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Reagent Controlled Synthesis of 1,2-cis-Oligosaccharides

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Reagent Controlled Synthesis of 1,2-*cis*-Oligosaccharides

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To my family

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List of abbreviations

Ac	acetyl	DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
All	allyl	DTBS	di- <i>tert</i> -butylsilylidene
aq.	aqueous	eq.	molar equivalent
Ar	aryl	Et	ethyl
Arom	aromatic	GATED	proton decoupling applied only during relaxation
BAIB	(diacetoxyiodo)benzene	Gal	galactose
Bn	benzyl	Glc	glucose
bs	broad singlet	GlcA	glucuronic acid
Bu	butyl	GlcN	glucosamine
Bz	benzoyl	GlcN ₃	2-azido-2-deoxy glucose
C	chair	GlcNAc	<i>N</i> -acetyl glucosamine
cat.	catalytic	h	hour(s)
CBz	carboxybenzyl	HFIP	hexafluoro- <i>iso</i> -propanol
COSY	correlation spectroscopy	HMBC	heteronuclear multiple-bond correlation spectroscopy
CSA	camphor-10-sulfonic acid	HPLC	high performance liquid chromatography
Cy	cyclohexyl	HRMS	high-resolution mass spectroscopy
δ	chemical shift (ppm)	HSQC	heteronuclear single quantum coherence
d	doublet	IR	infrared
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	<i>J</i>	coupling constant
DCE	1,2-dichloroethane	KIE	kinetic isotope effect
DCM	dichloromethane	LC-MS	liquid chromatography-mass spectrometry
dd	double doublet	LG	leaving group
DFT	density function theory	M	molar
DIPEA	diisopropylethylamine	m	multiplet
DIPF	<i>N,N</i> -diisopropylformamide	m/z	mass over charge ratio
DMA	<i>N,N</i> -dimethylacetamide	min	minutes
DMAP	4-dimethylaminopyridine		
DMF	<i>N,N</i> -dimethylformamide		
DMSO	dimethylsulfoxide		
DPSO	diphenyl sulfoxide		
dq	double quartet		
dt	double triplet		

Man	mannose	S _N 1	uni-molecular	nucleophilic
ManA	mannuronic acid		substitution	
Me	methyl	S _N 2	bi-molecular	nucleophilic
MPF	<i>N</i> -methyl- <i>N</i> -phenylformamide		substitution	
M.S.	molecular sieves	SSIP	solvent-separated ion pair	
Nap	2-methylnaphthyl	t	triplet	
NBS	<i>N</i> -bromosuccinimide	TBAF	tetrabutylammonium fluoride	
NFM	<i>N</i> -formylmorpholine	TBAB	tetrabutylammonium bromide	
NFP	<i>N</i> -formylpiperidine	TBAI	tetrabutylammonium iodide	
NIS	<i>N</i> -iodosuccinimide	TBS	<i>tert</i> -butyldimethylsilyl	
NMR	nuclear magnetic resonance	TBDPS	<i>tert</i> -butyldiphenylsilyl	
NOESY	nuclear Overhauser effect spectroscopy	TCA	trichloroacetyl	
	Nu nucleophile	TES	triethylsilyl	
<i>p</i>	para	TEMPO	2,2,6,6-tetramethylpiperidine	
PG	protection group	TFA	trifluoroacetic acid	
Ph	phenyl	THF	tetrahydrofuran	
Phth	phthaloyl	TLC	thin layer chromatography	
PMB	4-methoxybenzyl	TMS	trimethylsilyl	
ppm	parts per million	TMSI	trimethylsilyl iodide	
q	quartet	TMU	tetramethylurea	
rt	room temperature	Tol	tolyl; 4-methylphenyl	
R _f	retention factor	td	triple doublet	
RRV	relative reactivity value	tt	triple triplet	
s	singlet	TTBP	2,4,6-tri- <i>tert</i> -butylpyrimidine	
sat.	saturated	UV	ultraviolet	

Chapter 1

Modulating Glycosylation with Additives and Its Application in Synthesis of Oligosaccharides

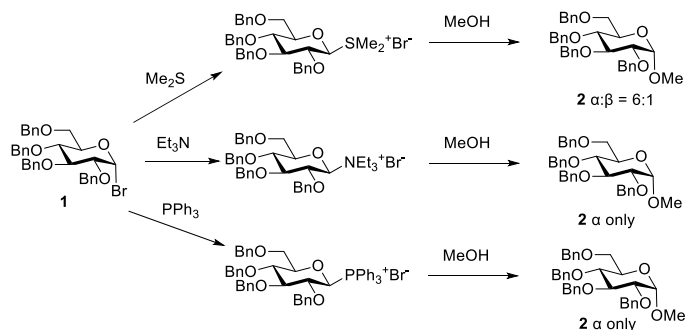
1. Introduction

Carbohydrates, polysaccharides and glycoconjugates are widely found in nature, and they play crucial roles in diverse biological processes such as cellular adhesion, migration, development, disease progression, pathogen detection, and immune response.^[1] To better understand the mechanism of action of these biomolecules, well-defined oligosaccharides and glycoconjugate libraries need to be investigated.^[2] However, extracting well defined oligosaccharides from natural sources can be extremely difficult, if not impossible, because of the heterogeneity of many naturally occurring oligosaccharides/glycoconjugates. Therefore, chemical synthesis has become an important method to provide these compounds.

The key step in oligosaccharide synthesis is the stereoselective formation of the glycosyl bond through the union of a donor and acceptor building blocks.^[3] Even after 140 years from the first chemical glycosylation reaction, reported by Arthur Michael and Emil Fischer,^[4] this step still presents a great challenge. In a glycosylation reaction, a new stereocenter is formed and while 1,2-trans glycosides can generally be reliably formed using a participating protecting group (such as an acyl type protecting group), the stereoselective formation of 1,2-cis glycosides and linkages of 2-deoxy sugars still presents a great challenge.^[5] To solve these problems, various strategies have been developed^[6] including the use of participating solvents,^[7] coordinating metal catalysts^[8], organocatalysis,^[6d, 9] remote participation by protecting groups placed at the C3, C4 and/or C6 positions,^[10] cyclic protecting group, such as benzylidene^[11] and silylidene groups,^[12] and chiral auxiliaries at the C2 position.^[5c, d, 13] However, no general solution exists yet, for the stereoselective construction of all types of glycosidic bonds. One of the main reasons for the lack of a universal stereoselective glycosylation method is the varying reactivity of different donor-acceptor glycoside combinations. The immense diversity in functional and protecting group patterns on the densely functionalized carbohydrate rings, creates an enormous diversity in reactivity in glycosylation systems and can make it difficult to translate a given glycosylation procedure from one system to another. In this regard, the introduction of nucleophilic additives to modulate the condensation reaction has been an important step forwards as this opens up the way to match donor and acceptor reactivity. This Thesis describes the use of additives for the stereoselective construction of 1,2-cis-glycosidic linkages, with a focus on glucosyl and galactosyl bonds in the context of oligosaccharide assembly. This introductory Chapter provides an overview of additive modulated glycosylations and glycosylation strategies developed to date.

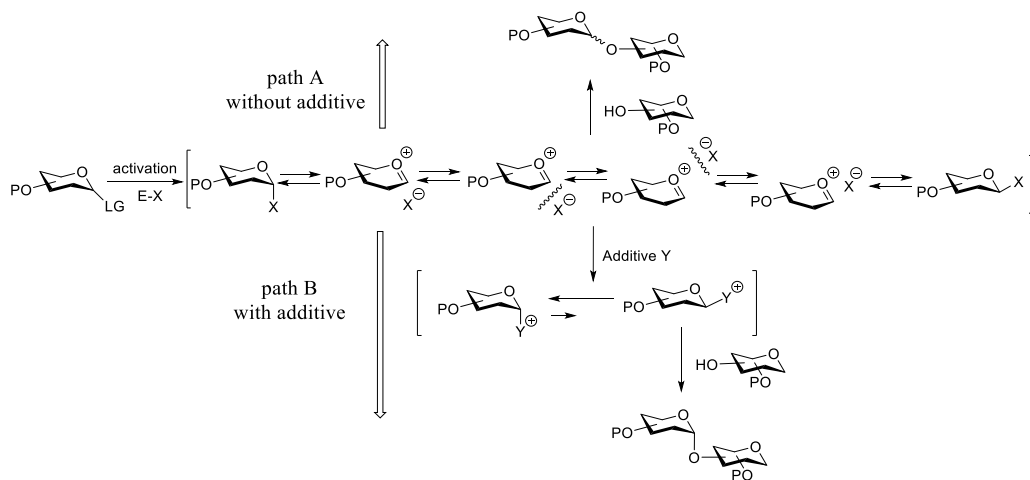
2. The proposed mechanism of additive mediated glycosylation reactions

The first glycosylation reactions using nucleophilic additives to modulate the selectivity dates back to 1973 (Scheme 1).^[14] West and Schuerch reported that the methanolysis of α -glucosyl bromide **1**, modulated by dimethyl sulfide (Me₂S), triethylamine (Et₃N), and triphenyl phosphine (Ph₃P) nucleophiles proceeded in a stereoselective manner to form the α -glycoside **2** through the intermediacy of the β -glucosyl sulfonium, ammonium and phosphonium adducts, respectively. West and Schuerch reasoned that the electropositive anomeric substituents would occupy an equatorial position for steric reasons. Then the direct S_N2-type inversion of the anomeric leaving group should lead to the desired 1,2-cis-linked products. The reactions of the ammonium and phosphonium ions indeed proceeded in a stereoselective manner, while the sulfonium ion was proved to be somewhat less selective ($\alpha/\beta = 6:1$). After these pioneering experiments, various nucleophilic additives have been probed, including sulfides, sulfoxides, phosphine and phosphine oxides, amides and formamides and iodide based reagents and several stereoselective 1,2-cis-glycosylation procedures have been reported based on their use.



Scheme 1. Use of Me_2S , Et_3N , and Ph_3P as additive modulate glycosylation.

There isn't one general reaction mechanism to describe all glycosylation reactions, as many factors affect the glycosylation reaction, including the nature of the substrates, reagents, solvent, concentration, temperature and pressure.^[15] The mechanism of a glycosylation reaction can be described with the continuum of reaction pathways depicted in Scheme 2 (path A). Upon activation of the leaving group with an electrophilic activator the donor can be transformed into a series of reactive intermediates, including covalent species or contact/solvent-separated ion pairs. The nature of these species enables different reaction pathway ranging from $\text{S}_{\text{N}}1$ - to $\text{S}_{\text{N}}2$ -type substitutions. In the presence of a nucleophilic additive, these intermediate species will react with the additive to form an intermediate adduct (Scheme 2, path B). In general, the axial adduct is formed predominantly (and can often be observed and characterized by spectroscopic techniques such as NMR). The use of (a large) excess of the external nucleophilic additive however allows for the formation of sufficient amounts of the more reactive equatorial adduct, which can react to provide the 1,2-*cis*-linked products.



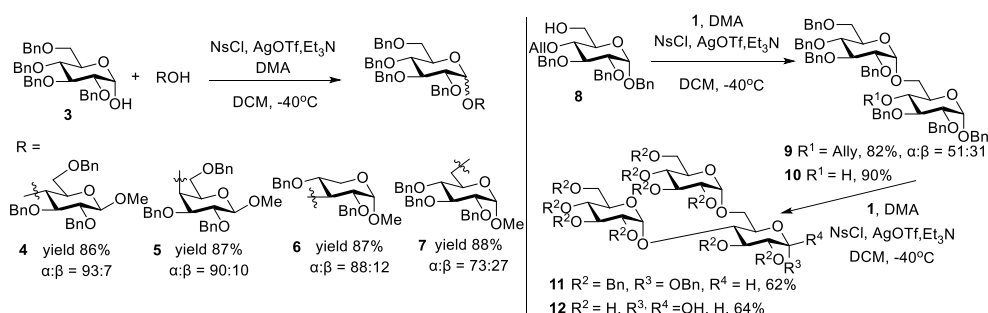
Scheme 2. Proposed continuum of reaction mechanisms in the presence or absence of external nucleophilic additives.

According to this mechanism, and the use throughout this Thesis, the “additive” in glycosylation reactions, is a nucleophilic reagent that plays an important role in the glycosylation mechanism, but that cannot activate (or catalyze) the glycosylation reaction independently. In the next sections different nucleophilic additives (or “modulators”) will be discussed, including amide, phosphate and sulfur reagents as well as quaternary ammonium halides.

3. Glycosylations modulated with amide reagents

3.1 *N,N*-dimethylacetamide (DMA)

The first use of an amide reagent to modulate glycosylation reactions can be traced to 1982, when Koto and coworkers reported DMA modulated glucosylations to proceed with good α -selectivity.^[16] They reported that reactions of 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose **3** with secondary and primary glucosyl acceptors formed α -glycosides, when a four component active system consisting of *p*-nitrobenzenesulfonyl chloride (NsCl), silver trifluoromethanesulfonate (AgOTf), *N,N*-dimethylacetamide (DMA, 2.5 eq for secondary and 5.0 eq for primary alcohol acceptors), and triethylamine (Et₃N) in dichloromethane (DCM), was used. The use of the corresponding ternary mixture (NsCl, AgOTf, Et₃N) without DMA led to the predominant formation of β -glucosides. Koto and coworkers speculated that the stereochemical course of the reaction in the presence of DMA, was due to the intermediacy of the β -imidinium ion. Besides a small set of disaccharides they also generated a branched trisaccharide **12** using the NSDT-system (Scheme 3).^[17]

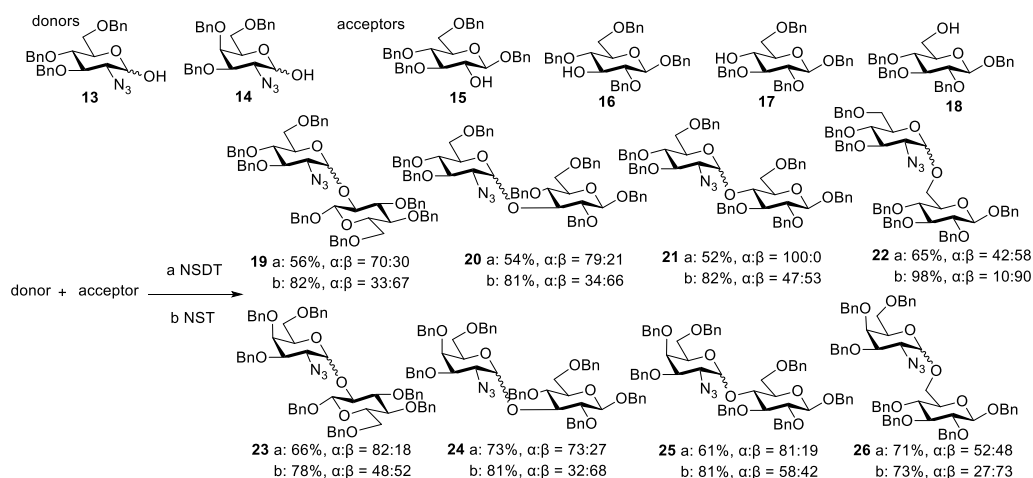


Scheme 3. Glycosylation with DMA.

Next, Koto and coworkers explored the NSDT (NsCl, AgOTf, DMA and Et₃N) and NST (NsCl, AgOTf, and Et₃N) systems with more substrates^[18] including 2-azido-sugar donors **13** and **14**, in combination with glucosyl acceptors (**15**–**18**, Scheme 4).^[19] The use of the NSDT system led to the formation of more α -product than the use of the NST system. The 1,2-*cis*-selectivity of the glycosylations involving the primary alcohol acceptors was generally lower than the glycosylations of the (less reactive) secondary alcohol acceptors.

3.2 *N,N*-dimethylformamide (DMF)

N,N-dimethylformamide (DMF) is not only an excellent solvent for reactions involving polar reagents and reaction intermediates, it can also serve as the source for key reactive intermediates, such as the Vilsmeier-Haack reagent.^[20] It has been widely used as an additive in glycosylation reactions, after Mong's systematically study of its use as a glycosylation additive in 2011^[21] owing to the good selectivity it provides. Dourtoglou and Gross were the first to describe the use of DMF in glycosylation reactions, when they explored the Vilsmeier-Haack reagent, formed from DMF and oxalyl chloride, to effect glycosylation reactions.^[22] They described the detection of α - and β -furanosyl imidinium adducts by NMR spectroscopy. In 1984, DMF was used as additive for the first time by Koto and coworkers, but only to serve as reference for the DMA system (*vide supra*).^[17] Later glycosyl imidinium adducts were detected by NMR by Kobayashi in glycosylation reactions, in which lactol donors were activated using Appel reagents (Ph_3P , CBr_4).^[23]

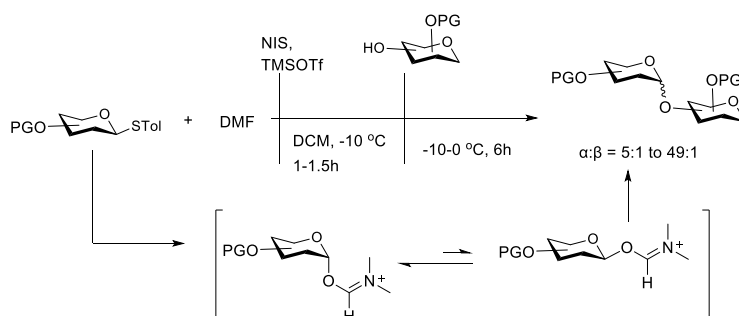


Scheme 4. Glycosylations of 2-azido-donors and glucosyl acceptors using the NSDT and NST system.

In 2009, Mong and co-workers noted that DMF (present as a contamination in the reaction originating from the donor glycoside) increased the α -selectivity of a Koenig-Knorr glycosylation.^[24] Inspired by these results, Mong and co-workers systematically evaluated the use of DMF as an additive in glycosylation reactions using thio-glycosyl donors and a pre-activation protocol as depicted in Scheme 5.^[21]

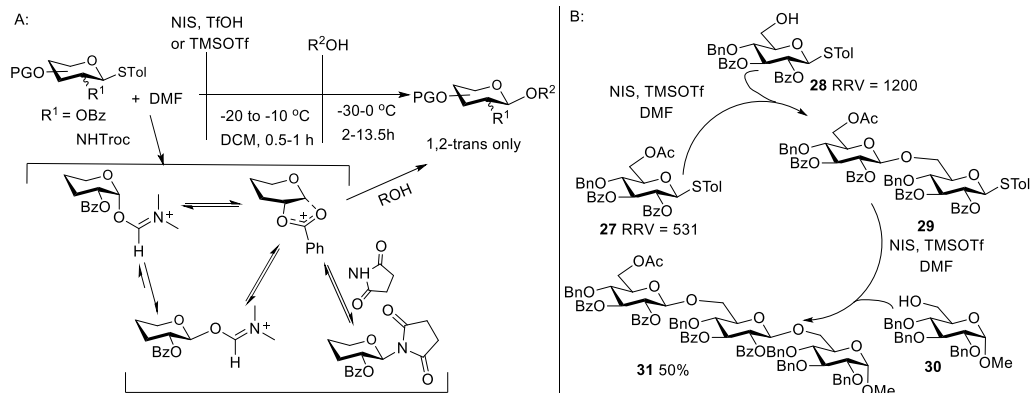
In this protocol, the thio-donor first mixed with DMF prior to the addition of NIS and TMSOTf. After complete activation of the thio-donor (1-1.5 h), the acceptor was added. The substrate scope of this protocol was shown to be quite broad with α -selectivity ranging from 5:1 to 49:1. The

authors only detected the α -glycosyl imidinium ion by NMR spectroscopy when reactive donor glycosides were used. In later research, Mong and co-workers also found β -glycosyl imidinium ions, when disarmed donors were used^[25] (Scheme 6, 9 and 10) and corresponds to the results of Chapter 6. Based on these glycosylations, Mong and coworkers proposed the mechanism depicted in Scheme 5, in which an equilibrium is set up between α - and β -imidinium ions, in which the latter is more reactive than the former and thus substituted in a selective manner to provide the α -glycoside products. They coined the term DMF-modulated glycosylations for this type of reactions.



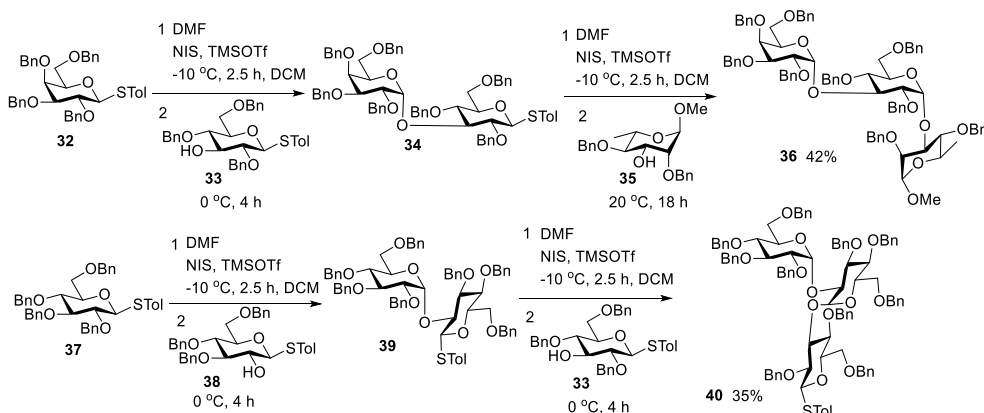
Scheme 5. Glycosylations mediated by DMF.

After this initial work, Mong and co-workers explored whether DMF can react with dioxonium ions, formed through neighboring group participation from a 2-acyl donor, to modulate the glycosylations of disarmed donors, giving *trans*-selectivity. They investigated the glycosylation of disarmed donors with armed acceptors in the presence of DMF (Scheme 6A).^[25a] When 1.2 eq DMF was used, the desired products were obtained with good yield and complete *trans*-selectivity. In an NMR study, α - and β -glucosyl imidinium adducts, and β -glucosyl *N*-succinimide were detected with a ratio of 1:7:1. Although the β -adducts were shown to be the major species in the equilibrium, the *trans*-products were obtained exclusively. Therefore, the authors proposed the dioxolenium ion to be the key player in the glycosylation reaction. This “disarmed-armed” glycosylation strategy enables the synthesis of oligosaccharide in a one pot fashion, where the order of the coupling partners does not depend on decreasing reactivity as it does in “traditional” armed-disarmed one-pot glycosylation sequences. To prove the utility of the method, three trisaccharides were synthesized using the disarmed-armed glycosylation strategy (Scheme 6B).



Scheme 6. Disarmed donors glycosylate armed acceptors in the presence of DMF.

Building on the application of DMF-modulation in pre-activation based glycosylation reactions, Mong and co-workers have developed iterative one-pot glycosylation methods to sequentially construct α,α -, β,α -, and α,β -linkages using one-pot glycosylation protocols.^[26] Several saccharides were synthesized using DMF to modulate the stereoselectivity illustrating the applicability of their method in the synthesis of oligosaccharides (Scheme 7).^[26] And a tetrasaccharide glycolipid from *Meiothermus taiwanensis* was assembled using a one-pot glycosylation protocol, in which the α -linked disaccharide building block was prepared using DMF-mediated reaction conditions.^[27]

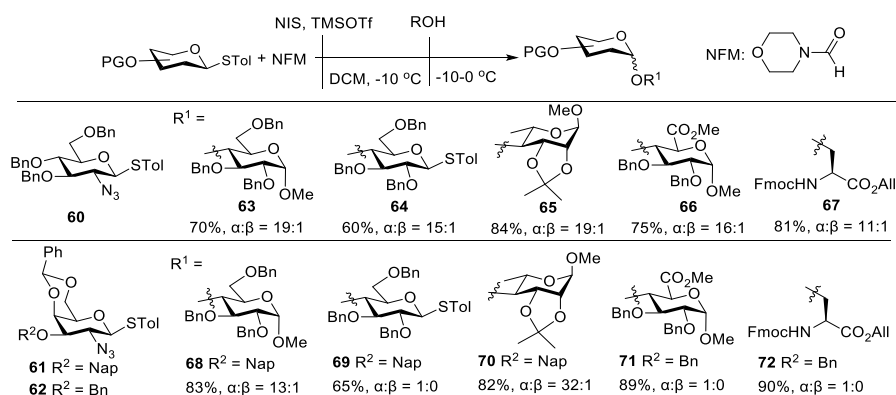


Scheme 7. One-pot α -glycosylations with DMF modulation.

In 2014, Mong's group reported an α -selective glycosylation method for 2-deoxy- and 2,6-dideoxythioglycoside donors based on DMF modulation (Scheme 8A).^[28] As 2-deoxy-donors are more reactive than fully oxygenated donors, it is more challenging to control the selectivity to generate either α - or β -glycosides. In this study, the desired glycoside products were obtained with an excellent $\alpha:\beta$ ratio, ranging from 7:1 to α only. A tetrasaccharide composed of 2-deoxyglucosides and a trisaccharide built up from 2-deoxygalactosides were assembled using

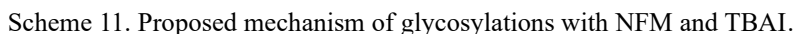
3.3 *N*-formylmorpholine (NFM)

Although the scope of donors and acceptors is quite broad in glycosylations modulated by DMF, it presents limitation for highly reactive building blocks such as primary alcohol acceptors and donor glycosides that are less reactive, such as 2-azido-2-deoxyglycosides. To overcome the low reactivity of the latter systems, a new additive, *N*-formylmorpholine (NFM), was introduced by Mong's group in 2013 (Scheme 10).^[25b] Glycosylations of 2-azido-glucosyl and galactosyl donors **60-62** were explored in combination with various additives, and the use of 16 equivalents of NMF proved to be the most effective to provide the desired products with optimal α -selectivity and yield. With NMR spectroscopy, both α - (major) and β -glycosyl (minor) imidium adducts were detected using DMF, NMF or di-*iso*-propylformamide (DIPF).



Scheme 10. Glycosylation using NFM-modulation.

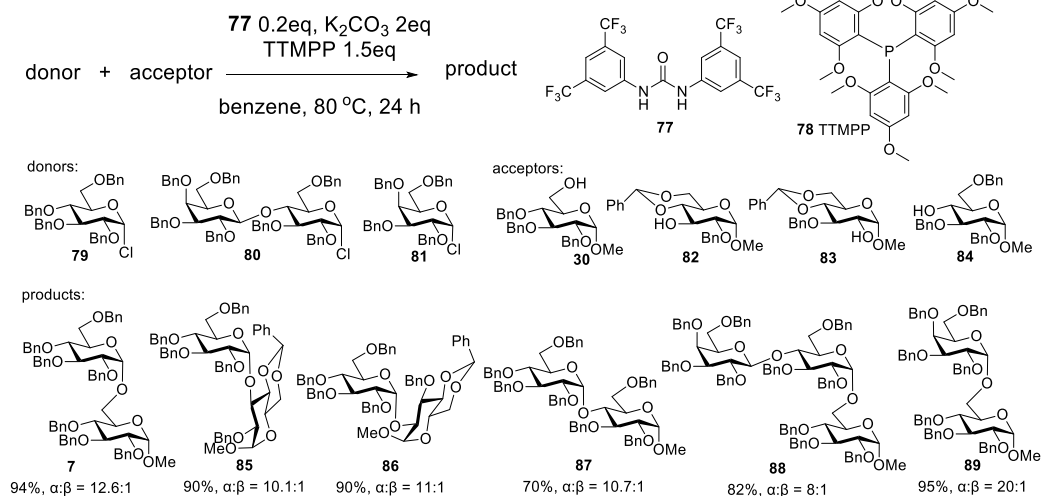
Mong's group found that DMF or NFM-modulation did not work well for glycosylations involving reactive acceptors like primary alcohols. Therefore they introduced the combination of NFM and TBAI in glycosylations of thio-donors with primary alcohol acceptors in 2017.^[25c] Various building blocks including 2-azido-2-deoxyglycosyl donors were examined under these conditions and found to provide excellent α -selectivity. The mechanism of the reactions was explored using low temperature NMR to detect potential reactive species. Glycosyl iodides were formed after the glycosyl imidinium adducts were treated with TBAI and therefore they proposed the mechanism depicted in Scheme 11A. Glucosyl trisaccharide **76** was synthesized using these conditions (Scheme 11B).



Other amide additives that have been used to steer the stereoselectivity of glycosylation reactions include *N,N*-diisopropylformamide (DIPF),^[25b] tetramethylurea (TMU),^[23b, 25b, 30] *N*-formylpiperidine (NFP),^[25b, 30a] and *N*-methyl-*N*-phenylformamide (MPF). They all play a similar role as DMF in the reported glycosylation reactions, but have been found to be less selective or provide lower yields.

Many different phosphine reagents have been used in glycosylation reactions, as catalyst,^[31] ligand^[32] or additive to influence the stereochemistry. Here below, only phosphine or phosphine oxide reagents that have been used as additives are introduced. The use of (chiral) phosphoric acid catalysis and phosphine ligands in transition metal catalyzed glycosidic bond forming reactions has recently been reviewed.^[6d]

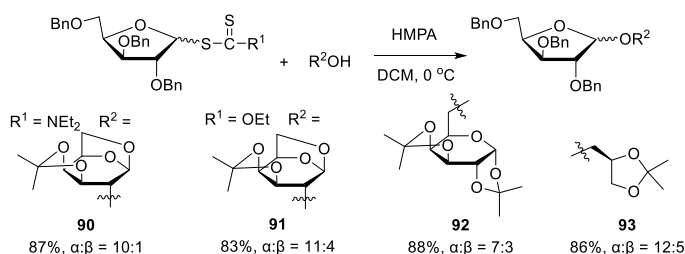
The use of phosphine additives was first reported in 1973, as described above (Scheme 1).^[14] In this study per-benzyl protected glucosyl bromide was coupled with methanol in the presence of Ph_3P to stereoselectively provide the α -product. Ye and co-workers explored various phosphine additives in glycosylations of glucosyl chlorides, activated by urea **77** (Scheme 12).^[33] They found tri-(2,4,6-trimethoxyphenyl)-phosphine (TTMPP) **78** to be the best additive, providing glycosylation reactions with excellent α -selectivity ($\alpha:\beta = 8:1$ to $20:1$) as shown in Scheme 12.



Scheme 12. Glycosylations Modulated by TTMP.

4.2 Phosphine oxide reagents

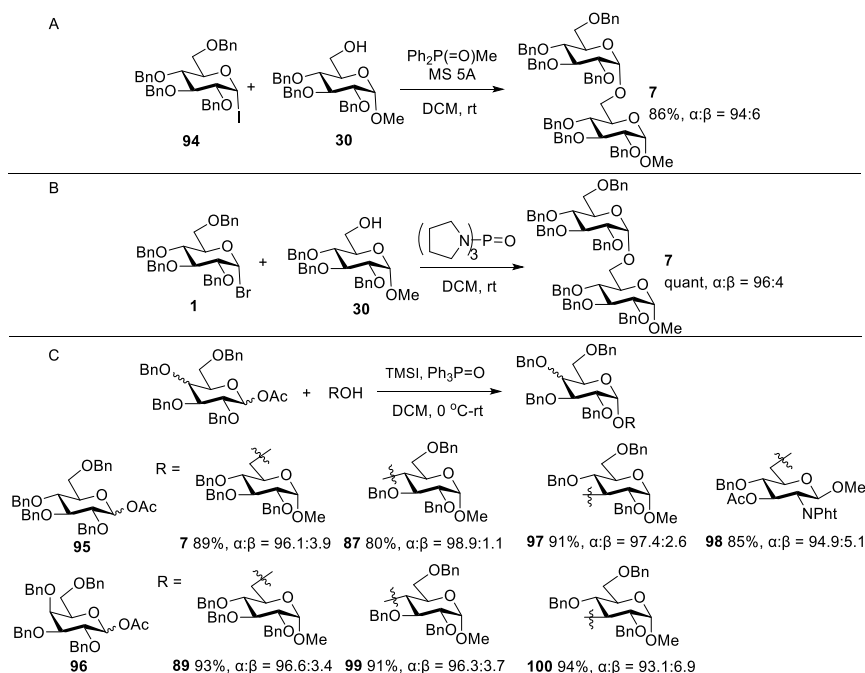
Phosphine oxide additives have been widely explored to synthesize 1,2-*cis*-glycosides. The first publication on the use of phosphine oxide as an additive dates back to 1997. Bogusiak and Szeja reported the glycosylation of *N,N*-diethyl *S*-(2,3,5-tri-*O*-benzyl-D-xylofuranosyl)-dithiocarbamate and 1,6-anhydro-3,4-*O*-isopropylidene- β -D-galactopyranose using hexamethylphosphoric triamide (HMPA) as additive (Scheme 13).^[30b] The desired disaccharide was obtained in 87% yield with good stereoselectivity ($\alpha:\beta = 10:1$). When *O*-ethyl *S*-(2,3,5-tri-*O*-benzyl-D-xylofuranosyl)-dithiocarbonate was used as donor, the selectivity decreased.



Scheme 13. Glycosylations using HMPA as additive.

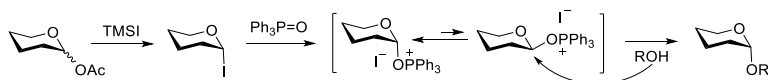
Mukaiyama and co-workers also systematically studied the application of various phosphine oxide additives, including $\text{Ph}_2\text{P}(=\text{O})\text{Me}$, $\text{Bu}_3\text{P}=\text{O}$, $\text{Ph}_3\text{P}=\text{O}$, HMPA, tripyrrolidinophosphine oxide and $(\text{PhO})_3\text{P}=\text{O}$.^[34] Three kinds of donor glycosides, iodides, bromides and acetates, were explored with different acceptors in the presence of the phosphine oxides. First, Mukaiyama group found that glucosyl iodides **94** could be coupled with 2,3,4-tri-*O*-benzyl-D-

glucopyranoside in the presence of $\text{Ph}_2\text{P}(=\text{O})\text{Me}$ to form the disaccharide with excellent α -selectivity (Scheme 14A). Because glycosyl iodides are generally quite unstable, they switched to use the more stable glycosyl bromides. It was found that tripyrrolidinophosphine oxide performed best as a nucleophilic additive, promoting glycosylations to proceed with excellent yield and selectivity. Different building blocks were investigated and all found to react with excellent yield and selectivity (Scheme 14B). To further improve on the protocol, they explored glycosylations of glycosyl acetates **95** and **96**, that were activated by TMSI, to provide the anomeric iodides *in situ*, in the presence of $\text{Ph}_3\text{P}=\text{O}$ (Scheme 14C).



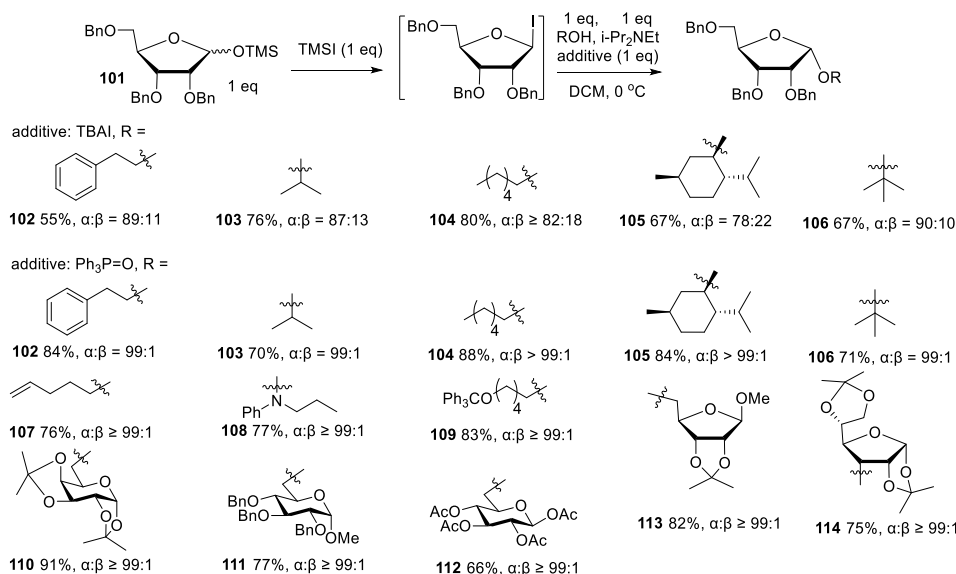
Scheme 14. Glycosylations of glycosyl acetate with phosphine oxide additives.

Mukaiyama and co-workers also studied the mechanism of glycosylation modulated by TMSI- $\text{Ph}_3\text{P}=\text{O}$. The proposed mechanism is depicted in Scheme 15. First, a glycosyl iodide is formed from the glycosyl acetate donor and TMSI which is then treated with the phosphine oxide to form the intermediate adduct. In line with the general additive controlled glycosylation mechanism, described in Scheme 2, the incoming acceptor then attacks the more reactive β -adduct to afford the α -product. Mukaiyama and co-workers tried to detect the glycosyl phosphonium iodide as the key intermediate adduct, but were unable to find this by NMR spectroscopy. That may indicate that only a very small amount of the glycosyl phosphonium iodide is formed or that the phosphine oxide only serves as a catalyst to assist in the formation of a β -iodide species.



Scheme 15. Proposed mechanism for glycosylations modulated by TMSI- $\text{Ph}_3\text{P}=\text{O}$.

In 2014, Oka and co-workers applied TMSI- $\text{Ph}_3\text{P}=\text{O}$ in the glycosylation of 1-*O*-trimethylsilyl-2,3,5-tri-*O*-benzyl-D-ribofuranose **101** to form α -ribofuranosides.^[35] The desired products were obtained in excellent yield with good α -selectivity (Scheme 16). They compared the TMSI- $\text{Ph}_3\text{P}=\text{O}$ conditions with the TMSI-TBAI conditions reported by Gervay in 1999^[36] and found that both the yield and α -selectivity decreased using the TMSI-TBAI conditions. The authors also tried to detect the glycosyl phosphonium iodide but did not succeed.

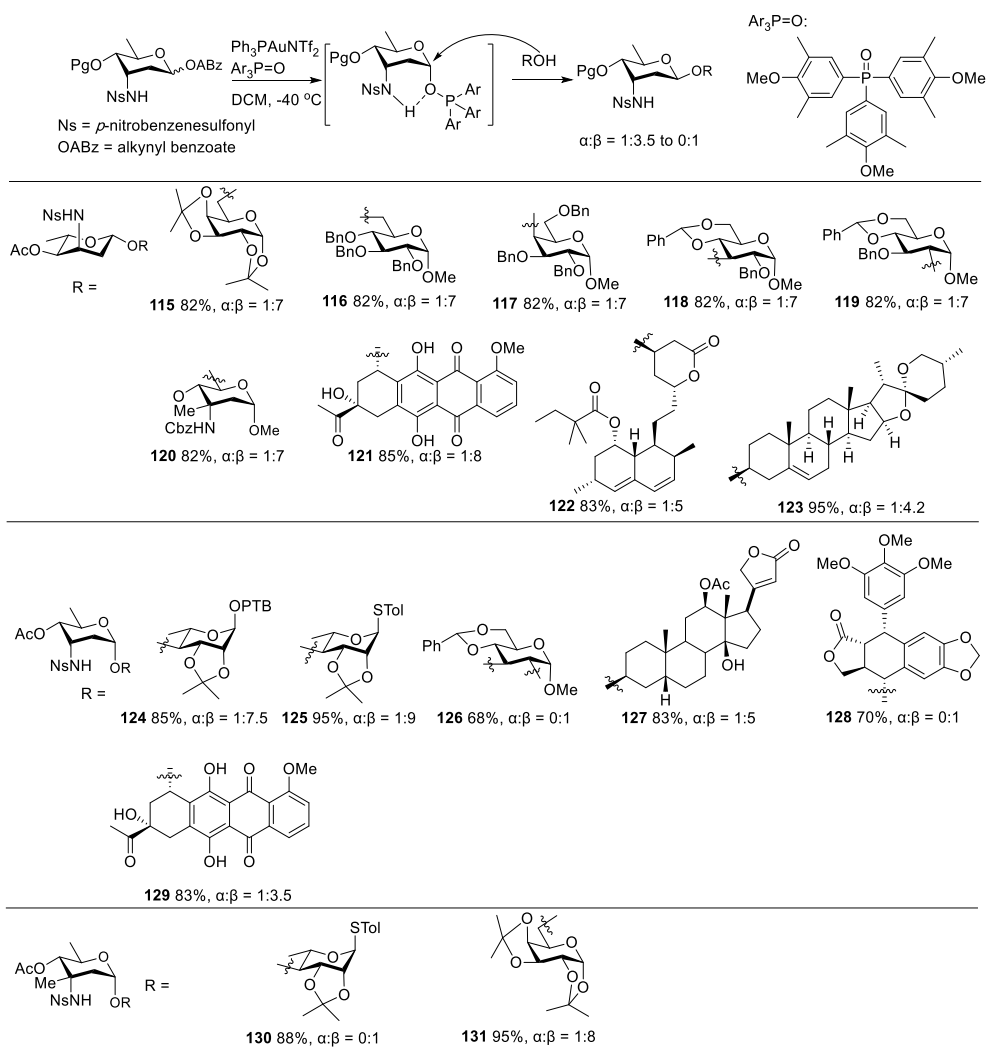


Scheme 16. Ribofuranosylation using TMSI- $\text{Ph}_3\text{P}=\text{O}$ activation.

In 2016, Wang and co-workers reported glycosylations of glycals using TMSBr- $\text{Ph}_3\text{P}=\text{O}$ activation conditions to form α -2-deoxyglycosides.^[37] They explored different additives, such as DMF, dimethyl sulfide (DMS), 2,4,6-tri-*tert*-butylpyridine (TTBP), triphenylphosphine (TPP), trimethyl phosphine oxide (TMPO) and $\text{Ph}_3\text{P}=\text{O}$, and found $\text{Ph}_3\text{P}=\text{O}$ to be the best one. It was reported that armed and disarmed glucal and galactal acceptors could be used to provide the desired products with good yield and selectivity.

Very recently, Wan and co-workers reported a β -selective glycosylation procedure for 3-amino-2,3,6-trideoxy sugars, using gold catalysis and phosphine oxide additives (Scheme 17).^[38] It was found that a nosyl protecting group was crucial to the outcome of the glycosylation reactions. The mechanism proposed by Wan and co-workers, differs from the TMSI- $\text{Ph}_3\text{P}=\text{O}$ system, as it invokes a hydrogen bond between the amino group and oxygen of $\text{Ph}_3\text{P}=\text{O}$ interacting with the

anomeric carbon on the α -face. The desired products were obtained with good selectivity (β : α = 3.5:1 to 1:0) and yield.



Scheme 17. Proposed mechanism of glycosylations of 3-amino-2,3,6-trideoxy sugars.

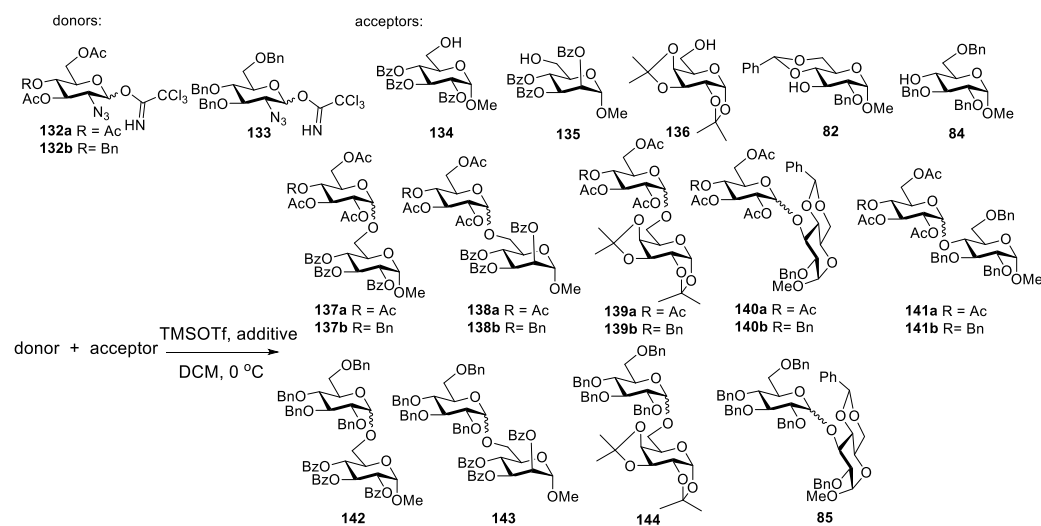
5. Glycosylations modulated with sulfur additives

5.1 Thio-ether additives

As described above, the first glycosylation using a thio-ether as additive was reported by West and Schuerch in 1973 (Scheme 1).^[14] Diethyl sulfide was applied in the glycosylation of glucosyl bromide **1** to afford methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **2** in 86% yield with a 86:14 α : β ratio. After 34 years, Boons and coworkers reported on the glycosylation of 2-azido-2-

deoxy-glucosyl trichloroacetimidates using PhSEt or thiophene as additive,^[39] inspired by the success of sulfur based C2-chiral auxiliaries^[13, 40] for 1,2-*cis*-glycosylations. The desired disaccharides were obtained with excellent yields and selectivity when using disarmed donors in the presence of PhSEt or thiophene (Table 1). The 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl trichloroacetimidate donor **133** gave poor α -selectivity because of the high reactivity of this donor. It was shown that a β -substituted anomeric sulfonium ion was formed upon activation of donor in the presence of PhSEt.

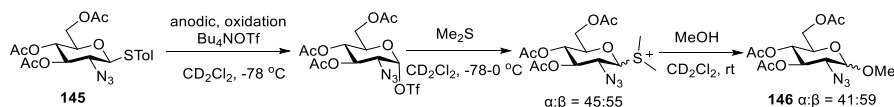
Table 1. Glycosylations of 2-azido-2-deoxy-glucosyl donors with PhSEt or thiophene.



entry	donor	acceptor	additive	product	yield %	α : β
1			none		92	8:1
2	132a	134	PhSEt	137a	94	20:1
3			thiophene		91	1:0
4			none		85	10:1
5	132a	135	PhSEt	138a	92	14:1
6			thiophene		95	18:1
7			none		87	2:1
8	132a	136	PhSEt	139a	92	5:1
9			thiophene		95	14:1
10	132a	82	none	140a	56	10:1
11			thiophene		60	15:1
12	132a	84	none	141a	40	1:0
13			thiophene		43	1:0
14	132b	134	none	137b	90	12:1
15			thiophene		93	20:1
16			none		95	10:1

17	132b	135	thiophene	138b	92	20:1
18	132b	136	none	139b	98	10:1
19			thiophene		96	15:1
20	132b	82	none	140b	52	11:1
21			thiophene		50	15:1
22	132b	84	none	141b	35	1:0
23			thiophene		34	1:0
24	133	132	none	142	80	3:1
25			thiophene		80	3:1
26	133	134	none	143	83	3:1
27			thiophene		81	4:1
28	133	135	none	144	95	2:1
29			thiophene		96	2:1
30	133	82	none	85	45	2:1
31			thiophene		48	1:1

Encouraged by Boons' aforementioned work, Yoshida and coworkers studied the role of Me₂S in glycosylation reactions, in which the thioglycosides were electrochemically activated, using low temperature NMR (Scheme 18).^[41] To this end, the glycosyl triflate formed from 2-azido-3,4,6-tri-acetyl-glucosyl donor **145** was treated with Me₂S in CD₂Cl₂. The intermediate sulfonium adduct was formed as a mixture of α : β -anomers in a 45:55 ratio. The anomeric composition did not change upon varying the temperature from -80 °C to 0 °C. When methanol was added to the solution at room temperature, the methyl glycoside **146** was obtained as an anomeric mixture (α : β = 41:59), indicating that the α -glycosyl sulfonium ion is somewhat more reactive than the β -glycosyl sulfonium ion and that an *in situ* anomerisation scenario operates to some extent. Yoshida and coworkers also found that some glycosyl sulfonium ions, such as the ion made from a 2-*N*-phthalimide-3,4,6-tri-acetylglucosyl thio-donor and Me₂S, can be stored as stable reagents for glycosylation.^[42]

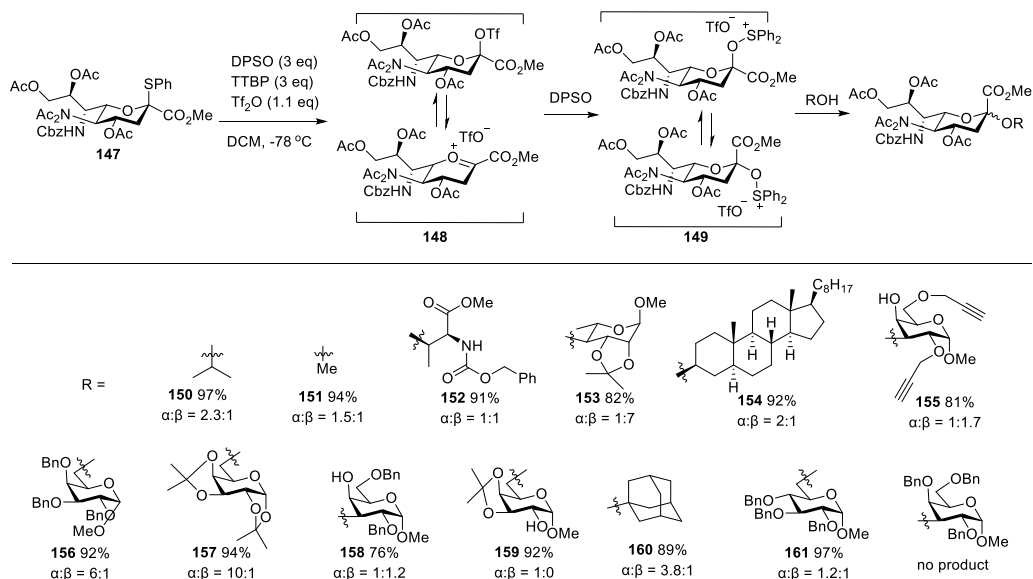


Scheme 18. Mechanism of glycosylations involving Me₂S.

5.2 Diphenyl sulfoxide (DPSO)

Diphenyl sulfoxide (DPSO) has been widely used in glycosylation reactions after the first dehydrative glycosylation using the DPSO-Tf₂O reagent combination by Gin in 1997.^[43] DPSO plays different roles in these glycosylations. It is part of the promoter system, but can also function as additive. In 2006, Crich and Li described that an excess of DPSO (3 eq) can be used in the

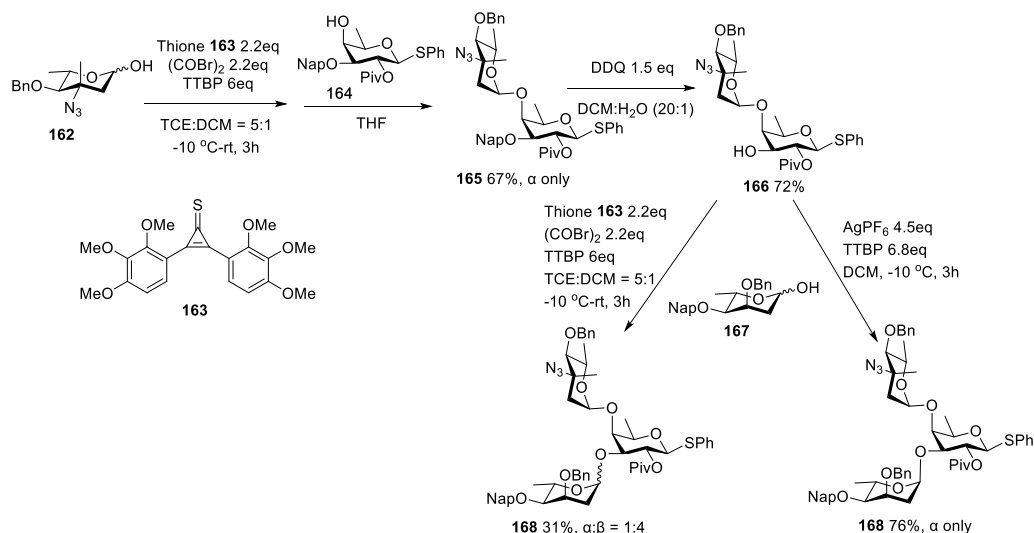
glycosylation of 2-thiosialic acid donors **147** to obtain the α -linked products with excellent yield and good α -selectivity.^[44] It was shown that DPSO plays a crucial role in the glycosylation as adducts **149** were formed upon treatment of the glycosyl triflate **148** with an excess of DPSO (Scheme 19).



Scheme 19. Glycosylation of 2-thiosialic acid donors with an excess of DPSO.

5.3 Other sulfur containing additives

Bennett and co-workers applied 2,3-bis(2,3,4-trimethoxyphenyl)-cyclopropene-1-thione **163** as additive in a synthesis of a branched trisaccharide fragment of the antibiotic saccharomicin B (Scheme 20).^[45] Disaccharide **165** was synthesized from monosaccharides **162** and **164** in the presence of thione **163** as a single anomer. When the same conditions were used to synthesize trisaccharide **168**, an α/β mixture was obtained ($\alpha:\beta = 1:4$). Application of thio-donor **166** in combination with AgPF_6 activation and the use of TTBP as an acid scavenger provided the desired trisaccharide **168** with excellent α -selectivity.

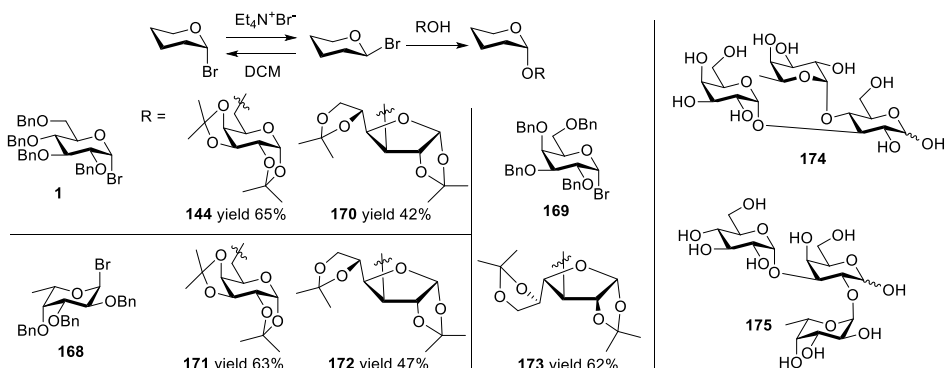
Scheme 20. Synthesis of trisaccharide **168**.

6 Glycosylations modulate with quaternary ammonium halide salt

The mechanism of quaternary ammonium salts in glycosylations is different with the other additives aforementioned. There isn't new intermediate species formed in the glycosylation modulated by quaternary ammonium salts. The halide ion (Br^- or I^-) from quaternary ammonium salt rebalance the glycosyl halide to offer more reactive β -anomer. That will be attacked by the acceptor to form α -glycosides. Originally quaternary ammonium salts were combined with glycosyl halides but have now been used as additives to many different types of glycosylations in the synthesis of 1,2-*cis*-oligosaccharides.

6.1 Tetraethylammonium bromide (TEAB) and tetrabutylammonium bromide (TBAB)

The first glycosylation mediated by quaternary ammonium bromide was reported by Lemieux and Hadd in 1975.^[46] Tetraethylammonium bromide (TEAB) was used in glycosylation of glycosyl bromides to form α -glycosides.^[46a] Two trisaccharides **174** and **175** were synthesized using this method, paving the way for more applications of quaternary ammonium salt in glycosylation reactions (Scheme 21).^[46b, c] It should be noted, however, that this glycosylation system is quite unreactive (because of the neutral nature of the intermediates as opposed to the cationic species generated in the previously described protocols), and therefore requires long reaction times and reactive nucleophiles for productive glycosylation reactions.



Scheme 21. Glycosylation of glucopyranosyl bromide with TEAB.

6.2 Tetrabutylammonium iodide (TBAI)

Inspired by Lemieux method, and building on improved methods to generate glycosyl iodides^[47], Gervay and co-workers described the use of these donors in combination with tetrabutylammonium iodide (TBAI) in glycosylation reactions.^[36] Compared to the TEAB-glycosyl bromide system, the TBAI-glycosyl iodide system is more efficient with shorter reaction times and higher yields. Hadd and Gervay described various iodide donors and reported that they reacted with good yield and α -selectivity (Table 2).

Table 2. TBAI modulate glycosylation of glycosyl iodide.

donors:								
acceptors:								
entry	donor	acceptor	solvent	additive	time (h)	product	yield %	$\alpha:\beta$
1	94	179	DCM	TBAI, DIEA	2	183	71	1:0
2	176	179	DCM	TBAI, DIEA	3	184	69	1:0
3	177	179	DCM	TBAI, DIEA	40 min	185	62	1:0
4	176	180	DCM	TBAI, DIEA	24	173	45	1:0
5	176	180	benzene	TBAI, DIEA	5.5	173	93	9:1
6	177	180	benzene	TBAI, DIEA	3	172	66	1:0
7	178	179	benzene	TBAI, DIEA	-	186	-	1:1
8	178	179	benzene	DIEA	-	186	-	1:1
9	178	180	benzene	DIEA	5.5	187	67	1:0

10	94	180	benzene	TBAI, DIEA	1.5	170	44	1:0
11	168	181	benzene	TEAB	4	188	quant	1:0
12	177	181	benzene	TBAI, DIEA	4	189	quant	1:0
13	177	182	DCM	TBAI, DIEA	5.5	190	91	1:0

In the same year, Hashimoto and co-workers applied TBAI in the glycosylation of glycosyl diethyl phosphites to construct 1,2-*cis*-glycosides.^[48] In their research, 2,6-di-tert-butylpyridinium iodide (DTBPI, 1.2 eq) was used as promoter and TBAI (1.2 eq) was used as additive, which transformed the glycosyl diethyl phosphites into the glycosyl iodide within 30 minutes as determined by TLC and ¹H-NMR. The desired products were obtained with excellent yield and α -selectivity (Table 3).

Table 3. Glycosylation of glycosyl diethyl phosphites with TBAI.

X = OP(OEt)₂, 1.1 eq 1.2 eq, 1.2 eq TBAI, DTBPI DCM 1.0 eq ROH

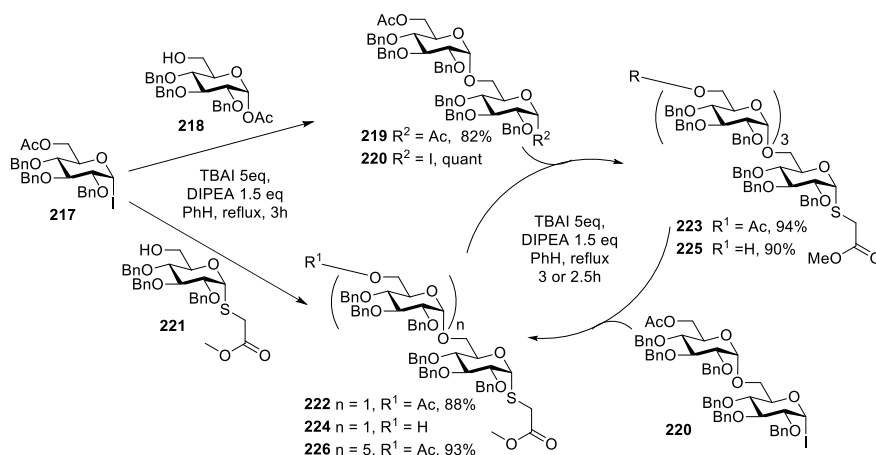
donors: 191 192 193 194 195 196 197 198

acceptors: 30 84 136 180 199 200 201 202 203 204

entry	donor	acceptor	time (h)	yield %	product	α : β
1	191	30	48	85	7	92:8
2	191	30	24	84	7	92:8
3	191	84	48	59	87	95:5
4	191	136	24	91	144	94:6
5	191	180	48	81	170	92:8
6	191	201	48	88	205	91:9
7	191	204	48	89	206	90:10
8	191	203	36	92	207	92:8
9	192	30	24	88	208	95:5
10	193	30	48	88	209	96:4
11	194	30	48	91	210	96:4
12	195	30	48	80	211	90:10
13	196	30	48	85	89	95:5
14	196	199	24	94	212	93:7

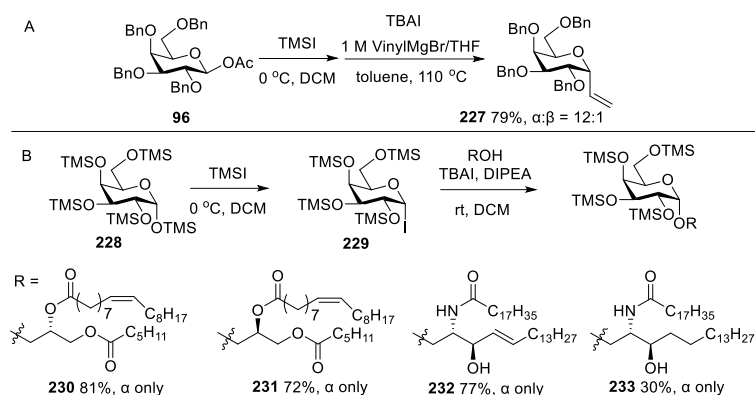
15	196	202	48	87	213	93:7
16	197	30	3	82	214	88:12
17	197	136	4	95	171	89:11
18	198	30	4	87	215	95:5
19	198	136	4	95	216	93:7

Afterwards, Gervay and co-workers studied the application of the TBAI-glycosyl iodide system in the solution and solid phase synthesis of oligosaccharides.^[49] Hexasaccharide **226** was assembled in solution using a [2+2+2] coupling strategy.^[49a] The glycosylation reactions were performed in refluxing benzene for 4h using 5 equivalents of TBAI and 1.5 equivalents of DIPEA (Scheme 22). Next, a tetrasaccharide was assembled using a solid phase approach, using the same reaction conditions.^[49b] Longer reaction times (up to 12 h) and more donor (7.5 equivalents in total) were needed to achieve good conversions.



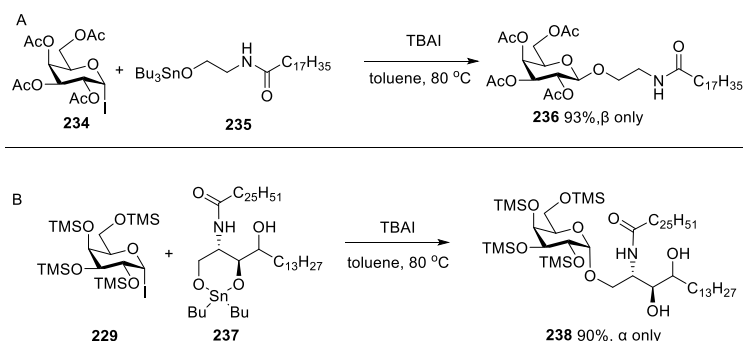
Scheme 22. TBAI-glycosyl iodide system in the synthesis of hexasaccharides.

Gervay and co-workers also used his method to synthesize a *C*-analogue of the bacterial glycolipid BbGL2.^[50] To this end a galactosyl iodide was generated from the galactosyl acetate by adding TMSI. The desired *C*-glycoside was obtained with good yield (79%) and α -selectivity ($\alpha:\beta = 12:1$) from the galactosyl iodide and vinyl magnesium bromide using TBAI in refluxing toluene (Scheme 23A). Afterwards, they synthesized α -*O*-glycolipids from per-*O*-silylated galactosyl iodides using TBAI as additive (Scheme 23B).^[51]



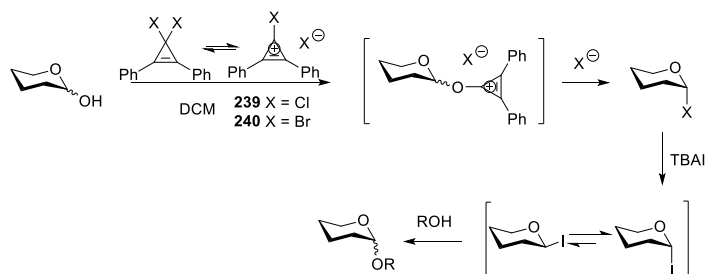
Scheme 23. Synthesis of glycolipid under influence of TBAI.

