure 3. Our conceptualized synthetic pathway towards target peptidoglycan.

transform amino protecting groups to their native acetamide form, then hydrolyze lactate function prior the peptide attachment (**G**).¹⁸⁰ Lastly, by removing the benzyl-type protecting group from the anhydromuramyl moiety and the base-labile protecting groups from the pendant pentapeptide, we hoped to obtain the naturally abundant peptidoglycan **H**. With the proposed pathway, we aimed to accomplish the total synthesis of *N*-Acetylglucosamine-1,6-anhydro-*N*-acetylmuramylpentapeptide found in Gram-negative bacteria through a markedly shorter route, shortening the existing 17-step pathway to a 12-step approach.

4.2.2 Synthesis of the Protected Form of *N*-Acetylglucosamine-1,6-Anhydro-*N*-Acetylmuramyl Moiety

Before we set out to investigate the feasibility of our synthetic pathway, we decided to accomplish the synthesis of disaccharide moiety **F** of the target natural product **H** on conventionally protected sugar donors, aiming to fine-tune the employed activator and *N*-protection strategy.

From the start of the synthesis up until arriving at the azido moiety **13**, we mainly followed Katavic's procedure (Figure 4).¹⁸¹ First, Zemplén deacetylation was carried out on commercially available D-glucal **10**. After which, the neutralized mixture of triol was treated with (Bu₃Sn)₂O in MeOH, and refluxed for 3 hs. The mixture was subsequently cooled down to 0 °C, thereafter I₂ was introduced into the reaction flask and continued stirring overnight while maintaining the set temperature. After quenching the excess iodine, repeated extraction of the crude mixture afforded target iodo compound **11** in excellent yield and purity. After dissolving it in DMF, the solution was treated with NaH and BnBr at -15 °C and stirred overnight. Column purification furnished Cerny epoxide **12**, which was subsequently dissolved in DMF:H₂O mixture, treated with NaN₃ and stirred at 120 °C over 3 days. Separation on column provided pure azido sugar **13**, which was consequently substituted with lactate triflate

reagent **14** under basic condition (**15**).¹⁷⁷ After which, the azido function was reduced and acetylated in a one-pot procedure, allowing us to obtain the benzyl protected sugar acceptor.¹⁸¹ While excellent yield was realized, *O*-benzyl group at C4 remained unaffected. Applying 100 psi or heating up the mixture to 50 °C did not bring any success, therefore we had to purify the crude product before proceeding to the benzyl removal. Gratifyingly, both high pressure as well as heating provided debenzylated sugar moiety **15**, with the latter procedure furnishing in nearly quantitative yield. To sum up, starting from easily accessible and affordable D-glucal **10**, the target 1,6-Anhydro-*N*-acetylmuramicacid methylester **16**¹⁸¹ was synthesized within 7 steps with a total 26 % yield, while 4 column chromatography were performed. Throughout the synthesis, each transformation has followed literature procedure as indicated, with acquired ¹H and ¹³C spectra in agreement with the reported data.

Figure 4. Synthesis of acceptor **16**.

With the sugar acceptor **16** in hand, we devised to explore the most suitable ancillary group on the protected sugar donor. The most commonly applied amino protection strategies are NHTroc, NHTCA and probably the most widely employed NPhth. Earlier in time, commencing our preliminary studies on the boron-masked glycosylation employing Troc-protected glucosamine,¹⁸⁴ we have observed primarily the formation of oxazolidine side product. Therefore, we devised to attempt glycosylation with trichloroacetate (TCA)¹⁸⁴ and phthaloyl (Phth) protected glucosamines (**17**,¹⁸⁵ **18**¹⁸⁶). We set NIS/TMSOTf as an activating

method throughout our study and began with TCA protected glucosamine donor. To our disappointment, most of the donor transformed into its oxazolidine form upon activation, drastically diminishing the yield for the desired disaccharide. On the contrary, phthaloyl protected armed **17** as well as disarmed **18** glucosamine donor afforded target disaccharide (**19**, **20**) in adequate yields (Figure 5). Those results prompted us to commence our studies on boron-masked glycosylation with slightly decorated *N*-phthaloyl sugar donor equipped with thioether anomeric leaving group. Additionally, we aimed to employ promoters, which were found to be useful throughout our methodology study reported in Chapter II.