Sergio Castillon and co-workers also reported the synthesis of α - and β -linked glycolipids using TBAI to modulate the reactivity of the glycosylations.^[52] The glycosylation of the disarmed tetra-*O*-acetyl- α -iodogalactose donor **234** with the tin ketal of the acceptor afforded the β -linked glycolipid, through direct displacement of the (relatively stable) α -iodide **234** (Scheme 24A). When the armed per-*O*-silylated galactosyl iodide donor **229** was used in combination with an excess TBAI (2 eq) and acceptor **237**, the α -glycolipid **238** was formed (Scheme 24B).



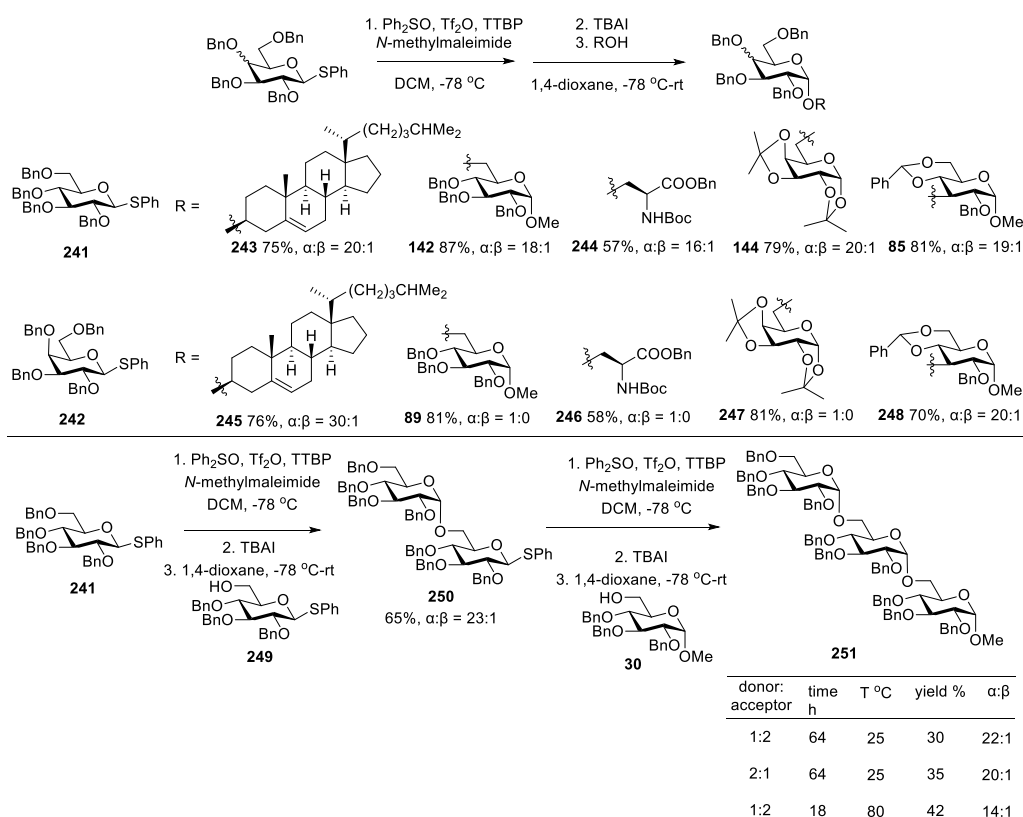
Scheme 24. Synthesis of glycolipid using TBAI condition.

Bennett and co-workers developed a dehydrative glycosylation procedure for deoxy-sugar donors promoted by 3,3-dichloro-1,2-diphenylcyclopropene **239** (1.5 eq) and TBAI (5 eq) to form α -glycosides.^[53] The mechanism that was proposed by the authors is depicted in Scheme 25. Upon treatment of the deoxy-sugar with 3,3-dichloro-1,2-diphenylcyclopropene **239**, the glycosyl chloride is formed, which is then treated with TBAI to form more reactivity glycosyl iodide. Acceptors attack the β -glycosyl iodide to give the α -glycosides. Various donors and acceptors were explored using these conditions. The desired products were obtained with good selectivity and yields. Later, they reported a new promoter 3,3-dibromo-1,2-diphenylcyclopropene **240** to further improve the α -selectivity.^[54]



Scheme 25. Mechanism of 3,3-dichloro-1,2-diphenylcyclopropene mediated dehydrative glycosylation of deoxy-sugar, modulated by TBAI.

In 2013, Bennett and co-workers reported a glycosylation protocol to construct 1,2-*cis*-glycosides from thio-donors.^[55] Per-benzylated thio-donors were activated by Ph_2SO and Tf_2O , and then treated with TBAI to form the intermediate glycosyl iodide. They also found that the addition of *N*-methylmaleimide to the reaction increases the yield. Scheme 26 depicts the scope of acceptors studied with per-benzyl glucosyl and galactosyl donors **241** and **242**. An 1,6-linked trisaccharide **251** was synthesized to illustrate the potential of the method in oligosaccharide synthesis.



Scheme 26. Glycosylations of thio-donors modulated by TBAI and *N*-methylmaleimide.

7 Conclusion

Tremendous progress has been made in the synthesis of oligosaccharides over the past decades. The use of exogenous nucleophiles (“additives”) to modulate the selectivity has opened up a new avenue for the stereoselective synthesis of oligosaccharides. This Chapter has summarized different additives that have been developed to date and that have found most applications. The prime advantage of additive controlled glycosylations is the fact that one can rely on the reactivity of an external agent instead of using specialized building blocks, bearing a specific protecting group pattern to control the stereochemistry of the glycosylation.^[56] In addition, the use of an external additive for reaction modulation enables the flexible tuning of the reactivity of the system and matching of donor and acceptor reactivity. Although the first “additive controlled” glycosylations were reported many years ago, the approach has received relatively limited attention until better mechanistic insight was recently gained, and reactive intermediates could be characterized by spectroscopic techniques. Still, relatively few applications of the methodology in the assembly of large and complex, branched oligosaccharides have been reported.

To date most additives have been used to afford α -selectivity, while the synthesis of β -glycosides modulated by additives has been only scarcely investigated, this could pose advantages for example in the context of the protecting group strategy followed. Besides applications in total synthesis of carbohydrates more insight is demanded into the reaction mechanism of additive controlled glycosylations and detailed kinetic studies are therefore required. In addition, knowledge of the reactivity of both coupling partners will enable better fine tuning of the reaction to optimally control the outcome of the reaction in terms of yield and stereoselectivity. The conception of an “additive toolbox” with modulators of known properties to match the reactivity of the donor and acceptor in a predictable manner will then be achievable.

8 Outline of this Thesis

This Thesis focuses on the development of additive controlled glycosylation and its use in assembly of biologically relevant oligosaccharides built up from 1,2-*cis*-linkages.

Chapter 2 describes an additive controlled glycosylation strategy built on the use of TfOH-DMF and TMSI-Ph₃P=O mediated glycosylation reactions of *N*-phenyltrifluoroacetamide donors. The different activator/additive combinations were used to match the reactivity of the donor and secondary and primary acceptor building blocks. To eliminate reactivity differences originating from different protecting groups, only benzyl type protecting groups (Bn, PMB, Nap) were used. To prove the utility of the devised synthesis strategy, a linear α -(1,4)-hexasaccharide and a branched α -glucan from *Mycobacterium tuberculosis* were assembled.

Encouraged by the results of chapter 2, an α -(1,3)-linked octasaccharide from the *Aspergillus*

fumigatus fungal cell wall was prepared using the TfOH-DMF mediated conditions as described in **Chapter 3**. The synthesis of α -(1,2)-linked glucans (“kojioligosaccharides”) using additives to control the selectivity of the required glycosylations is described in **Chapter 4**. The synthesis of α -galactosides is introduced in **Chapter 5**, where it is described that TMSI-Ph₃P=O conditions can be applied to a broad scope of substrates.

In **Chapter 6**, a new additive, *N*-methyl(phenyl) formamide (MPF) is introduced for glycosylations to form 1,2-*cis*-2-azido glycosides. A linear α -glucosazide tetrasaccharide and a linear Pel hexasaccharide, containing both α -glucosamines and α -galactosamines were synthesized using MPF as additive. **Chapter 7** provides a conclusion of this Thesis and an outlook for future research.

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Chapter 2

Reagent Controlled Stereoselective Synthesis of α -Glucans

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Introduction

As described in chapter 1, there exists still no general solution for the stereoselective construction of challenging glycosidic bonds, such as 1,2-*cis* and 2-deoxy linkages.¹ At the root of this persisting problem is the enormous variation in carbohydrate building blocks and the different mechanistic pathways that can be followed in the union of these.¹ Most glycosylation reactions rely on the activation of a glycosyl donor using a (Lewis) acid catalyst to generate a strong

electrophile that can either be a covalent species, a close ion pair or a solvent separated ion pair, in which the glycosyl oxocarbenium ion and the counter ion are fully dissociated (See Figure 1).^{2,3} Most often triflate-based activators are used and a multitude of covalently linked anomeric triflates has been described over the last two decades.³ These triflates may engage in a S_N2 type substitution reaction, but more often they act as a reservoir for the more reactive glycosyl cation-triflate ion pair, providing reactions with S_N1 -character. The equilibrium between the covalent species and ion pairs in combination with the reactivity of the incoming nucleophile -the acceptor- determines which pathway(s) will be followed. The reactivity of the donor building block depends on the nature and position of the functional groups on the carbohydrate ring and the different reactivity of donor glycosides has been called upon in reactivity based one-pot chemoselective glycosylation sequences.⁴ It is also well appreciated - but less well studied - that the reactivity of the acceptor alcohol can vary as a result of the protecting/functional group pattern on the ring and the intrinsic reactivity difference between primary and secondary alcohols often leads to a different stereochemical outcome when glycosylating these acceptors.⁵ It is a tremendous challenge to design a general glycosylation strategy that accommodates the varying reactivity of different donor-acceptor glycoside combinations and ensures a fully stereoselective glycosylation process.

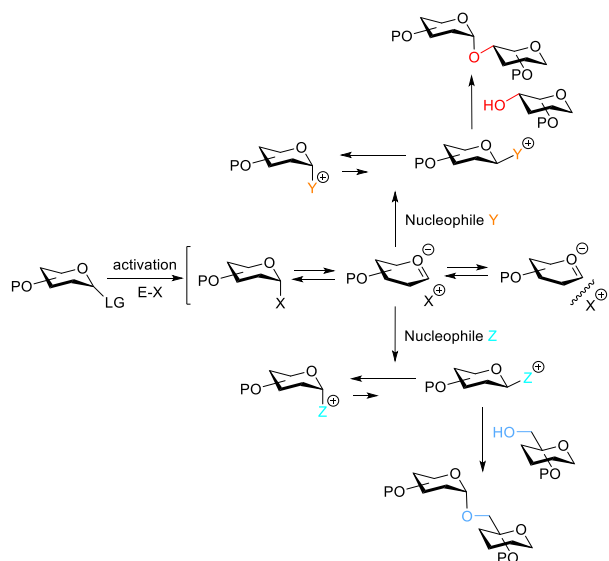


Figure 1. Additive controlled stereoselective glycosylations. The reactivity of the adducts of the different nucleophiles (Y and Z) are tuned to the reactivity of the incoming acceptor alcohol.

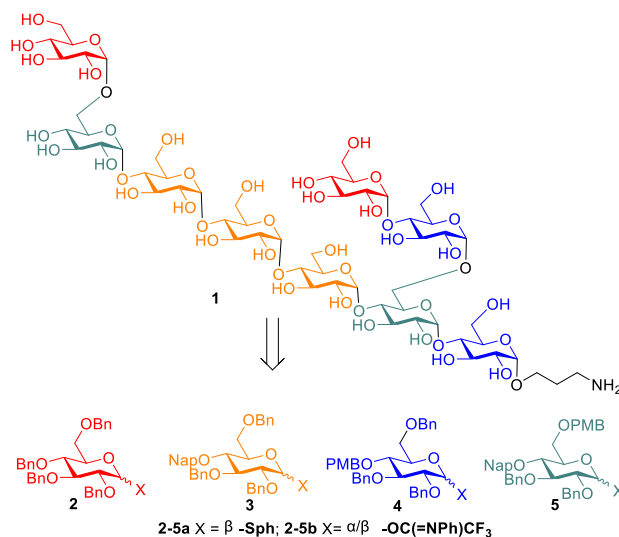
An attractive way to modulate the reactivity of a glycosyl donor is through the use of an exogenous nucleophile that can be added to the coupling reaction. These nucleophilic additives or reactivity modulators react with the activated donor to form a new covalent species (See Figure

1).⁶ Like introduced in chapter 1, various additives have been probed over the years, including sulfides,⁷ sulfoxides,⁸ phosphine oxides,⁹ amides and formamides¹⁰ and iodide based reagents¹¹ and several stereoselective 1,2-*cis*-glycosylation procedures have been reported based on their use. The most often invoked mechanistic rationale to account for the observed stereoselectivity involves the generation of a stable α -covalent species (often identified and characterized by NMR spectroscopy), that is in equilibrium with its less stable and more reactive β -counterpart (often not detected by NMR), following an *in situ* anomerisation kinetic scenario as first introduced by Lemieux and co-workers.¹² It is reasonable that modulation of donor reactivity through external nucleophiles would be very attractive to match the reactivity of acceptor alcohols of different nucleophilicity in order to achieve fully stereoselective glycosylation reactions with both partners. It is described here how a single type of donor glycoside can be used for the fully stereoselective glycosylation of both primary and secondary alcohol acceptors. Different additives have been used to accommodate the intrinsic reactivity difference between these two types of alcohols. Key to the success of the strategy is a protecting group strategy that ensures identical reactivity of the parent donor building blocks used, so that the reactivity of the system is under direct control of the activator/additive used. The applicability of this approach is showed in the assembly of *Mycobacterium tuberculosis* (Mtb) derived branched α -glucans. Mtb α -Glucans play an important role in allowing the bacterium to evade the human immune system, but the molecular details behind this process remain obscure.¹³ To unravel how α -glucans interact with our immune system, well-defined α -glucans fragments will be valuable tools. These structures represent excellent target molecules to test the proposed synthetic strategy, as they only contain 1,2-*cis* linkages and carry different branches, necessitating flexible building blocks and stereoselective glycosylation methodology for the construction of glycosidic linkages to both primary and secondary alcohol functions.

Results and Discussion

A glycosylation strategy was expected to be developed that is under full control of the used reagents and aimed to employ a single donor type, devoid of any stereodirecting protecting groups for the glycosylations of both the primary and secondary alcohol acceptors. Therefore, the used donors and acceptors were equipped solely with benzyl type protecting groups. This serves two purposes. Firstly, since all protecting groups on the building blocks are benzyl ethers, the reactivity of the building blocks is as similar as possible. The only factors influencing the relative reactivity of the acceptors are the intrinsic difference between the primary and secondary alcohols and the effect of the growing chain length on the reactivity of the acceptor. Secondly, global protection of the donor glycoside with benzyl ethers leads to a donor that is as reactive as possible. Previous reports employing nucleophilic additives in glycosylations have shown that this type of glycosylation is generally very slow.⁶ The reactive intermediates that are generated are relatively

stable necessitating long reaction times. The use of acyl type protecting groups would make the system less reactive leading to even longer reaction times. The target α -glucans of this study and the employed building blocks are depicted in Scheme 1. The most complex target, nonasaccharide **1**, features a hexa- α -glucan backbone with two different branches. This target saccharide was selected because its synthesis requires the introduction of all possible structural elements present in naturally occurring α -glucans. To be able to assemble this structure four different building blocks were designed: per-benzylated donor **2**, a chain-terminating synthon; donor **3** to build the growing α -(1,4)-chains; donor **4**, to build the branches; and finally, donor **5** to introduce the branches. The triad of benzyl ethers that was aimed to use include benzyl (Bn) ethers for permanent protection, only to remove at the end of the assembly; 2-methylnaphthyl (NAP) ethers that can be selectively removed with respect to the other benzyl ethers under acidic or oxidative conditions and finally the *para*-methoxybenzyl (PMB) ether that are the most labile of the three benzyl ethers and that can be selectively removed in the presence of the other two using mild acidic conditions, as described in recently publication of Volbeda et al.¹⁴



Scheme 1. Synthetic strategy for the assembly of Mtb α -glucan **1**.

The stereoselective construction of the α -(1,4)-glucosyl linkages was paid to attention firstly. To this end the condensation of tetra-*O*-benzyl thioglucoside **2a** and tri-*O*-benzyl- α -*O*-methyl glucose acceptor **6** were investigated using *N*-iodosuccinimide (NIS) and trimethylsilyl triflate (TMSOTf) activation.¹⁵ Following the seminal work of Mong and co-workers,¹⁰ several amides and formamide additives were explored, including *N,N*-dimethylformamide (DMF), *N*-formylpiperidine (NFP), *N*-formylmorpholine (NFM), *N,N*-dimethylacetamide (DMA) and tetramethylurea (TMU) as reactivity modulators. Phosphine oxides (triphenylphosphine oxide, Ph₃P=O) and sulfoxides (benzene sufanyl piperidine, BSP) also were probed. As shown in Table

1 (Entries 2-14), the stereoselectivity of the reactions with additives are better than the condensation reaction without nucleophilic additive (Entry 1), barred one: the reaction using $\text{Ph}_3\text{P}=\text{O}$. In line with the findings of the Mong laboratory,¹⁰ the formamide additives performed best and the use of a larger excess of these additives generally gave better results in terms of stereoselectivity.

Table 1. Glycosylations of perbenzylated glucose donors with secondary alcohols.

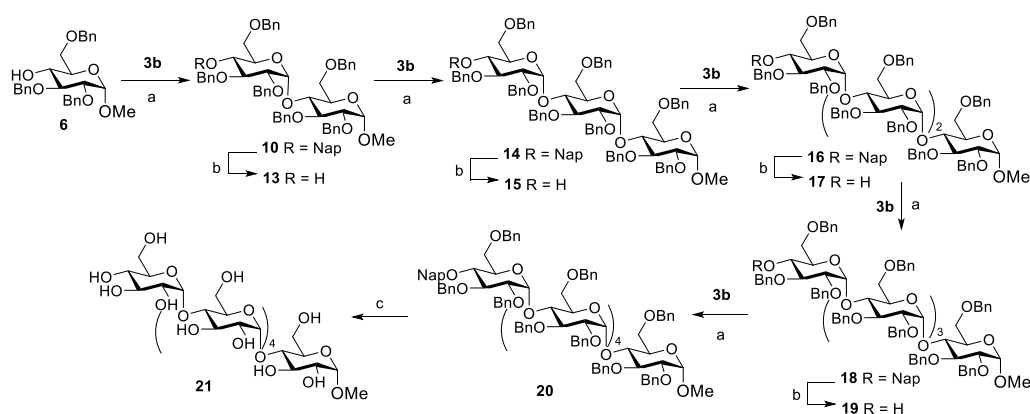
entry	donor	acceptor	promoter	additives	eq	product	yield	$\alpha:\beta$
1	2a	6	NIS, TMSOTf ^a	-	-	9	86%	2:1 ^c
2	2a	6	NIS, TMSOTf ^a	DMF	6	9	91%	37:1 ^c
3	2a	6	NIS, TMSOTf ^a		16	9	83%	>50:1 ^c
4	2a	6	NIS, TMSOTf ^a	NFP	6	9	72%	23:1 ^c
5	2a	6	NIS, TMSOTf ^a		16	9	69%	>30:1 ^c
6	2a	6	NIS, TMSOTf ^a	NFM	6	9	91.5%	15:1 ^c
7	2a	6	NIS, TMSOTf ^a		16	9	94%	19:1 ^c
8	2a	6	NIS, TMSOTf ^a	DMA	6	9	83%	9:1 ^c
9	2a	6	NIS, TMSOTf ^a		16	9	90%	19:1 ^c
10	2a	6	NIS, TMSOTf ^a	TMU	6	9	32%	4:1 ^c
11	2a	6	NIS, TMSOTf ^a		16	9	49%	3.5:1 ^c
12	2a	6	NIS, TMSOTf ^a	BSP	3	9	61%	3:1 ^c
13	2a	6	NIS, TMSOTf ^a		6	9	39%	3:1 ^c
14	2a	6	NIS, TMSOTf ^a	$\text{Ph}_3\text{P}=\text{O}$	6	9	60%	2:1 ^c
15	2b	6	TfOH ^b	DMF	16	9	94%	>20:1 ^d
16	3b	6	TfOH ^b	DMF	16	10	91%	>20:1 ^d
17	2b	7	TfOH ^b	DMF	16	11	85%	>20:1 ^d
18	2b	8	TfOH ^b	DMF	16	12	90%	>20:1 ^d

^aDCM, 0 °C, 24h. ^bDCM, -78-0 °C, 24h. ^cThe $\alpha:\beta$ ratio was determined by chiral HPLC analysis. ^dThe $\alpha:\beta$ ratio was determined by ¹H-NMR.

It was observed that the reactions with TMU and the phosphine oxide proceeded slower than the formamide and amide mediated condensations, resulting in diminished yields. This likely reflects

the greater stability of the formed covalent intermediates generated with these additives. As shown in Table 1, DMF performed best as additive and this reagent was further studied and the use of imidate donors was also explored as these represent a very powerful class of glycosylating agents.¹⁶ Where the *in situ* transformation of thioglycosides into reactive covalent species has been widely applied in glycosylation chemistry, the use of imidate donors for this purpose has not been explored. Gratifyingly, the additive controlled condensation of imidate donor **2b** and acceptor **6** proceeded in excellent yield and stereoselectivity to provide the desired disaccharide **9** (Table 1, entry 15). To test whether the acid labile naphthyl ether in donor **3b** is compatible with the developed reaction conditions, which employ a stoichiometric amount of TfOH, donor **3b** was next coupled with acceptor **6**. This glycosylation delivered the protected maltoside **10** in similar yield and with comparable stereoselectivity as the condensation of per-benzyl donor **2b** and acceptor **6** (Table 1, entry 16), showing that the Nap ether well tolerates the glycosylation conditions. The scope of the established conditions was briefly explored with two other secondary carbohydrate alcohols. Acceptors **7** and **8** could be glycosylated at the C-3 and C-2 OH, respectively, in good yield and with excellent stereoselectivity (Table 1, entries 17 and 18).

To probe the robustness of the established methodology, a longer α -glucan was assembled, as depicted in Scheme 2. To this end, the Nap-protecting group was removed from maltoside **10** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to furnish acceptor **13**. Compound **13** was glycosylated with donor **3b** using the DMF-conditions to give the desired trisaccharide **14** in 81% yield. Repetition of the deprotection and glycosylation reactions then provided the tetrasaccharide **16**, pentasaccharide **18** and hexasaccharide **20**. All through this reaction sequence the yields and stereoselectivity of the condensations did not erode showcasing the reliability of the methodology.

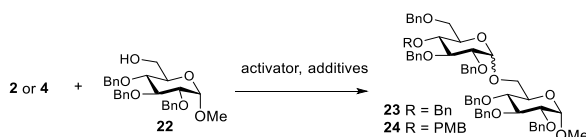


a) DMF, TfOH, DCM, -78 - 0 °C, **8**: 82%; **14**: 81%; **16**: 82%; **18**: 80%; **20**: 79%. b) DDQ, DCM/H₂O, **13**: 78%; **15**: 78%; **17**: 84%; **19**: 81%. c) Pd(OH)₂/C, H₂, THF:H₂O:t-BuOH, 3.5 atm, 80%.

Scheme 2. Synthesis of α -(1,4)-hexasaccharide **21**.

Then the attention was turned to the condensations of the primary acceptor. For this model acceptor **22** was used in combination with thioglycoside **2a** and the panel of additives described above. The higher reactivity of the primary alcohol **22** with respect to its secondary alcohol counterpart **6** leads to significant erosion of the stereoselectivity, when identical condensation conditions are used (Table 2, entries 1-5). It was surprised to see that the condensation using the phosphine oxide actually led to the formation of more β - than α -linked product. Cognizant of the work of Mukaiyama and co-workers on the use of phosphine oxides in highly stereoselective condensation reactions of perbenzylated glucosyl pyranosyl iodides,⁹ it was switched to the use of imidate donor **2b** that was transformed *in situ* into the anomeric iodide using trimethylsilyliodide (TMSI).¹⁷ Under these conditions, the disaccharide **23** was formed with moderate α -selectivity and in rather poor yield (Table 2, entry 6). The addition of 1.2 equivalent of diphenylmethyl phosphine oxide, as advocated by Mukaiyama and co-workers, led to a significant improvement of the stereoselectivity (α/β = 6:1, Table 2, entry 7).

Table 2. Glycosylations of primary alcohol **22**.



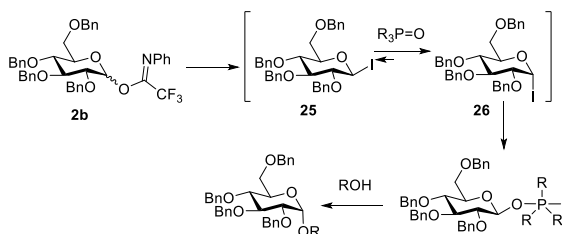
entry	donor	promoter	additive	eq	T	product	t(h)	yield	$\alpha:\beta^a$
1	2a	NIS, TMSOTf	DMF	16	0 °C	23	12	90%	2.7:1
2	2a	NIS, TMSOTf	NFM	16	0 °C	23	24	83%	2.1:1
3	2a	NIS, TMSOTf	DMA	16	0 °C	23	24	69%	1:1.3
4	2a	NIS, TMSOTf	TMU	6	0 °C	23	24	82%	1:1.1
5	2a	NIS, TMSOTf	Ph ₃ P=O	6	0 °C	23	24	70%	1:3
6	2b	TMSI	-	-	rt	23	24	41%	2:1
7	2b	TMSI	Ph ₂ (Me)P=O	1.2	rt	23	24	46%	6:1
8	4b	TMSI	Ph ₂ (Me)P=O	3	rt	24	24	82%	16:1
9	4b	TMSI	Ph ₂ (Me)P=O	6	rt	24	24	76%	20:1
10	4b	TMSI	Ph ₂ (Me)P=O	10	rt	24	24	73%	20:1
11	4b	TMSI	Ph ₂ (Me)P=O	16	rt	24	24	70%	20:1
12	4b	TMSI	Ph ₃ P=O	6	rt	24	24	78%	25:1
13	2b	TMSOTf	Ph ₂ (Me)P=O	6	rt	23	24	84%	3:2

^aThe $\alpha:\beta$ ratio was determined by ¹H-NMR.

As planned to use this activation system in combination with a donor glucoside bearing a relative acid labile PMB group, these conditions were explored for the coupling of donor **4b** and acceptor

22. The amount of phosphine oxide was increased to ensure that sufficient Lewis-basic reagent was present to protect the labile PMB. As displayed in Table 2, entry 8, the desired disaccharide **24** was obtained in good yield with improved stereoselectivity and the PMB group proved to be completely stable to the conditions used. Increasing the amount of the phosphine oxide additive to 6 equivalents led to a further increase in stereoselectivity (Table 2, entry 9). More phosphine oxide did not further improve the stereoselectivity (Table 2, entries 10 and 11). Triphenyl phosphine oxide performed equally well as an additive and the use of 6 equivalents of this reagent proved optimal for the condensation of donor **3b** and acceptor **22** (Table 2, entry 12).

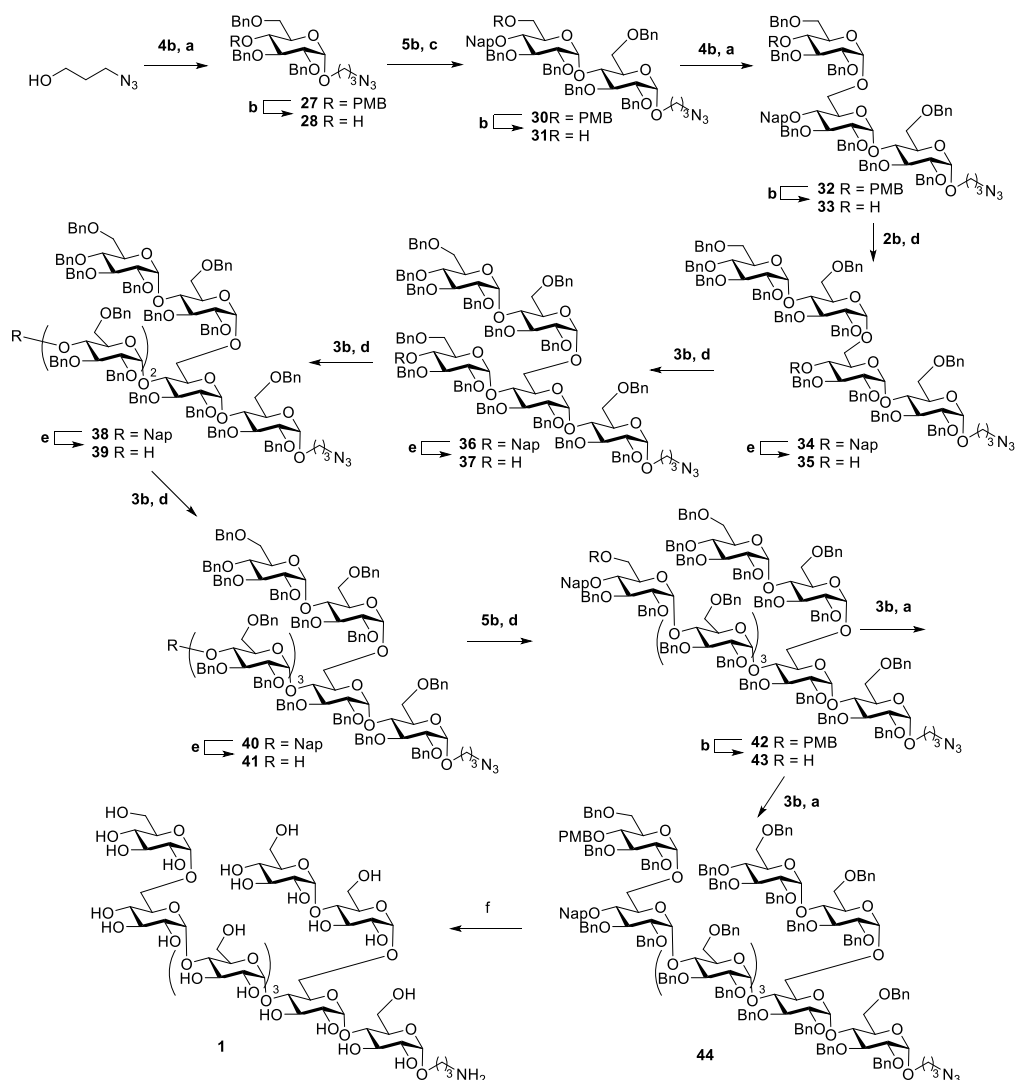
To explore the necessity of the intermediate iodide, the activation of imidate donor **2b** with TMSOTf instead of TMSI in the presence of 6 equivalents phosphineoxide was executed (Table 2, entry 13). This led to formation of the diglucoside **23** in good yield, but very poor selectivity, indicating that the anomeric iodide plays an important role in the coupling mechanism. To shed further light on the reactive intermediates formed with the TMSI-phosphine oxide reagent combination, the activation of donor **2b** was studied by NMR spectroscopy. When donor **2b** was activated with TMSI in CDCl₂ in the absence of a phosphine oxide additive, a mixture of two products was formed. The products were tentatively assigned as α -iodide **26** (Scheme 3, H-1: δ = 6.82 ppm; C-1: δ = 81.04 ppm; See SI for NMR spectra) and its β -counterpart **25** (H-1: δ = 5.68 ppm; C-1: δ = 61.42 ppm).¹⁸ In time ($\pm$ 45 min), the β -iodide **25** isomerized into its more stable α -congener **26**. Alternatively, treatment of a mixture of donor **2b** and Ph₂(Me)PO in CDCl₃ with TMSI, showed a clean conversion of the imidate into the anomeric α -iodide **26**. The β -iodide **25** was not observed, nor could be detected the presence of any anomeric phosphonium species. Given the importance of the phosphine oxide for the stereoselectivity of the reaction (compare Table 2, entries 6 and 9), it is suggested that the anomeric α -iodide serves a reservoir for the more reactive β -phosphonium iodide **25**, which is the actual glycosylating species (See Scheme 3). The phosphine oxide also catalyzes the transformation of the β -iodide **25** into α -iodide **26**.



Scheme 3. Proposed mechanism for the activation and glycosylation of imidate donors with TMSI and phosphineoxides.

Having identified the required reagents and conditions to stereoselectively construct *cis*-glucosidic linkages with both primary and secondary acceptor glucosyl alcohols, the attention was turned to assemble nonaglucoside **1** using the strategy outlined in Scheme 4.¹⁹ First 3-42

azidopropanol was condensed with donor **4b** using the Ph_3PO mediated glycosylation conditions to deliver monosaccharide **27** in 91% yield and 11:1 α/β selectivity (Scheme 4).



a) TMSI, $\text{Ph}_3\text{P}=\text{O}$, DCM, rt, **27**: 91%, $\alpha/\beta = 11:1$; **32**: 68%, $\alpha/\beta > 20:1$; **44**: 67%, $\alpha/\beta > 20:1$. b) 0.2M HCl/HFIP, DCM/HFIP, **28**: 85%; **31**: 85%; **33**: 83%; **43**: 88%. c) TMSOTf, DMF, 0 °C, **30**: 81%, $\alpha/\beta > 20:1$. d) TfOH, DMF, 0 °C, **34**: 81%, $\alpha/\beta > 20:1$; **36**: 91%, $\alpha/\beta > 20:1$; **38**: 93%, $\alpha/\beta > 20:1$; **40**: 91%, $\alpha/\beta > 20:1$; **42**: 80%, $\alpha/\beta > 20:1$. e) DDQ, DCM/ H_2O , **35**: 84%; **37**: 75%; **39**: 66%; **41**: 70%. f) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 (3.5 atm), $\text{THF}:\text{H}_2\text{O}:\text{t-BuOH}$, yield 61%.

Scheme 4. Stereoselective synthesis of branched α -nonasaccharide **1**.

The spacer-equipped glucoside **27** was then treated with a catalytic amount of HCl in a mixture of hexafluoro-*iso*-propanol (HFIP) and dichloromethane (DCM) to remove the PMB protecting group and liberate the C-4-alcohol. Acceptor **28** was then reacted with “branching” donor **5b**

using the DMF-mediated glycosylation conditions to provide disaccharide **30** in 81% yield and excellent α -selectivity.^{20,21} The PMB ether in disaccharide **30**, was chemoselectively removed using the aforementioned HCl/HFIP conditions. Of note, the Nap-ether at the C-4' position was completely stable under these acidic conditions. Disaccharide **31** was then elongated at its C-6'-OH with C-4-PMB-donor **4b** using the TMSI-Ph₃PO reagent combination to stereoselectively provide the trisaccharide **32**. Liberation of the C-4''-OH, again using HCl/HFIP, then set the stage for the elongation of the branching arm with perbenzyl donor **2b** under the *aegis* of TfOH and DMF. Having completed the first arm, it was continued to grow the α -(1,4)-backbone. To this end the Nap ether was oxidatively removed and the resulting secondary alcohol coupled to C-4-Nap donor **3b** with TfOH-DMF to give pentasaccharide **36**. Reiteration of this deprotection-coupling cycle led to hexasaccharide **38** and heptasaccharide **40** in a completely stereoselective fashion. To introduce the second α -(1,6)-arm the C-4-OH was unmasked and the heptasaccharide acceptor **41** was coupled to branching glucoside **5b** to deliver octamer **42**. Liberation of the primary alcohol was then followed by the final TMSI-Ph₃PO-condensation leading to the fully protected nonasaccharide **44**. Global deprotection of the nonasaccharide was accomplished in a single hydrogenation event to complete the total synthesis of branched α -glucan **1**.

Conclusion

In conclusion, a strategy was described to assemble α -glucans in a fully stereoselective manner, using a single type of donor, relying solely on the activating agents and additives to control the stereoselectivity of the glycosylation reactions. The reactivity of the donor building blocks was matched to the intrinsically different reactivity of primary and secondary alcohols through the use of different activator/additive combinations (TfOH or TMSOTf/DMF and TMSI/Ph₃PO). To keep the reactivity of all donor synthons on par, it was introduced the triad of benzyl, 2-methylnaphthyl and *para*-methoxybenzyl ethers, as a set of semi-orthogonal protecting groups that can be used to differentiate the hydroxyl groups on the building blocks that need permanent protection, that have to be extended to form the glycan backbone or removed to introduce branching.²² The applicability of the strategy has been illustrated by the fully stereoselective assembly of an Mtb nonasaccharide α -glycan, bearing two different branches. Matching the reactivity of both donor and acceptor through the use of external nucleophiles as reactivity moderators presents an important step towards the generation of a general glycosylation reaction. Increasing our insight into the reactivity of donor and acceptor building blocks in combination with the development of tailor made additives, covering a broad range of reactivity, will likely allow the fine tuning of many glycosylation systems in the future. Besides the stereoselective construction of *cis*-glycosidic linkages in a reagent controlled manner, it should be feasible to conceive nucleophilic additives that allow for the stereoselective formation of *trans*-glycosidic bonds using the same donor/acceptor pair, further broadening the scope of the methodology.

Experimental Section

Standard procedure for glycosylation of secondary alcohols with thiodonors (2a-5a) (procedure A)

The donor (1.0 eq, co-evaporated with toluene) was dissolved in dry DCM (see experimental description below for concentrations) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (16 eq) was added to the solution. The solution was cooled to 0°C, after which NIS (1.0 eq) and TMSOTf (1.0 eq) were added. After 1 h, the pre-activation was complete as indicated by TLC-analysis. Then acceptor (0.7 eq, see experimental description below for concentrations) was added to the solution. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction mixture was diluted and the reaction was quenched with saturated Na₂S₂O₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The products were purified by size exclusion (eluent (50/50) MeOH/DCM and silica gel column chromatography (See experimental description below for eluent system).

Standard procedure for glycosylation of secondary alcohols with imidate donors (2b-5b) (procedure B)

The donor (1.0 eq, co-evaporated with toluene) was dissolved in dry DCM (see experimental description below for concentrations) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (16 eq) was added to the solution. The solution was cooled to -78 °C, after which TfOH (1.0 eq) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor (0.7 eq, see experimental description below for concentrations) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The products were purified by size exclusion (eluent (50/50) MeOH/DCM and silica gel column chromatography (See experimental description below for eluent system).

Standard procedure for the glycosylation of primary alcohols (procedure C)

A mixture of donor (1.0 eq), acceptor (0.7 eq) was co-evaporated with toluene three times and together with Ph₃P=O (6 eq) dissolved in dry DCM (see experimental description below for concentrations) and stirred over fresh flame-dried molecular sieves 3A under nitrogen. Then TMSI (1.0 eq) was added slowly in the mixture. The reaction was stirred at room temperature until TLC-analysis indicated the reaction to be complete. The solution was diluted and the reaction quenched with saturated Na₂S₂O₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The products were purified by size exclusion (eluent (50/50) MeOH/DCM and silica gel column chromatography (See experimental description below for eluent system).

General procedure for deprotection of the Nap protecting group (general procedure D)

The starting material (1.0 eq) was dissolved in CH₂Cl₂(DCM):H₂O (10:1, 0.1 M). DDQ (1.1 eq) was added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material ($\pm$ 2h). Then the mixture was diluted with DCM and the reaction quenched with saturated Na₂S₂O₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column

chromatography (See experimental description below for eluent system).

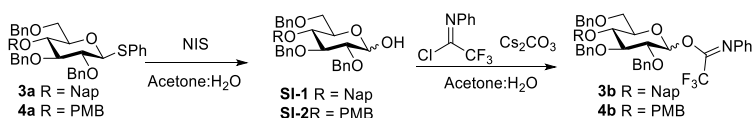
General procedure for deprotection of the PMB protecting group (general procedure E)

The starting material (1.0 eq) and triethylsilane (1.0 eq) were dissolved in DCM:HFIP (hexafluoro-*iso*-propanol) (1:1, 0.1 M). Then 0.2M HCl in HFIP (0.1 eq) was added to the mixture. The reaction was stirred until TLC-analysis indicated complete consumption of the starting material ($\pm$ 30 min.). Then the mixture was diluted with DCM and the reaction quenched with saturated Na_2CO_3 . The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography (See experimental description below for eluent system).

Experimental Procedures and Characterization Data of Products

For the synthesis procedure and data of known compounds **2a**²³, **2b**^{24,32}, **3a**²⁵, **4a**²⁶, **6**^{27,28}, **7**^{27,29}, **8**^{27,30}, **9**³², **11**³², **12**³², **22**^{27,31}, **23**³² see references. We used "a", "b", "c", "d", "e", "f", "g", "h" and "i" to specify the H-1 and C-13 NMR signals of sugar rings from the "reducing" to the "non-reducing" end and "o" to specify the H-1 and C-13 NMR signals of the spacer.

Scheme S1. Preparation of **3b** and **4b**



N-phenyl trifluoroacetimidate glucose donor **3b**

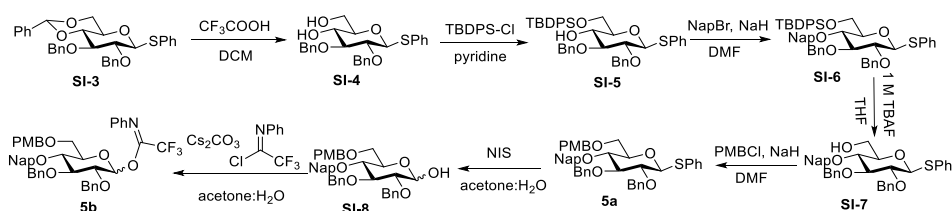
Compound **3a** (8.0 g, 11.7 mmol) was dissolved in acetone:H₂O (10:1, 120 mL). N-Iodosuccinimide (NIS) (5.27 g, 23.4 mmol) was added in one portion and the reaction was stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE:EA = 2:1). Compound **SI-1** (6.37 g, 92% yield) was obtained as a white solid. Next, compound **SI-1** (6.37 g, 10.8 mmol) was dissolved in acetone:H₂O (10:1, 110 mL). Cs_2CO_3 (5.27 g, 16.2 mmol) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (2.62 ml, 16.2 mmol) were added to the solution respectively. The reaction stirred overnight, then quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by column chromatography (PE:EA = 50:1-20:1). Compound **3b** (7.89 g, 96% yield, mixture of α and β , PE:EA = 10:1, R_f = 0.45-0.55) was obtained as yellow syrup. ¹H-NMR (CDCl_3 , 500 MHz, 60°C) δ 7.77-6.72(m, aromatic H), 6.46 (bs, 1 H, H-1 α), 5.61 (bs, 1 H, H-1 β), 5.00-4.71 (m, CHH), 4.58-4.43 (m, CHH), 4.06 (t, J = 9.0 Hz, 1 H, H- α), 3.99 (bd, 1 H, H- α), 3.80-3.68 (m), 3.42 (bs, 1 H). ¹³C-APT (CDCl_3 , 125 MHz, 60°C) δ 143.93, 143.73, 143.42, 138.94, 138.72, 138.32, 138.22, 138.14, 138.12, 135.91, 135.82, 133.57, 133.54, 133.28, 133.26 (aromatic C), 129.42, 128.81, 128.58, 128.55, 128.49, 128.46, 128.21, 128.17, 128.06, 128.05, 127.98, 127.94, 127.90, 127.80, 127.94, 127.90, 127.80, 127.74, 127.71, 127.68, 126.72, 126.70, 126.42, 126.17, 126.06, 126.00, 124.44, 124.30, 120.75, 119.66, 119.59 (aromatic CH), 116.50 (q, CF_3), 97.65 (C-1 β), 93.95 (C-1 α), 84.76 (β), 81.77 (α), 81.25 (β), 79.73 (α), 77.61 (β), 77.34 (α), 76.06 (β), 75.79, 75.60, 75.32, 46

75.07, 75.05, 73.72, 73.64, 73.57 (α), 73.52, 68.69 (C-6 α and β). HR-MS: Calculated for $C_{43}H_{42}F_3O_7N$ $[M-[O(C=NPh)CF_3]+OH+Na]^+$: 593.2510, found: 593.2516.

N-phenyl trifluoroacetimidate glucose donor 4b

Compound **4a** (10 g, 15.1 mmol) was dissolved in acetone:H₂O (10:1, 150 mL). N-Iodosuccinimide (NIS) (6.79 g, 30.2 mmol) was added in one portion and the reaction was stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated aqueous Na₂S₂O₃, then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE:EA = 2:1). Compound **SI-2** (7.40 g, 86% yield) was obtained as a white solid. Next, compound **SI-2** (7.40 g, 10.8 mmol) was dissolved in acetone:H₂O (10:1, 110 mL). Cs₂CO₃ (6.34 g, 19.4 mmol) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (3.15 ml, 19.4 mmol) were added to the solution respectively. The reaction stirred overnight, then quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by column chromatography (PE:EA = 50:1-20:1). Compound **4b** (9.14 g, 95% yield, mixture of α and β , PE:EA = 10:1, *R*_f = 0.34) was obtained as yellow syrup. ¹H-NMR (CDCl₃, 500 MHz, 60°C) δ 7.79-6.70 (m, aromatic *H*), 6.44 (bs, 1 H, H-1 α), 5.57 (bs, 1 H, H-1 β), 4.97-4.70 (m, CHH), 4.60-4.47 (m, CHH), 4.01 (t, *J* = 9.5 Hz, 1 H, H- α), 3.94 (bd, 1 H, H- α), 3.75-3.61 (m), 3.36 (bs, 1 H). ¹³C-APT (CDCl₃, 125 MHz, 60°C) δ 159.66, 143.94, 143.73, 139.00, 138.78, 138.38, 138.28, 138.14, 130.67, 130.57 (aromatic C), 129.68, 129.64, 129.46, 128.80, 128.57, 128.54, 128.51, 128.48, 128.46, 128.18, 127.96, 127.92, 127.80, 127.78, 127.74, 127.70, 127.66, 126.46, 124.43, 124.27, 120.78, 119.65, 119.58 (aromatic CH), 116.48 (q, CF₃), 114.12, 114.10 (aromatic CH), 97.64 (C-1 β), 93.91 (C-1 α), 84.78, 81.78, 81.25, 79.70, 77.32, 77.07, 76.07, 75.75, 75.58, 75.06, 74.95, 74.70, 73.72, 73.64, 73.56, 73.52, 68.71 (C-6), 68.69 (C-6), 55.39 (OCH₃), 55.38 (OCH₃). HR-MS: Calculated for $C_{46}H_{42}F_3O_6N$ $[M-[O(C=NPh)CF_3]+OH+Na]^+$: 613.2561, found: 613.2562.

Scheme S2. Preparation of **5b**.



CF₃COOH was added to the solution of **SI-3** (16.9 g, 31.2 mmol) in wet DCM (160 mL). After TLC-analysis showed complete consumption of the starting material, the reaction was quenched with Et₃N. Then the mixture was diluted with DCM, washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product **SI-4** (10.6 g, 75% yield) was purified by column chromatography (PE:EA = 2:1). Compound **SI-4** (10.6 g, 23.4 mmol) was dissolved in pyridine (60 mL). TBDPS-Cl (6.08 ml, 23.4 mmol) was added to the solution. After TLC-analysis showed complete consumption of the starting material, the reaction was quenched with saturated NaHCO₃. The mixture was diluted with DCM, washed with H₂O and brine, dried with anhydrous MgSO₄, filtered, concentrated *in vacuo*, purified by column chromatography (PE:EA = 20:1). Compound **SI-5** (12.9 g, 80% yield) was obtained as colorless solid. The

compound **SI-5** (12.9 g, 18.7 mmol) was dissolved in DMF (75 mL). Sodium hydride (1.34g, 56 mmol) and NapBr (5.37 g, 24.3 mmol) were added to the mixture at 0 °C under N₂. The reaction was stirred at room temperature until TLC-analysis showed complete consumption of the starting material. The mixture was poured in cold water, diluted with Et₂O, washed with H₂O and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The compound **SI-6** (14.4 g, 93% yield) was obtained as yellow syrup. Compound **SI-6** (14.4g, 17.3 mmol) was treated with 1M TBAF in THF (52.0 ml, 52.0 mmol). After TLC-analysis showed complete consumption of the starting material, the reaction was quenched with saturated NaHCO₃. The mixture was diluted with DCM, washed with H₂O and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude compound **SI-7** was dissolved in DMF (70 mL). Sodium hydride (1.25 g, 52 mmol) and PMBCl (3.52 ml, 26.0 mmol) were added to the mixture at 0 °C under N₂. The reaction was stirred at room temperature until TLC-analysis showed complete consumption of the starting material. The mixture was poured in cold water, diluted with Et₂O, washed with H₂O and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude compound was crystallization from EtOH. Compound **5a** (9.70g, 78% yield over two steps, PE:EA = 4:1, R_f = 0.63, melting point 90.4-91 °C) was obtained as a white solid. $[\alpha]_D^{20} +0.9$ (c=1, CHCl₃). IR (neat, cm⁻¹) ν 696, 744, 818, 1029, 1066, 1084, 1125, 1247, 1363, 1512, 1612, 2860, 2920. ¹H-NMR (CDCl₃, 400 MHz) δ 7.78-7.71 (m, 3 H, aromatic H), 7.602-7.57 (m, 3 H, aromatic H), 7.45-7.38 (m, 4 H, aromatic H), 7.33-7.20 (m, 14 H, aromatic H), 6.84-6.79 (m, 2 H, aromatic H), 4.96-4.84 (m, 4 H, 4 CHH), 4.75-4.67 (m, 3 H, H-1, 2 CHH), 4.54 (d, J = 11.6 Hz, 1 H, CHH), 4.42 (d, J = 11.6 Hz, 1 H, CHH), 3.77-3.69 (m, 7 H), 3.56-3.51 (m, 2 H). ¹³C-APT (CDCl₃, 100 MHz,) δ 159.18, 138.49, 138.08, 135.60, 133.98, 133.26, 132.99 (aromatic C), 131.88 (aromatic CH), 130.29 (aromatic C), 129.43, 128.94, 128.58, 128.47, 128.45, 128.25, 128.15, 127.95, 127.89, 127.78, 127.70, 127.69, 127.43, 126.61, 126.11, 125.96, 125.93, 113.91, 113.76 (aromatic CH), 87.54 (C-1), 86.79, 80.91, 79.12, 77.79, 75.82, 75.44, 75.04, 73.08, 68.61, 64.83 (C-6), 55.19 (OCH₃). HR-MS: Calculated for C₄₅H₄₄O₆S [M+Na]⁺: 735.2751, found: 735.2760.

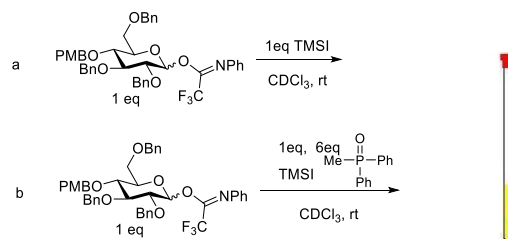
Compound **5a** (9.63g, 13.5 mmol) was dissolved in acetone:H₂O (10:1, 135 mL). NIS (6.08 g, 27.0 mmol) was added in a portion. The reaction was stirred at room temperature for 2 hours, after which the solution was diluted with DCM and the reaction quenched with saturated Na₂S₂O₃. Then the organic layer was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (PE:EA = 3:1). Compound **SI-8** (7.30 g, 87% yield) was obtained as white solid. Then compound **SI-8** (7.30 g, 11.7 mmol) was dissolved in acetone:H₂O (10:1, 120 mL). Cs₂CO₃ (5.75g, 17.6 mmol) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (2.86 mL, 17.6 mmol) were added to the solution respectively. The reaction was stirred overnight, then quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by column chromatography (PE:EA = 50:1-20:1). Compound **5b** (8.50 g, 91% yield, mixture of α and β , PE:EA = 10:1, R_f = 0.25-0.36) was obtained as yellow syrup. ¹H-NMR (CDCl₃, 500 MHz, 60 °C) δ 7.78-6.72 (m, aromatic H), 6.46 (bs, 1 H, H-1 α), 5.60 (bs, 1 H, H-1 β), 4.98-4.37 (m, CHH), 4.05 (t, J = 9.5 Hz, 1 H, H- α), 3.97 (bd, 1 H, H- α), 3.78-3.64 (m), 3.40 (bs, 1 H). ¹³C-APT (CDCl₃, 125 MHz, 60°C) δ 159.63, 159.59, 143.95, 143.75, 143.44, 138.97, 138.74, 138.15, 138.13, 135.95, 135.86, 133.58, 133.55, 133.28, 133.27, 130.41, 130.29 (aromatic C), 129.62, 129.56, 129.46, 128.81, 128.59, 128.55, 128.48, 128.46, 128.19, 128.08, 128.07, 127.98, 127.95, 127.80, 127.76, 127.71, 127.67, 126.66, 126.45, 126.16, 126.04, 125.99, 124.44, 124.30, 120.75, 119.68, 119.60 (aromatic CH), 116.50 (q, CF₃), 114.10, 114.08 (aromatic CH), 97.65 (C-1 β), 93.97 (C-1 α), 84.78, 81.78, 81.26, 79.71, 77.62, 77.34, 76.06, 75.79, 75.61, 75.30, 75.07, 75.05, 73.54, 73.52, 73.33, 73.27, 68.25 (C-6), 68.22 (C-6),

55.31 (OCH₃). HR-MS: Calculated for C₄₇H₄₄F₃O₇N [M-[O(C=NPh)CF₃]+OH+Na]⁺: 643.2666, found: 643.2676.

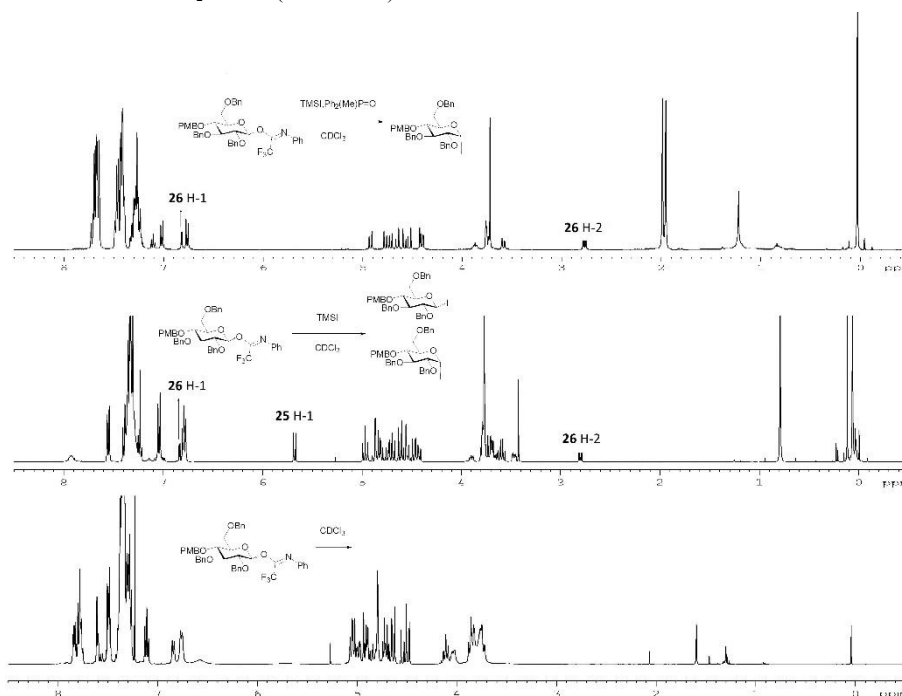
Activation of donor **4b** using TMSI with or without Ph₂MeP=O.

TMSI (10 μ L, 0.07 mmol) was added to a solution of donor **4b** (51 mg, 0.07 mmol), with or without Ph₂MeP=O (91 mg, 0.42 mmol) in CDCl₃ (0.6 mL) in a normal NMR tube under N₂ at room temperature. Spectra were recorded every 10 min.

Figure S1. Activation study of donor **4b** using NMR (for full NMR spectra: see below).



The following NMR spectra were obtained (from bottom to top): Starting donor; Activation with TMSI (after 5 min); Activation with TMSI and Ph₂MeP=O (after 55 min)



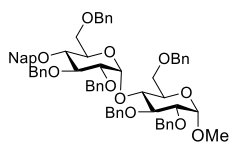
Synthesis of diglucoside **9** using NIS/TMSOTf

The donor **2a** (102 mg, 0.16 mmol) and acceptor **6** (50 mg, 0.11 mmol) were co-evaporated with toluene 3 times, then dissolved in dry DCM (2 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A. The solution was cooled to 0 °C, after which NIS (36 mg, 0.16 mmol) and TMSOTf (29 μ L, 0.16 mmol) were added. The reaction was

stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$, then the organic layer was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by size exclusion (DCM:MeOH = 1:1). Compound **9** (91mg, 86% yield, $\alpha:\beta$ = 2:1, PE:EA = 4:1, R_f = 0.32) was obtained as a colorless syrup.

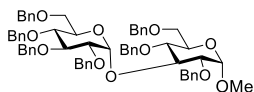
Synthesis of diglucoside **9** using NIS/TMSOTf + DMF

The donor **2a** (102 mg, 0.16 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (1 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (202 μL , 2.56 mmol) was added to the solution. The solution was cooled to 0 °C, after which NIS (36 mg, 0.16 mmol) and TMSOTf (29 μL , 0.16 mmol) were added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **6** (50 mg, 0.11 mmol, dissolved in a little DCM and washed 2 times with DCM (totally 1 mL) was added to the solution. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$, then the organic layer was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by size exclusion (DCM:MeOH = 1:1). Compound **9** (88 mg, 83% yield, $\alpha:\beta$ > 50:1) was obtained as a colorless syrup.

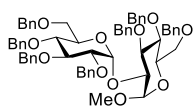


Synthesis of diglucoside **10**: The reaction was carried out according to the standard procedure B at -78 - 0 °C. The donor **3b** (1.34g, 1.96 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (20 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (2.47 mL, 31.4 mmol) was added to the solution.

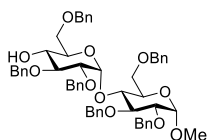
The solution was cooled to -78 °C, after which TfOH (173 μL , 1.96 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **6** (608mg, 1.31 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 6 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **10** (1113mg, 82% yield, $\alpha:\beta$ > 20:1, PE:EA = 4:1, R_f = 0.48) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +34.8$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 696, 735, 820, 857, 910, 1028, 1045, 1093, 1156, 1207, 1261, 1273, 1363, 1453, 1496, 2860, 3030. ^1H -NMR (CDCl_3 , 400MHz) δ 7.81-7.79 (m, 1 H, aromatic *H*), 7.74-7.70 (m, 2 H, aromatic *H*), 7.50 (bs, 1 H, aromatic *H*), 7.47-7.43 (m, 2 H, aromatic *H*), 7.30-7.18 (m, 31 H, aromatic *H*), 5.73 (d, J = 3.6 Hz, 1 H, H-1b), 5.05 (d, J = 11.6 Hz, 1 H, *CHH*), 4.91 (d, J = 10.8 Hz, 1 H, *CHH*), 4.81 (d, J = 10.8 Hz, 1 H, *CHH*), 4.70 (d, J = 12.0 Hz, 1 H, *CHH*), 4.63-4.49 (m, 8 H, 7 *CHH*, H-1a), 4.23 (d, J = 12.0 Hz, 1 H, *CHH*), 4.13-4.05 (m, 2 H, H-3a, H-4a), 3.94 (t, J = 9.2 Hz, 1 H, H-3b), 3.87-3.82 (m, 2 H, H-5a, H-6a_b), 3.73-3.59 (m, 4 H, H-5a, H-4b, H-2a, H-6a_b), 3.54-3.50 (m, 2H, H-2b, H-6b_a), 3.40-3.37 (m, 4 H, H-6b_b). ^{13}C -APT (CDCl_3 , 100 MHz) δ 139.01, 138.88, 138.22, 138.05, 137.96, 136.00, 139.29, 132.99 (aromatic C), 128.54, 128.45, 128.41, 128.35, 128.32, 128.31, 128.20, 128.04, 127.96, 127.88, 127.82, 127.78, 127.74, 127.69, 127.61, 127.46, 127.29, 127.21, 126.86, 126.61, 126.15, 126.10, 125.93 (aromatic CH), 97.86 (C-1a), 96.72 (C-1b), 82.19 (C-3b), 82.15 (C-3a), 80.28 (C-2a), 79.52 (C-2b), 77.65 (C-4b), 75.66, 75.11, 74.54, 73.54, 73.49, 73.35, 73.20 (7 CH_2), 72.17 (C-4a), 71.03 (C-5a), 69.57 (C-5b), 69.05 (C-6a), 68.12 (C-6b), 55.25 (OCH_3). HR-MS: Calculated for $\text{C}_{66}\text{H}_{68}\text{O}_{11}$ $[\text{M}+\text{Na}]^+$: 1059.4654 found: 1059.4681.



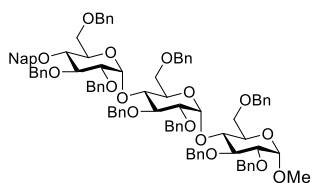
Synthesis of diglucoside **11**: The reaction was carried out according to the standard procedure B at $-78 - 0\text{ }^{\circ}\text{C}$. The donor **2b** (106 g, 0.15 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (1 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (188 μL , 2.39 mmol) was added to the solution. The solution was cooled to $-78\text{ }^{\circ}\text{C}$, after which TfOH (13 μL , 0.15 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **7** (46 mg, 0.10 mmol, dissolved in a little DCM and washed 2 times with DCM, totally 1 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at $0\text{ }^{\circ}\text{C}$ until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **11** (83 mg, 85% yield, α : β > 20:1, PE:EA = 4:1, R_f = 0.32) was obtained as a colorless syrup.



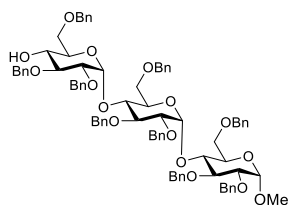
Synthesis of diglucoside **12**: The reaction was carried out according to the standard procedure B at $-78 - 0\text{ }^{\circ}\text{C}$. The donor **2b** (106 g, 0.15 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (1 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (188 μL , 2.39 mmol) was added to the solution. The solution was cooled to $-78\text{ }^{\circ}\text{C}$, after which TfOH (13 μL , 0.15 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **7** (46 mg, 0.10 mmol, dissolved in a little DCM and washed 2 times with DCM, totally 1 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at $0\text{ }^{\circ}\text{C}$ until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **12** (88 mg, 90% yield, α : β > 20:1, PE:EA = 4:1, R_f = 0.22) was obtained as a colorless syrup.