Figure 5. A brief study on the disaccharide formation.

4.2.3 Synthesis of the Semi-Protected Form of *N*-Acetylglucosamine-1,6-Anhydro-*N*-Acetylmuramyl Moiety

With the knowledge in hand gained from the conventional synthesis of the target disaccharides **19** and **20**, we set a few criteria for the synthetic scheme leading to NAG-AnhNAM. At first, utilizing Cerny epoxide **12** as a valuable intermediate was highly beneficial, therefore we decided to preserve its place in our synthetic scheme. However, we aimed to increase the yield from adequate to excellent by replacing BnBr with PMBCl during its synthesis.¹⁸² In the next step, we devised to open the epoxide function and subsequently install NPhth group,¹⁸² which greatly aided the following glycosylation. This anhydro moiety would serve as our key intermediate for the syntheses of both glycosyl acceptor and donor. To

markedly reduce to overall number of steps, we hoped to acquire the glycosyl acceptor by attaching the lactoyl moiety and subsequently deprotecting 4-*O*, as well as the glycosyl donor by utilizing Hanessian's strategy.¹⁸³

As previously described, we started our synthesis from D-glucal **10** and similarly acquired the iodo compound **11** (Figure 6). In the next step, we changed to Hsieh-Wilson's procedure, and were furnished with the target Cerny epoxide **21** in good yield.¹⁸² However, the subsequent transformation following Hsieh-Wilson's procedure failed to access our key intermediate **22**,¹⁸² therefore we devised to adapt Pericas's procedure developed for the syntheses of enantiopure aminoalcohols.¹⁸⁷ To our satisfaction, treating dioxane solution of Cerny epoxide with the aqueous solution of NH₄OH and stirring it for 3 days at 85 °C afforded us the aminoalcohol. After removing the solvent, the crude mixture was re-dissolved in MeOH and transformed into **23** applying common procedure. This method affords 3-OAc on **23** by its nature, therefore in the subsequent step, it had to be carefully hydrolyzed, freeing 3-*O*. Its well-known that NPhth group is base-labile, therefore Zemplén-deacetylation must be carried out at -20 °C to afford our key intermediate **24**. With **24** having synthesized, we proceeded to attempt transforming it to our sugar donor **25**. However, the ZnI₂-assisted one-step procedure from Hanessian's group did not furnish our targeted compound.¹⁸³ Nevertheless, we proceeded to pursue the syntheses of sugar acceptor **26**. However, S_N2 substitution on **24** with **14** triflate reagent surprisingly failed to occur,¹⁷⁷ therefore we attempted to attach the lactic acid **27** moiety first.¹⁸⁰ After which, lactic acid was esterified under mildly basic condition in a two-step one-pot procedure, while affording **26** in good yield. Methylating the acid function might look redundant, nonetheless we decided to carry out in order to avoid possible interference during glycosylation in future.¹⁸⁰ It should also be noted that NPhth group endured ring opening upon quenching the excess NaH with MeOH, thus aqueous NH₄Cl was used to neutralize the

mixture instead. Finally, removal of PMB group under mild condition furnished our target glycosyl acceptor **28** within 9 steps and with 13 % yield.¹⁸⁸

Figure 6. Synthesis of acceptor **28** and attempt towards donor **25**.