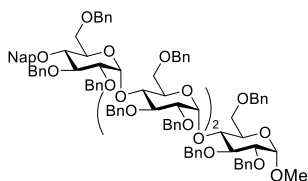
Synthesis of diglucoside **13**: The reaction was carried out according to the general procedure D, using **12** (750mg, 0.73 mmol, 0.1 M in DCM:H₂O) and DDQ (180 mg, 0.80 mmol). The product was purified by silica gel column chromatography (PE:EA = 6:1). Compound **13** (510mg, 78% yield, PE:EA = 4:1, R_f = 0.20) was obtained as a colorless syrup. $[\alpha]_D^{20} +38.4$ ($c=1$, CHCl_3), IR (neat, cm^{-1}) ν 696, 735, 764, 910, 1027, 1046, 1093, 1153, 1208, 1456, 2867, 2923. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.34-7.17 (m, 30 H, aromatic *H*), 5.71 (d, J = 3.6Hz, 1 H, H-1b), 5.05 (d, J = 11.6 Hz, 1 H, *CHH*), 4.90 (d, J = 11.6 Hz, 1 H, *CHH*), 4.71 (d, J = 11.6 Hz, 1 H, *CHH*), 4.69 (d, J = 11.6 Hz, 1 H, *CHH*), 4.61 (d, J = 3.6Hz, 1 H, H-1a), 4.59-4.47(m, 6 H, 6 *CHH*), 4.43 (d, J = 12.0 Hz, 1 H, *CHH*), 4.32 (d, J = 12.0 Hz, 1 H, *CHH*), 4.12-4.03 (m, 2 H, H-3a, H-4a), 3.88-3.83 (m, 2 H), 3.77-3.58 (m, 5 H), 3.54-3.51 (m, 2H), 3.46-3.42 (m, 2 H), 3.38 (s, 3 H, OCH_3). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 138.97, 138.81, 138.25, 137.97, 137.94, 137.90 (aromatic C), 128.51, 128.48, 128.38, 128.36, 128.30, 128.25, 128.13, 127.99, 127.90, 127.76, 127.69, 127.43, 127.36, 127.16, 126.75 (aromatic CH), 97.77 (C-1a), 96.58 (C-1b), 82.09 (C-3a), 81.30 (C-3b), 80.21 (C-2a), 79.02 (C-2b), 75.35, 74.43, 73.56, 73.38, 73.19, 73.12 (6 CH_2), 72.27 (C-4a), 71.48 (C-4b), 70.57 (C-5a), 69.77 (C-5b), 69.56 (C-6a), 69.03 (C-6b), 55.21 (OCH_3). HR-MS: Calculated for $\text{C}_{55}\text{H}_{60}\text{O}_{11}$ $[\text{M}+\text{Na}^+]$: 919.4028; found: 919.4058.



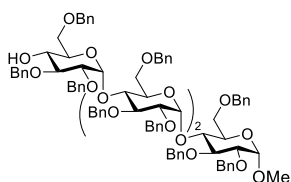
Synthesis of triglycoside **14**: The reaction was carried out according to the standard procedure B. The donor **3b** (1.04g, 1.53 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (10 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (1.90 mL, 24.4 mmol) was added to the solution. The solution was cooled to -78°C , after which TfOH (134 μL , 1.52 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **13** (680 mg, 0.76 mmol) dissolved in a little DCM and washed 3 times with DCM (totally 5 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **14** (906mg, 81% yield, $\alpha:\beta > 20:1$, PE:EA = 4:1, $R_f = 0.42$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +49.4$ (c=1, CHCl_3). IR (neat, cm^{-1}) ν 696, 749, 764, 1028, 1043, 1094, 1154, 1275, 2870, 3030. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.81-7.78 (m, 1 H, aromatic H), 7.74-7.68 (m, 2 H, aromatic H), 7.50 (bs, 1 H, aromatic H), 7.47-7.43 (m, 2 H, aromatic H), 7.30-7.09 (m, 46 H, aromatic H), 5.71 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.59 (d, $J = 3.6$ Hz, 1 H, H-1c), 5.04 (d, $J = 11.6$ Hz, 1 H, CHH), 4.93 (d, $J = 11.6$ Hz, 1 H, CHH), 4.91 (d, $J = 10.8$ Hz, 1 H, CHH), 4.85-4.68 (m, 5 H, 5 CHH), 4.60-4.40 (m, 12 H), 4.24 (d, $J = 12.0$ Hz, 1 H, CHH), 4.11-4.02 (m, 4 H), 3.95-3.83 (m, 4 H), 3.74-3.50 (m, 9 H), 3.40-3.37 (m, 4 H). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz.) δ 139.12, 138.95, 138.89, 138.42, 138.30, 138.12, 138.01, 137.85, 136.06, 133.31, 133.00 (aromatic C), 128.55, 128.42, 128.38, 128.36, 128.34, 128.31, 128.29, 128.19, 128.05, 127.97, 127.96, 127.78, 127.76, 127.7, 127.64, 127.62, 127.60, 127.55, 127.46, 127.22, 127.13, 126.89, 126.71, 126.59, 126.15, 126.12, 125.94 (aromatic CH), 97.90 (C-1a), 96.83 (C-1b), 96.37 (C-1c), 82.23, 82.01, 81.83 (3 C-3), 80.09, 79.71, 79.67 (3 C-2), 77.66 (C-4), 75.55, 75.11, 74.57, 74.15, 73.57, 73.48, 73.32, 73.12, 73.08 (CH_2), 73.03, 72.47 (2 C-4), 71.03, 70.83, 69.65 (3 C-5), 68.98, 68.87, 68.16 (3 C-6), 55.31 (OCH_3). HR-MS: Calculated for $\text{C}_{93}\text{H}_{96}\text{O}_{16}$ $[\text{M}+\text{Na}^+]$: 1491.6591; found: 1491.6603.



Synthesis of triglycoside **15**: The reaction was carried out according to the general procedure D, using **14** (800mg, 0.54 mmol, 0.1 M in DCM: H_2O) and DDQ (136 mg, 0.60 mmol). The product was purified by silica gel column chromatography (PE:EA = 6:1). Compound **15** (564mg, 78% yield, PE:EA = 4:1, $R_f = 0.20$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +41.0$ (c=1, CHCl_3). IR (neat, cm^{-1}) ν 696, 735, 1028, 1042, 1077, 1081, 1094, 1125, 1132, 1154, 1364, 1453, 2854, 2930. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.28-7.06 (m, 45 H, aromatic H), 5.71 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.60 (d, $J = 3.2$ Hz, 1 H, H-1c), 5.05 (d, $J = 11.6$ Hz, 1 H, CHH), 4.96 (d, $J = 11.6$ Hz, 1 H, CHH), 4.85-4.62 (m, 2 H, 2 CHH), 4.77-4.39 (m, 13 H), 4.33 (d, $J = 12.0$ Hz, 1 H, CHH), 4.13-4.03 (m, 5 H), 3.91-3.85 (m, 3 H), 3.77-3.52 (m, 9 H), 3.47-3.42 (m, 2 H), 3.38 (s, 3 H, OCH_3). $^{13}\text{C-APT}$ (CDCl_3 , 125 MHz.) δ 139.19, 138.97, 138.95, 138.51, 138.24, 138.21, 138.17, 137.05, 137.88 (aromatic C), 128.56, 128.55, 128.48, 128.39, 128.35, 128.32, 128.05, 127.99, 127.85, 127.79, 127.78, 127.75, 127.70, 127.67, 127.60, 127.54, 127.48, 127.23, 127.17, 127.92, 126.72 (aromatic CH), 97.95, 96.64, 96.37 (3 C-1), 82.01, 81.83, 81.47, 80.13, 79.74, 79.25, 75.32, 74.58, 74.08, 73.70, 73.49, 73.35, 73.27, 73.08, 72.94, 72.39, 71.69, 70.88, 70.53, 69.95, 69.73, 69.03, 68.93, 55.33 (OCH_3). HR-MS: Calculated for $\text{C}_{82}\text{H}_{88}\text{O}_{16}$ $[\text{M}+\text{Na}^+]$: 1351.5965; found: 1351.6018.

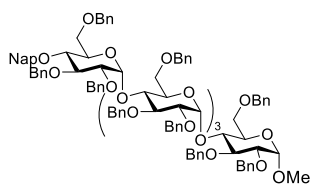


Synthesis of tetraglucoside **16**: The reaction was carried out according to the standard procedure B. The donor **3b** (620 mg, 0.91 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (5 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (1.13 mL, 14.5 mmol) was added to the solution. The solution was cooled to -78°C , after which TfOH (80 μL , 0.91 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **15** (680 mg, 0.76 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 3 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **16** (661mg, 82% yield, $\alpha:\beta > 20:1$, PE:EA = 4:1, $R_f = 0.33$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +64.8$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 696, 735, 1028, 1040, 1095, 1155, 1208, 1275, 1456, 2865, 3031, 3064. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.81-7.78 (m, 1 H, aromatic *H*), 7.74-7.68 (m, 2 H, aromatic *H*), 7.51 (bs, 1 H, aromatic *H*), 7.46-7.42 (m, 2 H, aromatic *H*), 7.30-7.09 (m, 61 H, aromatic *H*), 5.71 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.60 (m, 2 H, H-1c, H-1d), 5.04 (d, $J = 11.6$ Hz, 1 H, *CHH*), 4.94-4.69 (m, 9 H, 9 *CHH*), 4.61 (d, $J = 3.6$ Hz, 1 H, H-1b), 4.60-4.37 (m, 15 H), 4.23 (d, $J = 12.0$ Hz, 1 H, *CHH*), 4.14-4.01 (m, 6 H), 3.96 (t, $J = 9.2$ Hz, 1 H), 3.90-3.85 (m, 4 H), 3.79-3.71 (m, 4 H), 3.66-3.50 (m, 8 H), 3.40-3.37 (m, 4 H). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 139.09, 138.97, 138.93, 138.87, 138.42, 138.23, 138.14, 138.12, 138.09, 138.02, 137.96, 137.87, 136.02, 133.28, 132.97 (aromatic C), 128.49, 128.37, 128.27, 128.25, 128.22, 128.20, 128.14, 128.00, 127.98, 127.91, 127.73, 127.71, 127.66, 127.62, 127.58, 127.54, 127.48, 127.40, 127.16, 127.10, 127.02, 126.87, 126.73, 126.58, 126.12, 126.07, 125.90 (aromatic CH), 97.87 (C-1a), 96.94 (C-1b), 96.45, 96.32 (2 C-1), 82.19, 81.97, 81.85, 81.59 (4 C-3), 80.04, 79.79, 79.57, 79.42 (4 C-2), 77.67 (C-4), 75.52, 75.09, 74.56, 74.11, 74.05, 73.52, 73.41, 73.35, 73.31, 73.25 (CH_2), 73.18, 73.14 (2 C-4), 73.06, 73.02, 72.87 (CH_2), 72.53 (C-4), 70.99, 70.88, 70.81, 69.66 (4 C-5), 68.90, 68.84, 68.78, 68.15 (4 C-6), 55.26 (OCH_3). HR-MS: Calculated for $\text{C}_{120}\text{H}_{124}\text{O}_{21}$ $[\text{M}+\text{H}^+]$: 1901.8708; found: 1901.8695.



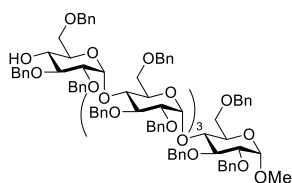
Synthesis of tetraglucoside **17**: The reaction was carried out according to the general procedure D, using **16** (590 mg, 0.31 mmol, 0.05 M in DCM:H₂O) and DDQ (80 mg, 0.35 mmol). The product was purified by silica gel column chromatography (PE:EA = 5:1). Compound **17** (460 mg, 84% yield, PE:EA = 4:1, $R_f = 0.18$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +59.2$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 695, 733, 747, 764, 910, 1027, 1039, 1094, 1152, 1207, 1260, 1456, 2855, 3923, 3031. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.29-7.10 (m, 60 H, aromatic *H*), 5.70 (d, $J = 3.2$ Hz, 1 H, H-1b), 5.61 (bd, 2 H, H-1c, H-1d), 5.05 (d, $J = 11.6$ Hz, 1 H, *CHH*), 4.94-4.78 (m, 5 H, 5 *CHH*), 4.73-4.37 (m, 18 H), 4.31 (d, $J = 12.0$ Hz, 1 H, *CHH*), 4.14-4.01 (m, 6 H), 3.90-3.86 (m, 4 H), 3.78-3.39 (m, 17 H). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 139.19, 139.05, 138.98, 138.95, 138.54, 138.34, 138.24, 138.20, 138.12, 138.07, 138.04, 137.97 (aromatic C), 128.57, 128.55, 128.48, 128.40, 128.35, 128.33, 128.29, 128.05, 127.99, 127.85, 127.83, 127.79, 127.77, 127.75, 127.72, 127.70, 127.67, 127.61, 127.59, 127.52, 127.47, 127.23, 127.17, 127.12, 126.97, 126.92, 126.81, 126.73, 126.64 (aromatic CH), 97.97, 96.79, 96.56, 96.34 (4 C-1), 82.03, 81.91, 81.63, 81.50 (4 C-3), 80.14, 79.86, 79.50, 79.17 (4 C-2), 75.36, 74.65, 74.15, 73.69, 73.50, 73.45 (C-4), 73.41, 73.38, 73.33, 73.27 (C-4), 72.93, 72.90, 72.40, 71.72 (C-4), 70.95, 70.91, 70.50 (3 C-5), 69.95 (C-6), 69.77 (C-5), 68.97, 68.88 (3 C-6), 55.35 (OCH_3). HR-MS:

Calculated for $C_{109}H_{116}O_{21}$ $[M+Na]^+$: 1783.7901; found: 1783.7969.



Synthesis of pentaglucofuranose **18**: The reaction was carried out according to the standard procedure B. The donor **3b** (380 mg, 0.56 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (2 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (700 μ L, 8.90 mmol) was added to the solution. The solution was cooled to -78°C , after which TfOH

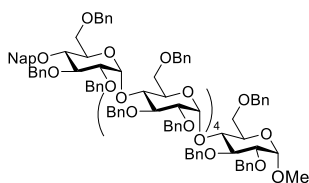
(49 μ L, 0.55 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **15** (680 mg, 0.76 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 3 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **18** (410mg, 80% yield, $\alpha:\beta > 20:1$, PE:EA = 4:1, $R_f = 0.26$) was obtained as a colorless syrup. $[\alpha]_D^{20} +92.7$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 695, 734, 820, 857, 910, 1027, 1037, 1094, 1154, 1207, 1363, 1453, 2862, 2927, 3031. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.81-7.79 (m, 1 H, aromatic *H*), 7.74-7.69 (m, 2 H, aromatic *H*), 7.50 (bs, 1 H, aromatic *H*), 7.46-7.44 (m, 2 H, aromatic *H*), 7.29-7.04 (m, 76 H, aromatic *H*), 5.72 (bs, 1 H, H-1), 5.63 (bs, 1 H, H-1), 5.59 (bs, 2 H, 2 H-1), 5.04 (d, $J = 11.6$ Hz, 1 H, *CHH*), 4.93-4.70 (m, 11 H, 11 *CHH*), 4.60-4.37 (m, 20 H), 4.22 (d, $J = 12.0$ Hz, 1 H, *CHH*), 4.11-3.47 (m, 29 H), 3.38-3.35 (m, 4 H). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 139.14, 139.00, 138.95, 138.89, 138.44, 138.28, 138.27, 138.14, 138.08, 137.99, 137.94, 137.90, 136.06, 133.30, 133.00 (aromatic C), 128.52, 128.40, 128.33, 128.21, 128.17, 128.02, 128.00, 127.94, 127.81, 127.77, 127.74, 127.71, 127.65, 127.59, 127.53, 127.50, 127.42, 127.18, 127.13, 127.05, 126.91, 126.77, 126.66, 126.59, 126.57, 126.15, 126.10, 125.93 (aromatic CH), 97.91 (C-1a), 97.01, 96.52, 96.46, 96.34 (4 C-1), 82.24, 81.98, 81.89, 81.68 (5 C-3), 80.05, 79.75, 79.57, 79.49 (5 C-2), 77.69 (C-4), 75.54, 75.12, 74.60, 74.12, 74.06, 73.55, 73.45, 73.41, 73.33, 73.29 (CH_2), 73.17 (2 C-4), 73.06 (CH_2), 72.95 (C-4), 72.91, 72.85 (CH_2), 72.50 (C-4), 71.02, 70.90, 70.85, 69.69 (5 C-5), 68.92, 68.86, 68.80, 68.73, 68.16 (5 C-6), 55.29 (OCH_3). MALDI-TOF: Calculated for $C_{147}H_{152}O_{26}$ $[M+H]^+$: 2356.0; found: 2357.9.



Synthesis of pentaglucofuranose **19**: The reaction was carried out according to the general procedure D, using **18** (590 mg, 0.25 mmol, 0.05 M in DCM:H₂O) and DDQ (63 mg, 0.28 mmol). The product was purified by silica gel column chromatography (PE:EA = 5:1). Compound **19** (415mg, 81% yield, PE:EA = 4:1, $R_f = 0.16$) was obtained as a colorless syrup. $[\alpha]_D^{20} +73.0$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 695, 733,

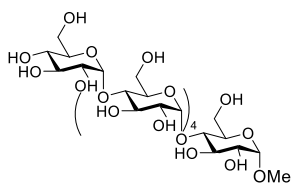
746, 763, 937, 1027, 1037, 1092, 1153, 1207, 1275, 1363, 1454, 2860, 2920, 3030, 3064. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.31-7.02 (450m, 75 H, aromatic *H*), 5.71 (d, $J = 3.6$ Hz, 1 H, H-1), 5.64 (d, $J = 3.6$ Hz, 1 H, H-1), 5.60 (bd, 2 H, 2 H-1), 5.05 (d, $J = 11.6$ Hz, 1 H, *CHH*), 4.95-4.36 (m, 29 H), 4.30 (d, $J = 12.0$ Hz, 1 H, *CHH*), 4.13-3.98 (m, 8 H), 3.91-3.86 (m, 5 H), 3.80-3.50 (m, 15 H), 3.45-3.37 (m, 5 H). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 139.56, 139.19, 139.03, 138.99, 138.95, 138.92, 138.50, 138.33, 138.20, 138.17, 138.11, 138.10, 138.00, 137.94 (aromatic C), 128.63, 128.53, 128.52, 128.45, 128.37, 128.31, 128.29, 128.27, 128.25, 128.22, 128.01, 127.96, 127.84, 127.80, 127.76, 127.30, 127.70, 127.69, 127.62, 127.55, 127.48, 127.44, 127.20, 127.15, 127.07, 126.94, 126.80, 126.69, 126.57 (aromatic CH), 97.95 (C-1a), 96.81, 96.55, 96.41, 96.36 (4 C-1), 81.99, 81.90, 81.68, 81.66, 81.50 (5 C-3), 80.10, 79.77, 79.58, 79.53, 79.13, 75.32, 74.62,

74.12, 74.04, 73.98, 73.66, 73.51, 73.46, 73.41, 73.37, 73.33, 73.22, 73.08, 73.02, 72.93, 72.91, 72.82, 72.35, 71.71, 70.93, 70.91, 70.46, 69.92, 69.74, 68.91, 68.77, 55.31 (OCH₃). MALDI-TOF: Calculated for C₁₃₆H₁₄₄O₂₆ [M+Na⁺]: 2216.0; found: 2220.0.



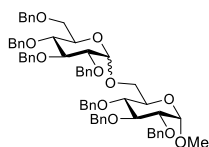
Synthesis of hexaglucofuranose 20: The reaction was carried out according to the standard procedure B. The donor **3b** (95 mg, 0.14 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (1 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (175 μ L, 2.25 mmol) was added to the solution. The solution was cooled to -78 $^{\circ}$ C, after which TfOH

(12 μ L, 0.14 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **15** (680 mg, 0.76 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 3 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 $^{\circ}$ C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **20** (104mg, 81% yield, α : β > 20:1, PE:EA = 4:1, *R*_f = 0.21) was obtained as a colorless syrup. [α]_D²⁰ +72.6 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 696, 738, 749, 764, 1028, 1039, 1095, 1154, 1208, 1261, 1456, 2859, 2922, 3031. ¹H-NMR (CDCl₃, 400 MHz) δ 7.82-7.79 (m, 1 H, aromatic *H*), 7.74-7.67 (m, 2 H, aromatic *H*), 7.50 (bs, 1 H, aromatic *H*), 7.47-7.43 (m, 2 H, aromatic *H*), 7.29-7.02 (m, 91 H, aromatic *H*), 5.71 (d, *J* = 3.6 Hz, 1 H, H-1), 5.64 (d, *J* = 3.2 Hz, 1 H, H-1), 5.61 (bt, 2 H, 2 H-1), 5.58 (d, *J* = 3.6 Hz, 1 H, H-1), 5.04 (d, *J* = 11.6 Hz, 1 H, CHH), 4.93-4.69 (m, 13 H, 11 CHH), 4.61-4.34 (m, 24 H), 4.21 (d, *J* = 12.0 Hz, 1 H, CHH), 4.13-3.46 (m, 35 H), 3.38-3.35 (m, 4 H). ¹³C-APT (CDCl₃, 100 MHz) δ 139.16, 138.98, 138.96, 138.91, 138.46, 138.30, 138.27, 138.16, 138.07, 138.00, 137.95, 137.92, 136.08, 133.32, 133.01 (aromatic C), 128.54, 128.41, 128.23, 128.19, 128.02, 127.97, 127.83, 127.80, 127.76, 127.73, 127.60, 127.58, 127.54, 127.50, 127.43, 127.21, 127.15, 127.06, 126.94, 126.79, 126.67, 126.64, 126.60, 126.58, 126.17, 126.11, 125.94 (aromatic CH), 97.93 (C-1a), 97.02, 96.55, 96.47, 96.34 (5 C-1), 82.25, 82.00, 81.92, 81.77, 81.73, 81.65 (6 C-3), 80.07, 79.77, 79.65, 79.58, 79.50, 77.71, 75.55, 75.13, 74.63, 74.07, 73.98, 73.56, 73.47, 73.37, 73.34, 73.30, 73.08, 72.99, 72.91, 72.63, 72.48, 71.02, 70.91, 70.85, 69.71, 68.88 (C-6), 68.72 (C-6), 68.18 (C-6), 55.31 (OCH₃). MALDI-TOF: Calculated for C₁₇₄H₁₈₀O₃₁ [M+Na⁺]: 2788.2; found: 2790.1.

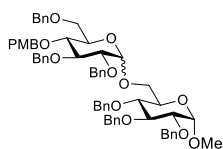


Synthesis of hexaglucofuranose 21: Compound **20** (31 mg, 0.011 mmol) was dissolved in THF/H₂O/*tert*-BuOH (4 ml/4 ml/1.6 ml) before a catalytic amount of Pd(OH)₂/C was added. The reaction mixture was stirred for 3 days under a H₂ atmosphere (3.5 bar), filtered and concentrated *in vacuo*. A white powder was obtained, which was purified by gel filtration (HW-40, 0.15M NH₄OAc in H₂O) to provide **21** (9mg,

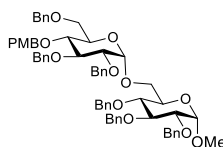
80%). ¹H-NMR (CDCl₃, 400 MHz) δ 5.37-5.36 (m, 5 H, 5 H-1), 4.77 (d, *J* = 4.0 Hz, 1 H, H-1a), 3.94-3.53 (m, 35 H), 3.41-3.35 (m, 4 H). ¹³C-APT (CDCl₃, 100 MHz) δ 96.68, 96.53, 99.40, 99.07 (6 C-1), 76.71, 76.64, 76.55, 73.50, 73.29, 72.81, 72.66, 71.68, 71.50, 71.12, 71.01, 70.00, 69.26, 60.41 (C-6), 60.34 (C-6), 55.04 (OCH₃). HR-MS: Calculated for C₃₇H₆₄O₃₁ [M+Na⁺]: 1027.3324; found: 1027.3348.



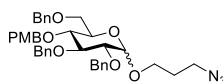
Synthesis of diglucoside **23** using NIS/TMSOTf+DMF: The donor **2a** (102 mg, 0.16 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (1 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (202 μ L, 2.56 mmol) was added to the solution. The solution was cooled to 0 $^{\circ}$ C, after which NIS (36 mg, 0.16 mmol) and TMSOTf (29 μ L, 0.16 mmol) were added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **22** (50 mg, 0.11 mmol, dissolved in a little DCM and washed 2 times with DCM (totally 1 mL) was added to the solution. The reaction was stirred at 0 $^{\circ}$ C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$, then the organic layer was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by size exclusion (DCM:MeOH = 1:1). Compound **23** (88 mg, 83% yield, $\alpha:\beta$ = 2.7:1, PE:EA = 4:1, R_f = 0.32) was obtained as a colorless syrup.



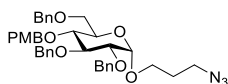
Synthesis of diglucoside **24** ($\alpha:\beta$ = 3:1): The donor **4b** (123 mg, 0.16 mmol) and acceptor **22** (70 mg, 0.15 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (2 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (50 μ L, 0.64 mmol) was added to the solution. Then TMSOTf (10 μ L, 0.05 mmol) was added. The reaction was stirred at rt until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **24** (144 mg, 94% yield, $\alpha:\beta$ = 3:1) was obtained as a white solid.



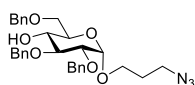
Synthesis of diglucoside **24**: The reaction was carried out according to the standard procedure C, using **4b** (90 mg, 0.15 mmol), **22** (40 mg, 0.09 mmol, 0.1 M in DCM), $\text{Ph}_3\text{P}=\text{O}$ (143 mg, 0.51 mmol) and TMSI (19 μ L, 0.12 mmol). The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **24** (79 mg, 90% yield, $\alpha:\beta$ = 25:1, PE:EA = 4:1, R_f = 0.34, melting point 117.5–118.6 $^{\circ}$ C) was obtained as a white solid. IR (neat, cm^{-1}) ν 696, 737, 747, 821, 1028, 1052, 1072, 1084, 1137, 1159, 1249, 1363, 1456, 1515, 1855, 2924, 3030. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.33–7.22 (m, 30 H, aromatic *H*), 7.04–7.01 (m, 2 H, aromatic *H*), 6.79–6.76 (m, 2 H, aromatic *H*), 4.99–4.89 (m, 4 H, 3 *CHH*, H-1), 4.82–4.54 (m, 10 H, 10 *CHH*), 4.43–4.37 (m, 2 H, *CHH*, H-1), 4.00–3.92 (m, 2 H), 3.84–3.52 (m, 12 H), 3.43 (dd, J_1 = 3.6 Hz, J_2 = 9.6 Hz, 1 H), 3.34 (s, 3 H). ^{13}C -APT (CDCl_3 , 100 MHz) δ 159.22, 138.98, 138.93, 138.55, 138.27, 138.10, 130.72 (aromatic C), 129.54, 128.51, 128.46, 128.25, 128.11, 128.07, 128.00, 127.95, 127.87, 127.74, 127.72, 127.67, 127.59, 113.78 (aromatic CH), 98.04 (C-1), 97.35 (C-1), 82.22, 81.80, 80.22, 80.07, 77.85, 77.42, 75.81, 75.57, 75.08, 74.68, 73.49, 73.48, 72.45, 70.47, 70.35, 68.56, 66.10, 55.35, 55.25. HR-MS: Calculated for $\text{C}_{63}\text{H}_{68}\text{O}_{12}[\text{M}+\text{Na}^+]$: 1039.4603; found: 1039.4642.



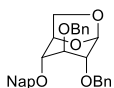
Synthesis of glucoside **27** ($\alpha:\beta$ = 1:1): The donor **4b** (123 mg, 0.16 mmol) and 3-aminopropanol (30 μ L, 0.32 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (2 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A. Then TMSOTf (5 μ L, 0.03 mmol) was added. The reaction was quenched with Et_3N after 3 h, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography (PE:EA = 10:1). Compound **27** (53 mg, 49% yield, $\alpha:\beta$ = 1:1) was obtained as a colorless syrup.



Synthesis of glucoside **27**: The reaction was carried out according to the standard procedure C, using **4b** (1.95 g, 2.63 mmol, 0.1 M in DCM), 3-aminopropanol (369 μ L, 3.94 mmol), $\text{Ph}_3\text{P}=\text{O}$ (4.39 g, 15.8 mmol) and TMSI (413 μ L, 2.89 mmol). The product was purified by silica gel column chromatography (PE:EA = 10:1). Compound **27** (1530 mg, 91% yield, $\alpha:\beta$ = 11:1, PE:EA = 4:1, R_f = 0.48) was obtained as a colorless syrup. An analytical sample of the pure α -anomer was obtained by careful silica gel column chromatography (PE:EA = 10:1). $[\alpha]_{\text{D}}^{20}$ +24.6 ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 749, 764, 823, 1014, 1028, 1040, 1071, 1158, 1249, 1257, 1456, 2096, 2867, 2910, 2923, 3031. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.33-7.22 (m, 15 H, aromatic H), 7.03 (d, J = 8.6 Hz, 2 H, aromatic H), 6.78 (d, J = 8.6 Hz, 2 H, aromatic H), 4.98 (d, J = 11.0 Hz, 1 H, CHH), 4.83 (d, J = 11.0 Hz, 1 H, CHH), 4.79-4.72 (m, 3 H, 2 CHH , H-1), 4.63 (d, J = 12.0 Hz, 1 H, CHH), 4.61 (d, J = 12.0 Hz, 1 H, CHH), 4.47 (d, J = 12.0 Hz, 1 H, CHH), 4.39 (d, J = 12.0 Hz, 1 H, CHH), 3.94 (t, $J_1 = J_2$ = 9.2 Hz, 1 H, H-3), 3.76 (s, 3 H, CH_3), 3.74-3.68 (m, 3H, H-5, H-6a, H-1 $^\circ$ a), 3.64-3.59 (m, 2H, H-6b, H-4), 3.55 (dd, J_1 = 3.6 Hz, J_2 = 9.6 Hz, 1 H, H-2), 3.48-3.33 (m, 3 H, H-1 $^\circ$ b, H-3 $^\circ$), 1.95-1.77 (m, 2 H, H-2 $^\circ$). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 159.33, 138.96, 138.32, 137.99, 130.39 (5 aromatic C), 129.73, 128.55, 128.48, 128.46, 128.09, 128.01, 127.99, 127.94, 127.79, 127.66, 113.86 (19 aromatic CH), 97.30 (C-1), 82.12 (C-3), 80.13 (C-2), 77.41 (C-4), 75.74, 74.85, 73.55, 73.38 (4 PhCH₂), 70.41 (C-5), 68.49 (C-6), 64.79 (C-1 $^\circ$), 55.33 (OCH₃), 48.38 (C-3 $^\circ$), 28.93 (C-2 $^\circ$). HR-MS: Calculated for $\text{C}_{38}\text{H}_{43}\text{O}_7\text{N}_3[\text{M}+\text{Na}^+]$: 676.2993; found: 676.3008.

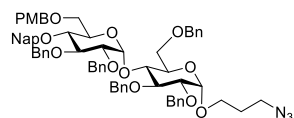


Synthesis of glucoside **28**: The reaction was carried out according to the general procedure E, using **27** (1605 mg, 2.51 mmol, 0.1 M in DCM:HFIP), triethylsilane (400 μ L, 2.52 mmol) and 0.2M HCl/HFIP (1.3 ml, 0.26 mmol). The product was purified by silica gel column chromatography (PE:EA = 6:1). Compound **28** (1138 mg, 85% yield, PE:EA = 2:1, R_f = 0.49) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20}$ +30.0 ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 749, 764, 1000, 1028, 1053, 1080, 1152, 1261, 1275, 1456, 2096, 2874, 2916, 3032. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.33-7.21 (m, 15 H, aromatic H), 4.99 (d, J = 11.4 Hz, 1 H, CHH), 4.76-4.71 (m, 3 H, 2 CHH , H-1), 4.61 (d, J = 12.0 Hz, 1 H, CHH), 4.58 (d, J = 12.0 Hz, 1 H, CHH), 4.52 (d, J = 12.0 Hz, 1 H, CHH), 3.81-3.66 (m, 5 H, H-6, H-5, H-1 $^\circ$ a), 3.60 (dt, J_1 = 2.2 Hz, J_2 = 9.2 Hz, 1 H, H-4), 3.52 (dd, J_1 = 3.6 Hz, J_2 = 9.6 Hz, 1 H, H-2), 3.47-3.33 (m, 3 H, H-1 $^\circ$ b, H-3 $^\circ$), 2.46 (d, J = 2.2 Hz, 1 H, OH), 1.94-1.82 (m, 2 H, H-2 $^\circ$). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 138.85, 138.18, 138.02 (3 aromatic C), 128.59, 128.52, 128.04, 128.02, 127.98, 127.94, 127.84, 127.68, 127.64 (15 aromatic CH), 97.21 (C-1), 82.42 (C-3), 79.80 (C-2), 75.39, 73.59, 73.07 (3 PhCH₂), 70.77 (C-4), 70.20 (C-5), 69.49 (C-6), 64.78 (C-1 $^\circ$), 48.35 (C-3 $^\circ$), 28.86 (C-2 $^\circ$). HR-MS: Calculated for $\text{C}_{30}\text{H}_{35}\text{O}_6\text{N}_3[\text{M}+\text{Na}^+]$: 556.2418; found: 556.2771.

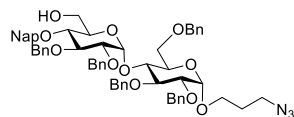


Characterization of anhydroglucose **29**: Compound **29** was obtained in the glycosylation reaction of **5b** and **28** as a side product. Compound **29** was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20}$ -21.1 ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 736, 819, 857, 898, 925, 953, 1027, 1071, 1089, 1173, 1197, 1315, 1337, 1454, 1718, 2858, 2895, 2922, 2956, 3060. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.85-7.78 (m, 3 H, aromatic H), 7.74 (s, 1 H, aromatic H), 7.51-7.46 (m, 3 H, aromatic H), 7.33-7.27 (m, 8 H, aromatic H), 7.20-7.17 (m, 2 H, aromatic H), 5.47 (s, 1 H, H-1), 4.47 (d, J = 12.4 Hz, 1 H, CHH), 4.71 (d, J = 12.4 Hz, 1 H, CHH), 4.62 (d, J = 5.4 Hz, 1 H, H-5), 4.58 (d, J = 12.4 Hz, 1 H, CHH), 4.54 (d, J = 12.4 Hz, 1 H, CHH), 4.42 (d, J = 12.4 Hz, 1 H, CHH), 4.37 (d, J = 12.4 Hz, 1 H, CHH), 3.89 (dd, J_1

= 0.8 Hz, $J_2 = 7.2$ Hz, 1 H, H-6a), 3.62 (dd, $J_1 = 5.4$ Hz, $J_2 = 7.2$ Hz, 1 H, H-6b), 3.61 (bs, 1 H, H-3), 3.36 (bd, 2 H, H-4, H-2), ^{13}C -APT (CDCl_3 , 100 MHz) δ 137.93, 135.47, 133.27, 133.16 (aromatic C), 128.56, 128.55, 128.45, 128.09, 127.98, 127.96, 127.94, 127.83, 127.71, 126.78, 126.35, 126.15, 125.92 (aromatic CH), 100.69 (C-1), 76.71 (C-4), 76.06 (C-3), 77.04 (C-2), 74.51 (C-5), 72.08, 71.90, 71.47 (3 CH_2), 65.469 (C-6). HR-MS: Calculated for $\text{C}_{31}\text{H}_{30}\text{O}_5$ [$\text{M}+\text{Na}^+$]: 505.1985; found: 505.1999.

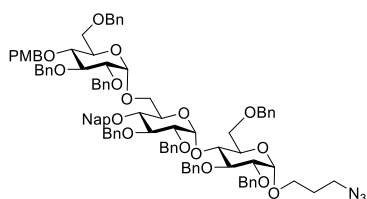


Synthesis of diglucoside 30: The reaction was carried out according to the standard procedure B. The donor **5b** (2.60 g, 3.28 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (35 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (2.80 mL, 35.5 mmol) was added to the solution. The solution was cooled to -78°C , after which TMSOTf (600 μL , 3.35 mmol) was added. After 60 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **28** (1.19 g, 2.23 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 10 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion ($\text{DCM}:\text{MeOH} = 1:1$). Compound **30** (2.05 g, 81% yield, $\alpha:\beta > 20:1$, Toluene (Tol):EA = 12:1, $R_f = 0.55$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +44.5$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 750, 764, 1014, 1029, 1038, 1093, 1156, 1261, 2096, 2868, 2925. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.81-7.78 (m, 1 H, aromatic H), 7.73-7.68 (m, 2 H, aromatic H), 7.47-7.42 (m, 3 H, aromatic H), 7.29-7.10 (m, 28 H, aromatic H), 6.76-6.72 (m, 2 H, aromatic H), 5.73 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.05 (d, $J = 11.6$ Hz, 1 H, CHH), 4.92 (d, $J = 10.8$ Hz, 1 H, CHH), 4.88 (d, $J = 11.2$ Hz, 1 H, CHH), 4.83 (d, $J = 11.6$ Hz, 1 H, CHH), 4.81 (d, $J = 11.2$ Hz, 1 H, CHH), 4.74 (d, $J = 3.6$ Hz, 1 H, H-1a), 4.67 (d, $J = 12.0$ Hz, 1 H, CHH), 4.61-4.46 (m, 7 H, 7 CHH), 4.16 (d, $J = 12.0$ Hz, 1 H, CHH), 4.11-4.05 (m, 2 H, H-3a, H-4a), 3.93 (t, $J = 8.8$ Hz, 1 H, H-3b), 3.86-3.82 (m, 2 H, H-5a, H-6a), 3.76-3.61 (m, 8 H, H-5b, H-4b, H-2a, H-1 $^\circ$, H-6a, OCH_3), 3.55-3.49 (m, 2 H, H-2b, H-6b), 3.48-3.34 (m, 4 H, H-1 $^\circ$, H-6b, H-3 $^\circ$), 1.92-1.85 (m, 2 H, H-2 $^\circ$). ^{13}C -APT (CDCl_3 , 100 MHz) δ 159.25, 139.02, 138.89, 138.23, 138.11, 137.98, 135.99, 133.26, 132.96 (aromatic C), 129.91 (aromatic CH), 129.88 (aromatic C), 128.52, 128.40, 128.36, 128.32, 128.29, 128.15, 128.00, 127.94, 127.93, 127.87, 127.80, 127.68, 127.55, 127.44, 127.27, 127.17, 126.79, 126.47, 126.04, 125.88, 113.72 (aromatic CH), 96.88 (C-1a), 96.84 (C-1b), 82.09 (C-3b), 81.97 (C-3a), 80.48 (C-2a), 79.42 (C-2b), 77.63 (C-4b), 75.59, 75.03, 74.36, 73.30, 73.25, 73.18, 73.07 (7 CH_2), 72.34 (C-4a), 71.01 (C-5b), 69.84 (C-5a), 69.02 (C-6a), 67.52 (C-6b), 64.86 (C-1 $^\circ$), 55.12 (OCH_3), 48.36 (C-3 $^\circ$), 28.90 (C-2 $^\circ$). HR-MS: Calculated for $\text{C}_{69}\text{H}_{73}\text{O}_{12}\text{N}_3$ [$\text{M}+\text{Na}^+$]: 1158.5086; found: 1158.5112.



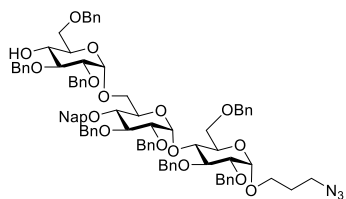
Synthesis of diglucoside 31: The reaction was carried out according to the general procedure E, using **30** (1.78 g, 1.57 mmol, 0.1 M in $\text{DCM}:\text{HFIP}$), triethylsilane (250 μL , 1.57 mmol) and 0.2M $\text{HCl}:\text{HFIP}$ (0.8 mL, 0.16 mmol). The product was purified by silica gel column chromatography (Tol:EA = 20:1). Compound **31** (1.36 g, 85% yield, Tol:EA = 12:1, $R_f = 0.21$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +30.4$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 696, 735, 748, 818, 1027, 1047, 1072, 1089, 1155, 1208, 1261, 1275, 1355, 1363, 1456, 2096, 2862, 2871, 2918, 2924, 3031. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.82-7.74 (m, 3 H, aromatic H), 7.68 (bs, 1 H, aromatic H), 7.48-7.43 (m, 2 H, aromatic H), 7.39 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.4$ Hz, 1 H,

aromatic *H*), 7.30-7.19 (m, 25 *H*, aromatic *H*), 5.63 (d, $J = 3.6$ Hz, 1 *H*, H-1b), 5.04 (d, $J = 11.2$ Hz, 1 *H*, *CHH*), 5.00 (d, $J = 10.8$ Hz, 1 *H*, *CHH*), 4.93 (d, $J = 10.8$ Hz, 1 *H*, *CHH*), 4.82 (d, $J = 10.8$ Hz, 1 *H*, *CHH*), 4.80 (d, $J = 10.8$ Hz, 1 *H*, *CHH*), 4.77 (d, $J = 11.2$ Hz, 1 *H*, *CHH*), 4.74 (d, $J = 3.6$ Hz, 1 *H*, H-1a), 4.68 (d, $J = 12.0$ Hz, 1 *H*, *CHH*), 4.61-4.50 (m, 5 *H*, 5 *CHH*), 4.09-4.04 (m, 2 *H*, H-3a, H-4a), 3.96 (t, $J = 8.8$ Hz, 1 *H*, H-3b), 3.86-3.82 (bd, 2 *H*, H-5a, H-6a), 3.76-3.51 (m, 7*H*, H-6b, H-5b, H-4b, H-6a_b, H-2a, H-1_a), 3.48-3.37 (m, 4 *H*, H-2b, H-1_b, H-3[°]), 1.93-1.87 (m, 2 *H*, H-2[°]). ¹³C-APT (CDCl₃, 100 MHz,) δ 139.01, 138.79, 138.10, 137.99, 137.95, 135.77, 133.32, 133.07 (aromatic *C*), 128.58, 128.48, 128.47, 128.40, 128.38, 128.28, 128.19, 128.08, 128.01, 127.94, 127.86, 127.83, 127.80, 127.67, 126.85, 126.71, 126.23, 126.12, 126.07 (aromatic *CH*), 96.90 (C-1a), 96.53 (C-1b), 82.00 (C-3a), 81.85 (C-3b), 80.41 (C-2a), 79.60 (C-2b), 77.59 (C-4b), 75.64, 75.31, 74.40, 73.50, 73.35 (6 *CH*₂), 72.31 (C-4a), 71.71 (C-5b), 69.91 (C-5a), 68.70 (C-6a), 64.94 (C-1[°]), 64.68 (C-6b), 48.41 (C-3[°]), 28.93 (C-2[°]). HR-MS: Calculated for C₆₂H₆₇O₁₁N₃ [M+Na⁺]: 1038.4511; found: 1038.4543.



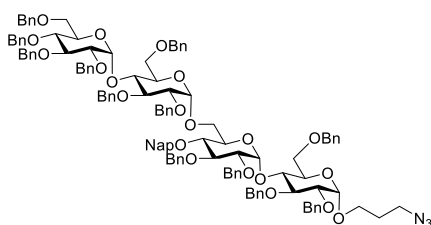
Synthesis of triglucoside **32**: The reaction was carried out according to the standard procedure C, using **4b** (1.80 g, 2.43 mmol), **31** (1.28 g, 1.26 mmol, 0.1 M in DCM), Ph₃P=O (4.00g, 14.4 mmol) and TMSI (382 μ L, 2.67 mmol). The product was purified by size exclusion (DCM:MeOH = 1:1).

Compound **32** (1.34 g, 68% yield, α : β > 20:1, Tol:EA = 12:1, R_f = 0.52) was obtained as a colorless syrup. [α]_D²⁰ +58.1 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 697, 749, 764, 820, 1028, 1051, 1073, 1084, 1156, 1208, 1251, 1261, 1275, 1465, 2096, 2868, 2923, 3031. ¹H-NMR (CDCl₃, 400 MHz) δ 7.78-7.68 (m, 4 *H*, aromatic *H*), 7.46-7.37 (m, 3 *H*, aromatic *H*), 7.32-7.10 (m, 40 *H*, aromatic *H*), 7.01 (bd, 2 *H*, aromatic *H*), 6.75-6.72 (m, 2 *H*, aromatic *H*), 5.63 (d, $J = 3.6$ Hz, 1 *H*, H-1b), 5.07 (d, $J = 3.6$ Hz, 1 *H*, H-1c), 5.03 (d, $J = 12.0$ Hz, 1 *H*, *CHH*), 5.02 (d, $J = 11.6$ Hz, 1 *H*, *CHH*), 4.93 (d, $J = 10.8$ Hz, 1 *H*, *CHH*), 4.88 (d, $J = 10.8$ Hz, 1 *H*, *CHH*), 4.80-4.72 (m, 6 *H*, H-1a, 5 *CHH*), 4.65-4.46 (m, 7 *H*, 7 *CHH*), 4.41-4.34 (m, 4 *H*, 4 *CHH*), 4.07-4.03 (m, 2 *H*, H-4a, H-3a), 3.96-3.56 (m, 17 *H*), 3.53 (dd, $J_1 = 3.2$ Hz, $J_2 = 9.6$ Hz, 1 *H*, H-2c), 3.48-3.37 (m, 4 *H*, H-6c, H-3[°]), 3.26 (dd, $J_1 = 3.6$ Hz, $J_2 = 9.6$ Hz, 1 *H*, H-2b), 1.91-1.85 (m, 2 *H*, H-2[°]). ¹³C-APT (CDCl₃, 100 MHz,) δ 159.20, 134.14, 139.03, 138.96, 138.54, 138.17, 138.13, 138.11, 138.03, 136.20, 133.36, 133.01, 130.77 (aromatic *C*), 129.62, 128.57, 128.45, 128.39, 128.36, 128.33, 128.22, 128.15, 128.05, 128.04, 127.80, 127.75, 127.70, 127.55, 127.50, 127.47, 127.38, 127.21, 126.61, 126.53, 126.15, 126.08, 125.87, 113.76 (aromatic *CH*), 97.20 (C-1c), 96.90 (C-1a), 96.29 (C-1b), 82.12 (C-3a), 81.98 (C-3b), 81.81 (C-3c), 80.38 (C-2a), 80.21 (C-2c), 80.00 (C-2b), 77.65 (C-4b), 77.31 (C-4c), 75.58, 75.50, 75.22, 74.77, 74.09, 73.54, 73.34, 73.29 (*CH*₂), 71.94 (C-4a), 71.84 (*CH*₂), 71.70 (C-5b), 70.27 (C-5c), 69.79 (C-5a), 69.14 (C-6a), 68.39 (C-6c), 65.24 (C-6b), 64.91 (C-1[°]), 55.33 (OCH₃), 48.41 (C-3[°]), 28.93 (C-2[°]). HR-MS: Calculated for C₆₂H₆₇O₁₁N₃ [M+Na⁺]: 1591.7162; found: 1591.6997.



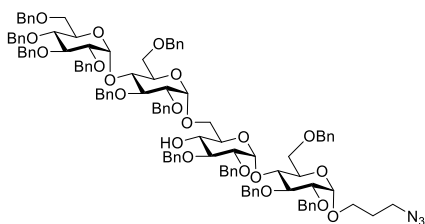
Synthesis of triglucoside **33**: The reaction was carried out according to the general procedure E, using **30** (1.90 g, 1.21 mmol, 0.1 M in DCM:HFIP), triethylsilane (302 μ L, 1.90 mmol) and 0.2M HCl/HFIP (0.95 ml, 0.19 mmol). The product was purified by silica gel column chromatography (Tol:EA = 25:1). Compound **33** (1456mg, 83% yield, Tol:EA = 12:1, R_f = 0.33) was

obtained as a colorless syrup. $[\alpha]_D^{20} +47.7$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 696, 737, 749, 764, 820, 857, 911, 1027, 1051, 1081, 1091, 1141, 1155, 1208, 1261, 1275, 2097, 2867, 2923. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.82-7.70 (m, 4 H, aromatic *H*), 7.49-7.39 (m, 3 H, aromatic *H*), 7.31-7.12 (m, 40 H, aromatic *H*), 5.64 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.06-5.03 (m, 3 H, H-1c, 2 *CHH*), 4.94 (d, $J = 11.6$ Hz, 1 H, *CHH*), 4.89 (d, $J = 10.8$ Hz, 1 H, *CHH*), 4.81-4.35 (m, 15 H, H-1a, 14 *CHH*), 4.09-4.03 (m, 2 H, H-4a, H-3a), 3.93-3.32 (m, 19 H), 3.26 (dd, $J_1 = 3.6$ Hz, $J_2 = 10.0$ Hz, 1 H, H-2b), 1.91-1.85 (m, 2 H, H-2°). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 139.04, 138.92, 138.42, 134.14, 138.09, 137.99, 136.15, 133.35, 133.02 (aromatic C), 128.55, 128.45, 128.40, 128.36, 128.32, 128.20, 128.17, 128.10, 128.05, 128.01, 127.82, 127.79, 127.69, 127.58, 127.53, 127.46, 127.38, 127.32, 127.23, 126.65, 126.59, 126.14, 125.93 (aromatic CH), 97.17 (C-1c), 96.85 (C-1a), 96.16 (C-1b), 82.15 (C-3a), 81.99 (C-3b), 80.86 (C-3c), 80.39 (C-2a), 80.01 (C-2b), 79.76 (C-2c), 77.71 (C-4b), 77.48, 77.16, 76.84, 75.52, 75.17, 74.12, 73.58, 73.33, 73.28 (CH_2), 71.69 (C-4a), 71.65 (C-5b), 71.58 (CH_2), 70.62 (C-5c), 70.70 (C-4c), 69.75 (C-5a), 69.36 (C-6a), 69.07 (C-6c), 65.34 (C-6b), 64.90 (C-1°), 48.38 (C-3°), 28.90 (C-2°). HR-MS: Calculated for $\text{C}_{62}\text{H}_{67}\text{O}_{11}\text{N}_3$ $[\text{M}+\text{H}^+]$: 1448.6629; found: 1448.6653.



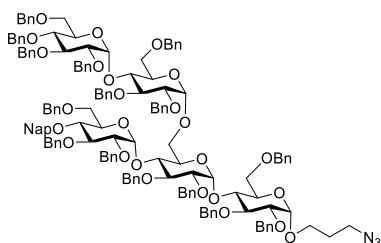
Synthesis of tetraglucose **34:** The reaction was carried out according to the standard procedure B. The donor **2b** (1.05 g, 1.47 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (10 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (1.86 mL, 23.6 mmol) was added to the solution. The solution was cooled to -78°C , after which TfOH (130

μL , 1.47 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **33** (1.07 g, 0.74 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 5 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **34** (1.18 g, 81% yield, $\alpha:\beta > 20:1$, Tol:EA = 12:1, $R_f = 0.57$) was obtained as a colorless syrup. $[\alpha]_D^{20} +60.7$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 696, 734, 749, 764, 819, 856, 909, 1027, 1047, 1072, 1091, 1155, 1207, 1261, 1275, 1363, 1456, 2090, 2095, 2863, 2923, 3031. $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 7.78-7.73 (m, 4 H, aromatic *H*), 7.48-7.37 (m, 3 H, aromatic *H*), 7.28-7.03 (m, 60 H, aromatic *H*), 5.73 (d, $J = 3.6$ Hz, 1 H, H-1d), 5.64 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.20 (d, $J = 3.6$ Hz, 1 H, H-1c), 5.08-5.00 (m, 3 H, 3 *CHH*), 4.90-4.29 (m, 23 H, H-1a, 22 *CHH*), 4.22 (d, $J = 12.4$ Hz, 1 H, *CHH*), 4.11-4.03 (m, 4 H, H-5b, H-4c, H-3a, H-3c), 3.95-3.31 (m, 23 H), 3.23 (dd, $J_1 = 3.6$ Hz, $J_2 = 9.2$ Hz, 1 H, H-2b), 1.91-1.85 (m, 2 H, H-2°). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 139.05, 139.04, 139.02, 138.85, 138.64, 138.38, 138.21, 138.07, 138.04, 138.01, 137.98, 136.24, 133.38, 133.05 (aromatic C), 128.57, 128.41, 128.35, 128.32, 128.31, 128.26, 128.21, 128.12, 128.06, 128.03, 127.93, 127.80, 127.76, 127.68, 127.63, 127.50, 127.46, 127.34, 127.24, 127.06, 126.93, 126.75, 126.54, 126.35, 126.08, 125.85 (aromatic CH), 96.90 (C-1a), 96.71 (2 C, C-1c and 1d), 96.18 (C-1b), 82.15 (2 C, C-3a and 3d), 81.88 (C-3b), 81.71 (C-3c), 80.38 (C-2a), 80.22 (C-2c), 79.98 (C-2b), 79.38 (C-2d), 77.65 (2 C, C-4b and 4d), 75.51, 75.41, 75.27, 74.99, 74.07, 74.01, 73.49, 73.43, 73.34, 73.23, 72.96 (CH_2), 72.06 (C-4a), 71.97 (C-4c), 71.54 (CH_2), 71.40 (C-5b), 70.91 (C-5d), 69.83 (C-5c), 69.70 (C-5a), 68.95 (2 C, C-6a and 6c), 68.15 (C-6d), 64.90 (C-1°), 64.55 (C-6b), 48.36 (C-3°), 28.90 (C-2°). HR-MS: Calculated for $\text{C}_{122}\text{H}_{127}\text{O}_{21}\text{N}_3$ $[\text{M}+\text{H}^+]$: 1970.9035; found: 1970.9066.



Synthesis of tetraglucoside **35**: The reaction was carried out according to the general procedure D, using **34** (1.20 g, 0.61 mmol, 0.05 M in DCM:H₂O) and DDQ (152 mg, 0.67 mmol). The product was purified by silica gel column chromatography (Tol:EA = 25:1). Compound **35** (928mg, 84% yield, Tol:EA = 12:1, R_f = 0.28) was obtained as a colorless syrup. [α]_D²⁰ +64.3 (c=1, CHCl₃). IR (neat,

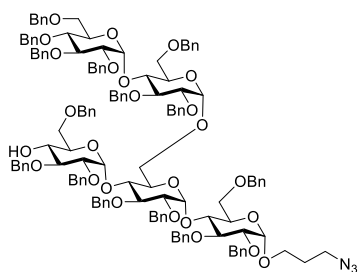
cm⁻¹) ν 695, 733, 747, 764, 911, 1026, 1044, 1092, 1155, 1208, 1261, 1275, 1355, 1363, 1456, 2095, 2868, 2926, 3031, 3064. ¹H-NMR (CDCl₃, 400MHz) δ 7.43-7.09 (m, 60 H, aromatic H), 5.70 (d, *J* = 3.6 Hz, 1 H, H-1d), 5.67 (d, *J* = 3.6 Hz, 1 H, H-1b), 5.04 (d, *J* = 12.0 Hz, 1 H, CHH), 4.99 (d, *J* = 11.6 Hz, 1 H, CHH), 4.89-4.39 (m, 23 H, H-1a, H-1c, 21 CHH), 4.25 (d, *J* = 12.4 Hz, 1 H, CHH), 4.11-3.97 (m, 4 H, H-4a, H-4c, H-3a, H-3c), 3.88-3.33 (m, 24 H), 1.93-1.86 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz) δ 139.09, 138.98, 138.86, 138.62, 138.19, 138.10, 138.06, 138.00, 137.97 (aromatic C), 128.77, 128.57, 128.51, 128.44, 128.43, 128.37, 128.35, 128.29, 128.20, 128.15, 128.05, 127.92, 127.90, 127.84, 127.79, 127.74, 127.70, 127.66, 127.64, 127.60, 127.54, 127.44, 127.23, 127.12, 126.75, 126.69 (aromatic CH), 97.53 (C-1a), 96.90 (C-1c), 96.82 (C-1d), 96.52 (C-1b), 82.06 (C-3d and 3c), 81.96 (C-3a), 81.37 (C-3b), 80.44 (C-2c), 80.04 (C-2a), 79.40 (C-2d), 79.26 (C-2b), 77.69 (C-4d), 75.63, 75.53, 75.02, 74.22, 73.54, 73.32, 73.27, 72.57 (CH₂), 72.03 (C-4a), 71.92 (C-4c), 71.72 (C-4b), 71.06 (C-5b), 70.94 (C-5d), 69.84 (C-5c and 5a), 68.92 (C-6a), 68.83 (C-6c), 68.17 (C-6d), 67.73 (C-6b), 64.90 (C-1°), 48.40 (C-3°), 28.93 (C-2°). HR-MS: Calculated for C₁₁₁H₁₁₉O₂₁N₃ [M+H⁺]: 1830.8409; found: 1830.8458.



Synthesis of pentaglucoside **36**: The reaction was carried out according to the standard procedure B. The donor **3b** (1.20 g, 1.57 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (6 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (1.98 mL, 25.1 mmol) was added to the solution. The solution was cooled to -78 °C, after which TfOH (139 μ L, 1.57 mmol) was added. After 30 min, the pre-activation was complete as indicated by

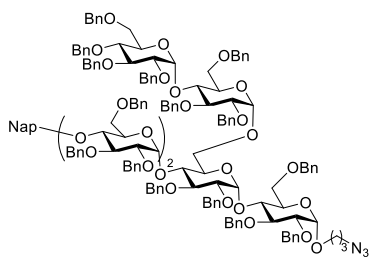
TLC-analysis. Acceptor **35** (860 mg, 0.47 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 3 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **36** (1.04 g, 91% yield, α : β > 20:1, Tol:EA = 12:1, R_f = 0.64) was obtained as a colorless syrup. [α]_D²⁰ +60.5 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 696, 749, 765, 1297, 1275, 2094, 2868, 2925, 3012. ¹H-NMR (CDCl₃, 400MHz) δ 7.69-7.62 (m, 3 H, aromatic H), 7.51 (s, 1 H, aromatic H), 7.39-7.36 (m, 2 H, aromatic H), 7.28-7.02 (m, 74 H, aromatic H), 6.97-6.95 (m, 2 H, aromatic H), 5.72-5.71 (bt, 2 H, H-1d, H-1e), 5.54 (d, *J* = 3.6 Hz, 1 H, H-1b), 5.35 (d, *J* = 3.6 Hz, 1 H, H-1c), 5.05 (d, *J* = 11.6 Hz, 1 H, CHH), 4.96-3.56 (m, 59H), 3.47-3.30 (m, 6H), 3.20 (dd, *J*₁ = 3.6 Hz, *J*₂ = 9.6 Hz, 1 H, H-2b), 1.91-1.85 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz) δ 139.12, 138.98, 138.89, 138.87, 138.72, 138.51, 138.25, 138.18, 138.16, 138.11, 138.07, 138.04, 137.72, 135.91, 133.29, 133.01 (aromatic C), 128.58, 128.43, 128.36, 128.34, 128.32, 128.27, 128.20, 128.18, 128.15, 128.12, 128.06, 127.98, 127.94, 127.90, 127.77, 127.72, 127.68, 127.65, 127.56, 127.47, 127.43, 127.31, 127.24, 127.04, 126.94, 126.79, 126.75,

126.61, 126.24, 126.05, 125.88 (aromatic CH), 97.14 (C-1a), 96.95 (C-1e), 96.63 (C-1d), 96.51 (C-1c), 95.80 (C-1b), 82.13 (C-3a), 81.98 (2 C, C-3d, C-3e), 81.78 (C-3c), 81.08 (C-3b), 80.34 (C-2a), 80.20 (2 C, C-2c, C-2d), 79.46 (C-2b), 79.25 (C-2e), 77.69 (C-4d), 77.57 (C-4e), 75.49, 75.24, 75.01, 74.43 (CH₂), 74.24 (C-4b), 74.12, 73.68, 73.49, 73.35, 73.24, 73.11, 72.89 (CH₂), 72.38 (C-4a), 72.24 (C-5e), 72.11 (C-5b), 71.76 (CH₂), 71.60 (C-4c), 70.99 (C-5d), 69.90 (C-5c), 69.80 (C-5a), 68.98 (C-6e), 68.80 (2 C, C-6a, C-6c), 68.20 (C-6d), 64.91 (C-1°), 64.30 (C-6b), 48.38 (C-3°), 28.91 (C-2°). MALDI-TOF: Calculated for C₁₄₉H₁₅₅O₂₆N₃ [M+H⁺]: 2403.1; found: 2397.7.



Synthesis of pentagluside **37**: The reaction was carried out according to the general procedure D, using **36** (1.10 g, 0.46 mmol, 0.05 M in DCM:H₂O) and DDQ (125 mg, 0.55 mmol). The product was purified by silica gel column chromatography (Tol:EA = 20:1). Compound **37** (777mg, 75% yield, Tol:EA = 12:1 =, R_f = 0.36) was obtained as a colorless syrup. [α]_D²⁰ +79.6 (c=1, CHCl₃). IR (neat, cm⁻¹) ν₆₉₇, 749, 764, 1028, 1045, 1098, 1155, 1261,

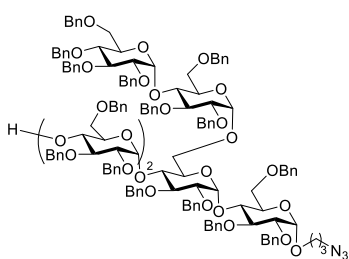
1275, 2098, 2855, 2923, 3031. ¹H-NMR (CDCl₃, 400MHz) δ 7.28-6.98 (m, 75 H, aromatic H), 5.74(d, *J* = 3.2 Hz, 1 H, H-1d), 5.63 (d, *J* = 3.2 Hz, 1 H, H-1e), 5.56 (d, *J* = 3.2 Hz, 1 H, H-1b), 5.32 (d, *J* = 3.2 Hz, 1 H, H-1c), 5.06 (d, *J* = 12.0 Hz, 1 H, CHH), 4.93-3.36 (m, 63H), 3.21 (dd, *J*₁ = 3.2 Hz, *J*₂ = 9.6 Hz, 1 H, H-2b), 1.92-1.86 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 12 MHz.) δ 139.02, 138.96, 138.92, 138.82, 138.55, 138.43, 138.34, 138.21, 138.17, 138.08, 138.03, 137.96, 137.59 (aromatic C), 128.53, 128.38, 128.28, 128.15, 128.08, 128.03, 127.88, 127.84, 127.76, 127.70, 127.68, 127.57, 127.45, 127.42, 127.38, 127.31, 127.20, 127.09, 127.02, 126.93, 126.79, 126.55 (aromatic CH), 96.90 (C-1a), 96.87 (C-1e), 96.55 (C-1c), 95.72 (C-1d), 95.68 (C-1b), 82.15 (C-3a), 82.00 (C-3e), 81.59 (C-3c), 81.41 (C-3d), 81.26 (C-3b), 80.14 (C-2a), 80.09 (C-2c), 79.74 (C-2b), 79.60 (C-2d), 79.31 (C-2e), 77.65 (C-4d), 75.50, 75.21, 74.92, 74.20, 74.08, 73.89, 73.76, 73.44, 73.29, 73.20, 73.07, 73.02, 72.96, 72.74, 72.64, 71.84, 71.79, 71.47 (CH₂), 71.44 (C-4b), 71.84 (2 C, C-4e, C-4a), 71.79 (2 C, C-5b, C-5d), 71.47 (CH₂), 71.44 (C-4c), 70.98 (C-4c), 70.85 (C-5e), 69.83 (C-5c), 69.76 (C-6), 69.70 (C-5a), 68.91, 68.60, 68.21 (3 C-6), 64.86 (C-1°), 64.20 (C-6b), 48.31 (C-3°), 28.87 (C-2°). MALDI-TOF: Calculated for C₁₃₈H₁₄₇O₂₆N₃ [M+H⁺]: 2263.0; found: 2259.9.



Synthesis of hexasaccharide **38**: The reaction was carried out according to the standard procedure B. The donor **3b** (860 mg, 1.13 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (3 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (1.30 mL, 16.5 mmol) was added to the solution. The solution was cooled to -78 °C, after which TfOH (100 μL, 1.13 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis.

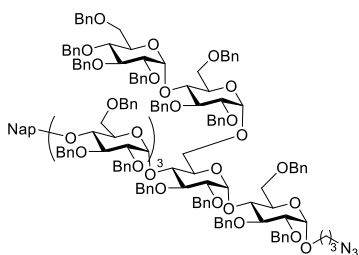
Acceptor **37** (620 mg, 0.27 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 3 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **38** (717mg, 93% yield, α:β 20:1, Tol:EA = 12:1 =, R_f = 0.64) was obtained as a colorless syrup. [α]_D²⁰ +62.6 (c=1, CHCl₃). IR (neat, cm⁻¹) ν₆₉₆, 749, 764, 1028, 1042,

1094, 1144, 1155, 1208, 1261, 1275, 1456, 2096, 2860, 2923, 3031. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.80-7.77 (m, 1 H, aromatic H), 7.71-7.67 (m, 2 H, aromatic H), 7.46-7.42 (m, 3 H, aromatic H), 7.34-6.92 (m, 91 H, aromatic H), 5.78 (d, $J = 3.6$ Hz, 1 H, H-1d), 5.74 (d, $J = 3.6$ Hz, 1 H, H-1e), 5.58 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.48 (d, $J = 3.6$ Hz, 1 H, H-1f), 5.33 (d, $J = 3.6$ Hz, 1 H, H-1c), 5.14 (d, $J = 10.8$ Hz, 1 H, CHH), 5.04 (d, $J = 11.6$ Hz, 1 H, CHH), 4.91-3.30 (m, 75 H), 3.25 (dd, $J_1 = 3.6$ Hz, $J_2 = 10.0$ Hz, 1 H, H-2b), 1.90-1.84 (m, 2 H, H-2°). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 139.37, 139.25, 139.00, 138.89, 138.78, 138.53, 138.40, 138.26, 138.23, 138.11, 138.08, 137.98, 137.93, 136.10, 133.35, 133.05 (aromatic C), 129.17, 128.59, 128.05, 127.71, 127.68, 127.41, 127.23, 127.04, 126.96, 126.75, 126.72, 126.58, 126.25, 126.11, 125.95, 125.43 (aromatic CH), 96.99 (C-1a, 1e, 1f), 96.84 (C-1d), 96.70 (C-1c), 96.28 (C-1b), 82.29, 82.16, 82.00, 81.87, 81.56 (5 C-3), 80.62 (C-2), 80.48 (C-3), 80.42, 80.35, 79.52, 79.25, 78.88 (5 C-2), 78.49, 77.78 (2 C-4), 75.58, 75.34, 75.17, 74.98, 74.30, 74.01, 73.58, 73.55, 73.44, 73.35, 73.29, 73.07 (CH_2), 72.90 (C-4), 72.81 (C-5), 72.64, 72.16 (CH_2), 72.02, 71.85 (2 C-4), 71.28, 71.08, 71.00, 70.04, 70.00 (5 C-5), 69.28, 69.11, 69.00, 68.26, 68.16 (5 C-6), 64.94 (C-1°), 64.83 (C-6b), 48.44 (C-3°), 28.95 (C-2°). MALDI-TOF: Calculated for $\text{C}_{176}\text{H}_{183}\text{O}_{31}\text{N}_3$ [$\text{M}+\text{H}^+$]: 2835.3; found: 2833.2.



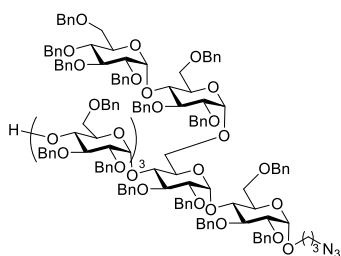
Synthesis of hexaglucoide **39**: The reaction was carried out according to the general procedure D, using **38** (700 g, 0.25 mmol, 0.05 M in $\text{DCM}:\text{H}_2\text{O}$) and DDQ (67 mg, 0.30 mmol). The product was purified by silica gel column chromatography (PE:EA = 20:1). Compound **39** (440 mg, 66% yield, Tol:EA = 12:1, $R_f = 0.38$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +67.8$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 696, 732, 734, 1016, 1028, 1050, 1094, 1152, 1363, 1453, 2093, 2872, 2927. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.30-6.93 (m, 90 H,

aromatic H), 5.78 (d, $J = 3.6$ Hz, 1 H, H-1d), 5.73 (d, $J = 3.6$ Hz, 1 H, H-1e), 5.58 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.53 (d, $J = 3.2$ Hz, 1 H, H-1f), 5.36 (d, $J = 3.6$ Hz, 1 H, H-1c), 5.09 (d, $J = 11.2$ Hz, 1 H, CHH), 5.05 (d, $J = 12.0$ Hz, 1 H, CHH), 4.91-3.31 (m, 75 H), 3.25 (dd, $J_1 = 3.6$ Hz, $J_2 = 9.6$ Hz, 1 H, H-2b), 1.92-1.86 (m, 2 H, H-2°). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 139.28, 139.19, 138.92, 138.86, 138.70, 138.49, 138.42, 138.17, 138.04, 137.95, 137.82 (aromatic C), 128.59, 128.51, 128.23, 128.18, 128.06, 128.01, 127.93, 127.86, 127.84, 127.82, 127.75, 127.59, 127.50, 127.45, 127.40, 127.34, 127.24, 127.04, 126.97, 126.69, 126.60, 126.55 (aromatic CH), 97.06 (C-1e), 96.96 (C-1a), 96.75 (C-1f), 96.64 (C-1c, 1d), 96.19 (C-1b), 82.09, 82.00, 81.83, 81.65, 81.58, 80.59 (6 C-3), 80.52, 80.36, 80.29, 79.13, 78.89 (6 C-2), 77.69 (2 C-4), 75.55, 75.29, 75.15, 74.99, 74.27, 74.02, 73.93, 73.60, 73.51, 73.37, 73.32, 73.25, 73.06, 72.98, 72.79, 72.65, 72.05, 71.91, 71.68, 71.57, 71.22, 70.59, 70.51, 69.98, 69.93, 69.69, 69.14, 68.96, 68.16, 64.92 (C-1°), 64.63 (C-6b), 48.41 (C-3°), 28.93 (C-2°). MALDI-TOF: Calculated for $\text{C}_{165}\text{H}_{175}\text{O}_{31}\text{N}_3$ [$\text{M}+\text{H}^+$]: 695.2; found: 2692.7.



Synthesis of heptaglucoide **40**: The reaction was carried out according to the standard procedure B. The donor **3b** (550 mg, 0.72 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (1 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (900 μL , 11.4 mmol) was added to the solution. The solution was cooled to -78°C , after which TfOH (63 μL , 0.71 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **39** (360 mg,

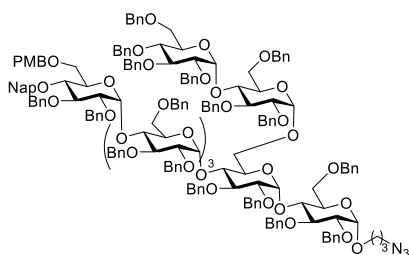
0.13 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 3 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **40** (397 mg, 91% yield, α : β = 20:1, Tol:EA = 12:1, *R_f* = 0.67) was obtained as a colorless syrup. $[\alpha]_D^{20}$ +67.5 (*c*=1, CHCl₃). IR (neat, cm⁻¹) ν 696, 733, 1027, 1035, 1078, 1082, 1093, 1132, 1141, 1145, 1155, 1361, 1453, 1496, 2098, 2864, 2928. ¹H-NMR (CDCl₃, 400 MHz) δ 7.80-7.78 (m, 1 H, aromatic *H*), 7.73-7.68 (m, 2 H, aromatic *H*), 7.50 (s, 1 H, aromatic *H*), 7.46-7.40 (m, 2 H, aromatic *H*), 7.28-6.88 (m, 106 H, aromatic *H*), 5.75 (d, *J* = 3.2 Hz, 1 H, H-1), 5.73 (d, *J* = 3.6 Hz, 1 H, H-1), 5.69 (d, *J* = 3.2 Hz, 1 H, H-1), 5.61 (d, *J* = 3.2 Hz, 1 H, H-1b), 5.49 (d, *J* = 2.8 Hz, 1 H, H-1), 5.34 (d, *J* = 3.2 Hz, 1 H, H-1c), 5.22 (d, *J* = 10.8 Hz, 1 H, *CHH*), 5.07 (d, *J* = 11.6 Hz, 1 H, *CHH*), 4.97-3.32 (m, 88 H), 3.25 (dd, *J*₁ = 3.6 Hz, *J*₂ = 10.0 Hz, 1 H, H-2b), 1.90-1.84 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz) δ 139.25, 139.13, 138.97, 138.89, 138.84, 138.78, 138.65, 138.45, 138.17, 138.12, 138.10, 138.08, 138.03, 137.95, 137.82, 137.78, 137.63, 136.03, 133.25, 132.93 (aromatic C), 128.51, 128.35, 128.30, 128.25, 128.21, 128.18, 128.12, 128.03, 127.97, 127.96, 127.89, 127.85, 127.82, 127.79, 127.67, 127.60, 127.54, 127.51, 127.47, 127.36, 127.26, 127.17, 127.03, 126.98, 126.88, 126.83, 126.66, 126.63, 126.53, 126.38, 126.10, 126.04, 125.87 (aromatic CH), 97.04, 96.89, 96.85, 96.77, 96.64, 96.25, 96.15 (7 C-1), 82.18, 82.07, 81.93, 81.84, 81.77, 81.26, 80.63, 80.34, 80.26, 80.20, 79.58, 79.52, 79.21, 78.79, 78.64, 77.64, 77.36, 75.55, 75.46, 75.05, 74.92, 74.22, 74.02, 73.93, 73.86, 73.48, 73.45, 73.40, 73.30, 73.24, 73.04, 72.97, 72.53, 72.46, 72.26, 72.19, 72.00, 71.84, 71.14, 70.92, 70.80, 69.90, 68.99, 68.85, 68.71, 68.08, 64.81 (C-1°), 64.69 (C-6b), 48.29 (C-3°), 28.83 (C-2°). MALDI-TOF: Calculated for C₂₀₃H₂₁₁O₃₆N₃ [M⁺]: 3266.5; found: 3266.2.



Synthesis of heptagluside **41**: The reaction was carried out according to the general procedure D, using **40** (260 g, 0.080mmol, 0.05 M in DCM:H₂O) and DDQ (20 mg, 0.09 mmol). The product was purified by silica gel column chromatography (Tol:EA = 20:1). Compound **41** (175mg, 70% yield, Tol:EA = 12:1, *R_f* = 0.40) was obtained as a colorless syrup. $[\alpha]_D^{20}$ +70.1 (*c*=1, CHCl₃). IR (neat, cm⁻¹) ν 695, 731, 1026, 1036, 1092, 1135, 1152, 1207, 1363, 1453, 1496, 2098, 2857, 2923. ¹H-NMR (CDCl₃, 500 MHz) δ 7.29-6.89 (m, 105 H,

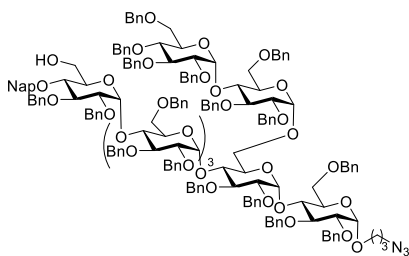
aromatic *H*), 5.73 (d, *J* = 3.0 Hz, 1 H, H-1), 5.67 (bd, 2 H, H-1), 5.59 (d, *J* = 3.0 Hz, 1 H, H-1b), 5.48 (bs, 1 H, H-1), 5.32 (bs, 1 H, H-1c), 5.19 (d, *J* = 11.0 Hz, 1 H, *CHH*), 5.04 (d, *J* = 11.5 Hz, 1 H, *CHH*), 4.93 (d, *J* = 11.5 Hz, 1 H, *CHH*), 4.88-3.32 (m, 86 H), 3.27 (bd, 1 H, H-2b), 2.52 (s, 1 H, OH), 1.89-1.88 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 125 MHz) δ 139.34, 139.24, 139.08, 139.00, 138.97, 138.95, 138.89, 138.78, 138.56, 138.52, 138.24, 138.22, 138.20, 138.16, 138.11, 138.07, 138.03, 137.93, 137.88, 137.72 (aromatic C), 128.60, 128.53, 128.46, 128.44, 128.39, 128.37, 128.34, 128.29, 128.26, 128.19, 128.12, 128.05, 127.98, 127.93, 127.90, 127.86, 127.81, 127.78, 127.71, 127.64, 127.60, 127.55, 127.52, 127.46, 127.38, 127.37, 127.24, 127.14, 127.04, 126.97, 126.91, 126.74, 126.61, 126.49 (aromatic CH), 97.12 (C-1), 97.00 (C-1), 96.85 (C-1), 96.76 (2 C-1), 96.38 (C-1), 96.21 (C-1), 82.16, 81.99, 81.88, 81.50, 81.34, 80.68, 80.43, 80.38, 80.30, 79.66, 79.35, 79.13, 78.79, 77.77, 75.63, 75.58, 75.00, 74.32, 74.02, 73.92, 73.67, 73.56, 73.47, 73.39, 73.35, 73.33, 73.12, 73.03, 73.00, 72.87, 72.75, 72.64, 72.43, 72.29, 72.11, 71.99, 71.70, 71.24, 71.03, 70.90, 70.45, 70.04, 70.01, 69.90 (C-6), 69.13 (C-6), 69.02 (C-6), 68.98 (C-6), 68.78 (C-6), 68.25 (C-6), 64.94 (C-1°), 64.81 (C-6b), 48.43 (C-3°), 28.96 (C-

2°). MALDI-TOF: Calculated for $C_{192}H_{203}O_{36}N_3$ [M^+]: 3126.4; found: 3126.1.



Synthesis of octaglucofuranose **42**: The reaction was carried out according to the standard procedure B. The donor **5b** (285 mg, 0.36 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (1 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (455 μ L, 5.78 mmol) was added to the solution. The solution was cooled to -78°C , after which TFOH (31 μ L, 0.35 mmol) was added. After 30 min, the pre-activation was complete as indicated

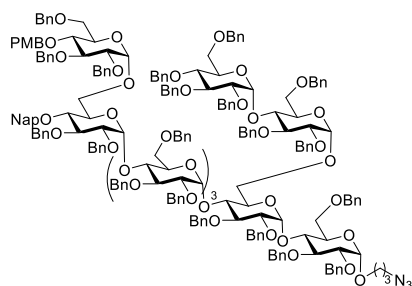
by TLC-analysis. Acceptor **15** (680 mg, 0.76 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 3 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **42** (135 mg, 80% yield, $\alpha:\beta > 20:1$, Tol:EA = 12:1, $R_f = 0.64$) was obtained as a colorless syrup. $[\alpha]_D^{20} +69.7$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 734, 1028, 1035, 1074, 1077, 1082, 1093, 1095, 1154, 1363, 2093, 2863, 2928. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.80-7.78 (m, 1 H, aromatic *H*), 7.72-7.68 (m, 2 H, aromatic *H*), 7.45-7.42 (m, 3 H, aromatic *H*), 7.30-6.86 (m, 118 H, aromatic *H*), 6.73-6.71 (m, 2 H, aromatic *H*), 5.75-5.71 (m, 3H, 3 H-1), 5.71 (bt, 2 H, 2 H-1), 5.46 (d, $J = 3.2$ Hz, 1 H, H-1), 5.33 (d, $J = 3.2$ Hz, 1 H, H-1), 5.21 (d, $J = 10.8$ Hz, 1 H, CHH), 5.05 (d, $J = 11.6$ Hz, 1 H, CHH), 4.92-3.24 (m, 104 H), 1.90-1.83 (m, 2 H, H-2°). $^{13}\text{C-APT}$ (CDCl_3 , 125 MHz) δ 159.29, 139.33, 139.23, 139.04, 139.01, 138.98, 138.85, 138.56, 138.32, 138.21, 138.12, 138.09, 138.06, 138.01, 137.89, 137.86, 137.74, 136.17, 133.34, 133.02, 130.01 (aromatic C), 129.95, 128.60, 128.42, 128.39, 128.36, 128.34, 128.30, 128.26, 128.20, 128.12, 128.06, 128.00, 127.97, 127.94, 127.90, 127.88, 127.84, 127.74, 127.70, 127.65, 127.59, 127.56, 127.54, 127.47, 127.42, 127.36, 127.25, 127.14, 127.05, 126.96, 126.90, 126.75, 126.72, 126.69, 126.61, 126.49, 126.46, 126.11, 125.92, 113.78 (aromatic CH), 97.07 (C-1), 96.99 (2 C-1), 96.73 (2 C-1), 96.34 (2 C-1), 96.16 (C-1), 82.27, 82.17, 82.01, 81.97, 81.88, 81.74, 81.38, 80.87, 80.40, 80.28, 79.82, 79.56, 79.43, 79.32, 78.87, 78.73, 77.76, 77.70, 75.64, 75.54, 75.08, 75.02, 74.30, 74.01, 73.88, 73.56, 73.44, 73.40, 73.35, 73.31, 73.14, 73.09, 73.03, 72.84, 72.75, 72.64, 72.52, 72.23, 72.11, 71.99, 71.79, 71.25, 71.00, 70.93, 70.02, 69.98, 69.12, 69.02, 68.94, 68.61, 68.22, 67.62, 64.91 (C-1°), 64.76 (C-6b), 55.21 (OCH₃), 48.41 (C-3°), 28.94 (C-2°). MALDI-TOF: Calculated for $C_{231}H_{241}O_{42}N_3$ [M^+]: 3728.7; found: 3728.9.



Synthesis of octaglucofuranose **43**: The reaction was carried out according to the general procedure E attt about 1 h, using **42** (70 mg, 0.019 mmol, 0.01 M in DCM:HFIP), triethylsilane (3 μ L, 0.018 mmol) and 0.1M HCl/HFIP (20 μ L, 0.19 mmol). The product was purified by silica gel column chromatography (Tol:EA = 20:1). Compound **43** (60 mg, 88% yield, Tol:EA = 12:1, $R_f = 0.29$) was obtained as a colorless syrup. $[\alpha]_D^{20} +79.3$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 696, 735, 1027, 1039,

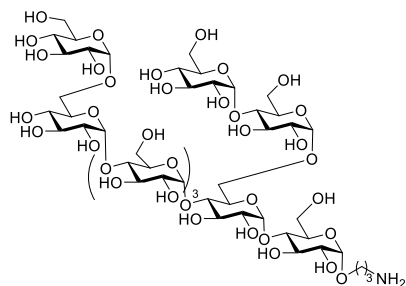
1042, 1078, 1094, 1138, 1155, 1363, 1454, 2097, 2858, 2927. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.81-7.72 (m, 3 H, aromatic *H*), 7.67 (s, 1 H, aromatic *H*), 7.46-7.38 (m, 3 H, aromatic *H*), 7.30-6.86 (m, 115 H, aromatic *H*), 5.75 (d, $J = 3.6$ Hz, 1

H, H-1), 5.73 (d, $J = 3.6$ Hz, 1 H, H-1), 5.65 (d, $J = 3.6$ Hz, 1 H, H-1), 5.61 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.56 (d, $J = 3.6$ Hz, 1 H, H-1), 5.48 (d, $J = 3.2$ Hz, 1 H, H-1), 5.34 (d, $J = 3.2$ Hz, 1 H, H-1c), 5.22 (d, $J = 11.6$ Hz, 1 H, CHH), 5.06 (d, $J = 12.0$ Hz, 1 H, CHH), 4.99 (d, $J = 11.2$ Hz, 1 H, CHH), 4.94 (d, $J = 11.6$ Hz, 1 H, CHH), 4.90-3.31 (m, 97 H), 3.27 (dd, $J_1 = 3.6$ Hz, $J_2 = 10.0$ Hz, 1 H, H-2b), 1.90-1.84 (m, 2 H, H-2°). ^{13}C -APT (CDCl_3 , 100 MHz), δ 139.29, 139.18, 138.98, 138.94, 138.80, 138.77, 138.72, 138.52, 138.26, 138.17, 138.13, 138.08, 138.03, 138.00, 137.93, 137.94, 137.81, 137.66, 135.80, 133.32, 133.07 (aromatic C), 128.59, 128.45, 128.42, 128.37, 138.31, 128.26, 128.20, 128.10, 128.06, 128.00, 127.94, 127.89, 127.87, 127.85, 127.80, 127.75, 127.71, 127.64, 127.62, 127.54, 127.46, 127.32, 127.24, 127.16, 127.11, 127.04, 126.95, 126.83, 126.71, 126.68, 126.64, 126.61, 126.41, 126.23, 126.11, 126.06 (aromatic CH), 97.07 (C-1), 96.97 (C-1), 96.68 (3 C-1), 96.29 (C-1), 96.17 (C-1), 96.10 (C-1), 82.15, 82.02, 81.96, 81.847, 81.36, 80.88, 80.36, 80.23, 79.61, 79.47, 79.26, 78.83, 78.66, 77.72, 77.65, 75.64, 75.53, 75.32, 75.01, 74.28, 74.10, 74.01, 73.88, 73.63, 73.53, 73.44, 73.39, 73.32, 73.27, 73.15, 73.06, 72.82, 72.41, 72.07, 71.87, 71.66, 71.21, 70.97, 70.86, 70.82, 69.96, 69.07, 68.89, 68.52, 68.37, 68.14, 64.88 (C-1°), 64.67 (C-6b), 61.73 (C-6), 48.38 (C-3°), 28.92 (C-2°). MALDI-TOF: Calculated for $\text{C}_{223}\text{H}_{233}\text{O}_{41}\text{N}_3$ [$\text{M}+\text{H}^+$]: 3609.6; found: 3604.8.



Synthesis of nonaglycoside **44**: The reaction was carried out according to the standard procedure C, using **4b** (100 mg, 0.13 mmol), **43** (40 mg, 0.011 mmol, 0.005 M in DCM), $\text{Ph}_3\text{P}=\text{O}$ (225 mg, 0.81 mmol) and TMSI (30 μL , 0.21 mmol). The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **44** (31 mg, 67% yield, $\alpha:\beta > 20:1$, Tol:EA = 12:1, $R_f = 0.65$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +86.6$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 696, 734, 1008, 1028, 1049, 1084, 1091, 1154, 1362, 2097, 2858, 2924. ^1H -NMR (CDCl_3 ,

500 MHz) δ 7.75 (bd, 1 H, aromatic H), 7.70 (bd, 1 H, aromatic H), 7.67-7.64 (m, 3 H, aromatic H), 7.43-7.36 (m, 3 H, aromatic H), 7.29-6.87 (31mg, 132 H, aromatic H), 6.76-6.73 (m, 2 H, aromatic H), 5.74 (d, $J = 3.5$ Hz, 1 H, H-1), 5.71 (d, $J = 3.5$ Hz, 1 H, H-1), 5.65 (d, $J = 3.5$ Hz, 1 H, H-1), 5.61 (d, $J = 3.5$ Hz, 1 H, H-1), 5.60 (d, $J = 3.5$ Hz, 1 H, H-1), 5.47 (d, $J = 3.5$ Hz, 1 H, H-1), 5.32 (d, $J = 3.5$ Hz, 1 H, H-1), 5.20 (d, $J = 11.0$ Hz, 1 H, CHH), 5.09 (d, $J = 3.5$ Hz, 1 H, H-1), 5.02 (bt, 2 H, CHH), 4.92-3.31 (m, 113 H), 3.27 (dd, $J_1 = 3.5$ Hz, $J_2 = 9.0$ Hz, 1 H, H-2), 3.23-3.20 (m, 1 H, H-2), 1.89-1.84 (m, 2 H, H-2°). ^{13}C -APT (CDCl_3 , 125 MHz), δ 159.24, 139.34, 139.24, 139.09, 139.05, 139.01, 138.87, 138.78, 138.58, 138.39, 138.32, 138.28, 138.24, 138.21, 138.19, 138.14, 138.12, 138.08, 137.96, 137.91, 137.87, 137.77, 136.42, 133.41, 133.04, 130.86 (aromatic C), 129.65, 128.60, 128.46, 128.44, 128.40, 128.34, 128.30, 128.21, 128.19, 128.12, 128.06, 128.04, 127.99, 127.97, 127.95, 127.90, 127.88, 127.80, 127.76, 127.74, 127.72, 127.69, 127.65, 127.61, 127.57, 127.54, 127.47, 127.42, 127.37, 127.35, 127.25, 127.15, 127.09, 127.05, 126.97, 126.91, 126.76, 126.74, 126.72, 126.48, 126.38, 126.19, 126.07, 125.84, 113.81 (aromatic CH), 97.25 (C-1), 97.08 (C-1), 97.00 (C-1), 96.76 (2 C-1), 96.33 (2 C-1), 96.20 (2 C-1), 82.14, 82.01, 81.89, 81.74, 81.38, 80.86, 80.42, 80.30, 80.25, 80.16, 79.78, 79.43, 79.36, 78.88, 78.76, 77.79, 77.54, 77.34, 75.64, 75.54, 75.35, 75.19, 75.02, 74.77, 74.31, 73.99, 73.88, 73.68, 73.57, 73.44, 73.38, 73.33, 73.15, 73.10, 72.83, 72.71, 72.66, 72.61, 72.13, 72.05, 71.84, 71.71, 71.27, 71.03, 70.91, 70.78, 70.35, 70.04, 70.01, 69.15, 69.02, 68.97, 68.85, 68.62, 68.45, 68.26, 65.05, 64.92 (C-1°), 64.79 (C-6), 55.38 (OCH_3), 48.42 (C-3°), 28.96 (C-2°). MALDI-TOF: Calculated for $\text{C}_{258}\text{H}_{269}\text{O}_{47}\text{N}_3$ [$\text{M}+\text{H}^+$]: 4161.8; found: 4161.7.



Synthesis of nonaglucoamide **1**: Compound **40** (20 mg, 0.0048 mmol) was dissolved in THF/H₂O/*tert*-BuOH (4 ml/4 ml/1.6 ml) before a catalytic amount of Pd(OH)₂/C was added. The reaction mixture was stirred for 3 days under a H₂ atmosphere (3.5 bar), filtered and concentrated *in vacuo*. A white powder **1** was obtained, which was purified by gel filtration (HW-40, 0.15M NH₄OAc in H₂O) to yield **1** (4.7 mg, 61%). ¹H-NMR (CDCl₃, 500 MHz) δ 5.40–5.38 (m, 3 H, 3 H-1), 5.35 (bt, 2 H, 2 H-1), 5.32 (d, J = 4.0 Hz, 1 H, H-1), 4.96–4.93 (m,

3 H, 3 H-1), 4.02–3.54 (m, 53 H), 3.49 (t, J = 9.5 Hz, 1 H), 3.44–3.39 (m, 2 H), 3.20–3.10 (m, 2 H), 2.02–1.97 (m, 2 H). ¹³C-APT (CDCl₃, 125 MHz), δ 100.03, 99.94, 99.83, 99.63, 99.56, 98.60, 98.11 (9 C-1), 78.86, 77.94, 77.57, 77.16, 76.78, 73.44, 73.02, 72.98, 72.79, 71.87, 71.83, 71.69, 71.53, 71.38, 71.31, 70.90, 70.57, 71.42, 70.23, 69.54, 69.41, 69.33, 67.55, 65.93, 60.79, 60.54, 60.49, 60.44, 37.85, 26.60. HR-MS: Calculated for C₅₇H₉₉O₄₆N [M+H⁺]: 1534.5511; found: 1534.5779.

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Chapter 3

Reagent Controlled Stereoselective Assembly of α -(1,3)-Glucans

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Chem. **2019**, 10, 1994-2003.

Introduction

The stereoselective construction of 1,2-*cis*-glycosidic bonds continues to be a great challenge in the assembly of oligosaccharides and glycoconjugates, and no general solution exists for the construction of these linkages.^[1] The large panel of diastereoisomeric monosaccharides in combination with the plethora of different functional and protecting group schemes generate a humongous diversity in carbohydrate building blocks.^[1] The structural variation translates to varying reactivity of both the donor glycoside^[2] and acceptor glycoside^[3] because of the large differences in the reactivity of both coupling partners it is often difficult to translate a productive

glycosylation reaction from one glycosylation couple to another. The introduction of nucleophilic additives to modulate the coupling reaction has been an important step forwards as this opens up the way to match donor and acceptor reactivity.^[4] Chapter 2 describes the fully stereoselective assembly of a *Mycobacterium tuberculosis* derived α -glucan **1**, built up from a 1,4-linked-hexa- α -glucose backbone, bearing a mono- and disaccharide α -glucose branch.^[5] The assembly of this nonasaccharide was accomplished using additive controlled glycosylation reactions and built on the following design parameters: 1) Only a single type of *N*-phenyltrifluoroimide building block was used, bearing a uniform protecting group pattern, solely relying on the use of benzyl type ethers; 2) A triad of benzyl ethers (namely the benzyl (Bn), para-methoxybenzyl (PMB) and 2-methylnaphthyl (Nap) ether) was used to discriminate the alcohol groups that required permanent protection or needed to be removed to introduce the branches or grow the α -(1,4)-backbone. 3) The intrinsic differences in reactivity between the primary and secondary alcohol acceptors was accommodated for in the coupling reaction using two different activator/additive couples: Trifluoromethanesulfonic acid (TfOH) in conjunction with dimethylformamide (DMF) for the condensation of the secondary alcohols and trimethylsilyliodide (TMSI) in combination with triphenylphosphine oxide for the coupling to the more reactive primary alcohols (See Figure 1). Besides the fact that all building blocks were of nearly identical reactivity, as a result of the chosen protecting group strategy, the use of solely benzyl ether-type protecting groups is beneficial at the stage of building block assembly - the benzyl ethers used are very robust and easily introduced - and at the final stage of the synthesis, as unmasking all groups can be achieved under mild condition in a single hydrogenation event. The successful assembly of the 1,4- α -glucan nonasaccharide was an incentive to explore the above described synthesis strategy for the assembly of the related α -(1,3)-glucans. These compounds are prominent components of fungal cell walls^[6] and they have been shown to interact with our immune system, through as yet undefined receptor(s).^[7] Nifantiev and co-workers recently reported the synthesis of an *Aspergillus fumigatus* α -(1,3)-glucan pentasaccharide, employing a long-range participation approach to ensure the stereoselective construction of the cis-glucosidic linkages.^[8] The spacer-equipped pentasaccharide was used for the generation of a BSA-conjugate vaccine and the polyclonal mouse serum raised with the conjugate could recognize α -(1,3)-glucan-expressing *A. fumigatus*.

This chapter describes the synthesis of the largest synthetic α -(1,3)-glucan to date, *i.e.* the assembly of octasaccharide **2** (Figure 1). To streamline the synthesis of large oligosaccharides using a nucleophilic additive glycosylation based on approach being further optimized the coupling protocol by showing that pre-activation of the donor glycoside can be omitted allowing for a much-simplified experimental procedure.

Results and Discussion

In line with the strategy outlined above, the synthetic approach is built on the use per-benzylated donor and acceptor building blocks. To temporarily mask the C-3-OH a 2-methylnaphthyl (Nap)-ether^[9] was used (building block **3**, See Figure 1). The assembly of the required building block for this study is depicted in Scheme 1A. The free alcohol in 1,2;5,6-di-*O*-isopropylidene- α -D-glucufuranose was used to introduce the Nap ether at this position. Acidic hydrolysis of both acetone ketals, ensuing acetylation, introduction of an anomeric thiophenol group and benzylation of the alcohols at C-2, C-4 and C-6 then delivered glucoside **5**. The anomeric thioacetal in this building block was hydrolyzed using N-iodosuccinimide in acetone/water to liberate the anomeric hydroxyl group, which could then be turned into the required N-phenyltrifluoroimidate **3**.

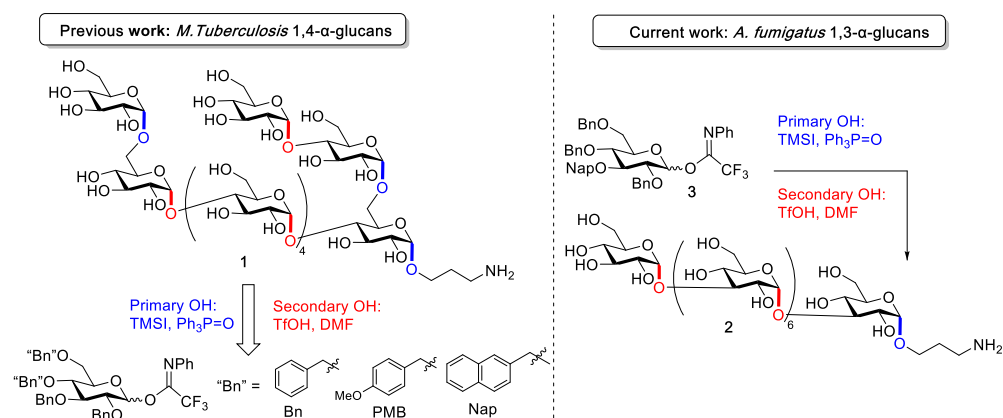
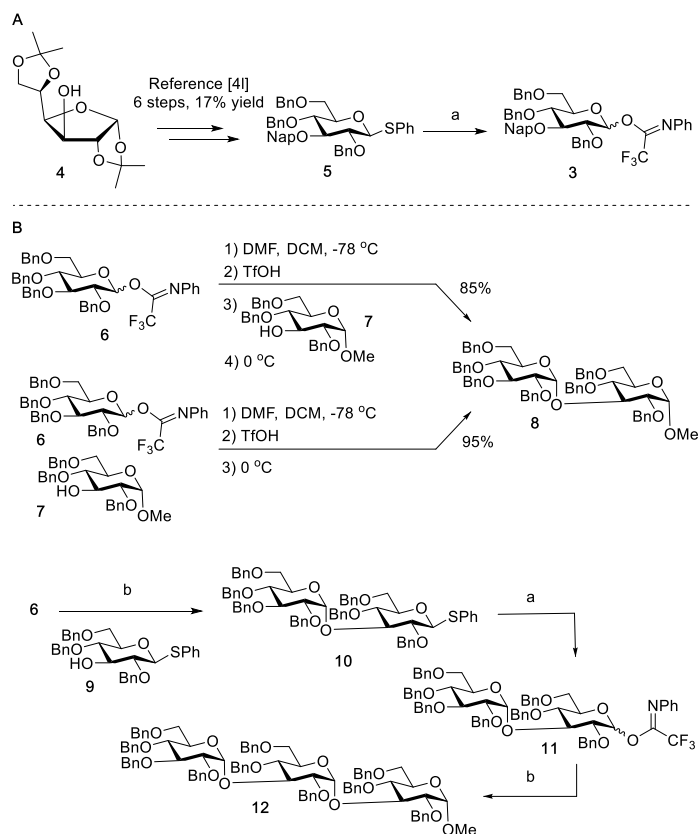


Figure 1. Schematic syntheses of branched 1,4- α -glucans (previously reported) and 1,3- α -glucans. The strategy hinges on the use of building blocks carrying solely benzyl-type protecting groups in combination with different activator/additive systems for glycosylations of primary (more reactive) or secondary (less reactive) alcohols.

With the required building block in hand, a series of glycosylations was performed to probe the feasibility of the DMF-mediated glycosylation conditions for the construction of the α -(1,3)-glucosyl bond (Scheme 1B). It was recently established by Van der Vorm that the glucosyl C-3-OH is somewhat more nucleophilic than its C-4-OH counterpart, which could impact the stereoselectivity of the projected glycosylation reactions.^[3a, 3c] Thus, donor **6** was activated at -78 °C using an equimolar amount of TfOH in the presence of 16 equivalents of DMF, as originally prescribed by Mong co-workers.^[4k] After 30 minutes C-3-OH acceptor **7** was added and the mixture warmed to 0 °C.

This protocol installed the desired α -glucosyl linkage with excellent stereoselectivity and generated diglucoside **8** in 85% yield. To allow for an operationally simpler protocol, it was examined whether the donor and acceptor could be premixed. Indeed, addition of TfOH to a mixture containing donor **6**, acceptor **7** and DMF at -78 °C and subsequent warming to 0 °C

proved feasible as the yield and stereoselectivity of the condensation remained excellent (See Scheme 1B). Especially in the generation of larger oligomers, using large and expensive acceptor building blocks (*vide infra*) this simpler protocol represents a significant improvement, as less manipulations are required on the side of the acceptor. It was also explored whether a chemoselective glycosylation could be achieved under these conditions, and to this end donor **6** and thioglucoside **9**, obtained by removal of the Nap ether in **5**, were coupled using TfOH/DMF to provide diglucoside **10** in 91%, again with excellent stereoselectivity. The resulting thiodisaccharide could be turned into *N*-phenyltrifluoroimide donor **11** and used in a subsequent glycosylation event. In the event disaccharide imide **11** and acceptor **7** were pre-mixed with DMF in dichloromethane (DCM), after which the activator was added and the mixture warmed to 0 °C. Trisaccharide **12** was obtained as a single anomer in 63 % yield.

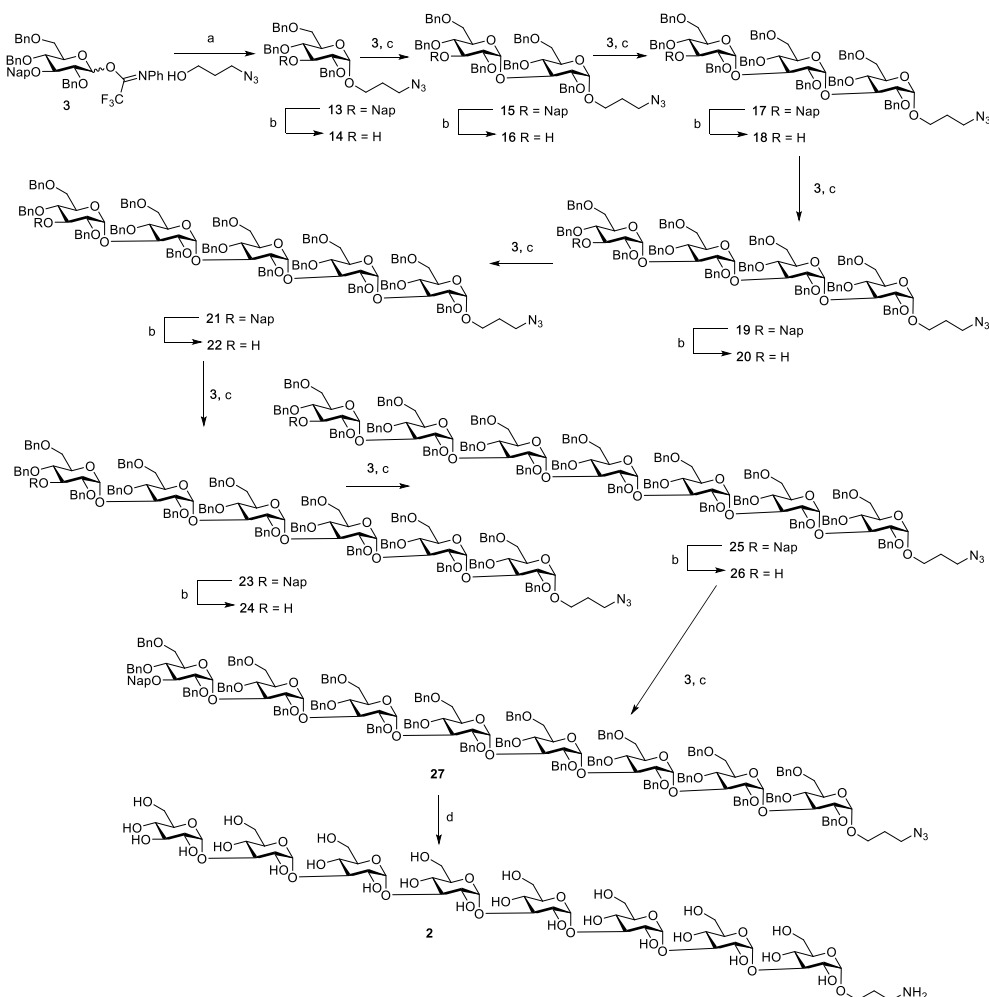


a) 1) NIS, acetone:H₂O = 10:1; 2) 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride, Cs₂CO₃, acetone, **3**: 90%; **11**: 80%. b) DMF, TfOH, DCM, -78-0 °C, **8**: α:β > 20:1; **10**: 91%, α:β > 20:1; **12**: 63%, α:β > 20:1.

Scheme 1. A) Synthesis of building block **3** and B) model glycosylations.

Next the attention was turned to the assembly of a longer and spacer-functionalized α-(1,3)-

glucan as depicted in Scheme 2. Firstly, the azidopropanol spacer was introduced. To this end donor **3** was activated using a combination of TMSI and $\text{Ph}_3\text{P}=\text{O}$ (6 equivalents). As described in chapter 2, these conditions work well to install the α -glucosidic linkage on reactive primary alcohols and also in this case the desired azidopropyl glucoside **13** was obtained in good yield and stereoselectivity ($\alpha/\beta = 10:1$). Deprotection of the C-3-O-Nap ether under oxidative conditions (dichlorodicyanobenzoquinone (DDQ) in $\text{DCM}/\text{H}_2\text{O}$, 10 : 1 v/v) proceeded uneventfully and set the stage for elongation of the azidopropyl glucoside which was purified with silica gel column chromatography to get pure α -anomer **14**.



a) TMSI, $\text{Ph}_3\text{P}=\text{O}$, DCM, rt, **13**: 80%, $\alpha/\beta = 10:1$. b) DDQ, $\text{DCM}/\text{H}_2\text{O}$, **14**: 80%; **16**: 90% (with two steps); **18**: 95%; **20**: 80%; **22**: 75%; **24**: 70%; **26**: 51%. c) DMF, TFOH, DCM, $-78-0^\circ\text{C}$, **15**: >90%, $\alpha/\beta > 20:1$; **17**: 81%, $\alpha/\beta > 20:1$; **19**: 84%, $\alpha/\beta > 20:1$; **21**: 81%, $\alpha/\beta > 20:1$; **23**: 90%, $\alpha/\beta > 20:1$; **25**: 90%, $\alpha/\beta > 20:1$; **27**: 98%, $\alpha/\beta > 20:1$. d) $\text{Pd}(\text{OH})_2$, H_2 (40 bar), $\text{THF}/\text{H}_2\text{O}/t\text{-BuOH}$, 40%.

Scheme 2. Assembly of an *A. fumigatus* α -(1,3)-octaglucan.

Activation of donor **3** with the TfOH/DMF combination and coupling with acceptor **14** delivered the desired disaccharide **15** as the sole anomer. The only side product that was detected was a 1,1'-coupled trehalose. Unfortunately, this side product was difficult to remove from the disaccharide product and therefore it was continued with the deprotection of **15** to give disaccharide alcohol **16**, which was now readily purified and obtained in 90% over the two steps. Elongation of the diglucoside proceeded smoothly and gave the trisaccharide **17** in 81% yield. Oxidative deprotection of the C-3'''-O-Nap ether and subsequent elongation with another copy of donor **3** delivered the tetrasaccharide **19**. Repetition of the deprotection-coupling cycle then generated pentasaccharide **21** and hexasaccharide **23**. Deprotection of the Nap ether again proceeded uneventfully to set the stage for the next glycosylation. From this stage on employing the donor-acceptor pre-mixing strategy and using the above described protocol, heptasaccharide **25** was generated as the sole anomer in 90% yield. De-naphthylation gave heptasaccharide alcohol **26**, which was elongated in a final glucosylation event, again under the donor-acceptor pre-mixing conditions, to give the all-*cis* octaglycoside **27** in 98% yield. Deprotection of the octasaccharide was accomplished in a single hydrogenation event to give **2** in 40% yield and complete the synthesis.

Conclusion

In summary the synthesis of a spacer-equipped octa- α -(1,3)-glucan was described using a strategy that is built on the use of benzyl ether protected building blocks in combination with appropriate activator-additive reagent combinations to install the desired glucosidic linkages. To stereoselectively install the linker on the first building block, the TMSI-Ph₃P=O reagent was used combination, while all other glycosylations, generating linkages to secondary alcohols, were promoted by the TfOH-DMF reagent system. It was shown that a pre-activation strategy, which encompasses the activation of the donor glycoside in the absence of the acceptor, is not required to achieve high yielding stereoselective glycosylation reactions. This has allowed the development of an effective α -glucosylation protocol that is operationally easier and requires less manipulation of (expensive) acceptor alcohols. Extension of the here reported glycosylation strategy to other *cis*-glycans is described in Chapter 4 and 5. The generated octasaccharide can be used as a synthetic antigen to raise antibodies at *A. fumigatus*

Experimental Section

General experimental procedures

All reagents were of commercial grade and used as received. All moisture sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of (NH₄)₆Mo₇O₂₄·4H₂O (25 g/L) and (NH₄)₄Ce(SO₄)₄·2H₂O (10 g/L) in 10%

sulfuric acid (aq.) followed by charring at ~ 150 °C. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20. High resolution mass (HRMS) was performed on a Thermo Finnigan LTQ Orbitrap mass spectrometer equipped with an electrospray ion source in positive ion mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 275 °C) resolution $R = 60,000$ at m/z 400 (mass range of 150-4000) and dioctylphthalate ($m/z = 391.28428$) as lock mass, or on a Waters Synapt G2-Si(OTF) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV) and LeuEnk ($m/z = 556.2771$). 1 μ l of 2,5-dihydroxybenzoic acid (2,5-DHB; Bruker Daltonics) matrix (20 mg/mL in ACN/water; 50:50 (v/v)) was applied on a 384-MTP target plate (Bruker Daltonics, Bremen, Germany) and air-dried. Subsequently, 1 μ l of xxx solution was spotted on the plate and the spots were left to dry prior MALDI-TOF analysis. An Ultraflex extreme MALDI-TOF (Bruker Daltonics), with Smartbeam-II laser was used to measure the samples in reflectron positive ion mode. The MALDI-TOF was calibrated using a peptide calibration standard prior to measurement. ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in CDCl_3 or D_2O . Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard (^1H NMR in CDCl_3) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. NMR peak assignments were made using COSY and HSQC experiments, where applicable Clean TOCSY, HMBC and GATED experiments were used to further elucidate the structure. The anomeric product ratios were analyzed through integration of proton NMR signals. IR spectra were recorded on a Shimadzu FTIR-8300 IR spectrometer and are reported in cm^{-1} . Specific rotations were measured on a Propol automatic polarimeter or an Anton-Paar MCP 100 modular circular polarimeter at 589 nm unless otherwise stated.

Standard procedure A for glycosylation of secondary alcohols: The donor (1.0 eq, co-evaporated with toluene) was dissolved in dry DCM under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (16 eq) was added to the solution. The solution was cooled to -78 °C, after which TfOH (1.0 eq) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor (0.7 eq) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Standard procedure B for glycosylation of secondary alcohols: A mixture of donor (1.0 eq), acceptor (0.7 eq) (donor and acceptor co-evaporated with toluene three times), DMF (6 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 °C, after which TfOH (1.0 eq) was added. After 30 min, the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

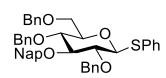
Standard procedure C for the glycosylation of primary alcohols: A mixture of donor (1.0 eq), acceptor (0.7 eq) (donor and acceptor co-evaporated with toluene three times), $\text{Ph}_3\text{P}=\text{O}$ (6 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. Then TMSI (1.0 eq) was added slowly in the mixture. The reaction was stirred at room temperature until TLC-analysis indicated the reaction to be complete. The solution was diluted and the reaction

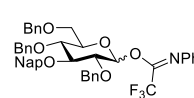
quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$. The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Standard procedure D for deprotection of the Nap protecting group: The starting material (1 eq) was dissolved in $\text{DCM}:\text{H}_2\text{O}$ (10:1, 0.1 M). DDQ (1.1 eq) was added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material ($\pm$ 2h). Then the mixture was diluted with DCM and the reaction quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$. The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography.

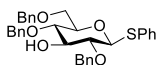
Experimental Procedures and Characterization Data of Products

For the synthesis procedure and data of known compounds **6**, **8** see reference 5. We used "a", "b", "c", "d", "e", "f", "g", and "h" to specify the H-1 and C-13 NMR signals of sugar rings from the "reducing" to the "non-reducing" end and "o" to specify the H-1 and C-13 NMR signals of the spacer.

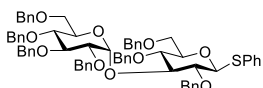
 **Phenyl 2,4,6-tri-O-benzyl-3-O-(naphthalen-2-ylmethyl)-1-thio-β-D-glucopyranoside (5):** $[\alpha]_{\text{D}}^{20} +8.1$, $c=1$, CHCl_3 . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.81-7.70 (m, 4 H, aromatic H), 7.61-7.59 (m, 2 H, aromatic H), 7.46-7.16 (m, 21 H, aromatic H), 5.05 (d, $J = 11.2$ Hz, 1 H, CHH), 4.99 (d, $J = 11.2$ Hz, 1 H, CHH), 4.91 (d, $J = 10.8$ Hz, 1 H, CHH), 4.85 (d, $J = 10.8$ Hz, 1 H, CHH), 4.75 (d, $J = 10.8$ Hz, 1 H, CHH), 4.69 (d, $J = 9.6$ Hz, 1 H, H-1), 4.61 (bd, 2 H, CHH), 4.54 (d, $J = 12.0$ Hz, 1 H, CHH), 3.81-3.67 (m, 4 H), 3.57-3.51 (m, 2 H). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz), δ 137.97, 137.73, 135.56, 133.52, 133.01, 132.65 (aromatic C), 131.62, 128.62, 128.14, 128.06, 127.91, 127.88, 127.63, 127.61, 127.57, 127.51, 127.38, 127.28, 127.14, 126.18, 125.78, 125.59, 125.55 (aromatic CH), 87.15 (C-1), 86.45, 80.53, 78.79, 77.49, 75.55 (PhCH₂), 75.16 (PhCH₂), 74.78 (PhCH₂), 73.11 (PhCH₂), 68.69 (C-6). HR-MS: Calculated for $\text{C}_{44}\text{H}_{42}\text{O}_5\text{S}$ $[\text{M}+\text{Na}]^+$: 705.2645; found: 705.2657.

 **2,4,6-Tri-O-benzyl-3-O-(naphthalen-2-ylmethyl)-α/β-D-glucopyranosyl phenyltrifluoroacetimidate (3):** Compound **5** (9.5 g, 13.9 mmol) was dissolved in $\text{acetone}:\text{H}_2\text{O}$ (10:1, 140 mL). N-Iodosuccinimide (NIS) (6.2 g, 27.6 mmol) was added in one portion and the reaction was stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$. Then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*, and the product purified by column chromatography (pentane : ethyl acetate (EA) = 3:1). The lactol (7.4 g, 90% yield) was obtained as a white solid. Next, the lactol (7.4 g, 12.5 mmol) was dissolved in acetone (120 mL). Cs_2CO_3 (6.1 g, 18.7 mmol) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (3.0 mL, 18.7 mmol) were added to the solution respectively. The reaction was stirred overnight, then quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by column chromatography (pentane:EA = 40:1-20:1). Compound **3** (9.1 g, 95% yield, $\alpha:\beta = 1:1.2$, pentane:EA = 10:1, $R_f = 0.45$ -0.55) was obtained as yellow syrup. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, 60°C) δ 7.79-6.72 (m, aromatic H), 6.47 (bs, 1 H, H-1 α), 5.60 (bs, 1 H, H-1 β), 5.11-4.74 (m, CHH), 4.61-4.48 (m, CHH), 4.08 (t, $J = 9.0$ Hz, 1 H, H- α), 3.97 (bd, 1 H, H- α), 3.78-3.68 (m), 3.40 (bs, 1 H). $^{13}\text{C-APT}$ (CDCl_3 , 125 MHz, 60°C) δ 143.97, 143.76, 138.48, 138.39, 138.38, 138.27, 138.65, 138.15, 136.45, 136.20, 133.69, 133.65, 133.29 (aromatic C), 129.52, 128.84, 128.63, 128.59, 128.54, 128.51, 128.21, 128.18, 128.12, 128.11, 128.00, 127.95, 127.85, 78

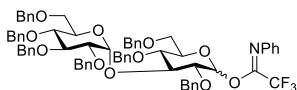
127.78, 126.69, 126.56, 126.51, 126.19, 126.18, 126.13, 125.99, 125.93, 124.47, 124.32, 120.77, 119.70, 119.63 (aromatic CH), 116.50 (q, CF₃), 97.69, 93.94, 84.77, 81.85, 81.29, 79.76, 77.67, 77.40, 76.09, 75.89, 75.69, 75.34, 75.11, 75.09, 73.78, 73.69, 73.60, 73.56, 68.73, 68.71.



Phenyl 2,4,6-tri-O-benzyl-1-thio- β -D-glucopyranoside (9): The reaction was carried out according to the general procedure D, using **5** (235 mg, 0.35 mmol, 0.1 M in DCM:H₂O) and DDQ (89 mg, 0.39 mmol). The product was purified by silica gel column chromatography (pentane:EA = 15:1). Compound **9** (168 mg, 87% yield, pentane:EA = 8:1, R_f = 0.44) was obtained as a colorless syrup. ¹H-NMR (CDCl₃, 400 MHz) δ 7.60-7.56 (m, 2 H, aromatic H), 7.41-7.22 (m, 18 H, aromatic H), 4.95 (d, J = 11.2 Hz, 1 H, CHH), 4.78 (d, J = 11.2 Hz, 1 H, CHH), 4.68-4.59 (m, 4 H, 3 CHH, H-1), 4.54 (d, J = 11.6 Hz, 1 H, CHH), 3.81-3.70 (m, 3 H, H-6, H-3), 3.56-3.46 (m, 2 H, H-4, H-5), 3.37 (dd, J_1 = 8.8 Hz, J_2 = 9.6 Hz, 1 H, H-2), 2.42 (d, J = 2.4 Hz, 1 H, OH). ¹³C-APT (CDCl₃, 100 MHz) δ 138.35, 138.33, 138.19, 133.94 (aromatic C), 131.89, 129.05, 128.73, 128.62, 128.48, 128.35, 128.20, 128.08, 128.00, 127.84, 127.72, 127.57 (aromatic CH), 87.18 (C-1), 80.70 (C-2), 878.91, 78.75, 77.48 (C-4), 75.25 (PhCH₂), 74.77 (PhCH₂), 73.55 (PhCH₂), 68.17 (C-6).

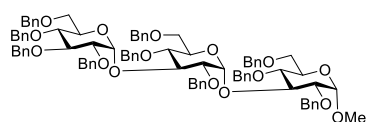


Phenyl 2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl-(1 $\rightarrow$ 3)-2,4,6-tri-O-benzyl-1-thio- β -D-glucopyranoside (10): The reaction was carried out according to the standard procedure B, using **6** (330 mg, 0.46 mmol), **9** (168 mg, 0.31 mmol, 0.1 M in DCM), DMF (580 μ L, 7.38 mmol) and TfOH (41 μ L, 0.46 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **10** (301 mg, 91% yield, α : β > 20:1, pentane:EA = 8:1, R_f = 0.46) was obtained as a colorless syrup. $[\alpha]_D^{20}$ +31.0, c=1, CHCl₃. IR (neat, cm⁻¹) ν 696, 745, 1028, 1071, 1090, 1361, 1454, 1497, 2862, 2910, 3030, 3063. ¹H-NMR (CDCl₃, 500 MHz) δ 7.60-7.57 (m, 2 H, aromatic H), 7.45 (bd, 2 H, aromatic H), 7.37-7.01 (m, 36 H, aromatic H), 5.68 (d, J = 3.5 Hz, 1 H, H-1b), 4.97-4.89 (m, 4 H, 3 CHH), 4.81 (d, J = 10.5 Hz, 1 H, CHH), 4.72-4.48 (m, 8 H, H-1a, 7 CHH), 4.40 (d, J = 10.5 Hz, 1 H, CHH), 4.11 (d, J = 11.5 Hz, 1 H, CHH), 4.14 (bd, 1 H), 4.10-4.04 (m, 2 H,), 3.85 (t, J = 9.5 Hz, 1 H), 3.75-3.65 (m, 3 H), 3.59-3.56 (m, 2 H, H-6), 3.50-3.48 (m, 2 H), 3.33-3.27 (m, 2 H). ¹³C-APT (CDCl₃, 125 MHz) δ 138.72, 138.58, 138.27, 138.14, 137.95, 137.80, 137.55, 133.81 (aromatic C), 131.81, 129.01, 128.87, 128.37, 128.33, 128.28, 128.25, 128.12, 127.94, 127.91, 127.76, 127.72, 127.60, 127.58, 127.53, 127.46, 127.39, 126.77 (aromatic CH), 97.30 (C-1b), 87.66 (C-1a), 79.42, 79.25, 78.95, 78.84, 78.20, 75.55, 75.20, 75.12, 73.91, 73.36, 73.31, 70.01, 68.73, 68.01.



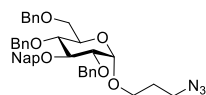
2,3,4,6-Tetra-O-benzyl- α -D-glucopyranosyl-(1 $\rightarrow$ 3)-2,4,6-tri-O-benzyl-1-thio- β -D-glucopyranosyl N-phenyltrifluoroacetimidate (11): Compound **10** (265 mg, 0.25 mmol) was dissolved in acetone:H₂O (10:1, 3.3 mL). N-Iodosuccinimide (NIS) (112 mg, 0.50 mmol) was added in one portion and the reaction was stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated aqueous Na₂S₂O₃, then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*, and the product purified by column chromatography (pentane:EA = 2:1). Compound Di-glucose alcohol (185 mg, 76% yield) was obtained as a white solid. Next, compound Di-glucose alcohol (185 mg, 0.19 mmol) was dissolved in acetone (2 mL).

Cs_2CO_3 (93 mg, 0.28 mmol) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (50 μL , 0.28 mmol) were added to the solution respectively. The reaction stirred overnight, then quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by column chromatography (pentane:EA = 50:1-20:1). Compound **11** (170 mg, 80% yield, $\alpha:\beta = 1.1:1$) was obtained as yellow syrup. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, 60°C) δ 7.31-7.01 (m, aromatic *H*), 6.77 (d, $J = 13.0$ Hz, 2 H), 6.68 (d, $J = 13.0$ Hz, 2 H), 6.48 (bs, 1 H α), 5.65 (bs, 1 H), 5.55 (d, $J = 3.5$ Hz, 1 H), 5.51 (d, $J = 3.5$ Hz, 1 H), 4.99 (d, $J = 11.5$ Hz, 1 H), 4.92-4.68 (m, CHH), 4.61-4.42 (m, CHH), 4.36-4.28 (m), 4.18 (bd, 1 H), 4.10-3.43 (m). $^{13}\text{C-APT}$ (CDCl_3 , 125 MHz, 60°C) δ 143.83, 143.73, 139.16, 139.07, 139.02, 138.91, 138.53, 138.49, 138.48, 138.41, 138.38, 138.37, 138.33, 138.20, 137.88, 137.71 (aromatic C), 128.81, 128.77, 128.52, 128.50, 128.46, 128.41, 128.38, 128.37, 128.35, 128.29, 128.22, 128.02, 128.00, 127.94, 127.90, 127.86, 127.83, 127.79, 127.72, 127.64, 127.62, 127.60, 127.58, 127.53, 127.48, 127.24, 127.16, 124.45, 124.31, 119.70, 119.61 (aromatic CH), 115.31 (q, CF_3), 97.78, 97.71, 97.61, 93.35, 82.49, 82.33, 80.31, 80.25, 79.83, 78.57, 78.55, 78.35, 78.20, 78.18, 76.24, 75.66, 75.56, 75.51, 75.10, 74.94, 74.73, 74.04, 73.89, 73.85, 73.77, 73.71, 73.64, 73.60, 73.46, 73.18, 70.90, 70.74, 68.96, 68.87, 68.63, 68.55.



Methyl 2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl-(1 $\rightarrow$ 3)-2,4,6-tri-O-benzyl- α -D-glucopyranoside (12**):** The reaction was carried out according to the

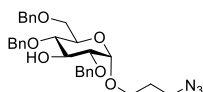
standard procedure B, using **11** (78 mg, 0.07 mmol), **7** (33 mg, 0.07 mmol, 0.1 M in DCM), DMF (87 μL , 1.12 mmol) and TfOH (7 μL , 0.07 mmol). The reaction was stirred at $-78-0^\circ\text{C}$ until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **12** (65 mg, 63% yield, $\alpha:\beta > 20:1$, pentane:EA = 4:1, $R_f = 0.50$) was obtained as a colorless syrup. $[\alpha]_D^{20} +60.1$, $c=1$ (10mg), CHCl_3 . IR (neat, cm^{-1}) ν 696, 735, 1028, 1072, 1157, 1362, 1454, 1497, 2864, 2916, 3031. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.39-6.87 (m, 50 H, aromatic *H*), 5.66 (bd, $J = 3.6$ Hz, 2 H, 2 H-1), 4.90-4.21 (m, 24 H), 4.08 (d, $J = 12.0$ Hz, 1 H, CHH), 4.01 (t, $J = 9.6$ Hz, 1 H), 3.85 (t, $J = 9.6$ Hz, 1 H), 3.74-3.48 (m, 10 H), 3.30-3.24 (m, 5 H). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 138.90, 138.71, 138.43, 138.18, 138.09, 137.90, 137.86 (aromatic C), 128.77, 128.51, 128.49, 128.39, 128.38, 128.32, 128.29, 128.24, 128.22, 128.18, 128.17, 128.11, 128.04, 127.99, 127.91, 127.83, 127.69, 127.62, 127.52, 127.44, 127.32, 127.13, 126.67 (aromatic CH), 97.70 (C-1), 97.43 (C-1), 96.21 (C-1), 82.35, 79.55, 79.24, 79.00, 78.90, 78.59, 78.12, 77.05, 75.76, 75.50, 74.71, 73.64, 73.60, 73.52, 73.37, 73.28, 73.09, 70.11 (C-5), 69.98 (C-5), 69.15 (C-a), 68.62 (2 C-6), 68.416 (C-6), 55.16 (CH_3).



3-Azidopropyl 2,3,4,6-tetra-O-benzyl- α -D-glucopyranoside (13**):** The reaction was carried

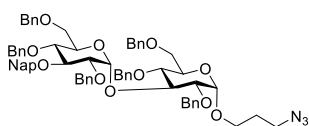
out according to the standard procedure C, using **3** (2500 mg, 3.28 mmol, 0.1 M in DCM), 3-aminopropanol (399 μL , 4.27 mmol), $\text{Ph}_3\text{P=O}$ (5.48 g, 19.7 mmol) and TMSI (516 μL , 3.61 mmol). The product was purified by silica gel column chromatography (pentane:EA = 15:1). Compound **13** (1716 mg, 80 % yield, $\alpha:\beta = 10:1$, pentane:EA = 4:1, $R_f = 0.74$) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 820, 1072, 1085, 1363, 1454, 2095, 2868, 2917, 3030. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.81-7.70 (m, 4 H, aromatic *H*), 7.48-7.39 (m, 3 H, aromatic *H*), 7.36-7.21 (m, 13 H, aromatic *H*), 7.13-7.10 (m, 4 H, aromatic *H*), 5.13 (d, $J = 11.2$ Hz, 1 H, CHH), 4.97 (d, $J = 11.2$ Hz, 1 H, CHH), 4.85 (d, $J = 10.4$ Hz, 1 H, CHH), 4.78 (d, $J = 8.4$ Hz, 1 H, CHH), 4.77 (s, 1 H, H-1), 4.65 (d, $J = 8.4$ Hz, 1 H, CHH), 4.60 (d, $J = 12.0$ Hz, 1 H, CHH), 4.49 (d, $J = 10.4$ Hz, 1 H, CHH), 4.47 (d, $J = 12.0$

Hz, 1 H, CHH), 4.03 (t, J = 9.2 Hz, 1 H, H-3), 3.78-3.57 (m, 6 H), 3.48-3.30 (m, 3H), 1.94-1.79 (m, 2 H, H-2°). ^{13}C -APT (CDCl₃, 100 MHz,) δ 138.21, 138.15, 137.85, 136.32, 133.34, 132.92 (aromatic C), 128.47, 128.37, 128.06, 128.00, 127.92, 127.88, 127.71, 127.66 (aromatic CH), 97.18 (C-1), 82.04 (C-3), 80.07 (C-2), 77.65 (C-4), 75.69, 75.11, 73.47, 73.24 (4 PhCH₂), 70.34 (C-5), 68.42 (C-6), 64.72 (C-1°), 48.26 (C-3°), 28.83 (C-2°). HR-MS: Calculated for C₄₁H₄₃O₆N₃ [M+Na⁺]: 696.3044; found: 696.3059.