With the acceptor being synthesized, we proceeded to assess the feasibility of our concept of boron-masked glycosylation performed on mildly decorated sugar donor (Figure 7). Since we failed to access donor moiety **25** from this synthetic pathway, we have chosen model compound **29**¹⁸⁹ bearing 2 free hydroxyl group similarly to the target donor **25**.¹⁹⁰ The position and the nature of the protecting group changed from the initially devised structure, however learning from our methodology studies (Chapter II) it should not affect conceivably the reactivity. With that in mind, we proceeded to attempt the glycosylation on semi-protected donor employing dibutylboron triflate as a masking reagent, together with various promoters. The reaction was able to provide desired product **30**, albeit together with complicated mixture of side products. Varying the nature of the activator did not entail significant improvement in yield, thus we deemed steric clash contributed to the poor yield. In examining the structure of the product **30**, we may notice that NPhth groups in the disaccharide are considerably pointing towards each other, therefore building up a repulsive force amongst them (Figure 7). To justify our hypothesis, but more importantly to achieve increment in yield, we changed acceptor **28** to

the sterically less congested **16** sugar acceptor. Disappointingly, switching the reacting partner did not bring any success, providing only a complex mixture of side products.

Figure 7. Attempts towards disaccharide **30**.

4.2.4 Divergent Syntheses Towards Lipid II Analogue and *N*-Acetylglucosamine-1,6-Anhydro-*N*-Acetyl-Muramylpentapeptide

Gaining interest in this field, we have encountered the biological relevance of Lipid II as well. By now, its distinguished role in the assembly of bacterial cell wall is known, however it is not fully understood.¹⁹¹⁻¹⁹⁸ One possible factor that withholds to reveal more details about Lipid II's involvement in biological processes may be the limited and laborious access to its intricate structure. Despite requiring tedious synthesis, few reports from: VanNieuwenhze,¹⁹⁹ Wong Chi-Huey,²⁰⁰ Schwartz²⁰¹ disclosed its accomplished total syntheses, and critical synthetic work has been done by Kahne²⁰² and Mobashery.²⁰³

We were keen to explore whether we could exploit more from the concise synthesis of disaccharide **20**. Devising to open anhydro motif of **20**, we set to provide a divergent syntheses arriving at both the NAG-AnhNAM pentatpetide **A** and Lipid II analogue **B** (Figure 8).

Figure 8. Divergent syntheses towards anhydro peptidoglycan **A** and LIPID II **B**.

As a first step, we proposed to transform ancillary group on **20** to its naturally abundant acetamide form **31**, following by the opening of the anhydro motif under acidic condition (Figure 9).²⁰⁴ Commencing the synthesis, dephthaloylation with hydrazine acetate and the concomitant acetylation went smoothly, however the anticipated transformation to **32** did not take place. Thus, we altered the sequence of reactions – to start with the acid-mediated anhydro ring opening - gratifyingly afforded **33** in high yield. In the next step, we had two choices; to either dephthaloylate **33** or hydrolyze anomeric acetate function in order to attach phosphate moiety. Considering the base sensitive nature of the anomeric acetate function, we set to hydrolyze it first before the phosphate attachment and the subsequent phthaloyl deprotection. Moreover, we should take the presence of methylester moiety on **33** into account, which is prone to undergo amidation when being treated with nucleophilic bases, such as methylamine,

Figure 9. Synthesis of Lipid II analogue **39** precursor.

benzylamine or ethylenediamine. Therefore, we had to set aside applying those bases to hydrolyze anomeric acetate function and instead, following Masatomo's protocol,²⁰⁵ we treated **33** with (NH₄)₂CO₃ in DMF, which afforded target **34** in decent yield. The success of arriving at disaccharide **34** prompted us to maintain future endeavors towards the total syntheses of biologically important structures, discussed in the following subchapter.

4.2.5 Future Plans Towards *N*-Acetylglucosamine-1,6-Anhydro-*N*-Acetyl-Muramylpentapeptide and Lipid II Analogue

Having a facile method in hand towards **31** motivated us to pursue a divergent total syntheses of **38** glycan as well as **39** Lipid II analogue (Figure 10). As per published procedure, hydrolysis of methylester function under basic condition would provide us with the acid form of the lactoyl moiety, moreover it would also hydrolyze 3,4,6-OAc groups. Continuing with the protecting group-free **31**, the attachment of peptide **37** is hoped to furnish the target **38** glycan within 13 steps, significantly shortening the existing 17-step approach.