3-Azidopropyl 2,4,6-tri-O-benzyl- α -D-glucopyranoside (14): The reaction was carried out according to the general procedure D, using **13** (1.67 g, 2.53 mmol, 0.1 M in DCM:H₂O) and DDQ (632 mg, 2.78 mmol). The product was purified by silica gel column chromatography

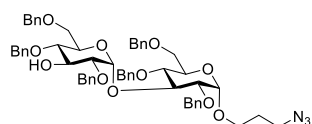
(pentane:EA = 8:1). Compound **14** (1.08 g, 80% yield, pentane:EA = 4:1, R_f = 0.33) was obtained as a colorless syrup. $[\alpha]_D^{20}$ +69.8, c = 1 (10mg), CHCl₃. IR (neat, cm⁻¹) ν 697, 734, 1028, 1070, 1154, 1453, 2096, 2869, 2918, 3031. ^1H -NMR (CDCl₃, 400 MHz) δ 7.31-7.19 (m, 15 H, aromatic H), 4.86 (d, J = 11.2 Hz, 1 H, CHH), 4.74 (s, J = 3.6 Hz, 1 H, H-1), 4.68 (d, J = 12.0 Hz, 1 H, CHH), 4.60 (d, J = 12.0 Hz, 1 H, CHH), 4.59 (d, J = 12.4 Hz, 1 H, CHH), 4.51 (d, J = 11.2 Hz, 1 H, CHH), 4.46 (d, J = 12.4 Hz, 1 H, CHH), 4.06 (t, J = 9.2 Hz, 1 H, H-3), 3.72-3.53 (m, 5 H), 3.41-3.28 (m, 4 H), 2.69 (bs, 1 H, OH), 1.86-1.75 (m, 2 H, H-2°). ^{13}C -APT (CDCl₃, 100 MHz,) δ 138.33, 137.99, 137.86 (aromatic C), 128.53, 128.35, 128.01, 127.91, 127.68 (aromatic CH), 96.58 (C-1), 79.62 (C-3), 77.35 (C-2), 74.61, 73.43 (2 PhCH₂), 73.42 (C-4), 72.92 (PhCH₂), 69.94 (C-5), 68.41 (C-6), 64.55 (C-1°), 48.17 (C-3°), 28.80 (C-2°). HR-MS: Calculated for C₃₀H₃₅O₆N₃ [M+Na⁺]: 556.2418; found: 556.2423.



3-Azidopropyl 2,4,6-tri-O-benzyl-3-O-(naphthalen-2-ylmethyl)- α -D-glucopyranosyl-(1→3)-2,4,6-tri-O-benzyl- α -D-glucopyranoside (15): The reaction was carried out according to the standard procedure A at -78 - 0 °C. The donor **3** (2.18 g, 2.86 mmol, co-evaporated with toluene 3 times) was dissolved in

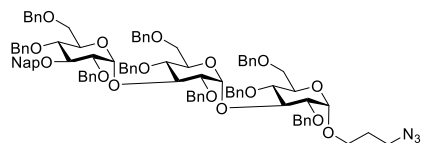
dry DCM (24 mL) under nitrogen and stirred over fresh flame-dried molecular sieves 3A, after which DMF (2.50 mL, 31.7 mmol) was added to the solution. The solution was cooled to -78 °C, after which TfOH (173 μ L, 1.96 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **14** (910 mg, 1.70 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 10 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Crude compound **15** (α : β > 20:1, pentane:EA = 4:1, R_f = 0.62) was obtained as a colorless syrup. ^1H -NMR (CDCl₃, 400 MHz) δ 7.79-7.64 (m, 4 H, aromatic H), 7.43-7.01 (m, 34 H, aromatic H), 5.62 (d, J = 3.6 Hz, 1 H, H-1b), 5.07 (d, J = 11.2 Hz, 1 H, CHH), 5.00 (d, J = 11.2 Hz, 1 H, CHH), 4.97 (d, J = 11.6 Hz, 1 H, CHH), 4.84-4.80 (bt, 2 H, H-1a, CHH), 4.72-4.57 (m, 5 H, 5 CHH), 4.51-4.32 (m, 6 H, 5 CHH, H-5), 4.28 (dd, J_1 = 8.4 Hz, J_2 = 9.2 Hz, 1 H, H-3a), 4.12 (t, J = 9.2 Hz, 1 H, H-3b), 3.84-3.56 (m, 8 H), 3.50-3.44 (m, 2H, H-6), 3.41-3.30 (m, 3 H, H-1°, H-3°), 1.85-1.79 (m, 2 H, H-2°). ^{13}C -APT (CDCl₃, 100 MHz,) δ 138.70, 138.36, 138.07, 138.04, 137.96, 137.85, 136.32, 133.33 (aromatic C), 128.55, 128.40, 128.30, 128.24, 128.23, 128.11, 128.04, 128.00, 127.95, 127.93, 127.87, 127.76, 127.67, 127.65, 127.61, 127.47, 127.43, 127.29, 126.89, 126.57, 126.52, 126.48, 126.40, 126.12, 126.08, 125.98, 125.95, 125.74 (aromatic CH), 97.40 (C-1b), 96.64 (C-1a), 82.33 (C-3b), 79.70 (C-2b), 78.77 (C-2a), 78.57 (C-4a), 78.20

(C-4b), 76.47 (C-3a), 75.51, 74.83, 73.67, 73.63, 73.52, 73.34, 73.01 (7 CH₂), 70.10 (C-5), 69.98 (C-5), 68.43 (C-6), 68.31 (C-6), 64.59 (C-1°), 48.28 (C-3°), 28.85 (C-2°).



3-Azidopropyl 2,4,6-tri-O-benzyl- α -D-glucopyranosyl-(1 $\rightarrow$ 3)-2,4,6-tri-O-benzyl- α -D-glucopyranoside (**16**):

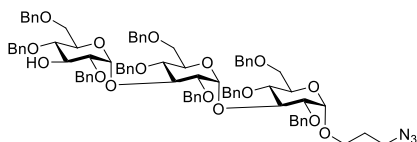
The reaction was carried out according to the general procedure D, using crude **15** (2 g, 1.81 mmol, 0.1 M in DCM:H₂O) and DDQ (451 mg, 1.99 mmol). The product was purified by silica gel column chromatography (pentane:EA = 8:1-5:1). Compound **15** (1.53 g, 90% yield with two steps, pentane:EA = 4:1, *R_f* = 0.32) was obtained as a colorless syrup. [α]_D²⁰ +78.6, *c*=1, CHCl₃. IR (neat, cm⁻¹) ν 696, 734, 1028, 1070, 1089, 1149, 1453, 1497, 2097, 2867, 2918, 3030. ¹H-NMR (CDCl₃, 400 MHz) δ 7.31-7.07 (m, 30 H, aromatic *H*), 5.59 (d, *J* = 3.6 Hz, 1 H, H-1b), 4.91 (d, *J* = 11.6 Hz, 1 H, CHH), 4.78 (d, *J* = 3.6 Hz, 1 H, H-1a), 4.71 (d, *J* = 11.2 Hz, 1 H, CHH), 4.62-4.55 (m, 4 H, 4 CHH), 4.48-4.40 (m, 5 H, 5 CHH), 4.32 (d, *J* = 12.0 Hz, 1 H, CHH), 4.28-4.23 (m, 2 H, H-3a, H-5b), 4.13 (t, *J* = 11.6 Hz, 1 H, H-3b), 3.79-3.51 (m, 7 H), 3.46-3.29 (m, 6 H), 2.34 (d, *J* = 1.6 Hz, 1 H, OH), 1.84-1.78 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz), δ 138.67, 138.27, 137.94, 137.84, 137.82 (aromatic C), 128.48, 128.34, 128.32, 128.23, 128.20, 128.10, 127.89, 127.85, 127.79, 127.69, 127.67, 127.57, 127.47, 127.25, 126.72 (aromatic CH), 96.86 (C-1b), 96.58 (C-1a), 79.14 (C-2b), 78.65 (C-2a), 78.53 (C-4a), 77.90 (C-4b), 76.28 (C-3a), 74.33 (CH₂), 73.68 (C-3b), 73.51, 73.43, 73.27, 73.09, 72.95 (5 CH₂), 69.92 (C-5a), 69.46 (C-5b), 68.32 (C-6), 68.18 (C-6), 64.50 (C-1°), 48.19 (C-3°), 28.77 (C-2°). HR-MS: Calculated for C₅₇H₆₃O₁₁N₃ [M+Na⁺]: 988.4355; found: 988.4391.



Synthesis of trisaccharide **17**: The reaction was carried out according to the standard procedure A at -78 - 0 °C. The donor **3** (1.78 g, 2.34 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (20 mL) under nitrogen and stirred over fresh flame-dried

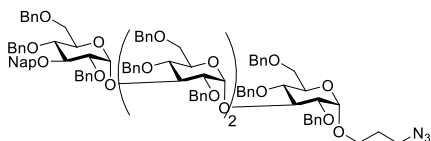
molecular sieves 3A, after which DMF (2.94 mL, 37.4 mmol) was added to the solution. The solution was cooled to -78 °C, after which TfOH (210 μ L, 2.38 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **16** (1.47 g, 1.52 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 10 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **17** (1.81 g, 81%, α : β > 20:1, pentane:EA = 4:1, *R_f* = 0.58) was obtained as a colorless syrup. [α]_D²⁰ +56.8, *c*=1, CHCl₃. IR (neat, cm⁻¹) ν 697, 750, 1028, 1072, 1088, 1155, 1364, 1454, 2096, 2865, 2927, 3030. ¹H-NMR (CDCl₃, 400 MHz) δ 7.77-7.62 (m, 4 H, aromatic *H*), 7.47-7.06 (m, 42 H, aromatic *H*), 6.99-6.94 (m, 4 H, aromatic *H*), 6.90-6.88 (m, 2 H, aromatic *H*), 5.69 (d, *J* = 3.6 Hz, 1 H, H-1c), 5.65 (d, *J* = 3.6 Hz, 1 H, H-1b), 5.01 (d, *J* = 11.2 Hz, 1 H, CHH), 4.94 (d, *J* = 11.2 Hz, 1 H, CHH), 4.90 (d, *J* = 12.0 Hz, 1 H, CHH), 4.81-4.23 (m, 21 H, H-1a, H-3a, H-3b, 2 H-5, 16 CHH), 4.12-4.05 (m, 2 H, 1 CHH, H-3c), 3.85 (t, *J* = 9.6 Hz, 1 H, H-4), 3.78-3.45 (m, 11 H), 3.39-3.24 (m, 5 H), 1.87-1.77 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz) δ 138.81, 138.61, 138.34, 138.15, 138.08, 138.05, 138.00, 137.83, 137.80, 136.28, 133.30, 132.86 (aromatic C), 128.50, 128.42, 128.32, 128.25, 128.21, 128.19, 128.15, 128.11, 128.06, 128.03, 127.96, 127.93, 127.87, 127.82, 127.77, 127.63, 127.55, 127.47, 127.37, 127.34, 127.23, 127.01, 126.60, 126.46, 126.04, 125.90, 125.70 (aromatic CH), 97.35 (C-1c),

96.60 (C-1a), 96.25 (C-1b), 82.18 (C-3c), 79.52, 79.21, 78.95, 78.91, 78.47, 78.01, 76.99 (C-3a), 75.75 (C-3b), 75.43, 74.62, 73.55, 73.46, 73.36, 73.23, 73.19, 73.15, 73.07, 69.93 (C-5b), 69.88 (C-5c), 69.54 (C-5a), 68.50 (C-6), 68.46 (C-6), 68.32 (C-6), 64.60 (C-1°), 48.29 (C-3°), 28.83 (C-2°). HR-MS: Calculated for $C_{95}H_{99}O_{16}N_3$ $[M+Na^+]$: 1560.6918; found: 1560.6923.



Synthesis of trisaccharide acceptor **18**: The reaction was carried out according to the general procedure D, using **17** (1.40 g, 0.95 mmol, 0.1 M in DCM:H₂O) and DDQ (238 mg, 1.05 mmol). The product was purified by silica gel column chromatography (pentane:EA = 8:1-

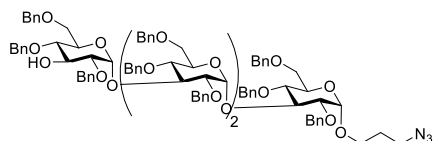
5:1). Compound **18** (1.27 g, 95% yield, pentane:EA = 4:1, R_f = 0.32) was obtained as a colorless syrup. $[\alpha]_D^{20} +80.0$, $c=1$, CHCl₃. IR (neat, cm⁻¹) ν 696, 735, 1029, 1071, 1089, 1153, 1454, 1497, 2095, 2868, 2921, 3030. ¹H-NMR (CDCl₃, 400 MHz) δ 7.33-7.07 (m, 39 H, aromatic H), 7.02-7.00 (m, 4 H, aromatic H), 6.88-6.86 (m, 2 H, aromatic H), 5.67 (d, J = 3.6 Hz, 1 H, H-1c), 5.62 (d, J = 3.6 Hz, 1 H, H-1b), 4.84-4.75 (m, 3 H, 2 CHH, H-1a), 4.68 (d, J = 11.2 Hz, 1 H, CHH), 4.81-4.05 (m, 20 H, H-3c, H-3a, H-3b, 2 H-5, 15 CHH), 3.82-3.18 (m, 17 H), 2.25 (s, 1 H, OH), 1.87-1.77 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz) δ 138.79, 138.57, 138.28, 138.03, 137.96, 137.79, 137.76 (aromatic C), 128.44, 128.40, 128.36, 128.30, 128.24, 128.18, 128.10, 128.02, 127.86, 127.79, 127.76, 127.73, 127.67, 127.61, 127.59, 127.53, 127.33, 127.30, 127.21, 127.10, 126.88, 126.51 (aromatic CH), 96.87 (C-1c), 96.56 (C-1a), 96.23 (C-1b), 79.19, 79.06, 78.87, 78.83, 78.49, 77.83, 76.82, 76.68, 74.18, 73.57, 73.54, 73.38, 73.34, 73.24, 73.09, 73.03, 73.01, 69.82 (C-5), 69.53 (C-5), 69.34 (C-5), 68.48 (C-6), 68.40 (C-6), 68.27 (C-6), 64.58 (C-1°), 48.28 (C-3°), 28.81 (C-2°). HR-MS: Calculated for $C_{84}H_{91}O_{16}N_3$ $[M+Na^+]$: 1420.6292; found: 1420.6320.



Synthesis of tetrasaccharide **19**: The reaction was carried out according to the standard procedure A at -78 - 0 °C. The donor **3** (1.10 g, 1.45 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (10 mL) under nitrogen and stirred over fresh

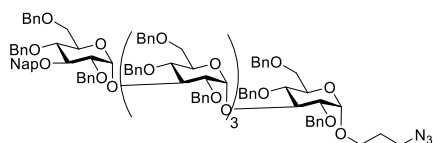
flame-dried molecular sieves 3A, after which DMF (1.83 mL, 23.2 mmol) was added to the solution. The solution was cooled to -78 °C, after which TfOH (128 μ L, 1.45 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **18** (1.01 g, 0.73 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 5 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **19** (1.20 g, 84%, α : β > 20:1, pentane:EA = 4:1, R_f = 0.46) was obtained as a colorless syrup. $[\alpha]_D^{20} +70.4$, $c=1$, CHCl₃. IR (neat, cm⁻¹) ν 697, 734, 1028, 1071, 1087, 1155, 1363, 1454, 1497, 2093, 2867, 2924, 3031. ¹H-NMR (CDCl₃, 400 MHz) δ 7.62-6.80 (m, 67 H, aromatic H), 5.71 (d, J = 3.6 Hz, 1 H, H-1), 5.61 (bd, 2 H, 2 H-1), 4.95 (d, J = 11.2 Hz, 1 H, CHH), 4.87 (d, J = 11.2 Hz, 1 H, CHH), 4.80-4.18 (m, 30 H), 4.11 (d, J = 12.0 Hz, 1 H, CHH), 3.99 (t, J = 9.6 Hz, 1 H, H-3), 3.83-3.22 (m, 21 H), 1.85-1.80 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz) δ 138.91, 138.71, 138.56, 138.32, 138.21, 138.12, 138.07, 138.05, 137.91, 137.89, 137.84, 136.35, 133.34, 132.91 (aromatic C), 128.52, 128.50, 128.48, 128.39, 128.32, 128.27, 128.25, 128.22, 128.12, 128.08, 128.04, 127.99, 127.97, 127.95, 127.87, 127.75, 127.68, 127.61, 127.59,

127.41, 127.38, 127.19, 127.13, 127.03, 126.92, 126.50, 126.45, 126.11, 125.92, 125.73 (aromatic CH), 97.33 (C-1), 96.63 (C-1), 96.33 (C-1), 96.12 (C-1), 82.21, 79.48, 79.36, 78.98, 78.95, 78.82, 78.72, 78.45, 78.04, 77.01, 75.64, 75.45, 74.56, 73.64, 73.50, 73.46, 73.37, 73.28, 73.13, 72.87, 72.72, 69.85 (C-5), 69.72 (C-5), 69.59 (2 C-5), 68.53 (3 C-6), 68.40 (C-6), 64.66 (C-1°), 48.37 (C-3°), 28.91 (C-2°). HR-MS: Calculated for $C_{122}H_{127}O_{21}N_3$ [$M+Na^+$]: 1992.8854; found: 1992.8793.



Synthesis of tetrasaccharide acceptor **20**: The reaction was carried out according to the general procedure D, using **19** (1.20 g, 0.61 mmol, 0.1 M in DCM:H₂O) and DDQ (152 mg, 0.67 mmol). The product was purified by silica gel column chromatography

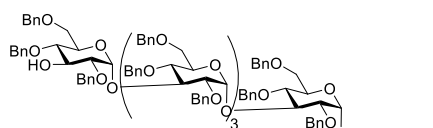
(pentane:EA = 5:1). Compound **20** (890 mg, 80% yield, pentane:EA = 4:1, R_f = 0.21) was obtained as a colorless syrup. $[\alpha]_D^{20} +87.8$, $c=1$, CHCl₃. IR (neat, cm⁻¹) ν 697, 735, 1028, 1091, 1154, 1364, 1453, 1497, 2098, 2866, 2924, 3029. ¹H-NMR (CDCl₃, 400 MHz) δ 7.35-6.78 (m, 60 H, aromatic *H*), 5.68 (d, J = 3.6 Hz, 1 H, H-1c), 5.61 (d, J = 3.6 Hz, 1 H, H-1b), 5.60 (d, J = 3.6 Hz, 1 H, H-1d), 4.79-4.76 (m, 2 H, H-1a, CHH), 4.72-4.18 (m, 28 H), 4.11 (bd, 2 H, 2 CHH), 4.00 (t, J = 9.2 Hz, 1 H, H-3d), 3.83-3.20 (m, 21 H), 2.19 (s, 1 H, OH), 1.86-1.80 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz) δ 138.85, 138.67, 138.49, 138.31, 138.09, 138.01, 137.88, 137.87, 137.82 (aromatic C), 128.40, 128.38, 128.23, 128.19, 128.18, 128.04, 127.99, 127.94, 127.84, 127.78, 127.75, 127.70, 127.65, 127.60, 127.48, 127.41, 127.33, 127.30, 127.28, 127.17, 127.08, 127.01, 126.96, 126.56, 126.40, 126.34 (aromatic CH), 96.86 (C-1d), 96.60 (C-1a), 96.29 (C-1b), 96.11 (C-1c), 79.35, 79.00, 78.91, 78.72, 78.68, 78.45, 77.85, 76.97, 75.53, 75.35, 74.11, 73.62, 73.56, 73.49, 73.40, 73.25, 73.11, 73.09, 72.95, 72.88, 72.67, 69.69 (C-5), 69.58 (C-5), 69.54 (C-5), 69.23 (C-5), 68.53 (C-6), 68.48 (2 C-6), 68.34 (C-6), 64.65 (C-1°), 48.35 (C-3°), 28.89 (C-2°). HR-MS: Calculated for $C_{111}H_{119}O_{21}N_3$ [$M+Na^+$]: 1852.8228; found: 1852.8154.



Synthesis of pentasaccharide **21**: The reaction was carried out according to the standard procedure A at -78 - 0 °C. The donor **3** (587 mg, 0.77 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (4 mL) under nitrogen and stirred over fresh

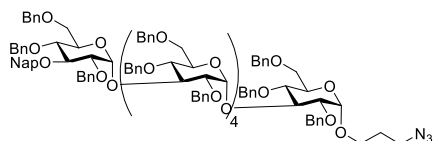
flame-dried molecular sieves 3A, after which DMF (970 mL, 12.3 mmol) was added to the solution. The solution was cooled to -78 °C, after which TfOH (68 μ L, 0.77 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **20** (705 mg, 0.38 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 4 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **21** (750 mg, 81%, α : β > 20:1, pentane:EA = 4:1, R_f = 0.36) was obtained as a colorless syrup. $[\alpha]_D^{20} +77.8$, $c=1$, CHCl₃. IR (neat, cm⁻¹) ν 697, 734, 1029, 1071, 1089, 1154, 1364, 1454, 1497, 2097, 2864, 2923, 3030. ¹H-NMR (CDCl₃, 400 MHz) δ 7.75-6.64 (m, 82 H, aromatic *H*), 5.69 (d, J = 3.2 Hz, 1 H, H-1c), 5.65 (d, J = 3.2 Hz, 1 H, H-1d), 5.61 (d, J = 3.6 Hz, H, H-1b), 5.57 (d, J = 3.2 Hz, 1 H, H-1e), 4.95 (d, J = 11.2 Hz, 1 H, CHH), 4.86 (d, J = 11.2 Hz, 1 H, CHH), 4.80-4.09 (m, 39 H), 3.97 (t, J = 9.6 Hz, 1 H, H-3e), 3.83-3.20 (m, 25 H), 1.88-1.81 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz) δ

139.28, 138.87, 138.68, 138.50, 135.35, 138.26, 138.17, 138.06, 138.03, 137.99, 137.90, 137.84, 137.77, 136.31, 133.29, 132.84 (aromatic C), 128.48, 128.44, 128.42, 128.33, 128.27, 128.25, 128.20, 128.14, 128.06, 127.98, 127.95, 127.93, 127.90, 127.80, 127.72, 127.70, 127.63, 127.61, 127.55, 127.50, 127.33, 127.29, 127.26, 127.19, 127.10, 127.00, 126.77, 126.51, 126.44, 126.34, 126.22, 126.06, 126.86, 125.66 (aromatic CH), 97.21 (C-1e), 96.54 (C-1a), 96.26 (C-1b), 96.11 (C-1c), 95.99 (C-1d), 82.10 (C-3e), 79.40, 79.20, 79.13, 78.91, 78.86, 78.78, 78.56, 78.51, 78.42, 77.98, 76.87, 75.53, 75.36, 75.06, 74.46, 75.58, 73.44, 73.31, 73.09, 72.99, 72.93, 72.70, 72.64, 72.51, 69.73 (C-5), 69.55 (C-5), 69.49 (2 C-5), 69.36 (C-5), 68.48 (2 C-6), 68.43 (2 C-6), 68.33 (C-6), 64.60 (C-1°), 48.29 (C-3°), 28.85 (C-2°). HR-MS: Calculated for $C_{149}H_{155}O_{26}N_3$ $[M+H]^+$: 2403.0972; found: 2403.0933.



Synthesis of pentasaccharide acceptor **22**: The reaction was carried out according to the general procedure D, using **21** (520 mg, 0.22 mmol, 0.1 M in DCM:H₂O) and DDQ (54 mg, 0.24 mmol). The product was purified by silica gel column chromatography (Tol:EA

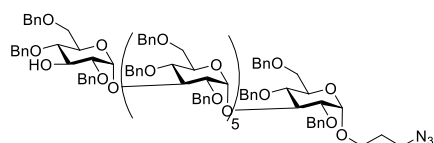
= 20:1). Compound **22** (370 mg, 75% yield, pentane:EA = 4:1, *R_f* = 0.20) was obtained as a colorless syrup. $[\alpha]_D^{20} +98.6$, *c*=1, CHCl₃. IR (neat, cm⁻¹) ν 696, 734, 1028, 1071, 1088, 1153, 1453, 1497, 2092, 2864, 2923, 3031. ¹H-NMR (CDCl₃, 400 MHz) δ 7.34-6.60 (m, 75 H, aromatic *H*), 5.69 (d, *J* = 3.6 Hz, 1 H, H-1c), 5.61 (bt, 2 H, H-1b, H-1d), 5.54 (d, *J* = 3.6 Hz, 1 H, H-1e), 4.79 (d, *J* = 3.6 Hz, 1 H, H-1a), 4.76 (d, *J* = 11.6 Hz, 1 H, *CHH*), 4.69-4.07 (m, 37 H), 3.98 (t, *J* = 9.6 Hz, 1 H, H-3e), 3.83-3.17 (m, 25 H), 2.17 (s, 1 H, OH), 1.87-1.80 (m, 2 H, H-2°). ¹³C-APT (CDCl₃, 100 MHz) δ 138.85, 138.67, 138.52, 138.47, 138.28, 138.06, 138.01, 137.91, 137.86, 137.85, 137.79 (aromatic C), 128.49, 128.47, 128.45, 128.36, 128.29, 128.23, 128.23, 128.16, 128.11, 128.09, 128.05, 127.99, 127.96, 127.92, 127.82, 127.80, 127.73, 127.67, 127.63, 127.57, 127.44, 127.29, 127.20, 127.01, 126.85, 126.79, 126.49, 126.27, 126.15 (aromatic CH), 96.79 (C-1e), 96.56 (C-1a), 96.28 (C-1), 96.10 (C-1), 96.01 (C-1), 79.22, 79.15, 78.95, 78.87, 78.77, 78.55, 78.44, 77.81, 76.87, 75.50, 75.02, 74.04, 73.61, 73.49 (C-3e), 73.47, 73.42, 73.38, 73.35, 73.30, 73.09, 73.01, 72.83, 72.69, 72.50, 69.57 (C-5), 69.48 (2 C-5), 69.37 (C-5), 69.14 (C-5), 68.51 (2 C-6), 68.44 (2 C-6), 68.31 (C-6), 64.63 (C-1°), 48.33 (C-3°), 28.88 (C-2°). HR-MS: Calculated for $C_{138}H_{147}O_{26}N_3$ $[M+H]^+$: 2263.0346; found: 2263.0291.



Synthesis of hexasaccharide **23**: The reaction was carried out according to the standard procedure A at -78 - 0 °C. The donor **3** (310 mg, 0.41 mmol, co-evaporated with toluene 3 times) was dissolved in dry DCM (1 mL) under nitrogen and stirred over fresh

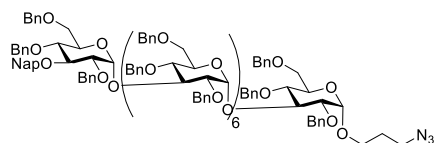
flame-dried molecular sieves 3A, after which DMF (512 μ L, 6.56 mmol) was added to the solution. The solution was cooled to -78 °C, after which TfOH (36 μ L, 0.41 mmol) was added. After 30 min, the pre-activation was complete as indicated by TLC-analysis. Acceptor **22** (260 mg, 0.12 mmol, dissolved in a little DCM and washed 3 times with DCM, totally 1 mL) was added to the solution and the mixture was placed in an ice bath. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **23** (293 mg, 90%, α : β > 20:1, pentane:EA = 4:1, *R_f* = 0.32) was obtained as a colorless syrup. $[\alpha]_D^{20} +78.7$, *c*=1, CHCl₃. IR (neat, cm⁻¹) ν 697, 734, 1029, 1072, 1089, 1154, 1363, 1454, 1497, m2097, 2863, 2926, 3029. ¹H-NMR (CDCl₃, 400

δ 7.74-6.58 (m, 112 H, aromatic H), 5.69 (d, J = 3.5 Hz, 1 H, H-1), 5.63-5.55 (m, 5 H, 5 H-1), 4.93 (d, J = 11.5 Hz, 1 H, CHH), 4.85 (d, J = 11.5 Hz, 1 H, CHH), 4.79-4.09 (m, 55 H), 3.96 (t, J = 9.0 Hz, 1 H, H-3g), 3.83-3.19 (m, 33 H), 1.85-1.79 (m, 2 H, H-2°). ^{13}C -APT (CDCl₃, 125 MHz) δ 138.84, 138.65, 138.49, 138.46, 128.23, 128.15, 138.03, 138.00, 137.84, 137.80, 137.74, 136.29, 133.24, 132.79 (aromatic C), 128.39, 128.38, 128.36, 128.27, 128.22, 128.21, 128.19, 128.14, 128.08, 128.03, 127.98, 127.96, 127.90, 127.86, 127.83, 127.72, 127.70, 127.64, 127.55, 127.48, 127.42, 127.32, 127.27, 127.21, 127.17, 127.04, 126.97, 126.78, 126.59, 126.64, 126.45, 126.37, 126.28, 126.24, 126.20, 126.11, 126.00, 125.79, 125.60 (aromatic CH), 97.11 (C-1g), 96.48 (C-1a), 96.17 (C-1), 95.99 (C-1), 95.92 (2 C-1), 95.87 (C-1), 82.03 (C-3g), 79.40, 79.17, 79.05, 79.00, 78.85, 78.75, 78.47, 78.38, 78.32, 77.95, 76.83, 75.46, 75.42, 75.28, 75.05, 74.94, 74.39, 73.52, 73.38, 73.31, 73.25, 73.22, 72.98, 72.93, 72.75, 72.61, 72.47, 72.35, 72.27, 69.67 (C-5), 69.52 (C-5), 69.43 (C-5), 69.36 (C-5), 69.30 (C-5), 69.11 (C-5), 69.06 (C-5), 68.44 (6 C-6), 68.29 (C-6), 64.56 (C-1°), 48.22 (C-3°), 28.79 (C-2°). MALDI-TOF: Calculated for C₂₀₃H₂₁₁O₃₆N₃ [M+K⁺]: 3305.4; found: 3306.1.



Synthesis of heptasaccharide acceptor **26**: The reaction was carried out according to the general procedure D, using **25** (300 mg, 0.09 mmol, 0.05 M in DCM:H₂O) and DDQ (23 mg, 0.10 mmol). The product was purified by silica gel column chromatography (Tol:EA

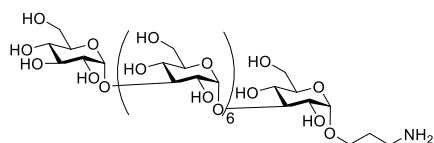
= 20:1). Compound **26** (145 mg, 51% yield, Tol:EA = 9:1, R_f = 0.25) was obtained as a colorless syrup. $[\alpha]_D^{20}$ +129.9, c =1, CHCl₃. IR (neat, cm⁻¹) ν 696, 733, 1028, 1071, 1089, 1153, 1364, 1454, 1497, 2096, 2863, 2926, 3031. ^1H -NMR (CDCl₃, 500 MHz) δ 7.33-6.54 (m, 105 H, aromatic H), 5.68 (d, J = 3.5 Hz, 1 H, H-1), 5.61 (bt, 2 H, 2 H-1), 5.58 (d, J = 3.5 Hz, 1 H, H-1), 5.55 (d, J = 3.5 Hz, 1 H, H-1), 5.52 (d, J = 3.5 Hz, 1 H, H-1g), 4.78 (bt, 2 H, H-1a, CHH), 4.69-4.06 (m, 53 H), 3.96 (t, J = 9.5 Hz, 1 H, H-3g), 3.82-3.15 (m, 33 H), 2.15 (bs, 1 H, OH), 1.84-1.80 (m, 2 H, H-2°). ^{13}C -APT (CDCl₃, 125 MHz) δ 138.88, 138.70, 138.55, 138.52, 138.29, 138.07, 138.04, 138.03, 137.96, 137.88, 137.82 (aromatic C), 128.47, 128.45, 128.43, 128.34, 128.29, 128.27, 128.21, 128.16, 128.14, 128.10, 128.05, 128.02, 127.97, 127.94, 127.89, 127.80, 127.77, 127.71, 127.63, 127.60, 127.54, 127.43, 127.39, 127.33, 127.30, 127.21, 127.14, 127.12, 127.05, 126.84, 126.81, 126.77, 126.68, 126.61, 126.51, 126.29, 126.28, 126.23, 126.08 (aromatic CH), 96.75 (C-1f), 96.56 (C-1a), 96.23 (C-1), 96.05 (C-1), 96.00 (C-1), 95.95 (2 C-1), 79.24, 79.10, 79.06, 78.97, 78.44, 78.41, 78.30, 77.82, 75.48, 75.11, 74.97, 74.01, 73.60, 73.46, 73.39, 73.36, 73.34, 73.29, 73.02, 72.79, 72.74, 72.65, 72.56, 72.51, 72.38, 72.31, 69.58 (C-5), 69.49 (C-5), 69.40 (C-5), 69.36 (C-5), 69.16 (C-5), 69.12 (2 C-5), 68.49 (6 C-6), 68.31 (C-6), 64.64 (C-1°), 48.33 (C-3°), 28.88 (C-2°). MALDI-TOF: Calculated for C₁₉₂H₂₀₃O₃₆N₃ [M+K⁺]: 3165.4; found: 3165.0.



Synthesis of octasaccharide **27**: The reaction was carried out according to the standard procedure B, using **3** (110 mg, 0.14 mmol), **24** (120 mg, 0.038 mmol, 0.025 M in DCM), DMF (182 μL , 2.31 mmol) and TfOH (13 μL , 0.15 mmol). The reaction was stirred at -

78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **27** (140 mg, 98% yield, α : β > 20:1, pentane:EA = 4:1, R_f = 0.17) was obtained as a colorless syrup. $[\alpha]_D^{20}$ +97.1, c =1, CHCl₃. IR (neat, cm⁻¹) ν 697, 734, 1028, 1071, 1154, 1208, 1364, 1455, 1497, 2097, 2864, 2925, 3030. ^1H -NMR (CDCl₃,

400 MHz) δ 7.75-6.56 (m, 127 H, aromatic H), 5.69 (d, J = 3.5 Hz, 1 H, H-1), 5.63-5.54 (m, 6 H, 6 H-1), 4.93 (d, J = 11.2 Hz, 1 H, CHH), 4.85 (d, J = 11.2 Hz, 1 H, CHH), 4.809-4.08 (m, 63 H), 3.95 (t, J = 9.2 Hz, 1 H, H-3h), 3.83-3.15 (m, 37 H), 1.84-1.80 (m, 2 H, H-2°). ^{13}C -APT (CDCl₃, 100 MHz) δ 139.17, 138.87, 138.67, 138.52, 138.49, 138.48, 138.34, 138.25, 138.17, 138.06, 138.02, 137.86, 137.80, 137.76, 136.32, 133.27, 132.82 (aromatic C), 128.47, 128.44, 128.42, 128.33, 128.27, 128.21, 128.17, 128.12, 128.07, 128.06, 128.03, 127.99, 127.95, 127.89, 127.80, 127.74, 127.71, 127.61, 127.53, 127.47, 127.38, 127.31, 127.27, 127.22, 127.16, 127.08, 127.04, 127.01, 126.83, 126.72, 126.46, 126.42, 126.28, 126.25, 126.17, 126.09, 126.05, 125.84, 125.65 (aromatic CH), 97.17 (C-1), 96.528 (C-1), 96.22 (C-1), 96.03 (C-1), 95.95 (4 C-1), 82.09 (C-3h), 79.37, 79.19, 79.02, 78.86, 78.73, 78.44, 78.39, 78.28, 77.95, 76.89, 75.51, 75.43, 75.35, 75.05, 74.97, 74.84, 74.43, 73.58, 73.44, 73.37, 73.30, 73.26, 72.99, 72.77, 72.64, 72.57, 72.46, 72.29, 69.67 (C-5), 69.52 (C-5), 69.45 (C-5), 69.35 (C-5), 69.31 (C-5), 69.10 (C-5), 69.03 (2 C-5), 68.41 (7 C-6), 68.29 (C-6), 64.60 (C-1°), 48.29 (C-3°), 28.84 (C-2°). MALDI-TOF: Calculated for C₂₃₀H₂₃₉O₄₁N₃ [M+K⁺]: 3737.6; found: 3737.5.



Synthesis of octasaccharide **2**: Compound **27** (20 mg, 0.0054 mmol) was dissolved in THF/H₂O/*tert*-BuOH (2 mL/2 mL/1 mL) before a catalytic amount of Pd(OH)₂/C was added. The reaction mixture was stirred for 2 days under a H₂ atmosphere (40 bar), filtered and

concentrated *in vacuo*. A white powder **2** was obtained, which was purified by gel filtration (HW-40, 0.15M NH₄OAc in H₂O) to yield **1** (2.9 mg, 40%). ^1H -NMR (CDCl₃, 500 MHz) δ 5.35 (bd, 7 H, 7 H-1), 4.91 (d, J = 3.5 Hz, 1 H, H-1), 4.02-3.53 (m, 53 H), 3.41 (t, J = 10.0 Hz, 1 H), 3.14-3.00 (m, 2 H), 1.96-1.91 (m, 2 H). ^{13}C -APT (CDCl₃, 125 MHz) δ 99.39, 99.23, 98.47, 79.94, 79.89, 79.75, 72.89, 71.84, 71.73, 71.62, 70.39, 69.93, 69.86, 69.74, 69.51, 65.91, 60.51, 60.39, 60.30, 37.88, 27.60. HR-MS: Calculated for C₅₁H₈₉O₄₁N [M+H⁺]: 1372.4983; found: 1372.5005.

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Chapter 4

Synthesis of Teichoic Acid α -(1,2)-Glucans

Introduction

α -Glucans, polysaccharides composed of glucose monosaccharides connected through α -glycosidic linkages, are widely found in natural products.^[1] The most abundant α -glucans are the α -(1,4)-glucans, that occur as starch and glycogen, and can be found as extracellular polysaccharides surrounding bacteria, such as *Mycobacterium tuberculosis*.^[2] α -(1,3)-Glucans are prominent members of the fungal cell wall and they have been implicated to play an important role in the interaction between the pathogenic fungus *Aspergillus fumigatus* and the host immune system.^[3] α -(1,2)-Glucans, also referred to as kojioligosaccharides, are the rarest member of the α -glucan family, but kojibiose and higher kojioligosaccharides have been found in koji extract, sake, beer and honey and they have also been encountered in bacterial cell walls.^[4] Kojibiose, kojitriose and kojitetraose have been found as part of the lipoteichoic acid (LTA) of *Enterococcus*

faecalis, which is a Gram-positive commensal bacterium.^[5] Although this bacterium is generally of low virulence, it is the causative agent of many life-threatening infections in immunocompromised patients and one of the most prominent hospital bacteria.^[6] LTA is an anionic polymer that is linked to the cell wall of the bacteria through a glycolipid anchor, and that is built up from glycerol phosphate repeating units, which can be substituted by glycans and D-alanine esters at the C2 position of the glycerols.^[7] Kojibiose is a prominent appendage of *E. faecalis* LTA (Figure 1), where it can be decorated with D-alanine esters at both C6-hydroxyl groups of the disaccharide.^[7] D-Alanylation plays a critical role in the virulence of the bacteria and it renders the bacteria less susceptible to (cationic) antimicrobial peptides. *E. faecalis* LTA fragments, containing a single α -glucosyl substituent have previously been explored as components in synthetic vaccine conjugates, and antibodies raised by these conjugates have been shown to be opsonophagocytic and capable of inducing killing of the bacteria in both active and passive immunization strategies.^[8] The microheterogeneity of naturally occurring LTA makes it challenging -if not impossible- to establish clear structure-activity relationships for these molecules, and therefore organic synthesis is the method of choice for the generation of well-defined single LTA molecules.

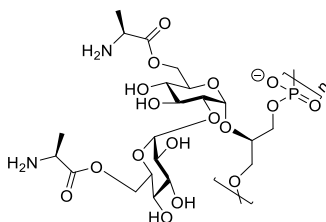
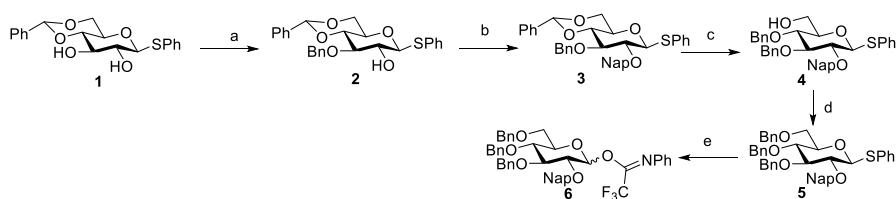


Figure 1. The structure of *E. faecalis* LTA.

Only few chemical syntheses of α -(1,2)-glucans have been reported. Takeo and Suzuki reported a procedure to assemble kojitriose, kojitetraose and kojipentaose based on the use of Koenigs-Knorr-type glycosylations, using anomeric chlorides under the activation of silver perchlorate.^[9] Hogendorf *et al.* relied on Crich's α -glucosylation protocol which involved the use of benzylidene glucose donors for the synthesis of a kojibiose glycerol building block.^[8] The work described in Chapter 2 and 3 has shown that additive controlled glycosylations of per-benzylated glucosyl donors can be used effectively for the introduction of α -(1,4)- and a α -(1,3)-glucosyl linkages,^[10] and it thus represents an attractive strategy for the assembly of α -(1,2)-linkages. This Chapter explores the use of additive controlled glycosylation methodology for the construction of α -(1,2)-glucans and the methodology is applied for, in combination with the triad of benzyl ether type protecting groups introduced in Chapter 2, the preparation of a D-Ala-kojibiose functionalized LTA (fragment of building block, depending on how far we get with the synthesis).

Results and Discussion

First the assembly of a spacer functionalized kojioligosaccharide was explored. To achieve this aim, donor **6** was designed and assembled, bearing three permanent benzyl ethers to mask the C3, C4 and C6 hydroxyls and a 2-methylnaphthyl (Nap) ether as a temporary protecting group at the C2-OH. The synthesis of this building block used benzylidene protected glucose building block **1** as starting compound. Selective protection of the C3-OH with benzyl ether was achieved through the formation of an intermediate tin ketal which was treated with benzyl bromide and cesium fluoride to give compound **2**. Protection of the remaining C2-OH with a Nap ether then provided compound **3**. Selective opening the benzylidene and protection of the liberated primary alcohol provided the fully benzylated thio donor **5**. The anomeric thio acetal in this building block was hydrolyzed using *N*-iodosuccinimide (NIS) in acetone/water to liberate the anomeric hydroxyl group, which could then be turned into the required *N*-phenyltrifluoroimidate **6**.

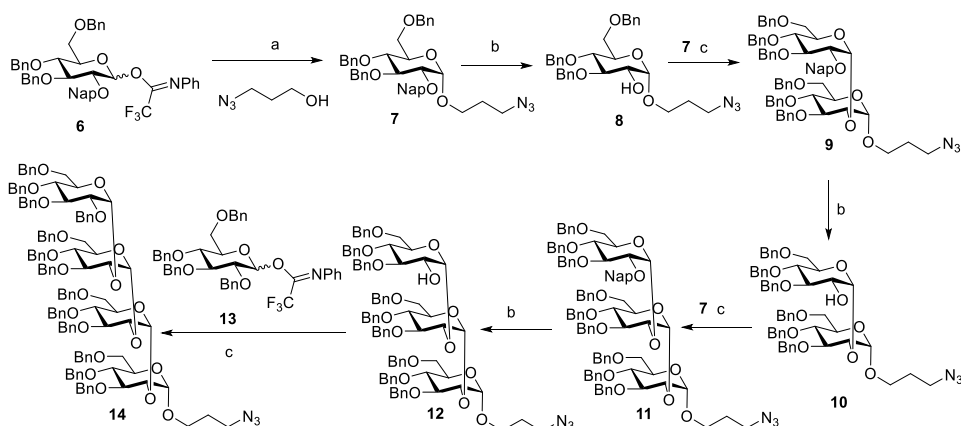


a) 1) Bu_2SnO , toluene, 120°C ; 2) CsF , BnBr , 76%. b) NapBr , NaH , DMF , 91%. c) $\text{BF}_3\cdot\text{Et}_2\text{O}$, TES , DCM , 72%. d) BnBr , NaH , DMF , 88%. e) 1) NIS , acetone: H_2O = 10:1 (v:v); 2) 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride, Cs_2CO_3 , acetone, 81% over two steps.

Scheme 1. The synthesis of donor **6**.

With the required donor **6** in hand, the assembly of kojioligosaccharides was explored as depicted in Scheme 2. Firstly, the donor **6** was glycosylated with azidopropanol under the $\text{TMSI-Ph}_3\text{P=O}$ condition to form the desired azidopropyl glucoside **7** in good yield and stereoselectivity ($\alpha:\beta$ = 10:1), in line with the results described previously. Deprotection of the C2-O-Nap ether under oxidative condition (dichlorodicyanobenzoquinone (DDQ) in $\text{DCM}/\text{H}_2\text{O}$, 10:1 v/v) provided alcohol **8** which was purified by silica gel column chromatography to deliver the pure α -anomer. Next the secondary alcohol acceptor **8** was glycosylated with donor **6** under the agency of TMSOTf and DMF to form the disaccharide **9** in 95% yield and a 15:1 $\alpha:\beta$ -ratio. Deprotection of the C2-O-Nap ether by DDQ to give disaccharide acceptor **10** proceeded in somewhat lower yield than the deprotection of the monosaccharide **8** (49% vs 75% yield). The third glycosylation, again performed under DMF mediated glycosylation conditions, then provided trisaccharide **11**. The stereoselectivity of this glycosylation, however, diminished slightly and **11** was formed as a 10:1 $\alpha:\beta$ mixture. The erosion of stereoselectivity developed further upon elongation of the trisaccharide. Thus, the DMF -mediated glycosylation of acceptor **12**, obtained after DDQ treatment of **11**, with per-benzyl donor **13** delivered tetrasaccharide **14** as a 2:1 $\alpha:\beta$ -mixture.

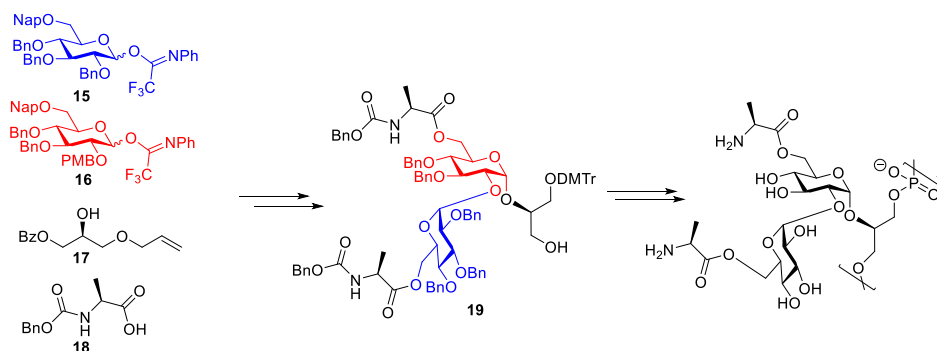
Possibly the overall structure of the twisted oligosaccharide is at the root of the erosion of stereoselectivity, with increasing steric demands leading to lower yields and poorer selectivity, indicating a limitation of the current glycosylation protocol.



a) TMSI, $\text{Ph}_3\text{P}=\text{O}$, DCM, 36 h, 75%, $\alpha:\beta = 10:1$. b) DDQ, DCM: $\text{H}_2\text{O} = 10:1$ (v:v), **8**: 75%; **10**: 49%; **12**: 47%. c) DMF, TfOH, DCM, **9**: 95%, $\alpha:\beta = 15:1$; **11**: 67%, $\alpha:\beta = 10:1$; **14**: 67%, $\alpha:\beta = 2:1$.

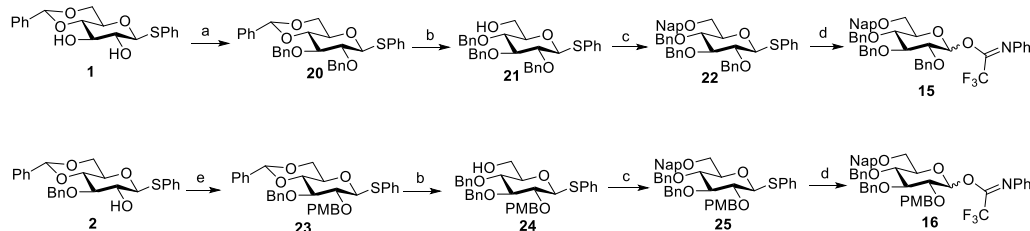
Scheme 2. The assembly of α -(1,2)-tetrasaccharide.

Although, the limitations of the DMF-mediated glycosylation protocol have come forward in the above described kojitetraose assembly, the synthesis also showed that the additive controlled glycosylation approach can provide a rapid entry into the assembly of kojibiose derivatives. Therefore, the assembly of an *E. faecalis* D-Ala-kojibiose LTA fragment was next explored. The synthesis of D-Ala-kojibiose LTAs requires the availability of compound **19** featuring the kojibiose, decorated with two D-alanine esters at both primary alcohols, attached to the glycerol through an α -bond with (Scheme 3). This intermediate compound **19** can be assembled from four building blocks: two benzyl type protected glucosyl donors, **15** and **16**, glycerol **17** protected with a benzoyl ester (Bz), allyl ether and *N*-benzyloxycarbonyl protected D-alanine **18** (Scheme 3). The glucosyl donors are protected with solely benzyl type ethers protecting group to keep the reactivity of these building blocks uniform throughout the assembly. The triad of benzyl, *para*-methoxybenzyl (PMB), and 2-methylnaphthyl ethers was used to discriminate the alcohol groups that required permanent protection or needed to be removed to introduce the next glucose residue of introduce the D-alanine esters.



Scheme 3. The required building blocks for synthesis of D-Ala kojibiose functionalized LTA-fragments of *Enterococcus faecalis*.

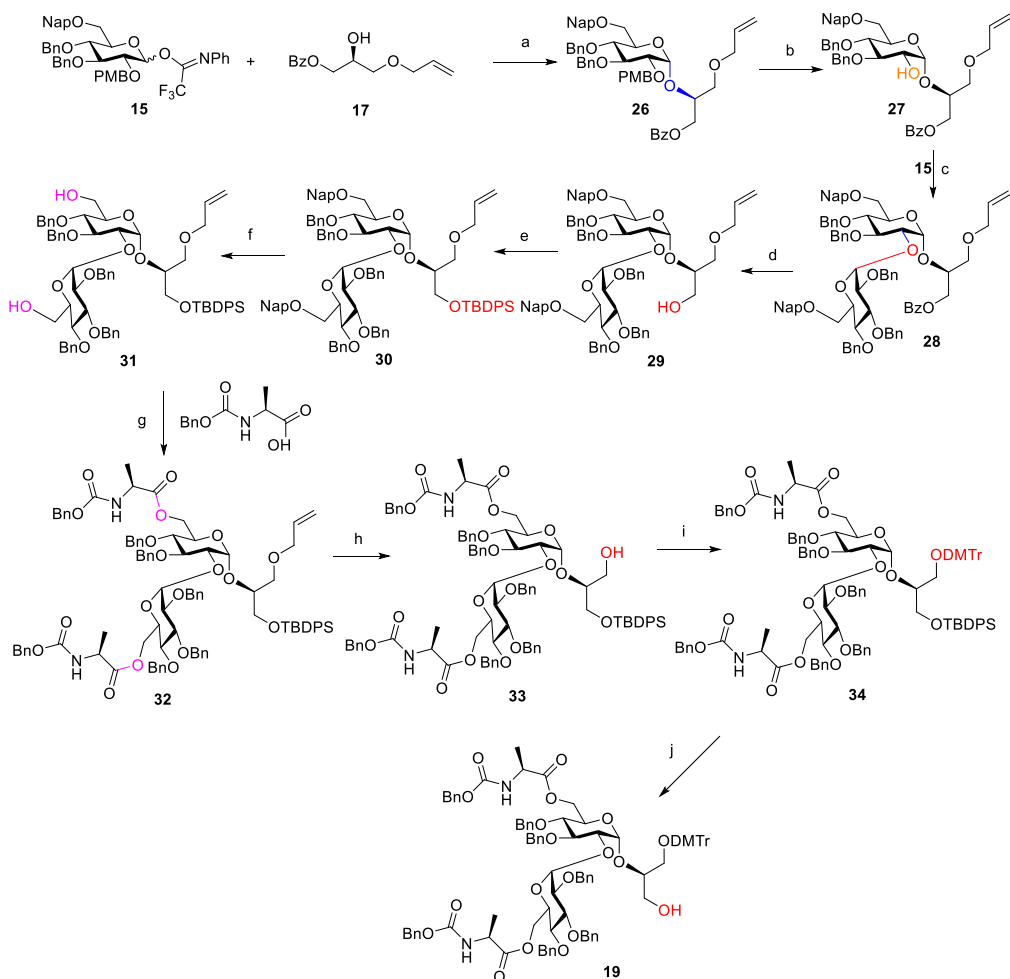
The synthesis of the required building blocks is depicted in Scheme 4. Firstly, donor **15** was synthesized from compound **1** by benzylation of the C2 and C3-hydroxyls, regioselective opening of the benzylidene acetal and protection of the liberated primary alcohol with a Nap-ether, to give thio donor **22**. Hydrolysis of the thioacetal and introduction of the 2,2,2-trifluoro-*N*-phenylacetimidate formed the desired donor **15**. Donor **16** was obtained from compound **2** following a similar sequence of reactions: Protection of the C2-OH with a PMB-ether, regioselective opening of the benzylidene acetal and installation of the C6-*O*-Nap ether provided thioacetal **25**, which was transformed into the corresponding imidate donor **16**.



a) BnBr, NaH, DMF, **20**: 96%. b) BH_3 /THF, $\text{Cu}(\text{OTf})_2$, **21**: 80%; **24**: 76%. c) NapBr, NaH, DMF, **22**: 91%; **25**: 93%. d) 1) NIS, acetone:H₂O = 10:1 (v:v); 2) 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride, Cs_2CO_3 , acetone, yield **15**: 86%; **16**: 84%. e) PMBCl, NaH, DMF, 94%.

Scheme 4. Synthesis of donor **15** and **16**.

With all the required building blocks available, the target kojibiose glycerol building block **19** was assembled as depicted in Scheme 5. Donor **15** was glycosylated with glycerol **17**, of which the primary alcohol groups were protected by a benzoate ester and an allyl ether, using the TMSI- $\text{Ph}_3\text{P}=\text{O}$ activation condition to give the compound **26** in good yield and excellent selectivity. Next, the C2-*O*-PMB was selectively removed using a catalytic amount of HCl in a mixture of hexafluoro-*iso*-propanol (HFIP) and DCM to give C2-OH acceptor **27** in 95% yield.^[11] All other benzyl ethers remained unaffected under these conditions.



a) TMSI, $\text{Ph}_3\text{P}=\text{O}$, DCM, 36 h, 76%, $\alpha:\beta > 20:1$. b) TES, HCl/HFIP , $\text{DCM}:\text{HFIP} = 1:1$ (v:v), 93%. c) DMF, TfOH , 24 h, 95%, $\alpha:\beta > 10:1$. d) CH_3ONa , $\text{DCM}:\text{CH}_3\text{OH} = 1:1$ (v:v), 92%. e) TBDPSCl , imidazole, DMF, 99%. f) DDQ , $\text{DCM}:\text{H}_2\text{O} = 10:1$ (v:v), 77%. g) PyBOP , NMI , DCM, 90%. h) 1) $\text{Ir}(\text{COD})(\text{Ph}_2\text{MeP})_2\text{PF}_6$, H_2 , THF, 2) I_2 , NaHCO_3 , 85%. i) DMTrCl , DIPEA , DCM, 95%. j) HF -pyridine, THF/pyridine, 86%.

Scheme 5. Synthesis of 6,6-di-alanyl- α -kojibiose **19**.

Acceptor **27** was then glycosylated with donor **15** using the DMF-mediated glycosylation condition to form the disaccharide **28** with good selectivity and excellent yield. To set the stage for the introduction of the D-alanyl esters, first the glycerol benzoate was replaced by a TBDPS ether, after which the two C-6-O-Nap ethers were removed to give diol **31**. The introduction of the two D-Ala esters was accomplished using PyBOP as a condensing agent to form 6,6-di-alanyl- α -kojibiose **32** in 90% yield. To transform this building block into a synthon suitable for the assembly of LTA-fragments, the allyl ether was replaced by a 4,4'-dimethoxytrityl (DMTr) group. To this end the allyl group was isomerized to the corresponding enol ether using an iridium

catalyst, which was subsequently hydrolyzed using I_2 in combination with sodium bicarbonate. The liberated primary alcohol was treated with DMTrCl in DCM to give compound **34**. Finally compound **34** was treated with HF-pyridine to give the 6,6-di-alanyl- α -kajibiose **19** in 86% yield.

Conclusion

In conclusion, this Chapter deals with DMF-mediated glycosylations for the construction of α -(1,2)-glucosyl linkages. After the successful construction of α -(1,3)-glucosyl and α -(1,4)-glucosyl linkages, reported in Chapter 3 and 2, respectively, it is shown that the developed conditions (activation of a per-benzylated glucosyl imidate donor with stoichiometric TfOH in the presence of an excess DMF) can be profitably used for the construction of kojibiosyl linkages. However, the assembly of a linear kojitetraose has revealed that the stereoselectivity of the glycosylation reactions decreases with growing chain length. A kojibiose was assembled with excellent stereoselectivity (α : β = 15:1) and elongation of this disaccharide proceeded with good selectivity (α : β = 10:1), but extension of the trisaccharide with a fourth residue led to an unproductive anomeric mixture (α : β = 2:1). Likely the secondary structure adopted by the trisaccharide acceptor caused this drop in selectivity. Using the methodology and building on a triad of benzyl-type protecting groups, a D-Ala-kajibiose functionalized LTA from the *E. faecalis* cell wall was synthesized. The generation of this structure will enable its evaluation as synthetic antigen for the generation of a synthetic vaccine, directed at this important nosocomial pathogen.

Experimental Section

General experimental procedures

All reagents were of commercial grade and used as received. All moisture sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4 \cdot 2H_2O$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20. ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in $CDCl_3$ or D_2O . Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard (^1H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. NMR peak assignments were made using COSY and HSQC experiments, where applicable Clean TOCSY, HMBC and GATED experiments were used to further elucidate the structure. The anomeric product ratios were analyzed through integration of proton NMR signals.

Standard procedure

Procedure A for the glycosylation of secondary alcohols:

A mixture of donor (1.0 eq), acceptor (0.7 eq) (donors and acceptors co-evaporated with toluene three times), DMF (16

eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 °C, after which TfOH (1.0 eq) was added. After 30 min, the reaction was stirred at 0 or -10 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Standard procedure B for the glycosylation of primary alcohols: A mixture of donor (1.0 eq), acceptor (0.7 eq) (donor and acceptor co-evaporated with toluene three times), Ph₃P=O (6 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. Then TMSI (1.0 eq) was added slowly in the mixture. The reaction was stirred at room temperature until TLC-analysis indicated the reaction to be complete. The solution was diluted and the reaction quenched with saturated Na₂S₂O₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Procedure C for deprotection of the PMB protecting group:

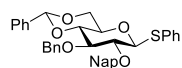
The starting material (1 eq) was dissolved in DCM:HFIP (1:1, 0.1 M). TES (1.0 eq) and 0.1M HCl/HFIP (0.1eq) were added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material (15min-2h). Then the mixture was diluted with DCM and the reaction quenched with saturated NaHCO₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography.

Standard procedure D for deprotection of the Nap protecting group:

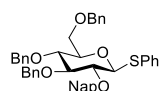
The starting material (1 eq) was dissolved in DCM:H₂O (10:1, 0.1 M). DDQ (1.1 eq) was added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material (± 2h). Then the mixture was diluted with DCM and the reaction quenched with saturated Na₂S₂O₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography.

Experimental Procedures and Characterization Data of Products

We used "a", "b", "c" and "d" to specify the H-1 and C-13 NMR signals of sugar rings from the "reducing" to the "non-reducing" end and "oo" to specify the H-1 and C-13 NMR signals of the spacer.

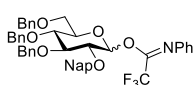


Phenyl 4,6-O-benzelidine-2-O-(naphthalen-2-ylmethyl)-3-O-benzyl-1-thio-β-D-glucopyranoside 3: ¹H-NMR (CDCl₃, 400 MHz) δ 7.80-7.77 (m, 4 H, aromatic *H*), 7.55-7.22 (m, 18 H, aromatic *H*), 5.54 (s, 1 H), 5.02-4.94 (m, 3 H, 3 CH*H*), 4.79-4.76 (m, 2 H, H-1, 1 CH*H*), 4.35 (dd, *J*₁ = 4.8 Hz, *J*₂ = 10.4 Hz, 1 H, H-6_a), 3.86-3.66 (m, 3 H, H-6, H-4, H-3), 3.56 (t, *J* = 8.4 Hz, 1 H, H-2), 3.47-3.41 (m, 1 H, H-5). ¹³C-APT (CDCl₃, 100 MHz), δ 138.34, 137.29, 135.56, 133.29, 133.18, 133.08 (aromatic C), 132.31, 129.05, 128.99, 128.41, 128.28, 128.12, 128.99, 128.87, 127.78, 127.73, 126.90, 126.26, 126.07, 126.03, 125.94 (aromatic CH), 101.08 (PhCH), 88.27 (C-1), 82.99 (C-3), 81.45 (C-4), 80.48 (C-2), 75.92, 75.28 (CH₂), 70.22 (C-5), 68.67 (C-6).



Phenyl 3,4,6-tri-O-benzyl-2-O-(naphthalen-2-ylmethyl)-1-thio-β-D-glucopyranoside 5: ¹H-NMR (CDCl₃, 400 MHz) δ 7.81-7.75 (m, 4 H, aromatic *H*), 7.62-7.18 (m, 23 H, aromatic *H*), 5.04 (d, *J* = 10.4 Hz, 1 H, 1 CH*H*), 4.93-4.82 (m, 4 H, 4 CH*H*), 4.71 (d, *J* = 9.6 Hz, 1 H, H-1), 4.62-4.52 (m, 3 H, 3 CH*H*), 3.81-3.65 (m, 4 H, H-6, H-4, H-3), 3.60-3.50 (m, 2 H, H-2, H-5). ¹³C-APT (CDCl₃, 100 MHz), δ 138.49, 98

138.37, 138.11, 135.62, 133.94, 133.37, 133.16 (aromatic C), 132.01, 129.02, 128.55, 128.45, 128.25, 128.07, 128.04, 127.92, 127.85, 127.79, 127.76, 127.67, 127.54, 127.00, 126.34, 126.12, 126.00 (aromatic CH), 87.57 (C-1), 86.86 (C-3), 80.92 (C-2), 79.18 (C-4), 77.89 (C-5), 75.93, 75.59, 75.16, 73.50 (CH₂), 69.08 (C-6).