Stemming from disaccharide **20**, we set to pursue the total syntheses of **39** Lipid II peptidoglycan analogue as well. For that, we planned to acquire disaccharide **34** first, which would be phosphorylated to obtain phosphoryldiester **35** (Figure 10).²⁰⁰ Having **35** in hand, we would carry out dephthaloylation and concomitant acetylation, followed by the 2-step attachment of lipid tail.²⁰⁰ As Chi-Huey and co-workers reported,²⁰⁶ the nature of the anchoring lipid tail does not affect substantially the biological interactions within the cell, therefore we may set aside carrying out the time-consuming synthesis of such complicated phospholipid moiety. Lastly, the hydrolysis of methylester/acetates would provide us with the free lipid-decorated disaccharide moiety,²⁰⁰ prior to the attachment of pentapeptide **37**. Lastly, global deprotection of the base labile protecting groups from the peptide moiety would end our

4.4 Experimental Session

4.4.1 General Methods

All reactions were conducted under an atmosphere of nitrogen, unless otherwise indicated. Anhydrous solvents were transferred via oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010-0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. Optical rotations were measured in CHCl₃ or CH₂Cl₂ with a 1 cm cell (c given in g/100 mL). High resolution mass spectra (HRMS) were recorded on Q-TOF mass spectrometer. Accurate masses are reported for the molecular ion [M+H]⁺, [M+Na]⁺, or a suitable fragment ion. Unless otherwise specified, NMR spectra were recorded at room temperature on a 400 MHz and 500 MHz NMR spectrometer. The residual solvent signals were taken as the reference (7.26 ppm for ¹H-NMR spectroscopy and 77.23 ppm for ¹³C-NMR spectroscopy). Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane (TMS). Chemical shift (δ) is referred in terms of ppm, coupling constants (*J*) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, br = broad or unresolved.

4.4.2 Syntheses and Characterization of Compounds

2-Phthalimido-(3,4,6-tri-*O*-benzyl)-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-1,6-anhydro-2-deoxy-3-*O*-[(1*R*)-1-carboxyethyl]-β-D-glucopyranose 19

Donor **17** (0.032 mmol, 1 eq.) was dissolved in dry DCM (2 mL) and was treated with 3Å molecular sieves and acceptor **16** (0.025 mmol, 0.77 eq.) at -5 °C. After 10 mins *N*-Iodosuccinimide (0.042 mmol, 1.3 eq.) and trimethylsilyl trifluoromethanesulfonate (0.001 mmol, 0.3 eq.) were added and stirred overnight at ambient temperature. After which the mixture was quenched with triethylamine (50 µL) and the molecular sieves were filtered off. The crude product was washed with sat. Na₂S₂O₃, water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded 12 mg of pure **19** as a white foam in 57 % yield. $[\alpha]_D^{20}$ -8.5 (c 0.8, CH₂Cl₂).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.62 (br, 4H), 7.32-6.76 (m, 16H), 5.83 (d, 1H, *J* = 9.7 Hz), 5.13 (d, 1H, *J* = 8.8 Hz), 4.86 (s, 1H), 4.77 (t, 2H, *J* = 11.7 Hz), 4.60-4.36 (m, 7H), 4.20-4.09 (m, 2H), 4.05-4.04 (m, 3H), 3.74-3.65 (m, 8H), 3.55 (t, 1H, *J* = 6.6 Hz), 3.50 (s, 1H), 1.29 (d, 3H, *J* = 6.8 Hz).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.8, 168.7, 134.0, 134.0, 131.6, 128.5, 128.49, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.4, 100.9, 96.5, 79.4, 78.8, 76.9, 75.1, 74.9, 74.5, 74.4, 73.6, 72.8, 68.6, 64.5, 56.2, 49.0, 23.00, 18.1.

HRMS (ESI): *m/z* calcd for C₄₇H₅₁N₂O₁₃ [M+H]⁺: 851.3391, found: 851.3359.

2-Phthalimido-(3,4,6-tri-*O*-acetyl)-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-1,6-anhydro-2-deoxy-3-*O*-[(1*R*)-1-carboxyethyl]-β-D-glucopyranose **20**

Donor **18** (1 mmol, 1 eq.) was dissolved in dry DCM (5 mL) and was treated with 3Å molecular sieves and acceptor **16** (0.7 mmol, 0.7 eq.) at -5 °C. After 10 mins *N*-Iodosuccinimide (1.4 mmol, 1.3 eq.) and trimethylsilyl trifluoromethanesulfonate (0.32 mmol, 0.3 eq.) was added and stirred overnight at ambient temperature. After which the mixture was quenched with triethylamine (160 µL) and the molecular sieves were filtered off. The crude product was

washed with sat. Na₂S₂O₃, water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded 281 mg of pure **20** as a white foam in 60 % yield.

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.83 (br, 2H), 7.74 (m, 2H), 5.97-5.85 (br, 1H), 5.43 (d, 1H, *J* = 8.5 Hz), 5.16 (t, 1H, *J* = 9.6 Hz), 4.97 (s, 1H), 4.39-4.28 (m, 2H), 4.28 – 4.19 (q, 1H, *J* = 6.8 Hz), 4.11-4.05 (m, 5H), 3.91-3.87 (m, 1H), 3.73 (s, 4H), 3.55 (t, 1H, *J* = 6.6 Hz), 3.50 (s, 1H), 2.10 (s, 3H), 2.06-1.98 (m, 6H), 1.87 (s, 3H), 1.39 (d, 3H, *J* = 6.8 Hz).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 172.9, 170.6, 170.0, 169.7, 169.5, 131.29, 100.9, 96.5, 75.6, 74.3, 72.9, 72.2, 70.0, 68.9, 64.6, 62.0, 54.8, 52.2, 49.1, 23.0, 20.7, 20.6, 20.4, 18.0.

2-Phthalimido-1,6-anhydro-2-deoxy-3-*O*-acetyl-4-*O*-*para*-methoxybenzyl-β-D-glucopyranose **23**

Cerny epoxide **21** (12.5 mmol, 1 eq.) was dissolved in dry dioxane, treated with NH₄OH_(aq) (500 mmol, 40 eq.) and stirred at 85 °C for 3 days. After which, the crude mixture was evaporated, and re-dissolved in MeOH. The methanolic solution of crude aminoalcohol was treated with Phthalic anhydride (15 mmol, 1.2 eq.) and stirred overnight at rt. After which the crude mixture was evaporated, dried, and treated with pyridine: Ac₂O 1:1 mixture, and stirred at 60 °C overnight. The solvent was removed from the crude mixture, then washed with 1 N HCl, H₂O and dried over Na₂SO₄ before subjecting to column chromatography, affording 2.27 g of pure **26** as a pale yellow powder in 40 % yield.

[α]_D²⁰ +2.6 (c 0.4, CH₂Cl₂).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.85-7.72 (m, 4H), 7.23 (d, 2H, *J* = 8.6 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 5.61 (s, 1H), 5.54 (dd, 1H, *J* = 9.6, *J* = 7.6 Hz), 4.66 (d, 1H, *J* = 5.2 Hz), 4.57 (dd, 2H, *J* = 14.4, *J* = 12 Hz), 4.12 (d, 1H, *J* = 9.3 Hz), 3.83 (s, 3H), 3.78-3.71 (m, 2H), 3.58 (d, 1H, *J* = 7.7 Hz), 1.89 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 170.4, 167.6, 159.5, 134.2, 131.7, 129.5, 129.5, 123.5, 114.0, 101.9, 81.3, 76.4, 71.5, 70.8, 67.8, 56.2, 55.3, 20.7.