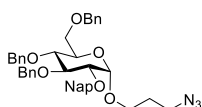


3,4,6-Tri-O-benzyl-2-O-(naphthalen-2-ylmethyl)- α/β -D-glucopyranosyl

N-

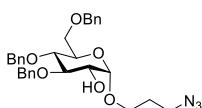
phenyltrifluoroacetimidate 6: Compound **5** (11.5 g, 16.8 mmol) was dissolved in acetone (200 mL). *N*-Iodosuccinimide (NIS) (7.5 g, 33.6 mmol) was added in one portion and the reaction

was stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated aqueous Na₂S₂O₃. Then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*, and the product purified by column chromatography. The lactol (8.7 g, 90% yield) was obtained as a white solid. Next, the lactol (8.7 g, 15.1 mmol) was dissolved in acetone (150 mL). Cs₂CO₃ (7.4 g, 22.6 mmol) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (3.5 mL, 25.1 mmol) were added to the solution respectively. The reaction was stirred overnight, then quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by column chromatography (pentane:EA = 40:1-20:1). Compound **6** (9.6 g, 92% yield, α/β = 1:1) was obtained as yellow syrup. ¹H-NMR (CDCl₃, 500 MHz, 60°C) δ 7.79-7.74 (m, aromatic *H*), 7.49- 7.01 (m, aromatic *H*), 6.83-6.73 (m, aromatic *H*), 6.40 (bs, 1 H, H-1 α), 5.58 (bs, 1 H, H-1 β), 4.96-4.53 (m), 4.02-3.95 (m), 3.79-3.59 (m), 3.40 (bs, 1 H). ¹³C-APT (CDCl₃, 125 MHz, 60°C) δ 159.77, 159.73, 143.96, 143.73, 143.42, 138.99, 138.77, 138.38, 138.31, 135.81, 135.70, 133.57, 133.32, 130.33, 130.26 (aromatic C), 129.86, 129.43, 128.80, 128.46, 128.43, 128.33, 128.28, 128.06, 127.98, 127.94, 127.91, 127.84, 127.78, 127.69, 127.65, 127.60, 126.78, 126.72, 126.22, 126.20, 126.01, 125.97, 124.41, 124.28, 119.69, 119.58, 114.20, 114.17 (aromatic CH), 117.62 (q, CF₃), 97.71, 94.00, 84.78, 81.75, 80.86, 79.41, 77.61, 77.36, 76.06, 75.31, 75.63, 75.55, 75.27, 75.02, 74.72, 73.82, 73.73, 73.48, 73.24, 68.73, 68.66, 55.83, 55.36. HR-MS: Calculated for C₄₆H₄₂F₃NO₆ [M-[O(C=NPh)CF₃]+OH+NH₄]⁺: 608.30066, found: 608.29853.



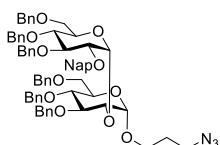
Synthesis of 7: The reaction was carried out according to the standard procedure B, using **6** (2000 mg, 2.6 mmol, 0.1 M in DCM), 3-aminopropanol (370 μ L, 3.9 mmol), Ph₃P=O (4.4 g, 15.8 mmol) and TMSI (371 μ L, 2.6 mmol). The product was purified by silica gel column

chromatography (pentane:EA = 10:1). Compound **7** (1300 mg, 75 % yield, α/β = 10:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 735, 818, 1027, 1155, 1358, 1454, 2095, 2866, 2922. ¹H-NMR (CDCl₃, 400 MHz) δ 7.83-7.74 (m, 4 H, aromatic *H*), 7.49-7.12 (m, 18 H, aromatic *H*), 5.02 (d, *J* = 11.2 Hz, 1 H, 1 CH*H*), 4.92 (d, *J* = 12.4 Hz, 1 H, 1 CH*H*), 4.86-4.77 (m, 3 H, 3 CH*H*), 4.74 (d, *J* = 3.6 Hz, 1 H, H-1), 4.59 (d, *J* = 11.6 Hz, 1 H, 1 CH*H*), 4.48-4.41 (m, 2 H, 2 CH*H*), 3.99 (t, *J* = 9.2 Hz, 1 H, H-2), 3.75-3.59 (m, 6 H, H-6, H-5, H-4, H-2, H-1^a), 3.48-3.35 (m, 3 H, H-3^o, H-1^b), 1.97-1.81 (m, 2 H, H-2^o). ¹³C-APT (CDCl₃, 100 MHz) δ 138.93, 138.25, 138.14, 127.98, 135.72, 133.29, 133.17 (aromatic C), 128.52, 128.49, 128.46, 128.40, 128.06, 128.00, 127.84, 127.79, 127.70, 127.03, 126.29, 126.13, 126.06 (aromatic CH), 97.31 (C-1), 82.10 (C-3), 80.10 (C-2), 77.75 (C-4), 75.81, 75.24, 73.57, 73.53 (CH₂), 70.43 (C-5), 68.50 (C-6), 64.83 (C-1^o), 48.41 (C-3^o), 28.96 (C-2^o). HR-MS: Calculated for C₄₁H₄₃N₃O₆ [M+NH₄]⁺: 691.34901, found: 691.34807.

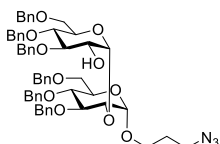


Synthesis of 8: The reaction was carried out according to the general procedure D, using **7** (1.3 g, 1.93 mmol, 0.1 M in DCM:H₂O) and DDQ (482 mg, 2.1 mmol). The product was purified by silica gel column chromatography. Compound **8** (770 mg, 75% yield) was obtained as a

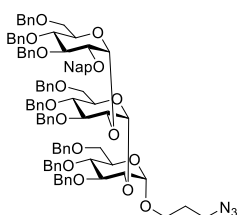
colorless syrup. $[\alpha]_D^{20} +90.5$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 735, 1027, 1066, 1038, 1359, 1454, 1497, 2095, 2870, 2923. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.39-7.13 (m, 15 H, aromatic H), 4.94-4.80 (m, 4 H, H-1, 3 CHH), 4.63 (d, $J = 12.4$ Hz, 1 H, 1 CHH), 4.52-4.48 (m, 2 H, 2 CHH), 3.85-3.61 (m, 7 H, H-6, H-5, H-4, H-3, H-2, H-3 ^{a}), 3.56-3.51 (m, 1 H, H-3 ^{b}), 3.43-3.32 (m, 2 H, H-1 ^{o}), 2.18 (d, $J = 7.6$ Hz, 1 H, OH), 1.94-1.82 (m, 2 H, H-2 ^{o}). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz), δ 138.69, 138.11, 137.93 (aromatic C), 128.50, 128.47, 128.02, 127.97, 127.96, 127.84, 127.80, 127.77 (aromatic CH), 98.66 (C-1), 83.31 (C-3), 77.46 (C-4), 75.43, 75.11, 73.59 (CH_2), 72.94 (C-2), 70.82 (C-5), 68.47 (C-6), 65.15 (C-1 ^{o}), 48.53 (C-3 ^{o}), 28.86 (C-2 ^{o}). HR-MS: Calculated for $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_6$ $[\text{M}+\text{NH}_4]^+$: 551.28641, found: 551.28604.



Synthesis of 9: The reaction was carried out according to the standard procedure B, using **6** (845 mg, 1.11 mmol), **8** (455 mg, 0.85 mmol, 0.05 M in DCM), DMF (1.4 mL, 17.7 mmol) and TfOH (98 μL , 1.11 mmol). The reaction was stirred at $-78-0^\circ\text{C}$ until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography ($\text{DCM}:\text{MeOH} = 1:1$). Compound **9** (1160 mg, 95% yield, $\alpha:\beta = 15:1$) was obtained as a colorless syrup. $[\alpha]_D^{20} +75.4$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 736, 1029, 1069, 1359, 1454, 1497, 2098, 2866, 2922. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.83-7.71 (m, 4 H, aromatic H), 7.49-7.45 (m, 3 H, aromatic H), 7.34-7.21 (m, 23 H, aromatic H), 7.16-7.03 (m, 7 H, aromatic H), 5.07 (d, $J = 3.2$ Hz, 1 H, H-1b), 5.05 (d, $J = 3.2$ Hz, 1 H, H-1a), 5.01-4.79 (m, 8 H, 8 CHH), 4.63-4.39 (m, 5 H, 5 CHH), 4.31 (d, $J = 12.4$ Hz, 1 H, 1 CHH), 4.11 (t, $J = 91.6$ Hz, 1 H, H-3b), 4.06-3.99 (m, 2 H, H-3a, H-5a), 3.83 (dd, $J_1 = 3.2$ Hz, $J_2 = 9.6$ Hz, 1 H, H-2a), 3.78-3.61 (m, 7 H, H-6, H-5b, H-4b, H-4a, H-2b, H-3 ^{a}), 3.55-3.39 (m, 3 H, H-6, H-3 ^{b}), 3.29-3.19 (m, 2 H, H-1 ^{o}), 1.84-1.70 (m, 2 H, H-2 ^{o}). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz), δ 138.81, 138.72, 138.32, 138.25, 138.00, 137.98, 135.69, 133.29, 133.11 (aromatic C), 128.49, 128.43, 128.42, 128.39, 128.29, 128.09, 128.03, 128.01, 127.97, 127.90, 127.81, 127.80, 127.71, 127.66, 127.62, 127.52, 126.87, 126.33, 126.12, 125.89 (aromatic CH), 96.06 (C-1a), 94.72 (C-1b), 82.17 (C-3b), 80.79 (C-3a), 79.14 (C-2b), 78.07 (C-4), 77.68 (C-4), 76.18, 75.71 (CH_2), 75.45 (C-2a), 75.20, 74.95, 73.60, 73.45, 72.99 (CH_2), 70.61 (C-5b), 70.44 (C-5a), 68.52 (C-6), 68.04 (C-6), 65.15 (C-1 ^{o}), 48.36 (C-3 ^{o}), 28.02 (C-2 ^{o}). HR-MS: Calculated for $\text{C}_{68}\text{H}_{71}\text{N}_3\text{O}_6$ $[\text{M}+\text{NH}_4]^+$: 1123.54269, found: 1123.54104.

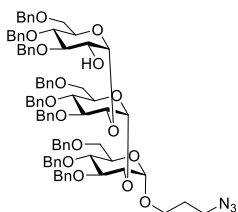


Synthesis of 10: The reaction was carried out according to the general procedure D, using **9** (970 mg, 0.88 mmol, 0.1 M in $\text{DCM}:\text{H}_2\text{O}$) and DDQ (217 mg, 0.96 mmol). The product was purified by silica gel column chromatography. Compound **10** (416 mg, 49% yield) was obtained as a colorless syrup. $[\alpha]_D^{20} +90.8$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 735, 1027, 1050, 1132, 1361, 1454, 2098, 2866, 2929. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.38-7.06 (m, 30 H, aromatic H), 5.02-4.97 (m, 3 H, H-1a, H-1b, 1 CHH), 4.87-4.75 (m, 5 H, 5 CHH), 4.63-4.44 (m, 5 H, 5 CHH), 4.32 (d, $J = 12.0$ Hz, 1 H, 1 CHH), 3.94-3.65 (m, 11 H), 3.53-3.33 (m, 5 H, H-6), 1.91-1.84 (m, 2 H, H-2 ^{o}). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz), δ 138.69, 138.61, 137.97, 137.86, 737.83 (aromatic C), 128.41, 128.39, 128.34, 128.30, 128.28, 128.16, 128.08, 127.97, 127.95, 127.87, 127.82, 127.78, 127.72, 127.65, 127.60, 127.55, 127.41 (aromatic CH), 96.21 (C-1b), 85.58 (C-1a), 83.28 (C-3b), 80.50 (C-3a), 77.79 (C-4), 76.94 (C-4), 76.00 (CH_2), 75.37 (C-2a), 75.12, 74.75, 73.48, 73.29 (CH_2), 72.79 (C-2b), 70.62 (C-5), 70.58 (C-5), 68.28 (C-6), 67.86 (C-6), 64.83 (C-1 ^{o}), 48.33 (C-3 ^{o}), 28.62 (C-2 ^{o}). HR-MS: Calculated for $\text{C}_{68}\text{H}_{71}\text{N}_3\text{O}_{11}$ $[\text{M}+\text{NH}_4]^+$: 983.48003, found: 983.47815.



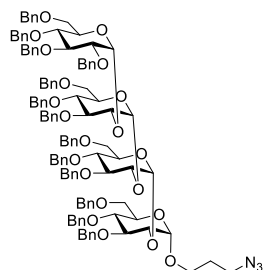
Synthesis of **11**: The reaction was carried out according to the standard procedure B, using **6** (547 mg, 0.72 mmol), **10** (347 mg, 0.36 mmol, 0.05 M in DCM), DMF (900 μ L, 11.4 mmol) and TfOH (64 μ L, 0.72 mmol). The reaction was stirred at -78 – 0 $^{\circ}$ C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **11** (372 mg, 67% yield, α : β = 10:1) was

obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +75.4$ ($c=1$, CHCl₃). IR (neat, cm⁻¹) ν 697, 736, 1029, 1069, 1359, 1454, 1497, 2098, 2866, 2922. $[\alpha]_{\text{D}}^{20} +96.5$ ($c=1$, CHCl₃). IR (neat, cm⁻¹) ν 697, 735, 1029, 1069, 1359, 1454, 1497, 2098, 2845, 2921. ¹H-NMR (CDCl₃, 400 MHz) δ 7.82 (s, 1 H, aromatic *H*), 7.71–7.62 (m, 3 H, aromatic *H*), 7.52–7.50 (m, 1 H, aromatic *H*), 7.41–7.37 (m, 1H, aromatic *H*), 7.32–6.96 (m, 46 H, aromatic *H*), 5.49 (d, J = 3.6 Hz, 1 H, H-1c), 5.41 (d, J = 3.6 Hz, 1 H, H-1b), 5.23 (d, J = 2.0 Hz, 1 H, H-1a), 5.16 (d, J = 12.0 Hz, 1 H, 1 CHH), 4.99–4.34 (m, 18 H, 18 CHH), 44.18–3.52 (m, 21 H), 3.31–3.22 (m, 2 H, H-3^o), 1.93–1.82 (m, 2 H, H-2^o). ¹³C-APT (CDCl₃, 100 MHz) δ 138.78, 138.76, 138.74, 138.45, 138.26, 138.16, 138.09, 137.98, 137.90, 136.09, 133.35, 132.94 (aromatic C), 128.72, 128.45, 128.44, 128.40, 128.38, 128.29, 128.26, 128.13, 128.06, 128.04, 127.93, 127.79, 127.72, 127.65, 127.60, 127.56, 127.51, 127.46, 126.11, 125.84, 125.77, 125.55 (aromatic CH), 95.84 (C-1c), 92.77 (C-1b), 92.09 (C-1a), 81.96 (C-3c), 81.45 (C-3a), 80.99 (C-3b), 79.97 (C-2c), 77.37 (2 C-4), 77.05 (C-4), 76.08, 75.99, 75.65, 74.94, 74.84 (CH₂), 74.71 (C-2), 74.60 (C-2), 73.58, 73.50, 71.60 (CH₂), 70.94 (C-5), 70.80 (C-5), 70.61 (C-5), 68.61 (C-6), 68.34 (C-6), 68.07 (C-6), 65.16 (C-1^o), 48.31 (C-3^o), 29.20 (C-2^o). HR-MS: Calculated for C₉₅H₉₉N₃O₁₆ [M+NH₄]⁺: 1555.73636, found: 1555.73599.

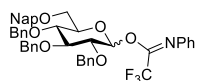


Synthesis of **12**: The reaction was carried out according to the general procedure D, using **11** (700 mg, 0.45 mmol, 0.1 M in DCM:H₂O) and DDQ (140 mg, 0.6 mmol). The product was purified by silica gel column chromatography. Compound **12** (300 mg, 47% yield) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +90.8$ ($c=1$, CHCl₃). IR (neat, cm⁻¹) ν 697, 735, 1027, 1050, 1132, 1361, 1454, 2098, 2866, 2929. $[\alpha]_{\text{D}}^{20} +122.1$ ($c=1$, CHCl₃). ¹H-NMR (CDCl₃, 400 MHz) δ 7.37–6.98 (m, 45 H, aromatic *H*), 5.18 (d, J = 3.2 Hz, 1 H, H-1b),

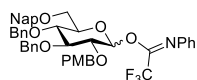
5.06 (d, J = 3.2 Hz, 1 H, H-1a), 5.00–4.90 (m, 3 H, H-1a, 2 CHH), 4.84–4.30 (m, 16 H, 16 CHH), 4.01–3.34 (m, 22 H), 2.41 (s, 1 H, OH), 2.06–1.85 (m, 2 H, H-2^o). ¹³C-APT (CDCl₃, 100 MHz) δ 138.89, 138.85, 138.56, 138.24, 138.22, 138.02, 137.96, 137.95, 137.89 (aromatic C), 128.56, 128.53, 128.51, 128.50, 128.42, 128.38, 128.36, 128.28, 128.08, 128.07, 127.86, 127.82, 127.79, 127.74, 127.63, 127.60, 127.50 (aromatic CH), 96.03 (C-1c), 95.04 (C-1a), 91.66 (C-1b), 83.42 (C-3c), 80.90 (C-3a), 80.62 (C-3b), 77.89 (C-4), 77.73 (C-4), 76.84 (C-4), 76.30, 76.25, 75.20, 75.15, 74.94, 74.92 (CH₂), 74.67 (C-2b), 74.00 (C-2a), 73.65, 73.59, 73.45 (CH₂), 72.67 (C-2c), 70.69 (C-5), 70.64 (C-5), 70.57 (C-5), 68.38 (C-6), 68.00 (C-6), 67.97 (C-6), 64.50 (C-1^o), 48.51 (C-3^o), 28.77 (C-2^o). HR-MS: Calculated for C₈₄H₉₁N₃O₁₆ [M+NH₄]⁺: 1415.67376, found: 1415.67378.



Synthesis of **14**: The reaction was carried out according to the standard procedure B, using **13** (190 mg, 0.27 mmol), **12** (70 mg, 0.05 mmol, 0.05 M in DCM), DMF (78 μ L, 0.99 mmol) and TfOH (23 μ L, 0.27 mmol). The reaction was stirred at -78-0 $^{\circ}$ C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **14** (64 mg, 67% yield, α : β = 2:1) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 1029, 1069, 1359, 1454, 1497, 2098, 2866, 2922. IR (neat, cm^{-1}) ν 695, 734, 1027, 1069, 1209, 1359, 1454, 1497, 1729, 2096, 2859, 2923. HR-MS: Calculated for C₁₁₈H₁₂₅N₃O₂₁ [M+NH₄]⁺: 1937.91438, found: 1937.91440.

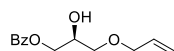


Synthesis of **15**: Compound **22** (1.0 g, 1.46 mmol) was dissolved in acetone:H₂O (10:1, 15 mL). *N*-Iodosuccinimide (NIS) (660 mg, 2.93 mmol) was added in one portion and the reaction was stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated aqueous Na₂S₂O₃. Then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*, and the product purified by column chromatography. The lactol was obtained as a white solid. Next, the lactol was dissolved in acetone (15 mL). Cs₂CO₃ (713 mg, 2.19 mmol) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (355 μ L, 2.19 mmol) were added to the solution respectively. The reaction was stirred overnight, then quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by column chromatography. Compound **15** (959 mg, 86% yield over two steps, α : β = 1:1) was obtained as yellow syrup. IR (neat, cm^{-1}) ν 695, 734, 1027, 1073, 1153, 1208, 1314, 1454, 1597, 1716, 2869, 2915. ¹H-NMR (CDCl₃, 400 MHz) δ 7.82-6.50 (m, aromatic *H*), 6.53 (bs, 1 H, H-1), 5.67 (bs, 1 H, H-1), 5.00-4.61 (m), 4.52-4.46 (m), 4.06-3.97 (m), 3.81-3.66 (m). ¹³C-APT (CDCl₃, 125 MHz) δ 143.78, 143.55, 138.67, 138.64, 137.92, 137.83, 135.45, 135.28, 133.35, 133.19, 133.16 (aromatic C), 129.51, 128.82, 128.64, 128.61, 128.57, 128.55, 128.49, 128.43, 128.36, 128.33, 128.13, 128.05, 127.99, 127.92, 127.88, 127.84, 127.81, 127.78, 127.00, 126.88, 126.49, 126.30, 126.26, 126.10, 126.08, 126.05, 124.39, 120.57, 119.44 (aromatic CH), 84.64, 81.62, 81.04, 79.37, 77.27, 76.94, 75.91, 75.82, 75.74, 75.44, 75.31, 75.17, 73.76, 73.65, 73.44, 73.19, 68.12.

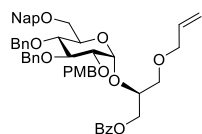


Synthesis of **16**: Compound **25** (4.8 g, 6.73 mmol) was dissolved in acetone:H₂O (10:1, 77 mL). *N*-Iodosuccinimide (NIS) (3.0 g, 13.3 mmol) was added in one portion and the reaction was stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated aqueous Na₂S₂O₃. Then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*, and the product purified by column chromatography. The lactol was obtained as a white solid. Next, the lactol was dissolved in acetone (70 mL). Cs₂CO₃ (6.3 g, 19.5 mmol) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (3.2 mL, 19.5 mmol) were added to the solution respectively. The reaction was stirred overnight, then quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by column chromatography. Compound **16** (4.48 g, 84% yield over two steps, α : β = 1:1) was obtained as yellow syrup. ¹H-NMR (CDCl₃, 500 MHz, 60 $^{\circ}$ C) δ 7.79-7.74 (m, aromatic *H*), 7.49- 7.01 (m, aromatic *H*), 6.83-6.73 (m, aromatic *H*), 6.40 (bs, 1 H, H-1 α), 5.58 (bs, 1 H, H-1 β), 4.96-4.53 (m), 4.02-3.95 (m), 3.79-3.59 (m), 3.40 (bs, 1 H). ¹³C-APT (CDCl₃, 125 MHz, 60 $^{\circ}$ C) δ 159.77, 159.73, 143.96, 143.73, 143.42, 138.99, 138.77, 138.38, 138.31, 135.81, 135.70, 102

133.57, 133.32, 130.33, 130.26 (aromatic C), 129.86, 129.43, 128.80, 128.46, 128.43, 128.33, 128.28, 128.06, 127.98, 127.94, 127.91, 127.84, 127.78, 127.69, 127.65, 127.60, 126.78, 126.72, 126.22, 126.20, 126.01, 125.97, 124.41, 124.28, 119.69, 119.58, 114.20, 114.17 (aromatic CH), 117.62 (q, CF₃), 97.71, 94.00, 84.78, 81.75, 80.86, 79.41, 77.61, 77.36, 76.06, 75.31, 75.63, 75.55, 75.27, 75.02, 74.72, 73.82, 73.73, 73.48, 73.24, 68.73, 68.66, 55.83, 55.36. HR-MS: Calculated for C₄₇H₄₄F₃NO₇ [M-[O(C=NPh)CF₃]+OH+Na]⁺: 643.26662, found: 643.26659.

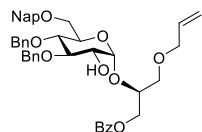


(S)-3-(allyloxy)-2-hydroxypropyl benzoate **17**: ¹H-NMR (CDCl₃, 400 MHz) δ 8.07-8.04 (m, 2 H, aromatic H), 7.58-7.53 (m, 1 H, aromatic H), 7.45-7.41 (m, 2 H, aromatic H), 5.95-5.85 (m, 1 H, H-5), 5.31-5.17 (m, 2 H, H-6), 4.45-4.36 (m, 2 H, H-1), 4.19-4.14 (m, 1 H, H-2), 4.05-4.03 (m, 2 H, H-4), 3.63-3.53 (m, 2 H, H-3), 3.01 (bs, 1 H, OH). ¹³C-APT (CDCl₃, 100 MHz), δ 166.69 (C=O), 134.30, 133.18 (aromatic CH), 129.87 (aromatic C), 129.80 (aromatic CH), 128.43 (C-5), 117.54 (C-6), 77.24, 71.02, 68.93 (C-2), 66.07. HR-MS: Calculated for C₁₃H₁₆O₄ [M+Na]⁺: 259.0941, found: 259.0948.



Synthesis of **26**: The reaction was carried out according to the standard procedure B, using **15** (1.5 g, 1.9 mmol), **17** (410 mg, 1.74 mmol, 0.1 M in DCM), Ph₃P=O (3.16 g, 11.4 mmol) and TMSI (270 μ L, 1.9 mmol). The product was purified by silica gel column chromatography.

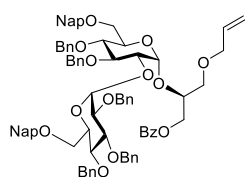
Compound **26** (1100 mg, 76 % yield, α : β > 20:1) was obtained as a colorless syrup. [α]_D²⁰ +38.9 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 698, 713, 820, 1037, 1072, 1095, 1249, 1272, 1452, 1513, 1720, 2865, 2912. ¹H-NMR (CDCl₃, 400 MHz) δ 7.99-7.97 (m, 2 H, aromatic H), 7.76-7.63 (m, 4 H, aromatic H), 7.46-7.08 (m, 16 H, aromatic H), 6.92 (bd, 2 H, aromatic H), 6.85-6.82 (m, 2 H, aromatic H), 5.93-5.84 (m, 1 H, H-5°), 5.31-5.25 (m, 1 H, H-6°_a), 5.19-5.16 (m, 2 H, H-1_a, H-6°_b), 4.99 (d, J = 10.8 Hz, 1 H, CHH), 4.81-4.77 (m, 2 H, 2 CHH), 4.70-4.63 (m, 3 H, 3 CHH), 4.57 (dd, J_1 = 3.6 Hz, J_2 = 11.6 Hz, 1 H, H-1°_a), 4.45-4.35 (m, 3 H, 2 CHH, H-1°_b), 4.28-4.24 (m, 1 H, H-2°), 4.04-3.99 (m, 4 H, H-3_a, H-5_a, H-4°), 3.74 (s, 3 H, OCH₃), 3.73-3.58 (m, 4 H, H-2_a, H-4_a, H-3°), 3.50 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 11.8 Hz, H-6_a), 3.37 (dd, 1 H, J_1 = 2.0 Hz, J_2 = 10.4 Hz, H-6_a_b). ¹³C-APT (CDCl₃, 100 MHz), δ 166.19 (C=O), 159.30, 138.91, 138.22, 135.16 (aromatic C), 134.38 (C-5°), 133.11, 132.96 (aromatic C), 132.88 (aromatic CH), 130.27, 129.84 (aromatic C), 129.62, 129.60, 128.31, 128.28, 128.11, 127.85, 127.82, 127.67, 127.48, 127.44, 126.80, 126.03, 125.97, 125.83 (aromatic CH), 117.19 (C-6°), 113.78 (aromatic CH), 96.13 (C-1_a), 81.83 (C-5_a), 79.26 (C-2_a), 77.47 (C-4_a), 75.59, 74.83 (CH₂), 73.59 (C-2°), 73.52, 72.43 (CH₂), 72.35 (C-4°), 70.23 (C-3_a), 69.59 (C-3°), 67.97 (C-6_a), 65.01 (C-1°), 55.16 (OCH₃). HR-MS: Calculated for C₅₂H₅₄O₁₀ [M+Na]⁺: 861.3609, found: 861.3647.



Synthesis of **27**: The reaction was carried out according to the general procedure C, using **26** (1000 mg, 1.19 mmol, 0.1 M in DCM:HFIP), triethylsilane (190 μ L, 1.19 mmol) and 0.1M HCl/HFIP (1.2 ml, 0.12 mmol). The product was purified by silica gel column chromatography (PE:EA = 6:1). Compound **27** (800 mg, 93% yield) was obtained as a colorless syrup. [α]_D²⁰

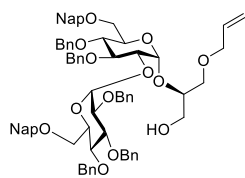
+73.0 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 710, 713, 738, 1027, 1070, 1095, 1272, 1452, 1721, 2866, 2915. ¹H-NMR (CDCl₃, 400 MHz) δ 8.02-8.00 (m, 2 H, aromatic H), 7.78-7.66 (m, 4 H, aromatic H), 7.49-7.09 (m, 14 H, aromatic H), 6.96-6.94 (m, 4 H, aromatic H), 5.93-5.84 (m, 1 H, H-5°), 5.32-5.26 (m, 1 H, H-6°_a), 5.23-5.19 (m, 1 H, H-6°_b), 5.12 (d, J = 3.2 Hz, 1 H, H-1_a), 4.99 (d, J = 11.2 Hz, 1 H, 1 CHH), 4.81 (d, J = 11.2 Hz, 1 H, 1 CHH), 4.78 (d, J = 11.2 Hz, 1 H, 1 CHH), 4.69 (d, J = 12.4 Hz, 1 H, 1 CHH), 4.49-4.38 (m, 4 H, 3 CHH, H-1°), 4.24-4.18 (m, 1 H, H-2°), 4.07-3.98 (m, 2 H, H-4°),

3.97-3.93 (m, 1 H, H-3a), 3.80-3.73 (m, 2 H, H-2a, H-5a), 3.68-3.57 (m, 4 H, H-3°, H-4a, H-6a), 3.42 (dd, 1 H, $J_1 = 2.0$ Hz, $J_2 = 10.4$ Hz, H-6a), 2.77 (d, 1 H, $J = 8.0$ Hz, OH). ^{13}C -APT (CDCl_3 , 100 MHz) δ 166.29 (C=O), 138.93, 138.25, 135.30 (aromatic C), 134.03 (C-5°), 133.24 (aromatic C), 133.18 (aromatic CH), 133.07, 129.83 (aromatic C), 129.75, 128.47, 128.41, 128.26, 127.99, 127.94, 127.80, 127.77, 127.61, 127.59, 126.86, 126.16, 126.05, 125.95 (aromatic CH), 117.92 (C-6°), 99.40 (C-1a), 83.53 (C-5a), 77.02 (C-4a), 76.14 (C-2°), 75.33, 74.95, 73.65 (CH_2), 73.44 (C-2a), 72.46 (C-4°), 71.08 (C-3a), 69.23 (C-3°), 68.11 (C-6a), 64.80 (C-1°). HR-MS: Calculated for $\text{C}_{44}\text{H}_{46}\text{O}_9$ $[\text{M}+\text{Na}]^+$: 741.3034, found: 741.3062.



Synthesis of **28:** The reaction was carried out according to the standard procedure B, using **15** (1210 mg, 1.59 mmol), **27** (760 mg, 1.05 mmol, 0.1 M in DCM), DMF (1.3 mL, 16.8 mmol) and TfOH (140 μL , 1.59 mmol). The reaction was stirred at -78°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion

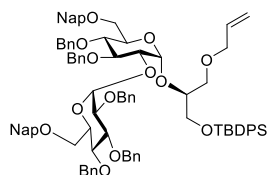
chromatography (DCM:MeOH = 1:1). Compound **28** (2.06 g, 95% yield, $\alpha:\beta > 10:1$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +75.1$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 698, 713, 820, 1046, 1070, 1095, 1272, 1359, 1454, 1721, 2863, 2919. ^1H -NMR (CDCl_3 , 400 MHz) δ 8.00-7.81 (m, 2 H, aromatic H), 7.78-7.63 (m, 8 H, aromatic H), 7.44-6.91 (m, 34 H, aromatic H), 5.81-5.76 (m, 1 H, H-5°), 5.46 (d, $J = 3.6$ Hz, 1 H, H-1a), 5.29 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.22-5.10 (m, 2 H, H-6°), 4.98-4.67 (m, 10 H, 10 CHH), 4.56-4.33 (m, 6 H, 4 CHH, H-1°), 4.29-4.23 (m, 1 H, H-2°), 4.14-4.04 (m, 4 H, H-5a, H-5b, H-3a, H-3b), 3.91-3.88 (m, 3 H, H-3a, H-4°), 3.80-3.43 (m, 9 H, H-3°, H-2b, H-4a, H-4b, H-6a, H-6b). ^{13}C -APT (CDCl_3 , 100 MHz) δ 166.23 (C=O), 138.69, 138.46, 138.34, 138.31, 138.27, 135.33, 135.22 (aromatic C), 134.27 (C-5°), 133.18, 133.15, 133.01, 132.99 (aromatic C), 132.91 (aromatic CH), 129.92 (aromatic C), 129.62, 128.41, 128.38, 128.35, 128.31, 128.19, 128.17, 128.15, 128.09, 127.92, 127.87, 127.74, 127.69, 127.63, 127.54, 127.51, 127.46, 127.43, 127.34, 126.88, 126.80, 126.09, 126.06, 125.98, 125.85, 125.84 (aromatic CH), 117.41 (C-6°), 99.70 (C-1b), 94.53 (C-1a), 82.10 (C-5b), 80.73 (C-5a), 79.35 (C-2b), 77.80 (C-4), 77.56 (C-4), 76.03, 75.54 (CH_2), 75.39 (C-2a), 74.85, 74.82, 73.54, 73.53 (CH_2), 73.14 (C-2°), 72.36, 72.22 (CH_2), 70.46 (C-3a and 3b), 69.23 (C-3°), 68.98 (C-6a and 6b), 64.96 (C-1°). HR-MS: Calculated for $\text{C}_{82}\text{H}_{82}\text{O}_{14}$ $[\text{M}+\text{Na}]^+$: 1313.5597, found: 1313.5624.



Synthesis of **29:** Compound **28** (1100 mg, 0.85 mmol) was dissolved in DCM:CH₃OH (1:1/v:v, 8.5 mL) stirring at room temperature. Then 5 drops of solution of CH₃ONa in CH₃OH (5.4 M) was added in the mixture. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material (3 h). Then the mixture was diluted with DCM. The organic phase was washed with water and brine, dried with anhydrous

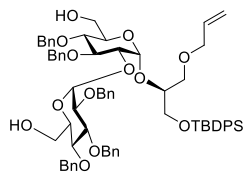
MgSO_4 , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **29** (930 mg, 92% yield) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +69.4$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 698, 737, 818, 1069, 1209, 1359, 1454, 2865, 2921. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.83-7.69 (m, 8 H, aromatic H), 7.49-7.09 (m, 25 H, aromatic H), 7.03-6.92 (m, 6 H, aromatic H), 5.86-5.76 (m, 1 H, H-5°), 5.31 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.22-5.10 (m, 3 H, H-6°, H-1a), 4.94-4.35 (m, 14 H, 14 CHH), 4.09-3.98 (m, 4 H, H-5a, H-5b, H-3a, H-3b), 3.89-3.45 (m, 14 H). ^{13}C -APT (CDCl_3 , 100 MHz) δ 138.73, 138.52, 138.31, 138.21, 137.98, 135.41, 135.20 (aromatic C), 134.56 (C-5°), 133.33,

133.29, 133.18, 133.12 (aromatic C), 128.60, 128.45, 128.42, 128.31, 128.22, 128.07, 128.04, 128.01, 127.95, 127.84, 127.81, 127.78, 127.74, 127.67, 127.64, 127.49, 126.98, 126.26, 126.19, 126.06, 126.04, 125.97 (aromatic CH), 117.25 (C-6°), 95.62 (C-1b), 95.08 (C-1a), 82.22 (C-5a), 80.73 (C-5b), 79.24 (C-2b), 78.89 (C-2b), 78.28 (C-4), 77.71 (C-4), 76.15 (CH₂), 75.73 (C-2°), 75.69, 75.16, 74.99, 73.70, 73.61, 72.86 (CH₂), 72.34 (C-4°), 70.86 (C-3b), 70.59 C-3a), 69.67 (C-3°), 68.64, 68.08 (C-6a and 6b), 63.61 (C-1°). HR-MS: Calculated for C₇₅H₇₈O₁₃ [M+Na]⁺: 1209.5335, found: 1209.5356.



Synthesis of 30: Compound **29** (350 mg, 0.3 mmol) was dissolved in DMF (6 mL) stirring at room temperature. Then TBDPSCl (153 μ L, 0.6 mmol) and imidazole (120 mg, 1.8 mmol) were added in the mixture. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material. Then the mixture was diluted with DCM. The organic phase was washed with water and brine, dried with

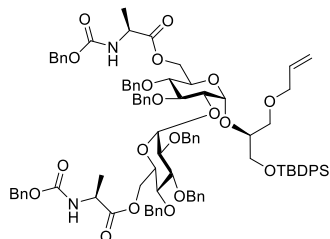
anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **29** (423 mg, 99% yield) was obtained as a colorless syrup. [α]_D²⁰ +62.1 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 698, 738, 818, 1047, 1070, 1361, 1454, 2858, 2928. ¹H-NMR (CDCl₃, 400 MHz) δ 7.80-7.62 (m, 12 H, aromatic H), 7.48-7.06 (m, 31 H, aromatic H), 6.97-6.94 (m, 6 H, aromatic H), 5.87-5.77 (m, 1 H, H-5°), 5.48 (d, J = 3.2 Hz, 1 H, H-1a), 5.34 (d, J = 3.2 Hz, 1 H, H-1b), 5.22-5.10 (m, 2 H, H-6°), 4.95-4.35 (m, 14 H, 14 CHH), 4.11-4.00 (m, 4 H, H-5a, H-5b, H-3a, H-2°), 3.89-3.84 (m, 4 H, H-3b, H-2a, H-4°), 3.78-3.40 (m, 11 H), 1.01 (s, 9 H, 3 CH₃). ¹³C-APT (CDCl₃, 100 MHz) δ 138.86, 138.70, 138.58, 138.54, 138.44 (aromatic C), 135.68 (aromatic CH), 135.52 (aromatic C), 134.70 (C-5°), 133.44, 133.43, 133.32, 133.13 (aromatic C), 129.77, 129.76, 128.68, 128.43, 128.40, 128.38, 128.31, 128.23, 128.19, 128.13, 128.05, 128.01, 127.98, 127.86, 127.84, 127.73, 127.60, 127.58, 127.45, 127.41, 126.98, 126.89, 126.23, 126.21, 126.15, 125.98, 125.93 (aromatic CH), 117.33 (C-6°), 94.22 (C-1a), 93.60 (C-1b), 82.16 (C-5b), 81.01 (C-5a), 79.44 (C-2b), 77.76 (C-4), 77.57 (C-4), 76.29, 75.67 (CH₂), 75.12 (C-2°), 74.94, 74.85 (CH₂), 74.79 (C-2a), 73.70, 72.28, 71.91 (CH₂), 70.43 (C-3b), 70.34 (C-3a), 69.29, 68.22, 63.77 (CH₂), 27.00 (3 CH₃), 19.30. HR-MS: Calculated for C₉₁H₉₆O₁₃Si [M+Na]⁺: 1447.6512, found: 1447.6539.



Synthesis of 31: The reaction was carried out according to the general procedure D, using **30** (460 mg, 0.32 mmol, 0.1 M in DCM:H₂O) and DDQ (170 mg, 0.75 mmol). The product was purified by silica gel column chromatography. Compound **31** (280 mg, 77% yield, pentane:EA = 4:1, R_f = 0.33) was obtained as a colorless syrup. [α]_D²⁰ +72.3 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 698, 737, 1027, 1072, 1209, 1361, 1454, 2858, 2929. ¹H-NMR (CDCl₃,

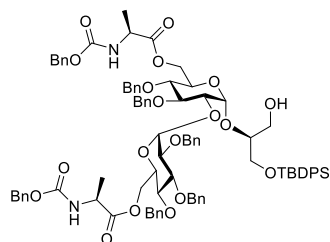
400 MHz) δ 7.66-7.63 (m, 4 H, aromatic H), 7.41-7.07 (m, 31 H, aromatic H), 5.88-5.78 (m, 1 H, H-5°), 5.44 (d, J = 3.2 Hz, 1 H, H-1a), 5.34 (d, J = 3.6 Hz, 1 H, H-1b), 5.23-5.13 (m, 2 H, H-6°), 4.99-4.58 (m, 10 H, 10 CHH), 4.11-4.00 (m, 3 H, H-5a, H-5b, H-2°), 3.92-3.88 (m, 3 H, H-3b, H-4°), 3.76-3.51 (m, 14 H), 1.76 (s, 1 H, OH), 1.64 (s, 1 H, OH), 1.04 (s, 9 H, 3 CH₃). ¹³C-APT (CDCl₃, 100 MHz) δ 138.69, 138.58, 138.44, 138.38, 138.35 (aromatic C), 135.62, 135.61 (aromatic CH), 134.52 (C-5°), 133.27, 133.24 (aromatic C), 129.81, 128.46, 128.44, 128.41, 128.38, 128.36, 128.05, 127.87, 127.84, 127.77, 127.70, 127.67, 127.62, 127.58 (aromatic CH), 117.28 (C-6°), 94.19 (C-1a), 93.40 (C-1b), 81.80 (C-5b), 80.69 (C-5a), 79.65 (C-2b), 77.31 (C-4), 77.25 (C-4), 76.09, 75.57 (CH₂), 75.04 (C-2°), 74.93 (CH₂), 74.90 (C-

2a), 72.24, 71.93 (CH₂), 71.25 (C-3b), 70.94 (C-3a), 69.84, 63.67, 61.68, 61.50 (CH₂), 26.93 (3 CH₃), 19.22. HR-MS: Calculated for C₆₉H₈₀O₁₃Si [M+Na]⁺: 1167.5260, found: 1167.5280.



Synthesis of **32**: Compound **31** (650 mg, 0.57 mmol) and **18** (633mg, 2.83 mmol) were dissolved in DCM (6 mL) stirring at room temperature. Then TPYBOP (1.48 g, 2.85 mmol) and NMI (454 μ L, 5.7 mmol) were added in the mixture. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material. Then the mixture was diluted with DCM. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered

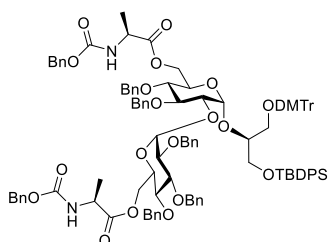
and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **29** (800 mg, 90% yield) was obtained as a colorless syrup. $[\alpha]_D^{20} +66.3$ (c=1, CHCl₃). IR (neat, cm⁻¹) ν 698, 738, 1029, 1070, 1171, 1208, 1251, 1454, 1498, 1725, 2858, 2931. ¹H-NMR (CDCl₃, 400 MHz) δ 7.67-7.63 (m, 4 H, aromatic *H*), 7.41-7.06 (m, 41 H, aromatic *H*), 5.85-5.75 (m, 1 H, H-5°), 5.42-5.34 (m, 3 H, H-1a, H-1b, H-6°), 5.21-4.73 (m, 13 H), 4.59-4.50 (m, 3 H), 4.35-3.45 (m, 22 H), 1.36 (d, *J* = 6.8 Hz, 1 H, CH₃), 1.25 (d, *J* = 7.2 Hz, 1 H, CH₃), 1.04 (s, 9 H, 3 CH₃). ¹³C-APT (CDCl₃, 100 MHz) δ 172.78, 172.69, 155.62 (4 C=O), 138.54, 138.32, 138.26, 138.19, 136.33 (aromatic C), 135.62, 135.60 (aromatic CH), 134.46 (C-5°), 133.20 (aromatic C), 129.86, 128.57, 128.46, 128.40, 128.35, 128.19, 128.10, 128.03, 127.88, 127.76, 127.70, 127.66, 127.60 (aromatic CH), 117.39 (C-6°), 96.64 (C-1a), 93.00 (C-1b), 81.86 (C-5b), 80.79 (C-5a), 79.60, 77.36, 76.12, 75.63, 74.96, 74.68, 72.22, 71.84, 69.30, 69.12, 68.71, 66.95, 63.73, 63.66, 63.50, 49.69 (2 CHNH), 29.34 (CH₃), 26.95 (3 CH₃), 19.23, 18.73 (CH₃). HR-MS: Calculated for C₉₁H₁₀₂N₂O₁₉Si [M+Na]⁺: 1577.67383, found: 1577.67285.



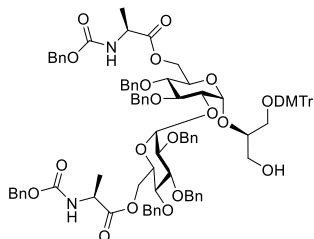
Synthesis of **33**: A solution of **32** (600 mg, 0.38 mmol) and freshly activated molecular sieves 3A in freshly distilled THF (4 ml) was stirred under argon for 30 min. After the addition of Ir(COD)(Ph₂MeP)₂PF₆ (33 mg, 10 mol %) the solution turned red and the mixture was purged with H₂ until the solution turned colourless again (5-15 seconds). After stirring under argon for 4 h, the solution was diluted with THF and satd aq NaHCO₃. After the addition of I₂ (73 mg, 0.57

mmol), the mixture was allowed to stir overnight at room temperature. The mixture was diluted with EtOAc and washed with satd aq Na₂S₂O₃ and brine, respectively. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Column chromatography afforded **33** (734 mg, 85%) as colorless syrup. $[\alpha]_D^{20} +55.9$ (c=1, CHCl₃). IR (neat, cm⁻¹) ν 697, 737, 1027, 1069, 1168, 1208, 1258, 1454, 1498, 1720, 2858, 2929. ¹H-NMR (CDCl₃, 400 MHz) δ 7.66-7.64 (m, 4 H, aromatic *H*), 7.43-7.07 (m, 41 H, aromatic *H*), 5.33 (d, *J* = 7.2 Hz, 1 H, NH), 5.26 (d, *J* = 7.6 Hz, 1 H, NH), 5.11-4.73 (m, 14 H, 12 CHH, H-1a, H-1b), 4.52 (bt, 2 H, 2 CHH), 4.32-4.25 (m, 2 H, 2 CHNH), 4.17-3.99 (m, 6 H, H-5a, H-5b, H-3, 3 CHH), 3.91-3.74 (m, 5 H, H-3, H-2°, 3 CHH), 3.67-3.61 (m, 3 H, H-2a, 2 CHH), 3.50-3.42 (m, 3 H, H-2b, H-4a, H-4b), 1.35 (d, *J* = 6.8 Hz, 1 H, CH₃), 1.28 (d, *J* = 7.2 Hz, 1 H, CH₃), 1.06 (s, 9 H, 3 CH₃). ¹³C-APT (CDCl₃, 100 MHz) δ 172.82, 172.65, 155.65, 155.57 (4 C=O), 138.38, 138.15, 137.92, 137.83, 137.55, 136.29 (aromatic C), 135.65, 135.62 (aromatic CH), 133.17, 133.09 (aromatic C), 128.71, 128.58, 128.52, 128.48, 128.43, 128.39, 128.22, 128.20, 128.18, 128.16, 127.98, 127.95, 127.93, 127.90, 127.77, 127.73 (aromatic CH), 96.63 (C-1a), 95.90 (C-1b), 82.27 (C-5b), 80.14 (C-5a), 79.57 (C-

2°), 77.97 (C-2b), 77.67 (C-4), 77.59 (C-4), 76.41 (C-2a), 75.95, 75.61, 75.08, 75.03, 73.81 (CH₂), 69.21 (C-3b), 69.06 (C-3a), 69.97, 63.84, 63.09, 63.03, 62.12 (CH₂), 49.68 (CHNH), 49.60 (CHNH), 26.94 (3 CH₃), 19.26, 18.70 (CH₃), 18.57 (CH₃). HR-MS: Calculated for C₈₈H₉₈N₂O₁₉Si [M+Na]⁺: 1537.64253, found: 1537.64262.



Synthesis of **34**: Compound **32** (610 mg, 0.4 mmol) and DMTrCl (273 mg, 0.8 mmol) were dissolved in DCM (4 mL) stirring at room temperature. Then DIPEA (283 μ L, 1.6 mmol) was added in the mixture. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material. Then the mixture was diluted with DCM. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **34** (691 mg, 95% yield) was obtained as a colorless syrup. $[\alpha]_D^{20} +118.8$ (c=1, CHCl₃). IR (neat, cm⁻¹) ν 698, 738, 827, 1029, 1070, 1175, 1209, 1249, 1454, 1508, 1607, 1724, 2931. ¹H-NMR (d-acetone, 400 MHz) δ 7.74-7.68 (m, 4 H, aromatic H), 7.55-7.12 (m, 50 H, aromatic H), 6.89 (bd, 4 H, aromatic H), 6.82 (d, J = 7.6 Hz, 1 H, NH), 6.79 (d, J = 8.0 Hz, 1 H, NH), 5.58 (d, J = 2.8 Hz, 1 H, H-1a), 5.25 (d, J = 2.8 Hz, 1 H, H-1b), 5.15-5.05 (m, 5 H, 5 CHH), 4.97-4.71 (m, 6 H, 2 CHH), 4.56-4.11 (m, 13 H), 3.91 (dd, J_1 = 2.8 Hz, J_2 = 9.6 Hz, 1 H, H-2a), 3.82-3.66 (m, 10 H), 3.59-3.52 (m, 2 H, H-2b, H-6a), 3.34-3.31 (m, 1 H, H-6b), 1.49-1.45 (m, 6 H, 2 CH₃), 1.04 (s, 9 H, 3 CH₃). ¹³C-APT (d-acetone, 100 MHz) δ 173.52, 173.41 (2 C=O), 159.55 (aromatic C), 156.90, 156.87 (2 C=O), 146.16, 139.99, 139.74, 139.68, 138.48, 139.32, 138.03, 137.98, 136.85, 136.69 (aromatic C), 136.40, 136.38 (aromatic CH), 134.06, 134.03 (aromatic C), 131.04, 131.00, 130.67, 130.65, 129.10, 129.07, 129.01, 128.95, 128.83, 128.67, 128.55, 128.40, 128.33, 128.26, 128.24, 128.17, 127.58, 114.08, 114.06 (aromatic CH), 94.97 (C-1a), 93.94 (C-1b), 87.37 (quaternary C), 82.55 (C-5a), 81.79 (C-5b), 80.87 (C-2b), 78.59 (C-4), 78.26 (C-4), 76.90 (C-2°), 76.58 (CH₂), 76.03 (C-2a), 75.86, 75.64, 75.53, 72.41 (CH₂), 70.29 (C-3b), 70.11 (C-3a), 66.93, 66.90, 64.59, 64.54, 63.86 (CH₂), 55.53 (2 OCH₃), 50.72 (2 CHNH), 27.39 (3 CH₃), 19.73 (quaternary C), 17.97 (CH₃), 17.93 (CH₃). HR-MS: Calculated for C₁₀₉H₁₁₆N₂O₂₁Si [M+Na]⁺: 1839.77321, found: 1839.77281.



Synthesis of **19**: Compound **33** (730 mg, 0.4 mmol) was dissolved in THF/pyridine (1:1 v/v, 6 mL) stirring at room temperature. Then HF-pyridine (0.4 mL) was added in the mixture. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material (10 h). Then the mixture was diluted with EtOAc. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **19** (548 mg, 86% yield) was obtained as a colorless syrup. $[\alpha]_D^{20} +64.0$ (c=1, CHCl₃). IR (neat, cm⁻¹) ν 698, 751, 830, 1029, 1070, 1176, 1213, 1251, 1302, 1454, 1508, 1608, 1724, 2928. ¹H-NMR (d-acetone, 400 MHz) δ 7.49-7.10 (m, 44 H, aromatic H), 6.87-6.73 (m, 5 H, 4 aromatic H, 1 NH), 6.74 (d, J = 7.6 Hz, 1 H, NH), 5.52 (d, J = 2.8 Hz, 1 H, H-1a), 5.26 (d, J = 2.8 Hz, 1 H, H-1b), 5.10-5.02 (m, 5 H, 5 CHH), 4.93-4.80 (m, 4 H, 2 CHH), 4.70-4.62 (m, 3 H), 4.56-4.48 (m, 2 H), 4.42-4.21 (m, 7 H), 4.17-4.01 (m, 4 H), 3.88-3.86 (m, 2 H), 3.75-3.47 (m, 12 H), 3.19 (dd, J_1 = 5.6 Hz, J_2 = 10.0 Hz, 1 H), 1.47-1.38 (m, 6 H, 2 CH₃). ¹³C-APT (d-acetone, 100 MHz) δ 173.50, 173.43 (2 C=O), 159.60, 159.58 (aromatic C), 156.99, 156.89 (2 C=O), 1146.16, 140.03, 139.77, 139.58, 139.50, 138.07, 138.04, 136.93, 136.71 (aromatic C), 131.07, 130.99, 129.25, 129.14, 129.13, 129.09, 129.07,

129.05, 129.04, 128.99, 128.83, 128.76, 128.67, 128.64, 128.43, 128.34, 128.25, 128.19, 128.62, 114.06, 114.04 (aromatic CH), 95.52 (C-1a), 93.96 (C-1b), 87.35 (quaternary C), 82.63, 81.72, 80.85, 78.83, 78.59, 78.29, 76.48, 76.06, 75.86, 75.63, 72.42, 70.34, 70.20, 66.92, 65.28, 64.32, 63.92, 63.43, 55.54 (2 OCH₃), 50.78 (CHNH), 50.74 (CHNH), 17.98 (2 CH₃). HR-MS: Calculated for C₉₃H₉₈N₂O₂₁ [M+NH₄]⁺: 1596.70003, found: 1596.69828.

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Chapter 5

α -Selective Galactosylation Using TMSI/Ph₃P=O Activation

Introduction

The construction of 1,2-*cis*-glycosidic linkages continues to be a major challenge in the synthesis of oligosaccharides and glycoconjugates.^[1] Despite tremendous progress that been made over the years in the development of new glycosyl donors, the introduction of novel activators alongside the growing mechanistic insight in the underlying reaction mechanisms, there is no general solution to form 1,2-*cis*-glycosidic bonds.^[2] The main reason for the lack of a general glycosylation procedure is the diversity of sugar substrates that leads to greatly varying results. The reactivity of both the glycosyl donor^[3] and acceptor^[4] is affected by the nature of the protecting groups and the orientation of the groups on the carbohydrate ring. The enormous variation in substitution patterns makes it difficult to translate a productive glycosylation reaction from one glycosylation couple to another. The use of additives to modulate glycosylation is an

attractive method to match donor and acceptor reactivity.^[5] The work described in Chapters 2, 3 and 4 has shown that additive controlled glycosylations of per-benzylated glucosyl donors can be used effectively for the introduction of α -(1,2)-, α -(1,3)-, α -(1,4)- and α -(1,6)- glucosyl linkages.^[6] The stereoselective glycosylations were achieved using two glycosylation systems, the first built on the use of triflic acid (TfOH) activation in combination with DMF as an additive,^[5b, 5k] while the second used trimethylsilyliodide (TMSI) as an activator and $\text{Ph}_3\text{P}=\text{O}$ as a reactivity moderator.^[5c-e, 5l] The first system was used for secondary alcohol acceptors, while the second activator set was employed to glucosylate more reactive primary alcohols. The assembly of longer and branched oligoglucosides was accomplished by the implementation of a protecting group strategy that employed a single type of protecting groups to keep the reactivity of the different substrates as similar as possible. The triad of benzyl (Bn), *para*-methoxybenzyl (PMB) and 2-methylnaphthyl (Nap) ethers was effectively exploited to discriminate the different hydroxyl groups on the building blocks.

The successful synthesis of α -glucans was an incentive to explore the above described methods in the synthesis of α -galactans. 1,2-*cis*-linked galactosides exist in many natural compounds. For example, pectin is a complex polysaccharide that is composed of a linear chain of α -(1,4)-linked galacturonic acids, and it is a prominent constituent of the plant cell wall.^[7] α -Galactosyl linkages are also frequently encountered in mammalian, bacterial and fungal polysaccharides. The opportunistic pathogenic fungus *Asperigillus fumigatus* produces galactosaminogalactans (GAGs), long linear polysaccharides composed of α -(1,4)-linked galactose, galactosamine and *N*-acetyl galactosamine monosaccharides, as part of a protective biofilm and the capsular polysaccharide of *Salmonella typhi*, the causative agent of typhoid fever is composed of repeating 1,4-linked α -*N*-acetyl galactosaminuronic acids.^[8] This Chapter was subject to the use of additive controlled glycosylation methodology for the construction of 1,2-*cis*-galactosides.

Results and discussion

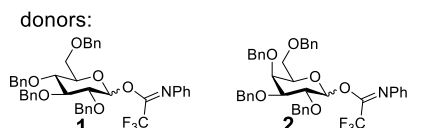
In previous work, per-benzylated donor and acceptor building blocks were used to assemble α -glucans and to match this approach, in this Chapter similarly protected building blocks for the introduction of 1,2-*cis*-galactosyl linkages were employed. First, attention was paid to the glycosylations between glucosyl- and galactosyl imidate donors **1** and **2**, respectively, and galactosyl acceptors **3**, **4** and **5** under DMF-mediated glycosylation conditions (See Table 1). The reactions were performed by combining the donor and acceptor with DMF in DCM, cooling to -78°C , after which TfOH was added. After stirring for 0.5h, the reactions were warmed to 0°C and allowed to proceed for 24h.

As shown in Table 1, the glycosylation between donor **1** and acceptor **3** proceeded in 70% yield and good selectivity ($\alpha:\beta = 15:1$; entry 1). The glycosylations of acceptor **4** and **5** with donor **1**

proceeded in excellent yields, but with less stereoselectivity ($\alpha:\beta$ = 7:1 and 6:1, respectively; entry 2 and 3). Next galactosyl imidate donor **2** was glycosylated with acceptors **3**, **4** and **5**. Disaccharide **9** was obtained in relatively poor yield and selectivity ($\alpha:\beta$ = 5:1, entry 4). Disaccharides **10** and **11** were obtained both with excellent yield and good selectivity ($\alpha:\beta$ = 13:1 and 12:1, respectively; entry 5 and 6). These results indicate that, across the board, the reactions of the galactosyl acceptors proceed with lower selectivity under DMF/TfOH activation. Therefore, attention was turned to the TMSI/ Ph₃P=O activation conditions, reasoning that these latter conditions generate intermediates that are less reactive than the intermediates generated upon TfOH/DMF activation, which could lead to improved stereoselectivity in the condensation reactions.

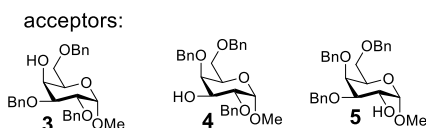
Table 1. Glycosylation under TfOH/DMF activation conditions.

donors:



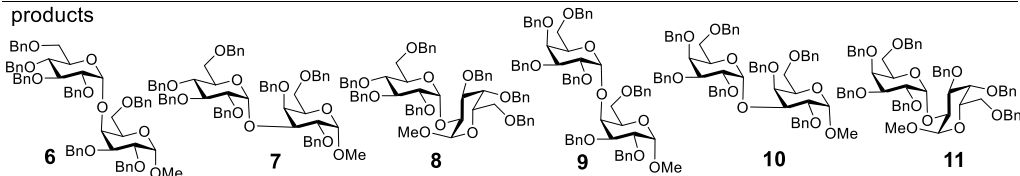
1 **2**

acceptors:



3 **4** **5**

products



6 **7** **8** **9** **10** **11**

donors + acceptors $\xrightarrow[\text{DCM, -78-0}^\circ\text{C}]{\text{DMF, TfOH}}$ products

Entry	Donor	Acceptor	Additive	Product	Yield ^a	α:β ^b
1	1	3	DMF	6	70%	15:1
2	1	4	DMF	7	95%	7:1
3	1	5	DMF	8	95%	6:1
4	2	3	DMF	9	55%	5:1
5	2	4	DMF	10	95%	13:1
6	2	5	DMF	11	98%	12:1

^a Isolated yield. ^b The α:β ratio was determined by ¹H NMR.

^a Isolated yield. ^b The $\alpha:\beta$ ratio was determined by ¹H NMR.

Previously, Ph₃P=O has been used as an additive to modulate glycosylation selectivity by Mukaiyama and coworkers^[5c-e], and Oka and coworkers reported α -selective ribofuranosylations using TMSI and Ph₃P=O.^[9] To be able to compare the TfOH/DMF and TMSI/Ph₃P=O systems, the set of glycosylation reactions, summarized in Table 2 was performed. The reactions were performed by mixing the donor, acceptor and Ph₃P=O in DCM, prior to the addition of TMSI and stirring for 24h at room temperature.

Table 2. Glycosylations under TMSI and Ph₃P=O activation.

acceptors:

products

donors (1 and 2) + acceptors (3-5 and 12-16) $\xrightarrow[\text{DCM, rt}]{\text{TMSI, Ph}_3\text{P=O}}$ products (6-11 and 17-26)

Entry	Donor	Acceptor	Additive	Product	Yield ^a	α:β ^b
1	1	12	Ph ₃ P=O	17	95%	>20:1
2	1	13	Ph ₃ P=O	18	95%	>20:1
3	1	3	Ph ₃ P=O	6	49%	>20:1
4	1	4	Ph ₃ P=O	7	92%	>20:1
5	1	5	Ph ₃ P=O	8	78%	>20:1
6	1	14	Ph ₃ P=O	21	61%	>20:1
7	1	15	Ph ₃ P=O	22	95%	>20:1
8	1	16	Ph ₃ P=O	23	60%	>20:1
9	2	12	Ph ₃ P=O	19	90%	10:1
10	2	13	Ph ₃ P=O	20	71%	15:1
11	2	3	Ph ₃ P=O	9	40%	10:1
12	2	4	Ph ₃ P=O	10	78%	10:1
13	2	5	Ph ₃ P=O	11	91%	15:1
14	2	14	Ph ₃ P=O	24	82%	>20:1
15	2	15	Ph ₃ P=O	25	93%	11:1
16	2	16	Ph ₃ P=O	26	98%	>20:1

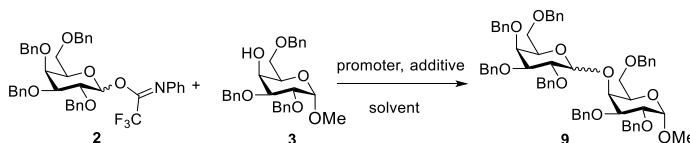
^a Isolated yield. ^b The α:β ratio was determined by ¹H NMR.

First, the reactions of glucosyl donor **1** were examined. In line with the results of the previous Chapters, the reactions with primary alcohol acceptors **12** and **13** proceeded in excellent yield and stereoselectivity (entry 1 and 2). Next the secondary galactosyl alcohols **3**, **4** and **5** were

exposed to the glucosylation conditions to provide disaccharides **6**, **7** and **8** with excellent selectivity (entries 3-5). Of note, the yield of the reaction of the C4-OH acceptor **3** (entry 3) was significantly lower than the reactions with the other two acceptors. The condensations with the secondary glucosyl acceptors **14**, **15** and **16** also proceeded in a highly stereoselective manner (entries 6-8). While the stereoselectivity of these reactions matched the stereoselectivity of the TfOH/DMF mediated glucosylations (Chapter 2), the reactions proceeded more slowly (requiring room temperature) and with somewhat diminished yields. Next the corresponding galactosylations were investigated. Entry 9 and 10 show that the TMSI/Ph₃P=O mediated galactosylations of the primary alcohol acceptors are somewhat less stereoselective than the corresponding glucosylations. The reactions with the secondary galactosyl acceptors **3**, **4** and **5** proceed with similar stereoselectivity. While the stereoselectivity of donor **2** with C4-OH galactose acceptor **3** is increased with respect to the TfOH/DMF system, the stereoselectivity of the reactions of the other two acceptors, **4** and **5**, is somewhat poorer under the TMSI/Ph₃P=O conditions. Finally, glucose acceptors **14**, **15** and **16** were combined with donor **2** and TMSI/Ph₃P=O activation to provide disaccharides **24**, **25** and **26** in good to excellent yields. Disaccharides **24** and **25** were formed with excellent stereoselectivity, while disaccharide **25** was obtained as a 11:1 mixture of α - and β -galactosides.