HRMS (ESI): m/z calcd for $C_{24}H_{23}NO_8Na$ $[M+Na]^+$: 476.1321, found: 476.1337

2-Phthalimido-1,6-anhydro-2-deoxy-3-*O*-[(1*R*)-1-carboxyethyl]-4-*O*-*para*-methoxybenzyl- β -D-glucopyranose **26**

Compound **23** (5 mmol, 1 eq.) was dissolved in DCM:MeOH 3:2 (25 mL) at -20 °C and treated with NaOMe (1 mmol, 0.2 eq.) and stirred for 30 mins, after which the mixture was quenched with Amberlyst® 15 acidic resin. Upon neutralizing the mixture, the resin was filtered off and the solvent was evaporated. The crude mixture of **24** (3.6 mmol) was re-dissolved in THF, and treated with 3 Å molecular sieves, NaH (60 % in mineral oil) (21.6 mmol, 6 eq.) and (*S*)-(-)-bromopropionic acid. The mixture was heated up to 50 °C and stirred overnight. After which the base was quenched with the $NH_4Cl_{(aq)}$ and evaporated. The crude mixture was extracted with EtOAc multiple times. The combined organic phases were dried over Na_2SO_4 and the residue was recovered from rotary evaporator. The crude mixture was re-dissolved again in dry DMF then treated with CsF (18 mmol, 5 eq.) and MeI (18 mmol, 5 eq.) and stirred overnight at ambient temperature. After which, the mixture was diluted with EtOAc and washed with $NH_4Cl_{(aq)}$, H_2O and dried over Na_2SO_4 . Purification by flash column chromatography afforded 1.36 g of pure **26** as a white powder in 72 % yield (from **24**).

$[\alpha]_D^{20}$ -1.6 (c 0.4, CH_2Cl_2).

1H -NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89-7.71 (m, 4H), 7.29 (d, 2H, $J = 8.8$ Hz), 6.91 (d, 2H, $J = 8.8$ Hz), 5.53 (s, 1H), 4.66-4.48 (m, 3H), 4.44 (q, 1H, $J = 6.9$ Hz), 4.14-4.07 (m, 1H), 3.82 (s, 3H), 3.78-3.65 (m, 3H), 3.53 (t, 1H, $J = 3.6$ Hz), 3.21 (s, 3H), 1.22 (d, 3H, $J = 6.9$ Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.4, 1678.0, 159.6, 133.8, 132.3, 129.8, 129.3, 123.2, 114.1, 102.3, 85.7, 75.3, 75.1, 71.7, 67.6, 56.5, 55.3, 51.4, 29.7, 19.1.

HRMS (ESI): m/z calcd for $C_{26}H_{27}NO_9Na$ $[M+Na]^+$: 520.1584, found: 520.1579.

2-Phthalimido-1,6-anhydro-2-deoxy-3-*O*-[(1*R*)-1-carboxyethyl]- β -D-glucopyranose **28**

Compound **26** (1 mmol, 1 eq.) was dissolved in the mixture of CH₂Cl₂:H₂O 9:1 (2 ml) at 0 °C and treated with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (1.2 mmol, 1.2 eq.). The mixture was warmed up to ambient temperature and filtered off after 6 hs. The crude product was evaporated, re-dissolved in EtOAc and washed with NH₄Cl_(aq), water, brine and dried over Na₂SO₄. Purification by flash column chromatography afforded 0.33 g of pure **28** as a white powder in 88 % yield.

$[\alpha]_D^{20} +46.8$ (c 1.0, CH₂Cl₂).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.89-7.77 (m, 4H), 5.51 (d, 1H *J* = 11.4 Hz), 5.32 (s, 1H), 4.67 (dd, 1H *J* = 6.1, *J* = 1.6 Hz), 4.55 (br, 1H), 4.24 (q, 1H, *J* = 6.9 Hz), 4.09 (dd, 1H, *J* = 7.2, *J* = 1.3 Hz), 3.83-3.76 (m, 2H), 3.62 (d, 1H, *J* = 11.5 Hz), 3.59 (s, 3H), 1.41 (d, 3H, *J* = 6.9 Hz).

¹³C NMR (126 MHz, CDCl₃) δ (ppm) 173.0, 168.1, 134.6, 131.5, 123.8, 101.2, 78.9, 77.4, 74.3, 70.8, 64.9, 53.3, 52.1, 18.9.

HRMS (ESI): *m/z* calcd for C₁₈H₁₉NO₈Na [M+Na]⁺: 400.1008, found: 400.1019

2-Phthalimido-3-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→4)-2-phthalimido-1,6-anhydro-2-deoxy-3-*O*-[(1*R*)-1-carboxyethyl]-β-D-glucopyranose **30**

To a magnetically stirred DCM:toluene 0.5:1 (1.5 mL) solution of donor **29** (0.09 mmol, 1 eq.), AgOTf (3 eq., co-evaporated with toluene prior the addition) and 2,4,6-tri-*tert*-butylpyrimidine (3 eq.) were added at -20 °C. After which, to the mixture was added dropwise with 1 M DCM solution of dibutylboryl trifluoromethanesulfonate (2.2 eq.), then subsequently the temperature was lowered to -60 °C. After reaching set temperature, *p*-nitrobenzenesulfonyl chloride (1.2 eq.) was added, thereafter 5 mins the mixture was treated with acceptor **28** (1.2 eq.) dissolved in 0.5 ml of DCM. The temperature was elevated to -40 °C and stirred for 12 hs. After which the mixture was quenched with triethylamine (50 μL) and the inorganic materials were filtered

off. The crude product was washed with water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded 0.05 g of pure **30** as a white powder in 6 % yield.

$[\alpha]_D^{20}$ -22.8 (c 0.5, CH₂Cl₂).

¹H NMR (500 MHz, CDCl₃) δ (ppm) δ 7.84-7.66 (m, 8H), 7.08-6.98 (m, 5H), 5.46 (s, 1H), 5.43-5.37 (m, 1H), 4.61 (dd, 2H, $J = 66.7$, $J = 12.1$ Hz), 4.41 (q, 1H, $J = 6.9$ Hz), 4.26 (t, 1H, $J = 3.5$ Hz), 4.20-3.73 (m, 10H), 3.59-3.55 (m, 1H), 3.22 (s, 3H), 2.68-2.64 (m, 1H), 2.27 (d, 1H, $J = 7.5$ Hz), 1.27 (d, 3H, $J = 6.9$ Hz).

¹³C NMR (126 MHz, CDCl₃) δ (ppm) 168.0, 133.8, 132.2, 128.4, 127.9, 127.8, 123.2, 102.1, 96.0, 83.5, 79.1, 77.3, 77.2, 75.5, 74.9, 74.6, 74.3, 72.7, 67.8, 62.73, 56.1, 55.6, 51.5, 18.9.

HRMS (ESI): m/z calcd for C₃₉H₃₈N₂O₁₄Na [M+Na]⁺: 781.2221, found: 781.2215

2-Phthalimido-(3,4,6-tri-*O*-acetyl)-2-deoxy- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-1,6-di-*O*-acetyl-2-acetamido-2-deoxy-3-*O*-[(1*R*)-1-carboxyethyl]- β -D-glucopyranose **33**

Compound **20** (0.05 mmol, 1 eq.) was dissolved in Ac₂O (0.5 mL) at 0 °C and treated with BF₃·OEt₂ (0.25 mmol, 5 eq.). The mixture was warmed up to ambient temperature and stirred overnight. After which the acid was quenched with triethylamine (20 μ L) and the solvent was removed under reduced pressure. The crude product was re-dissolved in EtOAc and washed with water, brine and dried over Na₂SO₄. Purification on flash chromatography afforded 37 mg of pure **33** as a transparent oil in 94 % yield.