As described above, the α -(1,4)-polygalactose motif is a prominent structure in many relevant polysaccharides. The results in Table 1 and 2 show that the glycosylations of the galactosyl C4-OH is more challenging than the other condensation reactions, likely as the result of the poor nucleophilicity of this alcohol. Therefore, the construction of the galactose- α -(1,4)-galactose was further investigated. Table 3 shows that conditions were screened to optimize the reaction between donor **2** and acceptor **3**. First the glycosylation of donor **2** and acceptor **3** was explored without additive at 0°C. Although, the yield of this reaction was quite good, the stereoselectivity was poor (α : β = 3:1, entry 1). Next, the glycosylation was performed under the activation of TMSOTf-Ph₃P=O. These conditions led to a similar yield but reduced selectivity (α : β = 2:1; entry 2). Because the stereoselectivity of this reaction was significantly lower than the stereoselectivity of the TMSI-Ph₃P=O mediated reaction (Table 2, entry 11), different additives were next investigated using TMSI as promoter. Disaccharide **9** was formed with poor yield and selectivity when TBAI was used as an additive (entry 4). By combining Ph₃P=O and TBAI the yield and α -selectivity of the latter reaction both increased (entry 5), although the α -selectivity of this reaction was lower than when solely Ph₃P=O was used. The use of different phosphine oxides, Me₃P=O and tri(pyrrolidin-1-yl)phosphine oxide (entry 6 and 7) did not lead to the desired improvement. In fact, when tri(pyrrolidin-1-yl)phosphine oxide was used, no disaccharide was formed at all. The use of Ph₃P=S gave a similar selectivity as Ph₃P=O, but the yield decreased to 27% (entry 8). Because no improvement could be found through the use of different additives, attention was directed to optimizing the yield for the TMSI/Ph₃P=O reaction. To this end, different solvents and

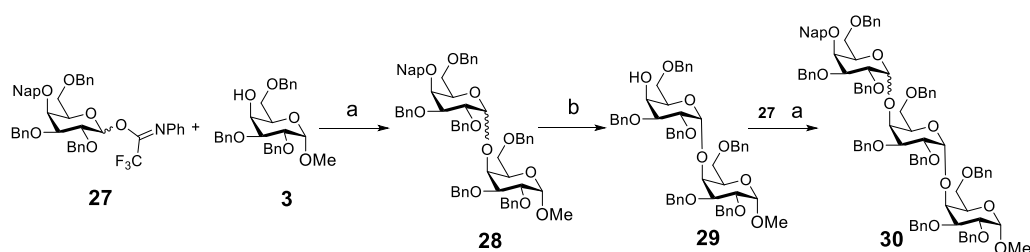
reaction temperatures were screened. The yield and α -selectivity were decreased slightly when DCE was used (entry 9). While the α -selectivity increased to 12:1 when using DCM/Et₂O, the yield dropped to 23%. Finally, the glycosylation was explored at higher temperature. Refluxing the reaction mixture in DCM improved the yield of the reaction to 67% while the stereoselectivity (α : β = 10:1) was maintained. Raising the temperature further, by refluxing the reaction mixture in DCE led to a poor yield and stereoselectivity.

Table 3. Glycosylation of donor **2** and acceptor **3**.

Entry	Promoter	Additive	Solvent	T(°C)	t(h)	Yield ^a	α : β ^b
1	TfOH	-	DCM	0	0.5	78%	3:1
2	TMSOTf	Ph ₃ P=O	DCM	rt	18	75%	2:1
3	TMSI	Ph ₃ P=O	DCM	rt	24	40%	10:1
4	TMSI	TBAI	DCM	rt	24	23%	3:1
5	TMSI	TBAI/Ph ₃ P=O	DCM	rt	24	49%	6:1
6	TMSI	Me ₃ P=O	DCM	rt	24	51%	5:1
7	TMSI		DCM	rt	24	-	-
8	TMSI	Ph ₃ P=S	DCM	rt	24	27%	9:1
9	TMSI	Ph ₃ P=O	DCE	rt	24	37%	7:1
10	TMSI	Ph ₃ P=O	DCM/Et ₂ O	rt	24	23%	12:1
11	TMSI	Ph ₃ P=O	DCM	reflux	24	67%	10:1
12	TMSI	Ph ₃ P=O	DCE	reflux	24	28%	3:1

^a Isolated yield. ^b The $\alpha:\beta$ ratio was determined by ¹H NMR.

To explore the applicability of the optimal conditions in the synthesis of an oligosaccharide, a linear trisaccharide was assembled as depicted in Scheme 1. First acceptor **3** was glycosylated with donor **27**, bearing a Nap-ether at the C-4 position to form the desired disaccharide **28** ($\alpha:\beta = 10:1$). Because the disaccharide could not be purified from the 1,1-linked disaccharide side product, the Nap-ether was removed using DDQ in DCM/H₂O to provide **29**. The pure α -disaccharide was obtained in 42% yield over two steps. Finally, disaccharide acceptor **29** was coupled with donor **27** under the conditions established above to give the trisaccharide **30** in 64% yield and $\alpha:\beta = 8:1$.



a) TMSI, Ph₃P=O, DCM, reflux, **28**: α : β = 10:1; **30**: 64%, α : β = 8:1. b) DDQ, DCM/H₂O, **29**: 42% with two steps.

Scheme 1. Synthesis of trisaccharide.

Conclusion

In summary, this Chapter has explored additive mediated glycosylations for the construction of α -glucosyl and galactosyl linkages. Because TfOH/DMF mediated glucosylations and galactosylations of galactosyl acceptors proceeded with lower selectivity than the systems explored in the previous Chapters, TMSI-Ph₃P=O mediated glycosylation conditions were probed. It was found that the use of this activation cocktail can be used with a broad substrate scope. Both primary and secondary alcohol acceptors can be stereoselectively condensed with glucosyl and galactosyl donors. The galactosyl C4-OH proved to be a challenging alcohol to glycosylate and elevated temperatures were required to achieve a synthetically useful glycosylation with this acceptor. A linear galactosyl trisaccharide was synthesized using optimal TMSI-Ph₃P=O mediated glycosylation conditions.

Experimental Section

General experimental procedures

All reagents were of commercial grade and used as received. All moisture sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of (NH₄)₆Mo₇O₂₄·4H₂O (25 g/L) and (NH₄)₄Ce(SO₄)₄·2H₂O (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20. High resolution mass (HRMS) was performed on a Thermo Finnigan LTQ Orbitrap mass spectrometer equipped with an electrospray ion source in positive ion mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 275 °C) resolution R= 60.000 at m/z 400 (mass range of 150-4000) and dioctylphthalate(m/z=391.28428) as lock mass, or on a Waters Synpat G2-Si(OTf) equipped with an electrospray ion source in positive mode (source voltage 3.5kV) and LeuEnk (m/z = 556.2771). 1 μ l of 2,5-dihydroxybenzoic acid (2,5-DHB; Bruker Daltonics) matrix (20 mg/mL in ACN/water; 50:50 (v/v)) was applied on a 384-MTP target plate (Bruker Daltonics, Bremen, Germany) and air-dried. Subsequently, 1 μ l of xxx solution was spotted on the plate and the spots were left to dry prior MALDI-TOF analysis. An Ultraflextreme MALDI-TOF (Bruker

Daltonics), equipped with Smartbeam-II laser was used to measure the samples in reflectron positive ion mode. The MALDI-TOF was calibrated using a peptide calibration standard prior to measurement. ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in CDCl_3 or D_2O . Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard (^1H NMR in CDCl_3) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. NMR peak assignments were made using COSY and HSQC experiments, where applicable Clean TOCSY, HMBC and GATED experiments were used to further elucidate the structure. The anomeric product ratios were analyzed through integration of proton NMR signals. IR spectra were recorded on a Shimadzu FTIP-8300 IR spectrometer and are reported in cm^{-1} . Specific rotations were measured on a Propol automatic polarimeter or an Anton-Paar MCP 100 modular circular polarimeter at 589 nm unless otherwise stated.

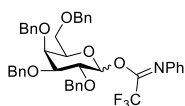
Standard procedure A: A mixture of donor (1.0 eq), acceptor (0.7 eq) (donor and acceptor co-evaporated with toluene three times), DMF (16 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78°C , after which TfOH (1.0 eq) was added. After 30 min, the mixture was placed in an ice bath. The reaction was stirred at 0°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Standard procedure B: A mixture of donor (1.0 eq), acceptor (0.7 eq) (donor and acceptor co-evaporated with toluene three times), $\text{Ph}_3\text{P}=\text{O}$ (6 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. Then TMSI (1.0 eq) was added slowly in the mixture. The reaction was stirred at room temperature until TLC-analysis indicated the reaction to be complete. The solution was diluted and the reaction quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$. The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Standard procedure C for deprotection of the Nap protecting group: The starting material (1 eq) was dissolved in $\text{DCM}:\text{H}_2\text{O}$ (10:1, 0.1 M). DDQ (1.1 eq) was added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material ($\pm 2\text{h}$). Then the mixture was diluted with DCM and the reaction quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$. The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography.

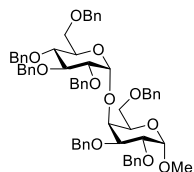
Experimental Procedures and Characterization Data of Products

We used "a", "b" and "c" to specify the H-1 and C-13 NMR signals of sugar rings from the "reducing" to the "non-reducing" end.

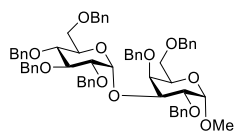


Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-galactopyranoside 2: IR (neat, cm^{-1}) ν 694, 731, 751, 1027, 1097, 1150, 1206, 1318, 1452, 1497, 1550, 1600, 1716, 2870, 3031. ^1H -NMR (CDCl_3 , 500 MHz, 60°C) δ 7.51-6.70 (m, aromatic *H*), 6.40 (bs, 1 H, H-1 α), 5.59 (bs, 1 H, H-1 β), 4.94-4.40 (m), 4.19-3.87 (m), 3.46 (t), 3.67-3.50 (m). ^{13}C -APT (CDCl_3 , 125 MHz, 60°C) δ 144.05, 143.84, 139.01, 138.90, 138.81, 138.79, 138.76, 138.51, 138.46, 138.20, 138.18, 135.38 (aromatic *C*), 129.47, 128.78, 128.76,

128.55, 128.53, 128.51, 128.47, 128.39, 128.34, 128.22, 128.19, 128.08, 127.98, 127.92, 127.89, 127.86, 127.83, 127.72, 127.69, 127.64, 126.50, 124.29, 124.25, 120.82, 119.78, 119.58 (aromatic CH), 98.08, 97.90, 92.16, 82.44, 78.66, 78.48, 76.12, 75.51, 75.21, 75.10, 74.97, 74.80, 73.96, 73.70, 73.65, 73.47, 73.33, 72.60, 69.97, 69.24, 68.83, 68.60. HR-MS: Calculated for C₄₃H₄₂F₃O₇N [M-[O(C=NPh)CF₃]+OH+Na]⁺: 593.2510, found: 593.2516.

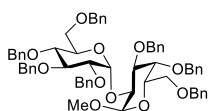


Synthesis of **6**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **1** (106 mg, 0.15 mmol), **3** (45 mg, 0.1 mmol, 0.1 M in DCM), DMF (189 μ L, 2.4 mmol) and TfOH (13 μ L, 1.59 mmol). The reaction was stirred at -78-0 $^{\circ}$ C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **6** (67 mg, 70% yield, α : β = 15:1) was obtained as a colorless syrup. Under condition B, using **1** (105 mg, 0.15 mmol), **3** (45 mg, 0.1 mmol, 0.1 M in DCM), Ph₃P=O (250 mg, 0.9 mmol) and TMSI (21 μ L, 0.15 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **6** (47 mg, 49 % yield, α : β > 20:1) was obtained as a colorless syrup. [α]_D²⁰ +75.1 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 697, 734, 1027, 1050, 1093, 1359, 1454, 1497, 2923. ¹H-NMR (CDCl₃, 400 MHz) δ 7.41-7.09 (m, 35 H, aromatic H), 5.10 (d, J = 3.6 Hz, 1 H, H-1b), 4.91 (d, J = 10.8 Hz, 1 H, CHH), 4.85-4.67 (m, 9 H, 8 CHH, H-1a), 4.48 (d, J = 12.4 Hz, 1 H, CHH), 4.40 (d, J = 10.8 Hz, 1 H, CHH), 4.28-4.11 (m, 5 H, 3 CHH, H-4a, H-5b), 3.98-3.84 (m, 5 H, H-6a_a, H-5a, H-4b, H-3b, H-2a), 3.73 (t, J = 10.0 Hz, 1 H, H-3a), 3.57 (dd, J = 3.6, 10.0 Hz, 1 H, H-2b), 3.51 (dd, J = 5.6, 9.2 Hz, 1 H, H-6a_b), 3.41-3.36 (m, 4 H, H-6b_a, OCH₃), 3.06 (dd, J = 2.0, 10.4 Hz, 1 H, H-6b_b). ¹³C-APT (CDCl₃, 100 MHz) δ 139.02, 138.97, 138.75, 138.46, 138.36, 138.28, 138.08 (aromatic C), 128.51, 128.48, 128.45, 128.36, 128.35, 128.19, 127.95, 127.93, 127.88, 127.82, 127.70, 127.63, 127.59, 127.52 (aromatic CH), 98.83 (C-1b), 98.88 (C-1a), 82.30 (C-3b), 80.39 (C-2b), 77.98 (C-3a), 77.89 (C-2a), 76.66 (C-4a), 75.54 (CH₂), 75.06 (C-4b), 74.99, 74.02, 73.46, 73.40, 73.10, 72.98 (CH₂), 70.80 (C-5b), 69.45 (C-5a), 68.15 (C-6a), 67.68 (C-6b), 55.43 (OCH₃). HR-MS: Calculated for C₆₂H₆₆O₁₁ [M+NH₄]⁺: 1004.49434, found: 1004.49243.



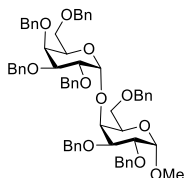
Synthesis of **7**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **1** (105 mg, 0.15 mmol), **4** (45 mg, 0.1 mmol, 0.1 M in DCM), DMF (189 μ L, 2.4 mmol) and TfOH (13 μ L, 1.59 mmol). The reaction was stirred at -78-0 $^{\circ}$ C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **7** (91 mg, 95% yield, α : β = 7:1) was obtained as a colorless syrup. Under condition B, using **1** (106 mg, 0.15 mmol), **4** (46 mg, 0.1 mmol, 0.1 M in DCM), Ph₃P=O (250 mg, 0.9 mmol) and TMSI (21 μ L, 0.15 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **7** (88 mg, 92 % yield, α : β > 20:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 698, 737, 1027, 1050, 1096, 1274, 1356, 1454, 1497, 1724, 2925, 3032. [α]_D²⁰ +69.4 (c=1, CHCl₃). ¹H NMR (500 MHz, CCl₄) δ 7.43-7.06 (m, 35H, aromatic H), 5.15 (d, J = 3.3 Hz, 1H, H-1b), 5.08 (d, J = 11.2 Hz, 1H, CHH), 4.90 (d, J = 11.0 Hz, 1H, CHH), 4.84-4.76 (m, 3H, 3 CHH), 4.72-4.66 (m, 3H, 2 CHH, H-1a), 4.58-4.54 (m, 2H, 2 CHH), 4.48 (d, J = 11.8 Hz, 1H, CHH), 4.44 (d, J = 11.0 Hz, 1H, CHH), 4.40-4.36 (m, 2H, 2 CHH), 4.30 (d, J = 12.1 Hz, 1H, CHH), 4.17 (bd, J = 10.1 Hz, 1H, H-5b), 4.14-4.07 (m, 2H, H-3a,

H-3b), 3.99 (dd, $J = 10.2, 3.6$ Hz, 1H, H-2a), 3.93 (bd, 1H, H-4a), 3.89-3.84 (t, $J = 6.5$ Hz, 1H, H-5a), 3.73 (t, $J = 9.5$ Hz, 1H, H-4b), 3.65 (dd, $J = 9.8, 3.4$ Hz, 1H, H-2b), 3.55-3.49 (m, 3H, 2 H-6a, H-6b), 3.45-3.39 (m, 1H, H-6b), 3.32 (s, 3H, OCH₃). ¹³C NMR (125 MHz, CDCl₃) δ 139.07, 138.86, 138.78, 138.31, 138.19, 138.17, 138.09 (aromatic C), 128.58, 128.54, 128.51, 128.49, 128.45, 128.43, 128.36, 128.29, 128.23, 128.19, 128.16, 128.13, 128.11, 128.06, 127.98, 127.81, 127.79, 127.75, 127.67, 127.62, 127.51, 127.36 (aromatic CH), 98.45 (C-1a), 96.44 (C-1b), 82.27 (C-3b), 80.30 (C-2b), 78.09 (C-4b), 76.52 (C-3a), 75.68 (C-2a), 75.58 (CH₂), 75.00 (CH₂), 74.94 (C-4a), 74.88, 74.18, 73.53, 73.41, 73.33 (CH₂), 70.49 (C-5b), 69.32 (C-5a), 69.07 (C-6a), 68.25 (C-6b), 55.33 (OCH₃). HR-MS: Calculated for C₆₂H₆₆O₁₁ [M+NH₄]⁺: 1004.49434, found: 1004.49343.



Synthesis of **8**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **1** (105 mg, 0.15 mmol), **5** (45 mg, 0.1 mmol, 0.1 M in DCM), DMF (190 μ L, 2.4 mmol) and TfOH (13 μ L, 1.59 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N,

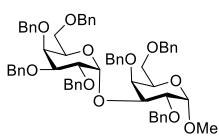
filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **8** (95 mg, 99% yield, $\alpha:\beta = 6:1$) was obtained as a colorless syrup. Under condition B, using **1** (106 mg, 0.15 mmol), **5** (46 mg, 0.1 mmol, 0.1 M in DCM), Ph₃P=O (250 mg, 0.9 mmol) and TMSI (21 μ L, 0.15 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **8** (76 mg, 78 % yield, $\alpha:\beta > 20:1$) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 737, 1027, 1050, 1093, 1275, 1358, 1454, 1497, 1724, 2866, 2926. [α]_D²⁰ +73.2 ($c=1$, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.20 (m, 30H), 7.12 – 7.05 (m, 5H), 4.98 (d, $J = 10.5$ Hz, 1H, CHH), 4.93 (m, 2H, H-1b, H-1a), 4.86 (d, $J = 11.5$ Hz, 1H, CHH), 4.84 – 4.64 (m, 6H, 6 CHH), 4.56 – 4.49 (m, 3H, 3 CHH), 4.44 (m, 2H, 2 CHH), 4.35 (dd, $J_1 = 10.0$ Hz, $J_2 = 3.5$ Hz, 1H, H-2a), 4.30 (d, $J = 12.5$ Hz, 1H, CHH), 4.13 – 4.07 (m, 2H, H-5b, H-3b), 4.03 – 4.00 (m, 2H, H-4a, H-3a), 3.94 (t, $J = 6.5$, 1H, H-5a), 3.68 (t, $J = 10.0$ Hz, 1H, H-4b), 3.59 – 3.56 (m, 3H, 2 H-6a, H-2b), 3.49 (dd, $J_1 = 11.0$ Hz, $J_2 = 2.5$ Hz, 1H, 1 H-6b), 3.44 (s, 3H, OCH₃), 3.40 (dd, $J_1 = 11.0$ Hz, $J_2 = 2.0$ Hz, 1H, 1 H-6b). ¹³C NMR (126 MHz, CDCl₃) δ 139.01, 138.89, 138.80, 138.60, 138.17, 138.08, 138.03 (aromatic C), 128.51, 128.44, 128.42, 128.35, 128.31, 128.23, 128.18, 128.13, 128.12, 128.09, 128.01, 127.93, 127.90, 127.86, 127.78, 127.65, 127.61, 127.59, 127.56, 127.42 (aromatic CH), 97.05 (C-1a), 94.40 (C-1b), 82.34 (C-3a), 79.35 (C-2b), 77.83 (C-3a), 77.78 (C-4b), 75.73 (CH₂), 74.80 (2 CH₂, C-4a), 73.68 (CH₂), 73.44 (CH₂), 73.39 (CH₂), 72.96 (CH₂), 71.66 (C-2a), 69.97 (C-5b), 69.39 (C-5a), 69.16 (C-6a), 68.06 (C-6b), 55.15 (OCH₃). HR-MS: Calculated for C₆₂H₆₆O₁₁ [M+NH₄]⁺: 1004.49434, found: 1004.49334.



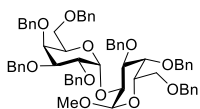
Synthesis of **9**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **2** (105 mg, 0.15 mmol), **3** (45 mg, 0.1 mmol, 0.1 M in DCM), DMF (190 μ L, 2.4 mmol) and TfOH (13 μ L, 1.59 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography

(DCM:MeOH = 1:1). Compound **9** (53 mg, 55% yield, $\alpha:\beta = 5:1$) was obtained as a colorless syrup. Under condition B, using **2** (97 mg, 0.14 mmol), **3** (42 mg, 0.09 mmol, 0.1 M in DCM), Ph₃P=O (240 mg, 0.86 mmol) and TMSI (20 μ L, 0.14 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **9** (36 mg, 40 %

yield, $\alpha:\beta = 10:1$) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 1029, 1050, 1098, 1359, 1454, 1497, 2923, 3031. $[\alpha]_{\text{D}}^{20} +34.0$ ($c=1$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.42-7.16 (m, 35 H, aromatic H), 4.99 (d, $J = 3.6$ Hz, 1 H, H-1b), 4.91-4.67 (m, 9 H, 8 CHH, H-1a), 4.60 (d, $J = 12.4$ Hz, 1 H, CHH), 4.41 (dd, $J = 4.8, 9.2$ Hz, 1 H, H-5b), 4.21 (s, 2 H, 2 CHH), 4.13-4.05 (m, 5 H, 2 CHH, H-4a, H-4b, H-2b), 3.93-3.80 (m, 5 H, H-6a_b, H-5a, H-3a, H-3b, H-2a), 3.56-3.46 (m, 2 H, H-6a_b, H-6b_a), 3.36 (s, 3 H, OCH_3), 3.21 (dd, $J = 4.8, 8.0$ Hz, 1 H, H-5b). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 139.08, 138.88, 138.79, 138.67, 138.34, 138.23 (aromatic C), 128.46, 128.41, 128.39, 128.24, 128.23, 128.16, 127.95, 127.77, 127.69, 127.66, 127.60, 127.54, 127.48, 127.46, 127.39 (aromatic CH), 100.45 (C-1b), 98.89 (C-1a), 79.60 (C-3b), 78.09 (C-3a), 76.66 (C-4b), 76.33 (C-4a), 77.17 (C-2b), 75.04 (CH_2), 74.71 (C-2a), 74.28, 73.48, 73.28, 73.05, 72.76, 72.37 (CH_2), 69.59 (C-5a), 67.89 (C-5b), 68.25 (C-6a), 67.89 (C-6b), 55.42 (OCH_3). HR-MS: Calculated for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{NH}_4]^+$: 1004.49434, found: 1004.49353.

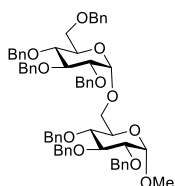


Synthesis of 10: The reaction was carried out according to the standard procedure A or B. Under condition A, using **2** (105 mg, 0.15 mmol), **4** (45 mg, 0.1 mmol, 0.1 M in DCM), DMF (190 μL , 2.4 mmol) and TfOH (13 μL , 1.59 mmol). The reaction was stirred at $-78-0^\circ\text{C}$ until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **9** (91 mg, 95% yield, $\alpha:\beta = 13:1$) was obtained as a colorless syrup. Under condition B, using **2** (106 mg, 0.15 mmol), **4** (46 mg, 0.1 mmol, 0.1 M in DCM), $\text{Ph}_3\text{P}=\text{O}$ (250 mg, 0.9 mmol) and TMSI (21 μL , 0.15 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **9** (76 mg, 78 % yield, $\alpha:\beta > 10:1$) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 698, 737, 1027, 1050, 1097, 1274, 1454, 1497, 1724, 2872, 2925. $[\alpha]_{\text{D}}^{20} +72.1$ ($c=1$, CHCl_3). $^1\text{H NMR}$ (500 MHz, CCl_4) δ 7.34–7.11 (m, 35H, aromatic H), 5.21 (d, $J = 3.5$ Hz, 1H, H-1b), 4.98 (d, $J = 11.5$ Hz, 1H, CHH), 4.92 (d, $J = 11.5$ Hz, 1H, CHH), 4.84 (d, $J = 11.5$ Hz, 1H, CHH), 4.73-4.66 (m, 4H, 4 CHH), 4.60 – 4.53 (m, 3H, 2 CHH, H-1a), 4.45 (d, $J = 12.0$ Hz, 1H, CHH), 4.37-4.30 (m, 5H, 4 CHH, H-5a), 4.15-4.11 (m, 2H, H-3a, H-2b), 4.00 (dd, $J = 10.5, 3.0$ Hz, 1H, H-3b), 3.96 (dd, $J = 10.5, 3.5$ Hz, 1H, H-2a), 3.92 (bd, 2H, H-4a, H-4b), 3.82 (t, $J = 6.5$ Hz, 1H, H-5b), 3.56-3.41 (m, 4H, 2 H-6a, 2 H-6b), 3.27 (s, 3H, OCH_3). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 139.15, 138.92, 138.82, 138.80, 138.49, 138.41, 138.25 (aromatic C), 128.47, 128.39, 128.37, 128.31, 128.15, 128.06, 127.92, 127.78, 127.74, 127.71, 127.66, 127.61, 127.60, 127.58, 127.49, 127.34 (aromatic CH), 98.68 (C-1a), 97.20 (C-1b), 79.13 (C-3b), 76.87 (C-2b), 76.31 (C-3a), 75.94 (C-2a), 75.21 (C-4), 75.12 (C-4), 74.97, 74.82, 74.30, 73.46, 73.39, 73.12, 72.52 (CH_2), 69.43 (C-5a), 69.34 (C-5b), 69.22 (C-6b), 68.72 (C-6a), 55.28 (OCH_3). HR-MS: Calculated for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{NH}_4]^+$: 1004.49434, found: 1004.49331.

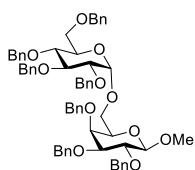


Synthesis of 11: The reaction was carried out according to the standard procedure A or B. Under condition A, using **2** (105 mg, 0.15 mmol), **5** (45 mg, 0.1 mmol, 0.1 M in DCM), DMF (190 μL , 2.4 mmol) and TfOH (13 μL , 1.59 mmol). The reaction was stirred at $-78-0^\circ\text{C}$ until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **9** (94 mg, 98% yield, $\alpha:\beta = 12:1$) was obtained as a colorless syrup. Under condition B, using **2** (106 mg, 0.15 mmol), **5** (46 mg, 0.1 mmol, 0.1 M in DCM), $\text{Ph}_3\text{P}=\text{O}$ (250 mg, 0.9 mmol) and TMSI (21 μL , 0.15 mmol). The product

was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **9** (89 mg, 91 % yield, $\alpha:\beta = 15:1$) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 1027, 1052, 1096, 1276, 1454, 1497, 1724, 2870, 2919. $[\alpha]_{\text{D}}^{20} +67.2$ ($c=1$, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.15 (m, 35H), 4.98 (d, $J = 3.5$ Hz, 1H, H-1b), 4.98 (d, $J = 3.5$ Hz, 1H, H-1a), 4.89 (d, $J = 11.5$ Hz, 1H, CHH), 4.88 (d, $J = 11.5$ Hz, 1H, CHH), 4.82-4.64 (m, 6H, 6 CHH), 4.56-4.48 (m, 3H, 3 CHH), 4.41 (d, $J = 11.5$ Hz, 1H, CHH), 4.36 (dd, $J = 10.0$, 3.5 Hz, 1H, H-2a), 4.33-4.24 (m, 3H, H-5b, 2 CHH), 4.04-3.90 (m, 5H, H-3a, H-5a, H-2b, H-3b, H-4), 3.85 (bd, 1H, H-4), 3.56 (bd, 2H, H-6a), 3.51 (bt, 1H, 1 H-6b), 3.44-3.38 (m, 4H, 1 H-6b, OCH_3). ^{13}C NMR (125 MHz, CDCl_3) δ 139.09, 139.01, 138.94, 138.81, 138.75 (aromatic C), 128.49, 128.43, 128.41, 128.31, 128.28, 128.20, 128.17, 128.98, 127.89, 127.82, 127.72, 127.58, 127.51, 127.48, 127.46 (aromatic CH), 97.15 (C-1a), 94.82 (C-1b), 79.07 (C-3b), 78.03 (C-3a), 76.05 (C-2b), 75.01 (C-4), 74.92 (C-4), 74.89, 74.62, 73.64, 73.22, 73.18, 73.01, 72.87 (CH_2), 71.42 (C-2a), 69.44 (C-5a), 69.23 (C-6a), 68.83 (C-5b), 68.40 (C-6b), 55.21 (OCH_3). HR-MS: Calculated for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{NH}_4]^+$: 1004.49434, found: 1004.49357.

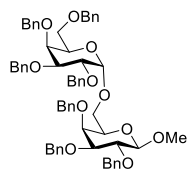


Synthesis of **17**: The reaction was carried out according to the standard procedure B, using **1** (106 mg, 0.15 mmol), **12** (46 mg, 0.1 mmol, 0.1 M in DCM), $\text{Ph}_3\text{P}=\text{O}$ (250 mg, 0.9 mmol) and TMSI (20 μL , 0.14 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **17** (93 mg, 95 % yield, $\alpha:\beta > 20:1$) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 1027, 1072, 1089, 1159, 1361, 1454, 1497, 2866, 2925. $[\alpha]_{\text{D}}^{20} +52.0$ ($c=1$, CHCl_3). ^1H -NMR (500 MHz, CDCl_3) δ 7.34-7.10 (m, 35H, aromatic H), 4.99-4.89 (m, 4 H, H-1b, 3 CHH), 4.84-4.55 (m, 9 H, CHH, H-1a), 4.46-4.39 (m, 2 H, 2 CHH), 4.01-3.94 (m, 2 H, H-3a and 3b), 3.85-3.52 (m, 9 H, H-5b, H-5a, H-4b, H-4a, H-2b, H-6b, H-6a), 3.45 (dd, $J = 9.6$, $J = 3.6$ Hz, 1H, H-2a), 3.51 (s, 3H, OCH_3). ^{13}C -NMR (126 MHz, CDCl_3) δ 138.86, 138.52, 138.49, 138.23, 138.02 (aromatic C), 128.49, 128.43, 128.39, 128.35, 128.08, 128.05, 127.96, 127.92, 127.80, 127.79, 127.71, 127.70, 127.67, 127.64, 127.61, 127.58 (aromatic CH), 98.02 (C-1a), 97.32 (C-1b), 82.19 (C-3a), 81.73 (C-3b), 80.19 (C-2), 80.03 (C-2), 77.81 (C-4), 77.66 (C-4), 75.79, 75.57, 75.03, 74.97, 73.46, 73.44, 72.44 (CH_2), 70.41 (C-5), 70.29 (C-5), 68.50 (C-6b), 66.09 (C-6a), 55.23 (OCH_3). HR-MS: Calculated for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{NH}_4]^+$: 1004.49434, found: 1004.493378.

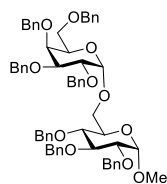


Synthesis of **18**: The reaction was carried out according to the standard procedure B, using **1** (90 mg, 0.13 mmol), **13** (39 mg, 0.08 mmol, 0.1 M in DCM), $\text{Ph}_3\text{P}=\text{O}$ (210 mg, 0.75 mmol) and TMSI (18 μL , 0.14 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **18** (79 mg, 95 % yield, $\alpha:\beta > 20:1$) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 734, 1029, 1073, 1156, 1206, 1362, 1454, 1497, 2866, 2915. $[\alpha]_{\text{D}}^{20} +25.4$ ($c=1$, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.10 (m, 35H, aromatic H), 4.98-4.58 (m, 13H, 12 CHH, H-1b), 4.45 (bt, 2H, 2 CHH), 4.25 (d, $J = 7.6$ Hz, 1H, H-1a), 3.97 (t, $J = 9.6$ Hz, 1H, H-3b), 3.82-3.45 (m, 14H, H-2a, H-2b, H-3a, H-4a, H-4b, H-5a, H-5b, H-6a, H-6b, OCH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 138.86, 138.82, 138.69, 138.57, 138.42, 138.18, 137.90 (aromatic C), 128.49, 128.46, 128.43, 128.38, 128.33, 128.24, 128.18, 128.14, 128.10, 128.06, 128.01, 127.78, 127.76, 127.70, 127.66, 127.64, 127.62, 127.58, 127.53 (aromatic CH), 104.95 (C-1a), 97.26 (C-1b), 82.09 (C-3a and 3b), 79.79 (C-2), 79.65 (C-2), 77.69 (C-4b), 77.57, 75.20, 75.00, 74.40 (CH_2), 73.93 (C-4a), 73.55, 73.36, 73.18 (CH_2), 73.16 (C-5a), 70.29 (C-5b), 68.38 (C-6b), 67.04 (C-6a), 57.08 (OCH_3). HR-MS: Calculated for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$

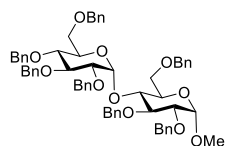
[M+NH₄]⁺: 1004.49434, found: 1004.49366.



Synthesis of **19**: The reaction was carried out according to the standard procedure B, using **2** (106 mg, 0.15 mmol), **13** (46 mg, 0.1 mmol, 0.1 M in DCM), Ph₃P=O (250 mg, 0.9 mmol) and TMSI (20 μL, 0.14 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **19** (88 mg, 90 % yield, α:β = 10:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 734, 1029, 1056, 1077, 1098, 1206, 1362, 1454, 1497, 2870, 2916. [α]_D²⁰ +24.3 (c=1, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.20 (m, 35 H, aromatic *H*), 4.94–4.86 (m, 3 H, 3 *CHH*), 4.81–4.71 (m, 6 H, 5 *CHH*, H-1b), 4.66–4.55 (m, 4 H, 4 *CHH*), 4.46 (d, *J* = 11.6 Hz, 1 H, *CHH*), 4.37 (d, *J* = 11.6 Hz, 1 H, *CHH*), 4.23 (d, *J* = 6.1 Hz, 1 H, H-1a), 4.03 (dd, *J* = 3.6 Hz, *J* = 10.0 Hz, 1 H, H-2b), 3.97 (bd, 1 H, H-4b), 3.92 – 3.90 (m, 2 H, H-5b, H-3b), 3.82 – 3.76 (m, 3 H, 1 H-6a, H-5a, H-2a), 3.57 – 3.48 (m, 7 H, 2 H-6b, 1 H-6a, H-a, OCH₃). ¹³C NMR (126 MHz, CDCl₃) δ 138.96, 138.79, 138.78, 138.68, 138.64, 137.99 (aromatic C), 128.53, 128.50, 128.44, 128.40, 128.33, 128.31, 128.22, 128.18, 128.15, 128.09, 127.99, 127.90, 127.83, 127.71, 127.64, 127.61, 127.57, 127.49 (aromatic CH), 104.95 (C-1a), 98.41 (C-1b), 82.14 (C-3a), 79.66 (C-2a), 79.06 (C-3b), 76.41 (C-2b), 75.17 (CH₂), 74.92 (C-4b), 74.85, 74.51 (2 CH₂), 74.05 (C-4a), 73.61, 73.58 (2 CH₂), 73.10 (CH₂, C-5a), 72.87 (CH₂), 69.47 (C-5b), 68.87 (C-6b), 66.40 (C-6a), 57.40 (OCH₃).

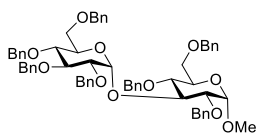


Synthesis of **20**: The reaction was carried out according to the standard procedure B, using **2** (106 mg, 0.15 mmol), **12** (46 mg, 0.1 mmol, 0.1 M in DCM), Ph₃P=O (250 mg, 0.9 mmol) and TMSI (20 μL, 0.14 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **20** (70 mg, 71 % yield, α:β = 15:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 737, 1027, 1096, 1159, 1275, 1359, 1454, 1497, 1724, 2876, 2919. [α]_D²⁰ +54.5 (c=1, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.41 – 7.12 (m, 35H, aromatic *H*), 5.00 (d, *J* = 3.6 Hz, 1H, H-1b), 4.94 (m, 2H, 2 *CHH*), 4.85 (d, *J* = 11.0 Hz, 1H, *CHH*), 4.82 – 4.77 (m, 2H, 2 *CHH*), 4.75 – 4.66 (m, 4H, 3 *CHH*, H-1a), 4.61 – 4.51 (m, 4H, 4 *CHH*), 4.42 (d, *J* = 11.8 Hz, 1H, *CHH*), 4.36 (d, *J* = 11.8 Hz, 1H, *CHH*), 4.03 (dd, *J* = 3.6 Hz, *J* = 9.5 Hz, 1H, H-2b), 3.99 – 3.88 (m, 4H, H-5b, H-4a, H-3a, H-3b), 3.82 – 3.70 (m, 3H, 2 H-6a, H-5a), 3.59 (t, *J* = 9.3 Hz, 1H, H-4b), 3.55 – 3.47 (m, 2H, 2 H-6b), 3.41 (dd, *J* = 9.6, *J* = 3.6 Hz, 1H, H-2a), 3.29 (s, 3H, OCH₃). ¹³C NMR (126 MHz, CDCl₃) δ 138.98, 138.95, 138.84, 138.81, 138.52, 138.30, 138.14 (aromatic C), 128.51, 128.48, 128.45, 128.43, 128.38, 128.36, 128.33, 128.29, 128.27, 128.24, 128.21, 128.19, 128.13, 128.05, 128.04, 127.95, 127.89, 127.84, 127.81, 127.77, 127.75, 127.73, 127.71, 127.67, 127.62, 127.60, 127.58, 127.54, 127.51, 127.44 (aromatic CH), 98.03 (C-1b), 97.97 (C-1a), 82.17 (C-3a), 80.27 (C-2a), 78.33 (C-3b), 78.08 (C-4b), 76.64 (C-2b), 75.77 (CH₂), 75.21 (C-4a), 75.08 (CH₂), 74.84 (CH₂), 73.43 (CH₂), 73.41 (CH₂), 72.90 (CH₂), 72.62 (CH₂), 70.41 (C-5a), 69.49 (C-5b), 69.03 (C-6b), 66.49 (C-6a), 55.12 (OCH₃). HR-MS: Calculated for C₆₂H₆₆O₁₁ [M+NH₄]⁺: 1004.49434, found: 1004.49307. HR-MS: Calculated for C₆₂H₆₆O₁₁ [M+NH₄]⁺: 1004.49434, found: 1004.49358.



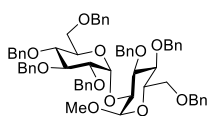
Synthesis of **21**: The reaction was carried out according to the standard procedure B, using **1** (102 mg, 0.14 mmol), **14** (45 mg, 0.1 mmol, 0.1 M in DCM), Ph₃P=O (240 mg, 0.86 mmol) and TMSI (20 μL, 0.14 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **21** (60 mg, 61 % yield, α:β > 20:1) was obtained as a

colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 1029, 1049, 1096, 1156, 1361, 1454, 1497, 2866, 2925, 3031. $[\alpha]_{\text{D}}^{20} +35.4$ ($c=1$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.35-7.08 (m, 35 H, aromatic *H*), 5.70 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.04 (d, $J = 11.6$ Hz, 1 H, *CHH*), 4.88 (d, $J = 10.8$ Hz, 1 H, *CHH*), 4.82-4.77 (m, 3 H, 3 *CHH*), 4.70 (d, $J = 12.0$ Hz, 1 H, *CHH*), 4.61-4.46 (m, 7 H, 6 *CHH*, H-1a), 4.42 (d, $J = 10.8$ Hz, 1 H, *CHH*), 4.27 (d, $J = 12.0$ Hz, 1 H, *CHH*), 4.12-4.03 (m, 2 H, H-3a, H-4a), 3.93-3.81 (m, 3 H, H-3b, H-5a, H-6), 3.72-3.58 (m, 4 H, H-2a, H-5a, H-4b, H-5b), 3.52-3.47 (m, 2H, H-2b, H-6a), 3.40-3.35 (m, 4 H, OCH_3 , H-6b). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz,) δ 139.04, 138.85, 138.57, 138.25, 138.06, 138.01 (aromatic C), 128.52, 128.41, 128.38, 128.34, 128.30, 128.12, 128.01, 127.91, 127.90, 127.79, 127.72, 127.66, 127.59, 127.45, 127.32, 127.17, 126.84 (aromatic CH), 97.85 (C-1a), 96.72 (C-1b), 82.13 (C-3b and 3a), 80.29 (C-2a), 79.54 (C-2b), 77.72 (C-4b), 75.63, 75.03, 74.51, 73.53, 73.46, 73.32, 73.22 (7 CH_2), 72.35 (C-4a), 71.04 (C-5b), 69.60 (C-5a), 69.09 (C-6a), 68.23 (C-6b), 55.23 (OCH_3). HR-MS: Calculated for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{NH}_4]^+$: 1004.49434, found: 1004.49331.



Synthesis of 22: The reaction was carried out according to the standard procedure B, using **1** (120 mg, 0.16 mmol), **15** (51 mg, 0.11 mmol, 0.1 M in DCM), $\text{Ph}_3\text{P}=\text{O}$ (263 mg, 0.94 mmol) and TMSI (24 μL , 0.16 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **22** (101 mg, 95 % yield, $\alpha:\beta > 20:1$)

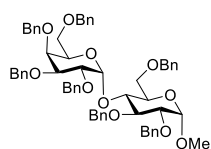
was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 1050, 1072, 1095, 1454, 1497, 2860, 2920. $[\alpha]_{\text{D}}^{20} +53.5$ ($c=1$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CCl_3) δ 7.34-6.99 (m, 35H, aromatic *H*), 5.60 (d, $J = 3.6$ Hz, 1H, H-1b), 4.96-4.79 (m, 4H, 4 *CHH*), 4.84-4.76 (m, 3H, 3 *CHH*), 4.70-4.57 (m, 6H, 5 *CHH*, H-1a), 4.52 (d, $J = 11.2$ Hz, 1H, *CHH*), 4.46-4.31 (m, 5H, 4 *CHH*, H-5b), 4.26 (t, $J = 8.4$ Hz, 1H, H-3a), 4.06 (t, $J = 9.2$ Hz, 1H, H-3b), 3.81-3.52 (m, 9H, H-2a, H-4a, H-5a, H-2b, H-3b, H-6a and 6b), 3.31 (s, 3H, OCH_3). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 138.87, 138.78, 138.42, 138.14, 138.08, 137.94, 137.92 (aromatic C), 128.84, 128.48, 128.45, 128.39, 128.35, 128.28, 128.21, 128.01, 127.98, 127.90, 127.85, 127.78, 127.75, 127.66, 127.55, 127.51, 127.31, 126.97 (aromatic CH), 97.65 (C-1a), 97.44 (C-1b), 82.37 (C-3b), 79.70, 78.82, 78.62, 78.19, 76.71 (C-3a), 75.57, 74.90, 73.59, 73.47, 73.37 (CH_2), 70.26 (C-5b), 69.54 (C-5a), 68.52 (C-6), 68.44 (C-6), 55.11 (OCH_3). HR-MS: Calculated for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{NH}_4]^+$: 1004.49434, found: 1004.49330.



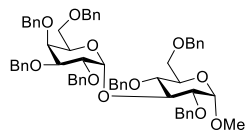
Synthesis of 23: The reaction was carried out according to the standard procedure B, using **1** (105 mg, 0.15 mmol), **16** (46 mg, 0.1 mmol, 0.1 M in DCM), $\text{Ph}_3\text{P}=\text{O}$ (250 mg, 0.9 mmol) and TMSI (21 μL , 0.15 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **23** (59 mg, 60 % yield, $\alpha:\beta > 20:1$) was obtained as a

colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 1029, 1048, 1069, 1090, 1159, 1361, 1454, 1497, 2865, 2923. $[\alpha]_{\text{D}}^{20} +60.0$ ($c=1$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39-6.98 (m, 35H), 5.00-4.90 (m, 4 H, 2 *CHH*, H-1a and 1b), 4.86-4.76 (m, 5 H, 5 *CHH*), 4.71 (d, $J = 12.0$ Hz, 1H, *CHH*), 4.60-4.42 (m, 5 H, 5 *CHH*), 4.32 (d, $J = 12.0$ Hz, 1H, *CHH*), 4.12-3.99 (m, 3 H, H-3a, H-3b, H-5), 3.85 (dd, $J_1 = 10.0$ Hz, $J_2 = 3.2$ Hz, 1H, H-2a), 3.80-3.54 (m, 6 H, H-6, H-5, H-4a, H-4b, H-2b), 3.55-3.45 (m, 5 H, H-6, OCH_3). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 138.82, 138.75, 138.50, 138.38, 138.20, 138.02, 137.97 (aromatic C), 128.57, 128.49, 128.46, 128.39, 128.38, 128.25, 128.06, 127.97, 127.94, 127.77, 127.73, 127.71, 127.69, 127.66, 127.60, 127.47 (aromatic CH), 97.40 (C-1a), 94.20 (C-1b), 82.23 (C-3b), 80.81 (C-3a), 79.06 (C-2b), 78.03 (C-4), 77.65 (C-4), 76.33, 75.77, 75.04, 74.94 (CH_2), 74.72 (C-2a), 73.58, 74.40, 72.95 (CH_2), 70.28 (C-5), 70.15 (C-5), 68.58 (C-6), 68.13 (C-6), 55.94 (OCH_3). HR-MS: Calculated for $\text{C}_{62}\text{H}_{66}\text{O}_{11}$ $[\text{M}+\text{NH}_4]^+$: 1004.49434, found:

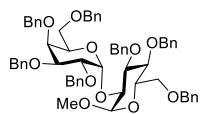
1004.49218.



Synthesis of **24:** The reaction was carried out according to the standard procedure B, using **2** (105 mg, 0.15 mmol), **14** (45 mg, 0.1 mmol, 0.1 M in DCM), Ph₃P=O (250 mg, 0.9 mmol) and TMSI (20 μL, 0.14 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **24** (78 mg, 82 % yield, α:β > 20:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 736, 1029, 1046, 1098, 1206, 1274, 1359, 1454, 1497, 1724, 2868, 2923. [α]_D²⁰ +39.5 (c=1, CHCl₃). ¹H-NMR (CDCl₃, 400 MHz) δ 7.31-7.17 (m, 35 H, aromatic H), 5.77 (d, *J* = 3.6 Hz, 1 H, H-1b), 4.98 (d, *J* = 11.6 Hz, 1 H, CHH), 4.87 (d, *J* = 11.6 Hz, 1 H, CHH), 4.81 (d, *J* = 11.6 Hz, 1 H, CHH), 4.72-4.52 (m, 9 H, 8 CHH, H-1a), 4.42 (d, *J* = 12.4 Hz, 1 H, CHH), 4.29 (d, *J* = 11.6 Hz, 1 H, CHH), 4.22 (d, *J* = 11.6 Hz, 1 H, CHH), 4.07 (t, *J* = 8.8 Hz, 1 H, H-3a), 4.01-3.93 (m, 3 H, H-4a, H-4b, H-2b), 3.88-3.80 (m, 3 H, H-5a, H-5b, H-3b), 3.72-3.63 (m, 2 H, H-6), 3.55 (dd, *J* = 3.6, 9.6 Hz, 1 H, H-2b), 3.50-3.41 (m, 2 H, H-6), 3.37 (s, 3 H, OCH₃), 3.21 (dd, *J* = 4.8, 8.0 Hz, 1 H, H-5b). ¹³C-APT (CDCl₃, 100 MHz,) δ 139.04, 138.69, 138.67, 138.43, 138.33, 138.06 (aromatic C), 128.49, 128.43, 128.40, 128.37, 128.29, 128.25, 127.98, 127.86, 127.78, 127.68, 127.59, 127.54, 127.46, 127.12, 126.81 (aromatic CH), 97.80 (C-1a), 97.53 (C-1b), 82.11 (C-3a), 80.23 (C-2a), 79.25 (C-3b), 75.69 (C-2b), 74.85 (CH₂), 74.68 (C-4b), 74.43, 73.89, 73.49, 73.45, 73.13, 72.82 (CH₂), 72.77 (C-4a), 69.93 (C-5b), 69.54 (C-5a), 69.48 (C-6), 68.74 (C-6), 55.18 (OCH₃). HR-MS: Calculated for C₆₂H₆₆O₁₁ [M+NH₄]⁺: 1004.49434, found: 1004.49345.

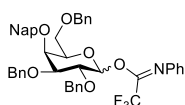


Synthesis of **25:** The reaction was carried out according to the standard procedure B, using **2** (105 mg, 0.15 mmol), **15** (45 mg, 0.1 mmol, 0.1 M in DCM), Ph₃P=O (250 mg, 0.9 mmol) and TMSI (20 μL, 0.14 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **25** (89 mg, 93 % yield, α:β = 11:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 736, 1029, 1055, 1093, 1274, 1454, 1497, 1724, 2870, 2911. [α]_D²⁰ +52.0 (c=1, CHCl₃). ¹H NMR (500 MHz, CCl₄) δ 7.34-6.98 (m, 35H, aromatic H), 5.59 (d, *J* = 3.2 Hz, 1H, H-1b), 4.96-4.89 (m, 2H, 2 CHH), 4.78-4.32 (m, 14H, 12 CHH, H-1a, H-5b), 4.25 (dd, *J* = 9.2, 8.4 Hz, 1H, H-3a), 4.07 (dd, *J* = 10.0, 3.2 Hz, 1H, H-2b), 4.01 (dd, *J* = 10.0, 2.4 Hz, 1H, H-3b), 3.96 (bs, 1H, H-4b), 3.77-3.50 (m, 7H, 2 H-6a, 2 H-6b, H-5a, H-4a, H-2a), 3.23 (s, 3H, OCH₃). ¹³C NMR (125 MHz, CDCl₃) δ 138.87, 138.78, 138.49, 138.44, 138.40, 138.35, 137.98 (aromatic C), 128.48, 128.44, 128.42, 128.35, 128.33, 128.30, 128.28, 128.25, 128.21, 128.16, 128.00, 127.98, 127.76, 127.57, 127.53, 127.43, 127.35, 127.22 (aromatic CH), 97.93 (C-1b), 97.83 (C-1a), 79.36 (C-3b), 79.16 (C-2a), 78.63 (C-4a), 76.34 (C-3a), 76.07 (C-2b), 75.24 (C-4b), 74.93, 73.88, 73.79, 73.56, 73.42, 73.19, 72.68 (CH₂), 69.56 (C-5a), 69.10 (C-5b), 68.91 (C-6), 68.54 (C-6), 55.01 (OCH₃). HR-MS: Calculated for C₆₂H₆₆O₁₁ [M+NH₄]⁺: 1004.49434, found: 1004.49324.



Synthesis of **26:** The reaction was carried out according to the standard procedure B, using **2** (105 mg, 0.15 mmol), **16** (45 mg, 0.1 mmol, 0.1 M in DCM), Ph₃P=O (250 mg, 0.9 mmol) and TMSI (20 μL, 0.14 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **26** (94 mg, 98 % yield, α:β > 20:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 737, 1027, 1047, 1095, 1274, 1362, 1454, 1497, 1724, 2920, 3032. [α]_D²⁰ +74.0 (c=1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.08 (m, 35H), 4.98 (d, *J* = 3.5 Hz, 1H, H-1b), 4.92 (d, *J* = 3.2 Hz, 1H, H-1a), 4.90 –

4.59 (m, 9H, 9 CHH), 4.51-4.40 (m, 3H, 3 CHH), 4.32 (d, $J = 11.8$ Hz, 1H, CHH), 4.27 (d, $J = 11.8$ Hz, 1H, CHH), 4.15 (t, $J = 11.8$, 1H, H-5b), 4.07-4.00 (m, 2H, H-3a, H-2b), 3.90 (dd, $J_1 = 10.0$ Hz, $J_2 = 2.8$ Hz, 1H, H-3b), 3.86 (dd, $J_1 = 10.0$ Hz, $J_2 = 3.2$ Hz, 1H, H-2a), 3.78-3.55 (m, 5H, H-5a, H-4b, H-4a, H-6), 3.49-3.35 (m, 5H, H-6, OCH₃). ¹³C NMR (100 MHz, CDCl₃) δ 138.99, 138.90, 138.88, 138.79, 138.44, 138.35, 138.09 (aromatic C), 128.55, 128.48, 128.45, 128.42, 128.37, 128.34, 128.27, 128.26, 128.03, 127.92, 127.78, 127.73, 127.66, 127.58, 127.56, 127.52, 127.44 (aromatic CH), 96.66 (C-1a), 94.86 (C-1b), 81.03 (C-3a), 78.86 (C-3b), 78.07 (C-4), 75.93 (C-2b), 75.68 (CH₂), 75.08 (C-4), 75.05 (CH₂), 74.88 (CH₂), 74.74 (C-2a), 73.63, 73.57, 73.01, 72.98, 72.95 (CH₂), 70.33 (C-5a), 69.16 (C-5b), 68.77 (C-6), 68.67 (C-6), 55.00 (OCH₃). HR-MS: Calculated for C₆₂H₆₆O₁₁ [M+Na]⁺: 1009.44973, found: 1009.44783.

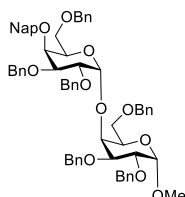


2,3,6-Tri-*O*-benzyl-4-*O*-(naphthalen-2-ylmethyl)- α/β -D-glucopyranosyl

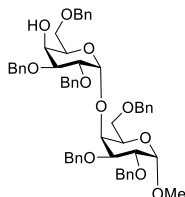
N-

phenyltrifluoroacetimidate **27**: IR (neat, cm⁻¹) ν 695, 734, 812, 909, 1027, 1097, 1152, 1208, 1319, 1454, 1497, 1598, 1717, 2870, 2921. ¹H-NMR (CDCl₃, 500 MHz, 60°C) δ 7.79-6.70 (m, aromatic H), 6.42 (bs, 1 H, H-1 α), 5.60 (bs, 1 H, H-1 β), 5.06 (bd), 4.85-4.68 (m), 4.47-4.35 (m),

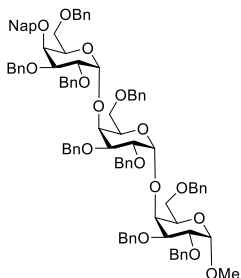
4.10-3.90 (m), 3.71-3.55 (m). ¹³C-APT (CDCl₃, 125 MHz, 60°C) δ 143.88, 138.50, 138.49, 138.17, 136.24, 133.57, 133.35 (aromatic C), 129.54, 128.79, 128.60, 128.54, 128.51, 128.27, 128.17, 128.12, 127.98, 127.92, 127.90, 127.87, 127.78, 127.75, 127.72, 126.99, 126.94, 126.54, 126.49, 126.43, 126.15, 126.10, 125.99, 124.31, 120.78, 119.81, 119.61 (aromatic CH), 97.94 (C-1), 92.23 (C-1), 82.55, 78.74, 78.58, 76.21, 75.57, 75.21, 75.17, 75.03, 74.83, 73.90, 73.71, 73.59, 73.46, 72.62, 68.83, 68.61. HR-MS: Calculated for C₄₆H₄₂F₃O₆N [M-[O(C=NPh)CF₃]+OH+Na]⁺: 613.25606, found: 613.25390.



Synthesis of **28**: The reaction was carried out according to the standard procedure B, using **27** (2066 mg, 2.7 mmol), **3** (420 mg, 0.9 mmol, 0.2 M in DCM), Ph₃P=O (2330 mg, 8.4 mmol) and TMSI (387 μ L, 2.7 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1) and silica gel column chromatography. Compound **28** (α/β = 10:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 736, 1029, 1050, 1098, 1454, 1497, 2872, 2923. HR-MS: Calculated for C₆₆H₆₈O₁₁ [M+NH₄]⁺: 1054.50999, found: 1054.50946.



Synthesis of **29**: The reaction was carried out according to the general procedure C, using crude compound **28** (0.1 M in DCM:H₂O) and DDQ (225 mg, 1.0 mmol). The product was purified by silica gel column chromatography. Compound **29** (340 mg, 42% yield over two steps) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 750, 1029, 1047, 1098, 1362, 1454, 2870, 2925. [α]_D²⁰ +55.1 (c=1, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.41-7.16 (m, 30 H, aromatic H), 5.01 (d, $J = 3.6$ Hz, 1 H, H-1b), 4.86 (d, $J = 12.0$ Hz, 1 H, CHH), 4.82-4.63 (m, 8 H, 7 CHH, H-1a), 4.35 (d, $J = 12.0$ Hz, 1 H, CHH), 4.30-4.77 (m, 1 H), 4.25-4.18 (m, 4 H), 4.06 (d, $J = 2.0$ Hz, 1 H, H-4a), 3.97 (dd, $J = 3.6$ Hz, $J = 10.0$ Hz, 1 H, H-2b), 3.93-3.81 (m, 5 H), 3.56-3.46 (m, 2 H), 3.36 (s, 3 H, OCH₃), 3.30 (dd, $J = 9.2$, $J = 4.0$ Hz, 1 H). ¹³C NMR (126 MHz, CDCl₃) δ 138.96, 138.75, 138.53, 138.42, 138.29, 137.95 (aromatic C), 128.49, 128.44, 128.41, 128.24, 128.06, 127.81, 127.78, 127.72, 127.68, 127.62, 127.53 (aromatic CH), 100.24 (C-1b), 98.69 (C-1a), 78.43 (C-3b), 77.75 (C-3a), 76.46 (C-4a), 76.13 (C-2b), 75.20 (C-2a), 74.31, 73.56, 73.25, 70.04, 72.94, 71.88 (CH₂), 69.70 (C-5a), 69.36 (C-6), 68.32 (C-5b), 68.17 (C-6), 55.40 (OCH₃). HR-MS: Calculated for C₅₅H₆₀O₁₁ [M+NH₄]⁺: 914.44739, found: 914.44635.



Synthesis of **30**: The reaction was carried out according to the standard procedure B, using **27** (130 mg, 0.17 mmol), **29** (50 mg, 0.06 mmol, 0.1 M in DCM), Ph₃P=O (140 mg, 0.5 mmol) and TMSI (25 μ L, 0.17 mmol). The product was purified by size exclusion chromatography (DCM:MeOH = 1:1). Compound **30** (52 mg, 64 % yield, α : β = 8:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 736, 1029, 1047, 1096, 1206, 1331, 1359, 1454, 1497, 1724, 2860, 2923. ¹H NMR (500 MHz, CDCl₃) δ 7.78-7.63 (m, 4 H, aromatic H), 7.45-7.05 (m, 48 H, aromatic H), 5.09 (d, J = 3.6 Hz, 1H, H-1), 5.05-4.97 (m, 2 H, CHH, H-1), 4.94-4.67 (m, 11 H, 10 CHH, H-1a), 4.56 (d, J = 12.8 Hz, 1H, 1 CHH), 4.47-4.41 (m, 2 H, 1 CHH, H-5), 4.35-4.28 (m, 3 H, 2 CHH, H-5), 4.25-3.77 (m, 17 H), 3.57-3.49 (m, 2 H), 3.35 (s, 3 H, OCH₃), 3.13-3.04 (m, 2 H). ¹³C NMR (126 MHz, CDCl₃) δ 139.09, 138.97, 138.92, 138.83, 138.76, 138.52, 138.47, 138.36, 138.22, 136.58, 133.32, 133.00 (aromatic C), 128.50, 128.42, 128.40, 128.39, 128.32, 128.28, 128.23, 128.18, 128.15, 127.99, 127.89, 127.76, 127.72, 127.68, 127.57, 127.54, 127.50, 127.47, 127.41, 127.32, 127.27, 127.20, 126.63, 126.45, 125.90, 125.71 (aromatic CH), 100.35 (2 C-1), 98.83 (C-1a), 79.66 (C-3), 78.98 (C-3), 77.97 (C-3), 76.51, 76.21, 75.34, 75.16, 75.04, 74.58, 74.25, 73.89, 73.40, 73.15, 73.08, 72.70, 72.62, 72.34, 72.24, 69.59, 69.20, 68.18, 67.67, 66.81, 55.41 (OCH₃). HR-MS: Calculated for C₉₃H₉₆O₁₆ [M+NH₄]⁺: 1486.70366, found: 1486.70388.

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Chapter 6

Reagent Controlled Glycosylations for the Assembly of Well-defined Pel Oligosaccharides

Introduction

Pel is one of the exopolysaccharides that forms the biofilm surrounding *Pseudomonas aeruginosa*, an opportunistic Gram-positive pathogen that is the major cause of morbidity and mortality in Cystic Fibrosis patients.^[1] Pel is a linear polysaccharide composed of 1,4-linked α -N-acetyl galactosamine (GalNAc) and α -N-acetyl glucosamine (GlcNAc) residues, present in a $\pm 6 : 1$ ratio, of which some of the residues have been de-acetylated to generate positively charged galactosamine (GalN) and glucosamine (GlcN) moieties (Figure 1).^[1b] Well-defined Pel fragments can be used to unravel their role in biofilm formation, to study their biosynthesis and possibly as synthetic antigens in the development of a (semi)-synthetic vaccine against *P. aeruginosa*. Because of the random distribution of the monosaccharides in Pel, it is impossible to

isolate well-defined oligosaccharides from natural sources and therefore organic synthesis is necessary to provide these structures.

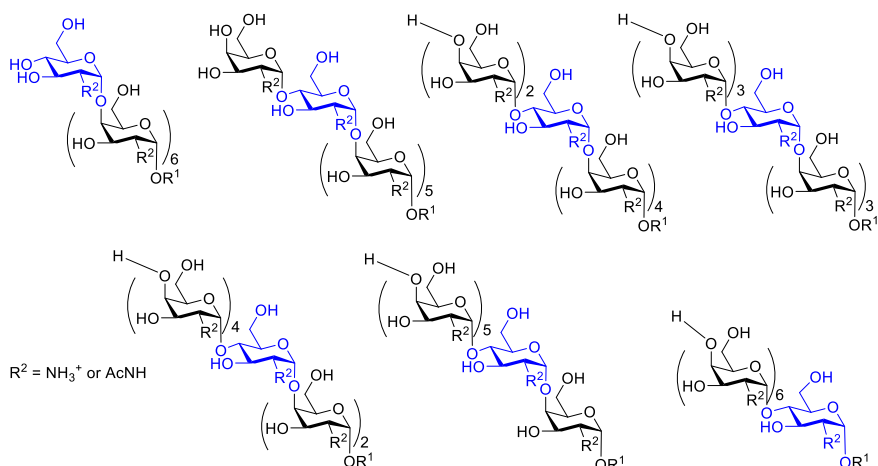
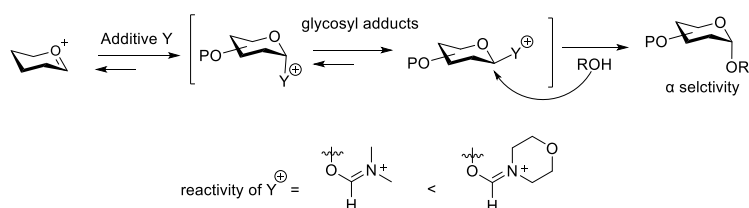


Figure 1. The repeating structures of Pel.