$[\alpha]_D^{20}$ +25.2 (c 1.0, CH₂Cl₂).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.86-7.76 (m, 5H), 6.36 (s, 1H), 5.81 (dd, 1H, $J = 10.5$ Hz, $J = 9.1$ Hz), 5.41 (d, 1H, $J = 8.4$ Hz), 5.20 (t, 1H, $J = 9.2$ Hz), 4.70 (q, 1H, $J = 6.9$ Hz), 4.51 (dd, 1H, $J = 12.4$, $J = 4.4$ Hz), 4.26 (dd, 1H, $J = 10.4$, $J = 8.4$ Hz), 4.17 (q, 2H, $J = 11.6$ Hz), 3.98 (t, 1H, $J = 9.3$ Hz), 3.91 (m, 2H), 3.81 (s, 3H), 3.57 (m, 3H), 2.09 (s, 6H), 2.05-1.96 (m, 9H), 1.85 (s, 3H), 1.50 (d, 3H, $J = 6.9$ Hz).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 176.5, 170.4, 170.0, 170.0, 169.6, 131.1, 97.8, 90.1, 75.2, 74.7, 72.1, 70.7, 70.6, 68.6, 61.7, 61.7, 55.2, 53.1, 52.4, 23.0, 20.9, 20.8, 20.7, 20.6, 20.34, 18.6.

HRMS (ESI): m/z calcd for $\text{C}_{36}\text{H}_{45}\text{N}_2\text{O}_{19}$ $[\text{M}+\text{H}]^+$: 809.2617, found: 809.2638

2-Phthalimido-(3,4,6-tri-*O*-acetyl)-2-deoxy- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-3-*O*-[(1*R*)-1-carboxyethyl]-6-*O*-acetyl- β -D-glucopyranose **34**

Compound **33** (0.019 mmol, 1 eq.) was dissolved in dry DMF and treated with $(\text{NH}_4)_2\text{CO}_3$ (0.19 mmol, 10 eq.) at 30 °C and stirred for 5 days. After which, solvent was removed under reduced pressure and the crude product was re-dissolved in EtOAc and washed with water, brine and dried over Na_2SO_4 . Purification on flash chromatography afforded 6 mg of pure **34** as a transparent oil in 43 % yield.

$[\alpha]_{\text{D}}^{20} +4.5$ (c 0.6, CH_2Cl_2).

^1H -NMR (400 MHz, CDCl_3) δ (ppm) 8.11 (br, 1H), 7.86 (br, 2H), 7.73-7.53 (m, 2H), 5.82 (dd, 1H, $J = 10.6$, $J = 9.0$ Hz), 5.60 (br, 1H), 5.42 (d, 1H, $J = 8.3$ Hz), 5.19 (t, 1H, $J = 9.6$ Hz), 4.69 (q, 1H, $J = 6.9$ Hz), 4.49 (dd, 1H, $J = 12.4$, $J = 4.4$ Hz), 4.31- 4.14 (m, 3H), 3.93 (m, 2H), 3.80 (s, 3H), 3.80-3.56 (m, 4H), 3.04 (s, 1H), 2.09 (d, 6H, $J = 7.0$ Hz), 2.03 (br, 6H), 1.85 (s, 3H), 1.51 (d, 3H, $J = 7.0$ Hz).

^{13}C NMR (126 MHz, CDCl_3) δ (ppm) 130.9, 128.8, 97.3, 77.2, 74.7, 70.6, 68.7, 68.6, 68.2, 61.7, 55.1, 54.8, 52.4, 38.8, 30.4, 29.7, 28.9, 23.8, 23.0, 20.8, 20.6, 20.4, 18.6, 11.0.

HRMS (ESI): m/z calcd for $\text{C}_{34}\text{H}_{43}\text{N}_2\text{O}_{18}$ $[\text{M}+\text{H}]^+$: 767.2511, found: 767.2518

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