To assemble Pel-fragments (Figure 1), four kinds of α -bonds, α -D-GlcN-(1 $\rightarrow$ 4)-D-GlcN, α -D-GlcN-(1 $\rightarrow$ 4)-D-GalN, α -D-GalN-(1 $\rightarrow$ 4)-D-GlcN and α -D-GalN-(1 $\rightarrow$ 4)-D-GalN, have to be constructed. Zhang *et al.* have recently reported an effective synthetic strategy to assembly galactosaminogalactans (GAGs), fungal polysaccharides composed of 1,4-linked α -D-Gal, α -D-GalN and α -D-GalNAc moieties.^[2] For the formation of the 1,2-*cis*-linkage, 4,6-di-*tert*-butylsilylene (4,6-*O*-DTBS) protected GalN-donors were used to control the selectivity.^[3] This strategy allowed the use of galactosamine donors bearing differently masked amine functionalities. Galactosazide and trichloroacetyl protected GalN donors were used to combine GalN and GalNAc at pre-determined sites in the target GAG oligosaccharides. Of note, the stereodirecting capacity of the DTBS group in GalN donors effectively overrides the neighboring group participation by C2-participating functionalities such as the trichloroacetamide. Thus, DTBS-GalN donors also represent attractive building blocks for Pel-assembly. For the stereoselective introduction of α -D-GlcN linkages no general solution exists, even though the construction of this type of glycosidic linkage has attracted significant attention,^[4] as it presents in many important natural polysaccharides and glycoconjugates, such as heparin, heparan sulfate,^[5] GPI anchors and various bacterial polysaccharides.^[6] Additive controlled glycosylations have been introduced for the stereoselective construction of glycosidic linkages.^[7] In these approaches the nature of the additive determines the reactivity of *in situ* formed glycosylating species and the reactivity of the additive can be tuned to match the reactivity of the glycosyl donor^[8] and acceptor^[9] building blocks. Chapter 2 and 3 of this Thesis have reported the fully stereoselective assembly of a branched α -glucan from *Mycobacterium tuberculosis* and α -

(1,3)-glucans from fungi cell wall.^[10] The synthetic strategy to the oligosaccharides is built on the use of additive controlled glycosylation reactions and the use of one single benzyl type protecting group (Bn, PMB, Nap). For glycosylations with relatively reactive primary alcohol acceptors, the trimethylsilyliodide (TMSI)-triphenylphosphine oxide ($\text{Ph}_3\text{P}=\text{O}$) activator couple was used, while the condensations with the less reactive secondary alcohols required the use of the trifluoromethanesulfonic acid (TfOH)-dimethylformamide (DMF) pair. The successful construction of multiple 1,4- α -glucosidic linkages was an incentive to explore this strategy for the assembly of the Pel oligosaccharides. Mong and co-workers have previously described how formamide additives can be used for the construction of 1,2-*cis*-GalN₃ and GlcN₃ linkages. They introduced *N*-formyl-morpholine (NFM) to modulate the reactivity of tri-*O*-benzyl GlcN₃ and 4,6-benzylidene-GalN₃ donors and showed that the glycosylations mediated by NFM proceeded with higher stereoselectivity than the corresponding DMF-modulated condensations.^[72n] Because of the stronger electron withdrawing effect of the azide group with respect to a benzyl ether, 2-azido donors are generally less reactive than their 2-*O*-benzyl counterparts. This lower reactivity can be counterbalanced by the use of a somewhat more reactive additive, explaining why NFM outperforms DMF in these glycosylations (See Scheme 1).



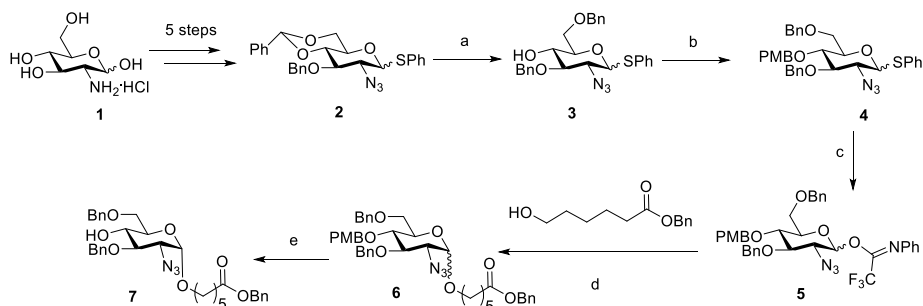
Scheme 1. The relative reactivity of DMF and NFM intermediates.

This Chapter describes a strategy to synthesize Pel oligosaccharides using additive-controlled glycosylations to match the reactivities of the GlcN₃-donor and the Pel acceptors. Because of the relatively low nucleophilicity of the GlcN₃-C4-OH and especially the GalN₃-C4-OH, a new additive is introduced that generates intermediates that are more reactive than the previously introduced DMF and NFM-imidinium ions.

Results and discussion

First, attention was paid to the formation of α -D-GlcN-(1→4)-D-GlcN linkages. In line with previous work, solely benzyl type protecting group (PMB, Nap, Bn) were used to generate orthogonally protected building blocks of uniform reactivity. The synthesis of D-GlcN building blocks is depicted in Scheme 2 and started from D-glucosamine **1**. Using the diazo transfer reagent imidazole-1-sulfonyl azide hydrogen sulfate,^[11] glucosazide was generated, which was acetylated and functionalized with an anomeric thiophenol group. Remove of the acetyl groups, introduction of a benzylidene acetal at C-4-*O* and C-6-*O* and benzylation of the remaining C-3-OH, delivered

the fully protected GlcN₃. Regioselective opening of the benzylidene acetal and masking of the liberated C4-OH as a PMB-ether provided compound **4**. The anomeric thio acetal in this building block was hydrolyzed using *N*-iodosuccinimide in acetone/water to liberate the anomeric hydroxyl group, which was then turned into the required *N*-phenyltrifluoroimidate donor **5**. To obtain the first acceptor, synthon **5** was coupled with benzyl 6-hydroxyhexanoate using the TMSI-Ph₃P=O conditions to provide compound **6** in 75% yield and a 5:1 α : β ratio. Deprotection of the PMB-masked C4-alcohol using a catalytic amount of HCl in hexafluoroisopropanol (HFIP) produced acceptor **7**.^[12] After purification by silica gel chromatography the desired α -product was obtained as a single anomer.



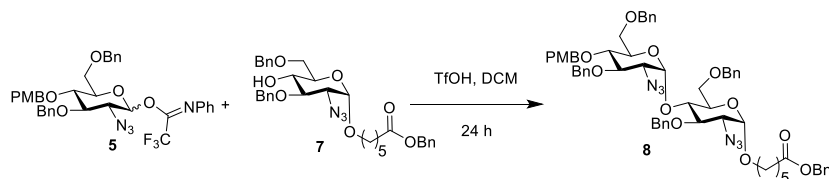
(a) BF₃·Et₂O, TES, DCM, **3**: 80%; (b) PMBCl, NaH, DMF, **4**: 95%; (c) 1) NIS, acetone, H₂O, 2) 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride, Cs₂CO₃, acetone, **5**: 83% with two steps; d) TMSI, Ph₃P=O, DCM, rt, **6**: 75%, α : β = 5:1; (e) 0.2 M HCl/HFIP, TES, HFIP, DCM, **7**: 60%.

Scheme 2. Synthesis of donor **5** and acceptor **7**.

With donor **5** and acceptor **7** in hand, DMF was investigated as an additive to control the selectivity according to previous successful experiments. Thus, donor α -D-GlcN **5**, acceptor **7** and the additive were mixed in DCM with molecular sieves and cooled to -78°C. Next, TfOH was added and after stirring for 0.5h, the mixture was placed at 0 °C and allowed to stir for 24h. As shown in Table 1, this produced the desired disaccharide product **8** with complete α -selectivity, but the yield was only 32% (entry 1). Performing the reaction at room temperature did not lead to erosion of stereoselectivity but only marginally improved the yield (entry 2). Likely, the low reactivity of the azido-donor and -acceptor led to the observed poor yields and therefore NFM was probed as an additive.^[6c] Use of this additive provided complete α -selectivity, and raised the yield of the condensation to 55% yield. To further improve the reaction, a more reactive additive was sought and *N*-methyl-*N*-phenylformamide (MPF) was explored. It was expected that the imidinium ion formed from this additive would be more reactive because the aniline-type nitrogen would be less capable of supporting the (partial) positive charge in the ion. The reaction of donor **5** and acceptor **7** proceeded with excellent yield (91%) when performed at 0°C, and the disaccharide **8** was obtained with 15:1 α : β -selectivity (entry 4). Although the stereoselectivity of

this condensation is somewhat less than the DMF or NFM mediated glyosylations, the improved yield allows for an overall more productive reaction.^[13]

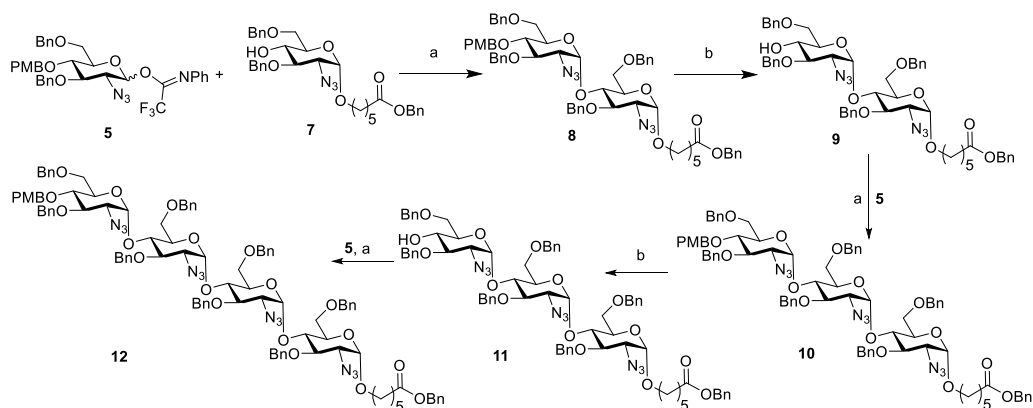
Table 1. Glycosylation between donor **5** and acceptor **7** under various additives.



entry	c(mmol/ml)	additive	T(°C)	product	yield ^a	$\alpha:\beta^b$
1	0.1	DMF	0	8	32%	>20:1
2	0.1	DMF	rt	8	38%	>20:1
3	0.1	NFM	rt	8	55%	>20:1
4	0.1	MPF	0	8	91%	~15:1

^a Isolated yield. ^b The $\alpha:\beta$ ratio was determined by ¹H NMR.

To probe the robustness of the MPF-mediated protocol in the synthesis of oligosaccharides, the assembly of an all-1,2-*cis* linked tetrasaccharide was explored as depicted in Scheme 3. Thus, donor **5** and acceptor **7** were coupled under the above identified reaction conditions to provide the desired disaccharide **8**. The PMB was removed using a catalytic amount of HCl to give disaccharide acceptor **9** in 88% yield. Next, compound **9** was glycosylated with donor **5** under the MPF-conditions to form the desired trisaccharide **10** in 83% yield and excellent stereoselectivity ($\alpha:\beta > 19:1$). Repetition of the deprotection and glycosylation reactions then uneventfully provided tetrasaccharide **12**. The successful assembly of this tetrasaccharide indicates that the yield and stereoselectivity don't decrease with the growing of the sugar chain.



(a) MPF, TfOH, DCM, -78-0°C, **8**: 91%, $\alpha:\beta = 15:1$; **10**: 83%, $\alpha:\beta > 19:1$; **12**: 90%, $\alpha:\beta > 20:1$. (b) 0.2 M HCl/HFIP, TES, HFIP/DCM, **9**: 88%; **11** 78%.

Scheme 3. Assembly of an α -glucosazide tetrasaccharide using MPF mediated glycosylations.

Next, attention was turned to the formation of the α -GlcN-(1 $\rightarrow$ 4)-GalN-linkage exploring the additives as described above. First donor **13** was coupled with acceptor **16** using DMF to provide product **20** in low yield and poor selectivity (Table 2, entry 1). The use of NFM instead of DMF did not improve the outcome of this glycosylation (entry 2). Likely the poor reactivity of the sterically encumbered GalN₃-C4-OH hampers the union of the two carbohydrate building blocks.

Table 2. Glycosylation between 2-azido Glu/Gal donors and 4-OH-2-azido Glu/Gal acceptors.

donors:

products:

acceptors:

donor + acceptor

$\xrightarrow[\text{DCM, 24h}]{\text{TfOH, additives}}$

product

entry	donor	acceptor	c(mmol/ml)	additive	T(°C)	product	yield ^a	α : β ^b
1	13	16	0.1	DMF	0	20	23%	6:1
2	13	16	0.1	NFM	0	20	24%	6:1
3	13	16	0.1	MPF	0	20	83%	5:1
4	13	16	0.1	MPF	-10	20	43%	10:1
5	13	16	0.2	MPF	-10	20	88%	10:1
6	14	17	0.1	MPF	-10	21	88%	8:1
7	14	18	0.1	MPF	-10	22	80%	4:1
8 ^c	15	19	0.1	-	0	23	70%	1:0

^a Isolated yield. ^b The α : β ratio was determined by ¹H NMR. ^c The reaction stirred 3 h.

Next, the use of MPF was explored. At 0°C, disaccharide **20** was obtained in high yield (83%), but with moderate α : β -selectivity (5:1). Performing the same reaction at -10°C increased the α -selectivity (α : β = 10 : 1), but led to a relatively low yield (43%, entry 4). To increase the yield of the reaction, the concentration was raised from 0.1 M to 0.2 M (entry 5). This led to the formation of the desired compound **20** with a yield of 88% and a 10:1 α : β ratio. Having defined adequate conditions for the construction of α -GlcN-(1 $\rightarrow$ 4)-GlcN and α -GlcN-(1 $\rightarrow$ 4)-GalN linkages, the use of MPF in combination with galactosazide donor **14** was explored for the construction of the target α -GalN-(1 $\rightarrow$ 4)-GlcN and α -GalN-(1 $\rightarrow$ 4)-GalN linkages. Under the conditions established above, donor **14** was coupled with glucosyl acceptor **17** to give the disaccharide **21** in excellent yield and 8:1 α / β -stereo selectivity (Table 2, entry 6). Contrary disaccharide **22**, formed from donor **14** and galactosyl acceptor **18**, was obtained in poor yield and poor selectivity (α : β = 4:1, entry 7). Because 4,6-*O*-DTBS protected galactosamine donors have been shown to reliably provide 1,2-*cis*-linkages, attention was next turned to this donor type. Thus, DTBS-donor **15** was glycosylated with acceptor **19** at 0 °C to give the desired disaccharide **23** with completely α -selectivity (entry 8).

With conditions in hand to construct all Pel-*cis* linkages the synthesis of Pel hexasaccharides **24** and **25** was undertaken. A [2+2+2] strategy was designed to streamline the assembly of the structures, building on MFP-mediated glycosylations of the GalN₃-GlcN₃ donor **26** (Figure 2). The procedure for the synthesis of the required building blocks **26** and **27** is depicted in Scheme 4 A and B. First donor **15** was coupled with glucoazide **19** to form disaccharide **23** as a single anomer. Next, the silylidene ketal was cleaved with HF-pyridine, after which a benzyl ether was regioselectively introduced under the aegis of Taylor's borinic acid catalyst.^[14] Protection of the remaining C4'-OH with a naphthyl group delivered compound **30**. Next the anomeric thiophenol group was removed using *N*-iodosuccinimide in acetone/water, and the resulting hydroxyl group turned into the desired *N*-phenyltrifluoroimidate functionality to provide donor **26**. Acceptor **27** was obtained from donor **15** and acceptor **7**. These two building blocks were united to stereoselectively provide disaccharide **32**. Removal of the silylidene ketal and introduction of the C6'-*O*-benzyl ether as described above provided **27**.

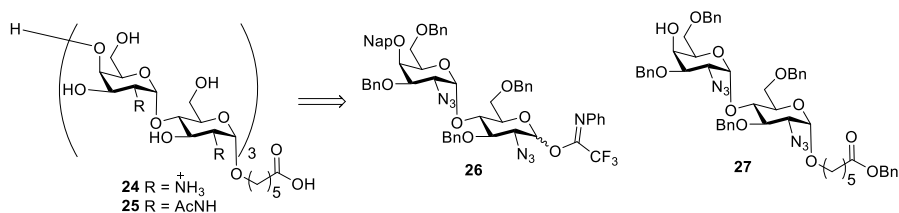
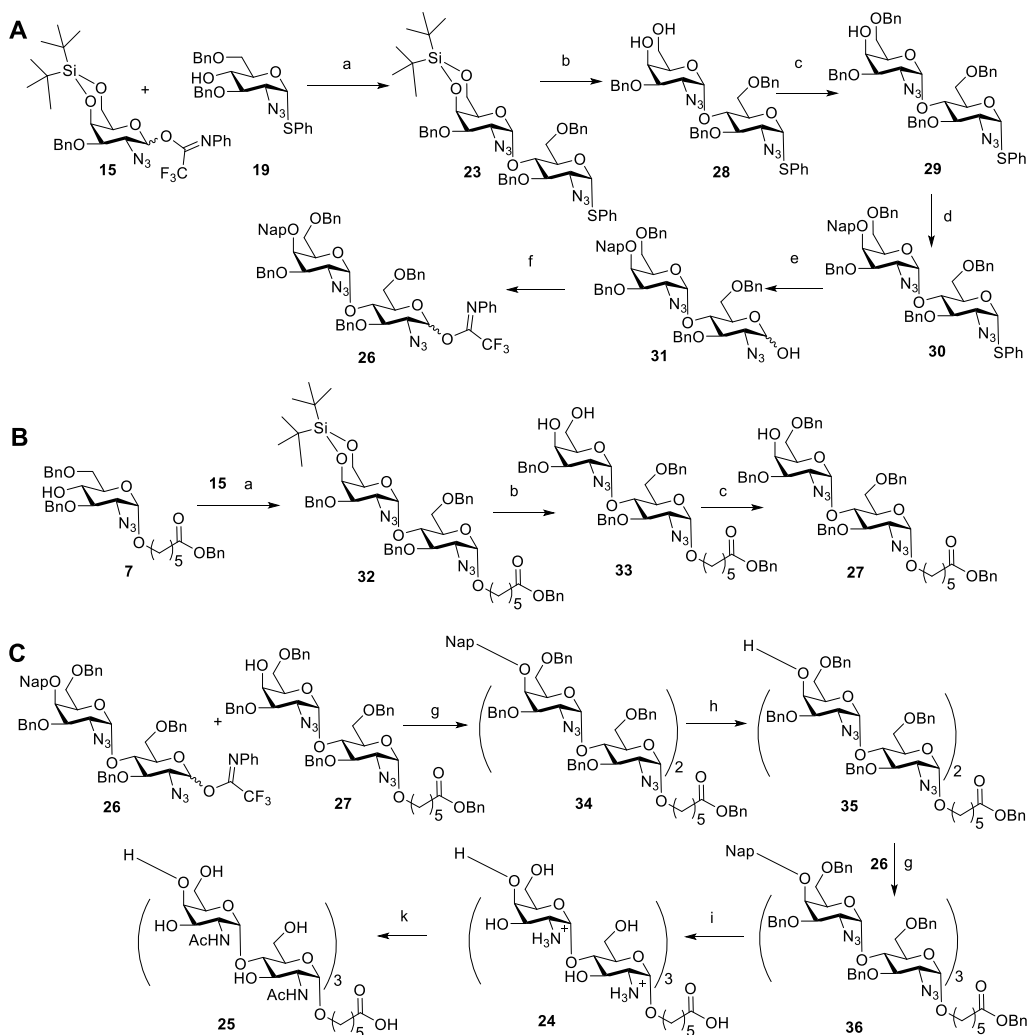


Figure 2. Retrosynthesis of the target Pel hexasaccharides **24** and **25**.

With building blocks **26** and **27**, the assembly of the target hexasaccharides **24** and **25** was started (Scheme 4C). First, donor **26** was glycosylated with acceptor **27** using MPF as additive at $-10\text{ }^{\circ}\text{C}$ at a 0.2 M concentration to form tetrasaccharide **34** in 89% yield as a 10:1 α/β -mixture.



(a) TfOH, DCM, **23**: 70%; **32**: 92%. (b) HF-pyridine, THF, **28**: 98%, **33**: 91%. (c) BnBr, borinic acid-catalyzed, K_2CO_3 , KI, CH_3CN , $60\text{ }^{\circ}\text{C}$, **29**: 96%; **27**: 95%. (d) NapBr, NaH, DMF, **30**: 93%. (e) NIS, acetone, H_2O . (f) 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride, Cs_2CO_3 , acetone, **26**: 83% over two steps. (g) MPF, TfOH, DCM, $-10\text{ }^{\circ}\text{C}$, 48 h, **34**: 89%, $\alpha/\beta = 10:1$; **36**: 91%, $\alpha/\beta = 10:1$. (h) 0.2 M HCl/HFIP, TES, HFIP/DCM, **35**: 73%. (i) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, CH_3COOH , THF/ H_2O /*t*-BuOH, **24**: 76%. (k) Ac_2O , NaHCO_3 , H_2O , **25**: 86%.

Scheme 4. A: Synthesis of donor **26**. B: synthesis of acceptor **27**. C: Assembly of Pel fragment.

Then the Nap ether was removed using HCl and triethylsilane in DCM/HFIP to give the tetrasaccharide acceptor **35**. Compound **35** was treated with donor **26** under the optimal MPF-

mediated glycosylation conditions to deliver hexasaccharide **36**. Reduction of the six azides and removal of the benzyl ester and ethers were accomplished in a one-step reduction to give the compound **24**, of which the amino groups were acetylated with acetic anhydride to afford the final compound **25**.

Conclusion

In conclusion, an effective procedure to assemble Pel fragments containing 1,4-linked GalNAc and GlcNAc residues, was developed. A [2+2+2] strategy was developed for the assembly of a Pel-hexasaccharide in which the α -GlcN linkages were constructed in glycosylation reactions using MPF as an additive. MPF was reported for the first time as a moderator to introduce α -GlcN₃ linkages. The required disaccharide synthons were synthesized using a 4,6-*O*-DTBS protected galactosazide donor. To probe the ability of MPF in the synthesis of oligosaccharides, a linear glucosazide tetrasaccharide has also been assembled, through highly stereoselective glycosylation reactions, using building blocks, solely equipped with benzyl type (Bn and PMB) hydroxyl protecting groups. The successful synthesis reported in this Chapter show that MPF is a valuable addition to the “additive toolbox”, which can be used to match the reactivity of donor and acceptor building blocks to attain stereoselective glycosylation reactions.

Experimental Section

General experimental procedures

All reagents were of commercial grade and used as received. All moisture sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of (NH₄)₆Mo₇O₂₄·4H₂O (25 g/L) and (NH₄)₄Ce(SO₄)₄·2H₂O (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20. ¹H and ¹³C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in CDCl₃ or D₂O. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard (¹H NMR in CDCl₃) or the residual signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. All ¹³C spectra are proton decoupled. NMR peak assignments were made using COSY and HSQC experiments, where applicable Clean TOCSY, HMBC and GATED experiments were used to further elucidate the structure. The anomeric product ratios were analyzed through integration of proton NMR signals.

Standard procedure

Procedure A for the glycosylation of secondary alcohols:

A mixture of donor (1.0 eq), acceptor (0.7 eq) (donors and acceptors co-evaporated with toluene three times), MPF (16 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 °C, after which TfOH (1.0 eq) was added. After 30 min, the reaction was stirred at 0 or -10 °C until TLC-analysis

showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Procedure B for the glycosylation of primary alcohols:

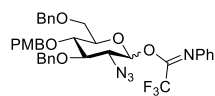
A mixture of donor (1.0 eq), acceptor (0.7 eq) (donors and acceptors co-evaporated with toluene three times), Ph₃P=O (6 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. Then TMSI (1.0 eq) was added slowly in the mixture. The reaction was stirred at room temperature until TLC-analysis indicated the reaction to be complete. The solution was diluted and the reaction quenched with saturated Na₂S₂O₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Procedure C for deprotection of the PMB and Nap protecting group:

The starting material (1 eq) was dissolved in DCM:HFIP (1:1, 0.1 M). TES (2.0 eq) and 0.2M HCl/HFIP (0.1-1eq) were added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material (15min-2h). Then the mixture was diluted with DCM and the reaction quenched with saturated NaHCO₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography.

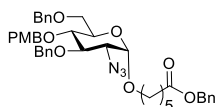
Experimental Procedures and Characterization Data of Products

For the synthesis procedure and data of known compounds **2**, **3**, **4** see references.^[15]

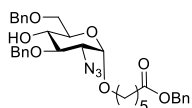


N-phenyl trifluoroacetimidate 2-*N*₃-glucose donor **5**: Compound **4** (9.1 g, 15.2 mmol) was dissolved in acetone:H₂O (10:1, 150 mL). *N*-Iodosuccinimide (NIS) (6.9 g, 30.5 mmol) was added in one portion and the reaction was stirred at room temperature for 2 hours. The solution

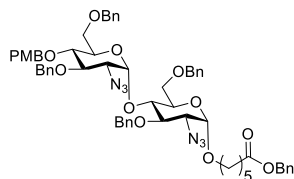
was diluted with DCM and the reaction was quenched with saturated aqueous Na₂S₂O₃. Then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*, and the product purified by column chromatography (pentane : ethyl acetate (EA) = 3:1). The lactol (7.2 g, 14.3 mmol) was obtained as colourless syrup. Next, the lactol was dissolved in acetone (150 mL). Cs₂CO₃ (7.0 g, 21.3 mmol) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (3.4 mL, 21.3 mmol) were added to the solution respectively. The reaction was stirred overnight, then quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by column chromatography (pentane:EA = 40:1-20:1). Compound **5** (8.5 g, 83% over two steps, pentane:EA = 10:1, R_f = 0.45-0.55) was obtained as yellow syrup. IR (neat, cm⁻¹) ν 697, 737, 1029, 1082, 1119, 1210, 1251, 1312, 1514, 1720, 2112 (N₃), 2872, 2912. ¹H-NMR (CDCl₃, 500 MHz, 60°C) δ 7.38-7.20 (m, aromatic *H*), 7.11-7.06 (m, aromatic *H*), 6.82-6.78 (m, aromatic *H*), 6.37 (bs, 1 H), 5.41 (bs, 1 H), 4.92-4.80 (m), 4.74-4.69 (m), 4.60-4.48 (m), 3.96 (t, *J* = 10.0 Hz, 1 H), 3.90 (bd, 1 H), 3.77-3.58 (m), 3.43 (t), 3.33 (bs, 1 H). ¹³C-APT (CDCl₃, 125 MHz, 60°C) δ 159.81, 159.77, 143.61, 143.49, 138.26, 138.20, 138.11, 130.31 (aromatic C), 129.66, 128.91, 128.60, 128.57, 128.54, 128.09, 128.03, 127.96, 127.94, 127.89, 127.84, 124.65, 124.57, 119.57, 114.22, 114.18 (aromatic CH), 96.23 (C-1), 94.35 (C-1), 83.29, 80.49, 77.70, 77.30, 76.36, 75.68, 75.03, 74.84, 73.92, 73.80, 73.71, 68.46, 65.81, 63.45, 55.43. Calculated for C₃₆H₃₅F₃O₆N₄ [M-[O(C=NPh)CF₃]+OH+Na]⁺: 582.21051, found: 582.20943.



Synthesis of monosaccharide **6**: The reaction was carried out according to the standard procedure B. A mixture of donor **5** (1.0 g, 1.5 mmol), benzyl 6-hydroxyhexanoate (520 mg) (donors and acceptors co-evaporated with toluene three times), $\text{Ph}_3\text{P}=\text{O}$ (2.6 g, 9.3 mmol) in dry DCM (15 mL) were stirred over fresh flame-dried molecular sieves 3A under nitrogen. Then TMSI (222 μL , 1.5 mmol) was added slowly in the mixture. The reaction was stirred at room temperature until TLC-analysis indicated the reaction to be complete. The solution was diluted and the reaction quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$. The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The products were purified by silica gel column chromatography. Compound **6** (800 mg, 75% yield, $\alpha:\beta = 5:1$, PE:EA = 8:1, $R_f = 0.63$) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 1002, 1029, 1037, 1075, 1150, 1248, 1358, 1454, 1611, 1733 ($\text{C}=\text{O}$), 2105 (N_3), 2866, 2933. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.40-7.21 (m, 15 H, aromatic *H*), 7.00 (bd, 2 H, aromatic *H*), 6.79 (bd, 2 H, aromatic *H*), 5.09 (s, 2 H, PhCH_2), 4.90 (d, $J = 3.6$ Hz, 1 H, H-1a), 4.88 (s, 2 H, PhCH_2), 4.71 (d, $J = 10.4$ Hz, 1 H, CHH), 4.63 (d, $J = 12.4$ Hz, 1 H, CHH), 4.49 (d, $J = 12.4$ Hz, 1 H, CHH), 4.43 (d, $J = 10.4$ Hz, 1 H, CHH), 3.975 (t, t, $J = 9.6$ Hz, 1 H, H-3a), 3.79-3.63 (m, 5 H, H-2a, H-4a, H-5a, H-6a, H-1 $^\circ$), 3.47-3.37 (m, 1 H, H-1 $^\circ$), 3.33 (dd, 1 H, $J_1 = 10.0$ Hz, $J_2 = 2.0$ Hz, H-2a), 2.36 (t, $J = 7.6$ Hz, 2H, H-5 $^\circ$), 1.70-1.58 (m, 4 H, H-2 $^\circ$, H-4 $^\circ$), 1.43-1.36 (m, 2 H, H-3 $^\circ$). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 173.43 ($\text{C}=\text{O}$), 159.36, 138.09, 137.88, 130.08 (aromatic C), 129.61, 128.57, 128.50, 128.45, 128.20, 127.99, 127.96, 127.85, 127.79, 113.87 (aromatic CH), 97.91 (C-1a), 80.22 (C-3a), 78.03 (C-4a), 75.32, 74.79, 73.55 (CH_2), 70.73 (C-5a), 68.30 (C-6a), 68.04 (C-1 $^\circ$), 66.13 (PhCH_2), 63.37 (C-2a), 55.28 (OCH_3), 34.161 (C-5 $^\circ$), 29.11 (C-2 $^\circ$), 25.70 (C-3 $^\circ$), 24.68 (C-4 $^\circ$). HR-MS: Calculated for $\text{C}_{41}\text{H}_{47}\text{N}_3\text{O}_8$ $[\text{M}+\text{NH}_4]^+$: 727.37014, found: 727.37015.

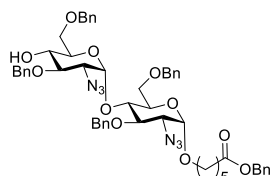


Synthesis of monosaccharide acceptor **7**: The reaction was carried out according to the standard procedure C. The starting material **6** (700 mg, 0.99 m mol) was dissolved in DCM:HFIP (1:1, 0.1 M). TES (314 mL) and 0.2M HCl/HFIP (0.5 mL) were added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material (15min). Then the mixture was diluted with DCM and the reaction quenched with saturated NaHCO_3 . The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **7** (350 mg, 60% yield, PE:EA = 4:1, $R_f = 0.34$) was obtained as a colorless syrup. $[\alpha]_D^{20} +59.3$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 737, 1050, 1147, 1455, 1734 ($\text{C}=\text{O}$), 2105 (N_3), 2866, 2926, 3478. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.41-7.23 (m, 15 H, aromatic *H*), 5.10 (s, 2 H, PhCH_2), 4.90 (d, $J = 11.2$ Hz, 1 H, CHH), 4.87 (d, $J = 3.6$ Hz, 1 H, H-1a), 4.81 (d, $J = 11.2$ Hz, 1 H, CHH), 4.59 (d, $J = 12.0$ Hz, 1 H, CHH), 4.53 (d, $J = 12.0$ Hz, 1 H, CHH), 3.86-3.64 (m, 6 H, H-2a, H-3a, H-4a, H-5a, H-6a, H-1 $^\circ$ a), 3.47-3.41 (m, 1 H, H-1 $^\circ$ b), 3.25 (dd, 1 H, $J_1 = 10.0$ Hz, $J_2 = 2.0$ Hz, H-2a), 2.37 (t, $J = 7.6$ Hz, 2H, H-5 $^\circ$), 1.72-1.61 (m, 4 H, H-2 $^\circ$, H-4 $^\circ$), 1.47-1.37 (m, 2 H, H-3 $^\circ$). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 173.59 ($\text{C}=\text{O}$), 138.24, 137.86, 136.09 (aromatic C), 128.66, 128.63, 128.51, 128.27, 128.25, 128.14, 128.05, 127.85, 127.73, 127.46 (aromatic CH), 98.00 (C-1a), 79.81 (C-3a), 75.04 (C-6a), 73.72 (CH_2), 72.24 (c-4a), 70.24 (c-5a), 69.76 (PhCH_2), 68.07 (C-1 $^\circ$), 66.23 (PhCH_2), 62.80 (C-2a), 34.21 (C-5 $^\circ$), 29.07 (C-2 $^\circ$), 25.74 (C-3 $^\circ$), 24.68 (C-4 $^\circ$). HR-MS: Calculated for $\text{C}_{33}\text{H}_{39}\text{O}_7\text{N}_3$ $[\text{M}+\text{NH}_4]^+$: 607.31263, found: 607.31238.



Synthesis of disaccharide **8**: The reaction was carried out according to the standard procedure A. A mixture of donor **5** (320 mg, 0.47 mmol), acceptor **7** (185 mg, 0.31 mmol) (donors and acceptors co-evaporated with toluene three times), MPF (610 μ L) in dry DCM (3 mL) were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 $^{\circ}$ C, after which TfOH (42 μ L) was added.

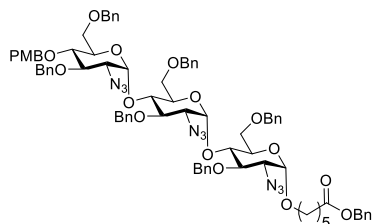
After 30 min, the reaction was stirred at -10 $^{\circ}$ C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **8** (304 mg, 91% yield, α : β = 15:1, PE:EA = 4:1, R_f = 0.51) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 736, 1027, 1147, 1249, 1358, 1454, 1514, 1734 (C=O), 2103 (N₃), 2866, 2928. ¹H-NMR (CDCl₃, 400 MHz) δ 7.39-7.21 (m, 25 H, aromatic *H*), 7.00 (bd, 2 H, aromatic *H*), 6.79 (bd, 2 H, aromatic *H*), 5.66 (d, *J* = 4.0 Hz, 1 H, H-1b), 5.11 (s, 2 H, PhCH₂), 4.98(d, *J* = 10.4 Hz, 1 H, CHH), 4.93 (d, *J* = 4.0 Hz, 1 H, H-1a), 4.89-4.82 (m, 3 H, 3 CHH), 4.66 (d, *J* = 10.0 Hz, 1 H, CHH), 4.54-4.47 (m, 3 H, 3 CHH), 4.37 (d, *J* = 10.4 Hz, 1 H, CHH), 4.23 (d, *J* = 10.4 Hz, 1 H, CHH), 4.07 (t, *J* = 9.2 Hz, 1 H, H-3a), 3.98 (t, *J* = 9.2 Hz, 1 H, H-4a), 3.87-3.61 (m, 10 H, H-3b, H-4b, H-5a, H-5b, H-6a, H-6b, OCH₃), 3.54-3.44 (m, 2 H, H-6b, H-1^a), 3.35-3.29 (m, 3 H, H-2a, H-2b, H-1^b), 2.38 (t, *J* = 7.6 Hz, 2H, H-5^o), 1.73-1.63 (m, 4 H, H-2^o, H-4^o), 1.46-1.38 (m, 2 H, H-3^o). ¹³C-APT (CDCl₃, 100 MHz) δ 173.53 (C=O), 159.39, 138.22, 138.03, 137.84, 137.82, 136.17, 130.24 (aromatic C), 129.66, 128.65, 128.46, 128.42, 128.23, 128.13, 128.00, 127.94, 127.84, 127.78, 127.64, 127.40, 113.85 (aromatic CH), 97.78 (C-1b), 97.73 (C-1a), 80.88 (C-3a), 80.33 (C-3b), 77.82 (C-4b), 75.45, 74.73, 74.47, 73.61, 73.50 (PhCH₂), 73.37 (c-4a), 71.60 (c-5b), 70.18 (C-5a), 69.09 (C-6a), 68.23 (C-6b), 67.89 (C-1^o), 66.23 (PhCH₂), 63.80 (C-2), 63.42 (C-2), 55.37 (OCH₃), 34.24 (C-5^o), 29.15 (C-2^o), 25.75 (C-3^o), 24.76 (C-4^o). HR-MS: Calculated for C₆₁H₆₈N₆O₁₂ [M+NH₄]⁺: 1094.52335, found: 1094.52388.



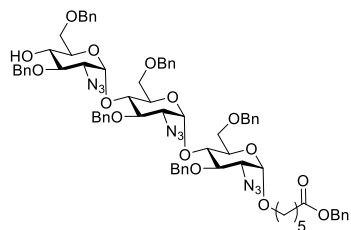
Synthesis of disaccharide **9**: The reaction was carried out according to the standard procedure C. Compound **8** (200 mg, 0.18 mmol) was dissolved in DCM:HFIP (1:1, 0.1 M). TES (60 μ L) and 0.2M HCl/HFIP (100 μ L) were added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material (30 min).

Then the mixture was diluted with DCM and the reaction quenched with saturated NaHCO₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **9** (152 mg, 88% yield, PE:EA = 5:1, R_f = 0.22) was obtained as a colorless syrup. [α]_D²⁰ +62.9 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 697, 736, 1029, 1043, 1146, 1261, 1454, 1734 (C=O), 2105 (N₃), 2868, 2926, 3491. ¹H-NMR (CDCl₃, 400 MHz) δ 7.42-7.20 (m, 25 H, aromatic *H*), 5.64 (d, *J* = 3.6 Hz, 1 H, H-1b), 5.11 (s, 2 H, PhCH₂), 4.98 (d, *J* = 10.4 Hz, 1 H, CHH), 4.93 (d, *J* = 3.6 Hz, 1 H, H-1a), 4.89-4.82 (m, 3 H, 3 CHH), 4.55 (d, *J* = 12.0 Hz, 1 H, CHH), 4.51 (d, *J* = 12.0 Hz, 1 H, CHH), 4.08 (dd, *J*₁ = 8.8 Hz, *J*₂ = 10.0 Hz, 1 H, H-3a), 3.99 (t, *J* = 8.8 Hz, 1 H, H-4a), 3.86-3.65 (m, 7 H, H-3b, H-4b, H-5a, H-5b, H-6b, H-6a), 3.53-3.44 (m, 2 H, H-6a, H-1^a), 3.40-3.33 (m, 2 H, H-2a, H-1^b), 3.24 (dd, *J*₁ = 3.6 Hz, *J*₂ = 10.0 Hz, 1 H, H-2b), 2.68 (bs, 1 H, OH), 2.38 (t, *J* = 7.6 Hz, 2H, H-5^o), 1.73-1.64 (m, 4 H, H-2^o, H-4^o), 1.47-1.39 (m, 2 H, H-3^o). ¹³C-APT (CDCl₃, 100 MHz) δ 173.56 (C=O), 138.23, 138.17, 137.79, 137.66, 136.15 (aromatic C), 128.67, 128.57, 128.54, 128.43, 128.29, 128.17, 128.08, 127.94, 127.89, 127.83, 127.79, 127.63, 127.35 (aromatic CH), 97.73 (C-1a), 97.63 (C-1b), 80.93 (C-3a), 79.70 (C-3b), 75.22, 74.47, 73.71, 73.40 (PhCH₂), 73.12 (C-4b), 72.77 (c-4a), 70.61 (c-5b), 70.15 (C-5a), 69.93 (C-6a),

69.01 (C-6b), 68.23 (C-1°), 66.26 (PhCH₂), 63.78 (C-2a), 62.75 (C-2b), 34.26 (C-5°), 29.15 (C-2°), 25.76 (C-3°), 24.77 (C-4°). HR-MS: Calculated for C₅₃H₆₀N₆O₁₁ [M+NH₄]⁺: 974.46583, found: 974.46576.



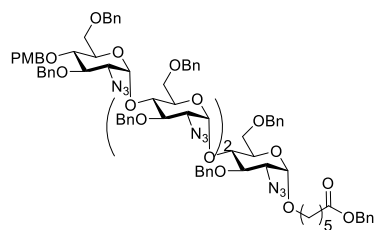
Synthesis of trisaccharide 10: The reaction was carried out according to the standard procedure A. A mixture of donor **5** (160 mg, 0.24 mmol), acceptor **9** (150 mg, 0.16 mmol) (donors and acceptors co-evaporated with toluene three times), MPF (307 mL) in dry DCM (1.5 mL) were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 °C, after which TfOH (300 µL) was added. After 30 min, the reaction was stirred at -10 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **10** (186 mg, 83% yield, α : β > 19:1, PE:EA = 4:1, R_f = 0.40) was obtained as a colorless syrup. [α]_D²⁰ +75.8 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 697, 736, 1029, 1147, 1249, 1359, 1454, 1514, 1734 (C=O), 2106 (N₃), 2866, 2932. ¹H-NMR (CDCl₃, 400 MHz) δ 7.39-7.21 (m, 35 H, aromatic *H*), 7.00 (bd, 2 H, aromatic *H*), 6.79 (bd, 2 H, aromatic *H*), 5.69 (d, *J* = 3.6 Hz, 1 H, H-1), 5.67 (d, *J* = 3.6 Hz, 1 H, H-1), 5.11 (s, 2 H, PhCH₂), 5.02-4.82 (m, 7 H, 6 *CHH*, H-1a), 4.66 (d, *J* = 10.0 Hz, 1 H, *CHH*), 4.56-4.46 (m, 3 H, 3 *CHH*), 4.39-4.33 (m, 2 H, 2 *CHH*), 4.26 (d, *J* = 12.0 Hz, 1 H, *CHH*), 4.18 (d, *J* = 12.0 Hz, 1 H, *CHH*), 4.14-3.98 (m, 4 H), 3.90-3.59 (m, 11 H), 3.56-3.44 (m, 3 H), 3.37-3.24 (m, 3 H), 2.38 (t, *J* = 7.6 Hz, 2H, H-5°), 1.73-1.63 (m, 4 H, H-2°, H-4°), 1.47-1.39 (m, 2 H, H-3°). ¹³C-APT (CDCl₃, 100 MHz) δ 173.49 (C=O), 159.36, 138.27, 138.17, 137.99, 137.79, 137.75, 137.55, 136.14, 130.25 (aromatic *C*), 129.61, 128.62, 128.57, 128.55, 128.42, 128.31, 128.26, 128.13, 127.92, 127.86, 127.81, 127.70, 127.63, 127.52, 127.41, 127.33, 113.82 (aromatic *CH*), 97.85, 97.73, 97.42 (C-1a, 1b and 1c), 81.04, 80.74, 79.89 (C-3a, 3b and 3c), 77.73 (C-4c), 75.26, 74.68, 74.57, 74.24, 73.57, 73.50 (PhCH₂), 72.96, 72.46 (C-4a and 4b), 71.45, 71.12, 70.16 (c-5a, 5b and 5c), 68.90, 68.65 (2 C-6), 68.24 (C-1°), 67.73 (C-6), 66.20 (PhCH₂), 63.89, 63.63, 63.13 (C-2a, 2b and 2c), 55.34 (OCH₃), 34.21 (C-5°), 29.13 (C-2°), 25.73 (C-3°), 24.74 (C-4°). HR-MS: Calculated for C₈₁H₈₉N₉O₁₆ [M+NH₄]⁺: 1461.67655, found: 1461.67594.



Synthesis of trisaccharide acceptor 11: The reaction was carried out according to the standard procedure C. The starting material **10** (320 mg, 0.22 mmol) was dissolved in DCM:HFIP (1:1, 0.1 M). TES (71 µL) and 0.2M HCl/HFIP (110 µL) were added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material (15min). Then the mixture was diluted with DCM and the reaction quenched with saturated NaHCO₃.

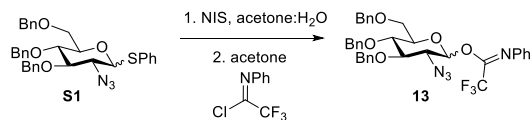
The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **11** (230 mg, 78% yield) was obtained as a colorless syrup. [α]_D²⁰ +51.0 (c=3mg/mL, CHCl₃). IR (neat, cm⁻¹) ν 697, 737, 1028, 1148, 1454, 1736 (C=O), 2106 (N₃), 2866, 2926. ¹H-NMR (CDCl₃, 400 MHz) δ 7.42-7.17 (m, 35 H, aromatic *H*), 5.67-5.65 (m, 2 H, H-1b and H-1c), 5.12 (s, 2 H, PhCH₂), 5.01-4.85 (m, 7 H, 6 *CHH*, H-1a), 4.56 (d, *J* = 12.0 Hz, 1 H, *CHH*), 4.50 (d, *J* = 12.0 Hz, 1 H, *CHH*), 4.37-4.32 (m, 3 H, 3 *CHH*), 4.22 (d, *J* = 12.0 Hz, 1 H, *CHH*), 4.14-3.99 (m, 4 H), 3.87-3.62 (m, 8 H), 3.56-3.43 (m, 3 H), 3.37-3.30 (m, 4 H), 3.18 (dd, *J*₁ = 3.6 Hz, *J*₂ = 10.0 Hz, 1 H, H-2c), 2.76 (bs, 1 H, OH), 2.39 (t, *J* = 7.6 Hz, 2H, H-5°), 1.74-1.64 (m, 4 H, H-2°, H-4°), 1.47-1.41 (m, 2 H, H-3°). ¹³C-APT (CDCl₃, 100 MHz) δ 173.56 (C=O), 138.28, 138.20, 138.17,

137.81, 137.61, 137.53, 136.17 (aromatic C), 138.69, 128.67, 128.61, 128.55, 128.49, 128.36, 128.31, 128.13, 128.09, 128.00, 127.95, 127.92, 127.79, 127.73, 127.54, 127.48, 127.26 (aromatic CH), 97.78, 97.72, 97.42 (C-1a, 1b and 1c), 81.13, 80.77, 79.14 (C-3a, 3b and 3c), 75.02, 74.59, 74.27, 73.71, 73.53, 73.38 (PhCH₂), 73.04, 72.95, 72.25 (C-4a, 4b and 4c), 71.09, 70.31, 70.18 (c-5a, 5b and 5c), 70.02, 68.92, 68.55 (C-6a, 6b and 6c), 68.30 (C-1°), 66.26 (PhCH₂), 63.93, 63.66, 62.46 (C-2a, 2b and 2c), 34.27 (C-5°), 29.17 (C-2°), 25.77 (C-3°), 24.79 (C-4°). HR-MS: Calculated for C₇₃H₈₁N₉O₁₅ [M+NH₄]⁺: 1341.61904, found: 1341.61923.



Synthesis of tetrasaccharide 12: The reaction was carried out according to the standard procedure A. A mixture of donor **5** (40 mg, 0.06 mmol), acceptor **11** (35 mg, 0.03 mmol) (donors and acceptors co-evaporated with toluene three times), MPF (52 μ L) in dry DCM (0.3 mL) were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 °C, after which TfOH (5 μ L) was added. After 30 min, the

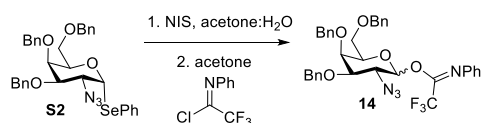
reaction was stirred at -10 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **12** (43 mg, 90% yield, α : β > 20:1) was obtained as a colorless syrup. [α]_D²⁰ +94.8 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 697, 737, 1029, 1148, 1251, 1359, 1454, 1514, 1735 (C=O), 2106 (N₃), 2868, 2928. ¹H-NMR (CDCl₃, 400 MHz) δ 7.42-7.15 (m, 45 H, aromatic H), 7.00 (bd, 2 H, aromatic H), 6.79 (bd, 2 H, aromatic H), 5.70-5.67 (m, 3 H, H-1b, 1c, 1d), 5.11 (s, 2 H, PhCH₂), 5.02-4.87 (m, 8 H, 7 CHH, H-1a), 4.81 (d, *J* = 10.4 Hz, 1 H, CHH), 4.66 (d, *J* = 10.4 Hz, 1 H, CHH), 4.54 (s, 2 H, PhCH₂), 4.65 (d, *J* = 12.0 Hz, 1 H, CHH), 4.38-4.28 (m, 4 H, 4 CHH), 4.22-4.00 (m, 8 H), 3.90-3.59 (m, 15 H), 3.52-3.44 (m, 3 H), 3.39-3.34 (m, 7 H), 2.38 (t, *J* = 7.6 Hz, 2H, H-5°), 1.73-1.64 (m, 4 H, H-2°, H-4°), 1.47-1.38 (m, 2 H, H-3°). ¹³C-APT (CDCl₃, 100 MHz) δ 173.54 (C=O), 159.41, 138.31, 138.23, 138.00, 137.84, 137.78, 137.55, 136.17, 130.29 (aromatic C), 129.66, 128.66, 128.65, 128.61, 128.59, 128.48, 128.45, 128.40, 128.33, 128.30, 128.16, 128.02, 127.98, 127.93, 127.87, 127.84, 127.74, 127.71, 127.58, 127.52, 127.43, 127.34, 113.86 (aromatic CH), 97.91, 97.76, 97.52, 97.48 (C-1a, 1b, 1c and 1d), 80.96, 80.88, 80.79, 79.95 (C-3a, 3b, 3c and 3d), 77.76 (C-4), 75.30, 74.73, 74.37, 74.31, 73.60, 73.56, 73.54, 73.51 (PhCH₂), 73.08 (C-4), 72.38 (C-4), 72.09 (C-4), 71.48, 71.20, 71.0570.20 (c-5a, 5b, 5c and 5d), 68.86, 68.61, 68.29 (3 C-6), 68.29 (C-1°), 67.75 (C-6), 66.25 (PhCH₂), 63.81, 63.70, 63.60, 63.19 (C-2a, 2b, 2c and 2d), 55.39 (OCH₃), 34.26 (C-5°), 29.17 (C-2°), 25.77 (C-3°), 24.79 (C-4°).



Synthesis of *N*-phenyl trifluoroacetimidate 2-N₃-glucose donor 13: Compound **S1** (8.5 g, 15 mmol) was dissolved in acetone:H₂O (10:1, 150 mL). *N*-

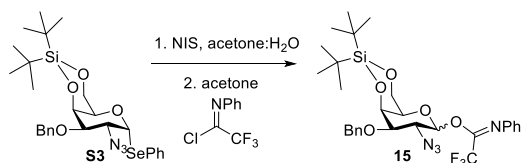
Iodosuccinimide (NIS) (6.7 g, 30 mmol) was added in one portion and the reaction was stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated aqueous Na₂S₂O₃. Then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*, and the product purified by column chromatography (pentane : ethyl acetate (EA) = 3:1). The lactol (6.1 g, 13 mmol) was obtained as colorless syrup. Next, the lactol was dissolved in acetone (150 mL). Cs₂CO₃ (6.4 g, 19.6 mmol) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (3.4 mL, 21.3 mmol) were added to the solution respectively. The reaction was stirred overnight, then quenched with Et₃N, filtered and concentrated *in vacuo*. The product

was purified by column chromatography (pentane:EA = 40:1-20:1). Compound **13** (7.3 g, 87%) was obtained as yellow syrup. IR (neat, cm^{-1}) ν 694, 734, 1027, 1073, 1116, 1150, 1208, 1312, 1361, 1452, 1490, 1497, 1598, 1717, 2110 (N_3), 2869, 3032. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, 60°C) δ 7.52-6.81 (m, aromatic H), 6.37 (bs, 1 H, H-1 α), 5.43 (bs, 1 H, H-1 β), 4.89-4.76 (m, CHH), 4.60-4.48 (m, CHH), 3.98 (t, $J = 9.5$ Hz, 1 H), 3.91 (bd, 1 H), 3.80-3.59 (m), 3.46 (t), 3.36 (bs, 1 H). $^{13}\text{C-APT}$ (CDCl_3 , 125 MHz, 60°C) δ 143.61, 143.50, 138.23, 138.16, 138.14, 138.12, 138.06 (aromatic C), 129.54, 128.92, 128.79, 128.62, 128.58, 128.54, 128.17, 128.14, 128.06, 128.04, 128.00, 127.97, 127.95, 127.91, 127.86, 126.54, 124.68, 124.60, 120.78, 119.59 (aromatic CH), 96.24 (C-1), 94.37 (C-1), 83.28, 80.49, 77.99, 77.62, 76.33, 75.74, 75.73, 75.37, 75.18, 73.90, 73.82, 73.74, 68.45, 65.83, 63.48. HR-MS: Calculated for $\text{C}_{35}\text{H}_{33}\text{F}_3\text{O}_5\text{N}_4$ $[\text{M}-[\text{O}(\text{C}=\text{NPh})\text{CF}_3]]+\text{OH}+\text{Na}]^+$: 498.19994, found: 498.19848.



Synthesis of *N*-phenyl trifluoroacetimidate 2- N_3 -galactose donor **14**: Compound **S2** (3.7 g, 6.0 mmol) was dissolved in acetone: H_2O (10:1, 150 mL). *N*-Iodosuccinimide (NIS) (2.7 g, 12 mmol) was added in one portion and the reaction was

stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$. Then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*, and the product purified by column chromatography (pentane:EA = 3:1). The lactol was obtained as colourless syrup. Next, the lactol was dissolved in acetone. Cs_2CO_3 (3.0 g, 9 mmol) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (1.5 mL, 9 mmol) were added to the solution respectively. The reaction was stirred overnight, then quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by column chromatography (pentane:EA = 40:1-20:1). Compound **14** (3.3 g, 86%) was obtained as yellow syrup. IR (neat, cm^{-1}) ν 695, 734, 751, 986, 1027, 1153, 1316, 1364, 1454, 1490, 1497, 1590, 1717, 2114 (N_3), 2870, 2915. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, 60°C) δ 7.56-6.79 (m, aromatic H), 6.35 (bs, 1 H, H-1), 5.49 (bs, 1 H, H-1), 5.28 (d), 4.90-4.84 (m, CHH), 4.78-4.31 (m), 4.15-3.83 (m), 3.76 (dd), 3.65-3.31 (m). $^{13}\text{C-APT}$ (CDCl_3 , 125 MHz, 60°C) δ 143.48, 143.36, 138.46, 138.30, 138.25, 138.17, 138.14, 137.73, 137.69, 137.64, 137.57, 137.38, 137.33, 135.19 (aromatic C), 129.48, 128.83, 128.67, 128.63, 128.60, 128.56, 128.48, 128.46, 128.43, 128.37, 128.34, 128.19, 128.17, 128.15, 128.14, 128.07, 128.03, 128.00, 127.95, 127.91, 126.48, 124.46, 120.62, 119.38 (aromatic CH), 96.53 (C-1), 92.46 (C-1), 80.89, 80.69, 77.44, 75.05, 74.93, 74.77, 74.75, 74.65, 73.81, 73.67, 73.65, 73.62, 73.53, 72.89, 72.67, 72.64, 72.46, 72.43, 72.30, 72.24, 71.90, 69.73, 69.30, 68.74, 68.27, 68.05, 64.67, 62.24, 60.43, 59.21. HR-MS: Calculated for $\text{C}_{35}\text{H}_{33}\text{F}_3\text{N}_4\text{O}_5$ $[\text{M}+\text{Na}]^+$: 669.22953, found: 669.22913.

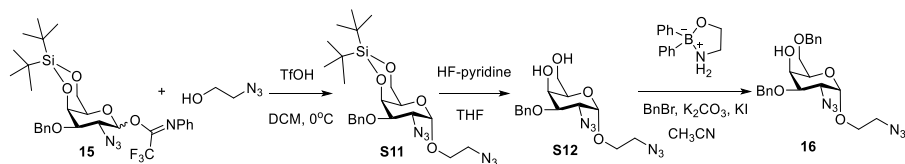


Synthesis of *N*-phenyl trifluoroacetimidate 2- N_3 -galactose donor **15**: NIS (9.15 g, 40.68 mmol) was added to the solution of compound **S3** (18 g, 31.3 mmol) in Acetone/ H_2O (210 ml/72ml) at 0°C . The reaction was slowly warmed to room temperature and stirred until

TLC-analysis indicated full consumption of the starting material (± 1 h). Then the mixture was diluted with DCM and washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The lactol was purified by silica gel column chromatography (PE:EA = 4:1). Cs_2CO_3 was added to the solution of the lactol (10.59g,

24.33 mmol) in 140 ml acetone. The mixture was stirred at 0 °C for 15 minutes. Then $\text{CF}_3\text{C}(\text{=NPh})\text{Cl}$ (6.06 g, 29.2 mmol) was added to the solution, which was slowly warmed to room temperature and stirred overnight. The reaction was quenched with Et_3N and concentrated *in vacuo*. The product **15** was purified by silica gel column chromatography (PE:Et₂O = 30:1 – 10:1). Compound **15** (13.3 g, a/b = 2:1, 90% yield, PE: Et₂O = 10:1, R_f = 0.45-0.55) was obtained as white solid. *a* isomer: ¹H-NMR (CDCl₃, 400 MHz) δ 7.50 – 7.24 (m, 7H, aromatic H), 7.15 – 7.05 (m, 1H, aromatic H), 6.84 (d, *J* = 7.7 Hz, 2H, aromatic H), 6.47 (bs, 1H, H-1), 4.78 (d, *J* = 11.4 Hz, 1H, CH₂Ph), 4.69 (d, *J* = 11.4 Hz, 1H, CH₂Ph), 4.63 (s, 1H, H-4), 4.22 (q, *J* = 12.8 Hz, 2H, H-6), 4.10 (t, *J* = 6.3 Hz, 1H, H-2), 3.89 (d, *J* = 9.5 Hz, 1H, H-3), 3.76 (s, 1H, H-5), 1.09-1.02 (m, 18H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 143.29, 137.45, 128.74, 128.56, 128.01, 127.91, 124.40, 119.35 (aromatic C/CH), 94.73 (C-1), 76.04 (C-3), 70.71 (CH₂Ph), 69.89 (C-5), 69.16 (C-4), 66.76 (C-6), 57.71 (C-2), 27.59 (CH₃), 27.23 (CH₃), 23.38 (C-Si), 20.73 (C-Si). *b* isomer: ¹H-NMR (CDCl₃, 400 MHz) δ 7.48 – 7.25 (m, 7H, aromatic H), 7.14 – 7.04 (m, 1H, aromatic H), 6.85 (d, *J* = 7.7 Hz, 2H, aromatic H), 5.50 (bs, 1H, H-1), 4.77 (d, *J* = 11.9 Hz, 1H, CH₂Ph), 4.66 (d, *J* = 11.9 Hz, 1H, CH₂Ph), 4.43 (s, 1H, H-5), 4.19 (s, 2H, H-6), 4.02 (s, 1H, H-4), 3.30 (s, 2H, H-2, 3), 1.15 – 1.00 (m, 18H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 143.45, 137.54, 128.83, 128.71, 128.17, 127.97, 124.48, 119.42 (aromatic C/CH), 95.82 (C-1), 79.55 (C-3), 72.18 (C-2), 70.99 (CH₂Ph), 68.57 (C-5), 66.84 (C-6), 60.79 (C-4), 27.72 (CH₃), 27.42 (CH₃), 23.55 (C-Si), 20.89 (C-Si). HR-MS: Calculated for C₂₉H₃₇F₃N₄O₅Si [M+Na]⁺: 629.2383, found: 629.2376.

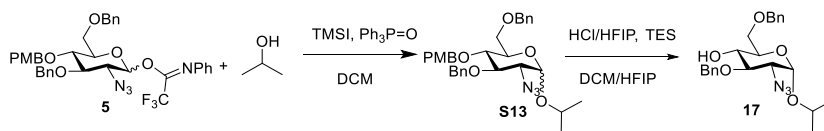
Synthesis of acceptor **16**



Donor **15** (620 mg, 1.0 mmol) and 2-azidoethanol (178 mg, 2.0 mmol) were dissolved in DCM, cooled to 0 °C and TfOH (15 μL, 0.1 mmol) was added. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the donor. The reaction was quenched with Et_3N after completed checking by TLC, filtered and concentrated *in vacuo*. Compound **S11** (370 mg, 73%) was obtained with full α-selectivity. Then compound **S11** was dissolved in THF. HF-pyridine was added to the solution. After TLC-analysis showed complete consumption of the starting material, the reaction was quenched with saturated NaHCO_3 . The mixture was diluted with ethyl acetate, washed with H₂O and brine, dried with anhydrous MgSO_4 , filtered, concentrated *in vacuo*. Crude compound **S12**, K_2CO_3 , KI, and borinic acid-catalyzed were mixed in CH₃CN, and then BnBr was added in the solution. The reaction was stirred at 60 °C until TLC-analysis showed complete conversion of the starting material. The reaction was quenched with H₂O after completed checking by TLC, filtered and concentrated *in vacuo*, purified by column chromatography. Compound **16** (280 mg, 84% yield over two steps) was obtained as colorless syrup. $[\alpha]_D^{20} +89.9$ (c=1, CHCl₃). IR (neat, cm⁻¹) ν 698, 738, 1052, 1096, 1146, 1454, 2108 (N₃), 2873, 2923, 3483. ¹H-NMR (CDCl₃, 500 MHz) δ 7.40-7.28 (m, 10 H, aromatic H), 4.95 (d, *J* = 3.5 Hz, 1 H, H-1a), 4.71 (d, *J* = 11.5 Hz, 1 H, CHH), 4.68 (d, *J* = 11.5 Hz, 1 H, CHH), 4.60 (d, *J* = 12.0 Hz, 1 H, CHH), 4.57 (d, *J* = 12.0 Hz, 1 H, CHH), 4.12 (t, *J* = 1.5 Hz, 1 H, H-4a), 3.98 (t, *J* = 6.0 Hz, 1 H, H-5a), 3.93 (dd, 1 H, *J*₁ = 10.5 Hz, *J*₂ = 3.0 Hz, H-3a), 3.90-3.86 (m, 1 H, H-1^a), 3.77-3.63 (m, 4 H, H-2a, H-6^a, H-1^b), 3.57-3.52 (m, 1 H, H-2^a), 3.37-3.33 (m, 1 H, H-2^b), 2.61 (bt, 1 H, OH), 1.21-1.18 (bt, 6 H, 2 CH₃). ¹³C-APT (CDCl₃, 125 MHz) δ 137.94, 137.28 (aromatic C), 142

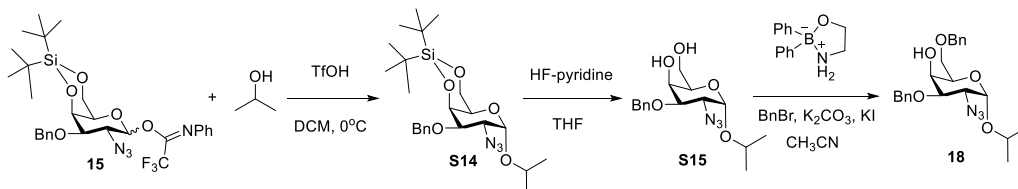
128.78, 128.58, 128.35, 128.23, 127.92, 127.83 (aromatic CH), 98.48 (C-1a), 76.02 (C-3a), 73.78, 72.13 (CH₂), 69.60 (C-6a), 69.21 (C-5a), 67.24 (C-1°), 66.83 (C-4a), 58.98 (C-2a), 50.76 (C-2°). HR-MS: Calculated for C₂₂H₂₆O₅N₆ [M+NH₄]⁺: 472.23029, found: 472.23003.

Synthesis of acceptor 17



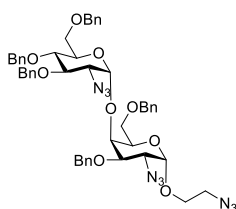
Donor **5** (820 mg, 1.2 mmol), isopropanol (200 μ L, 2.6 mmol) and Ph₃P=O (2 g) were dissolved in DCM (12 mL), and TMSI (173 μ L) was added at room temperature. The reaction was stirred at rt until TLC-analysis showed complete conversion of the donor. The reaction was quenched with Et₃N after completed checking by TLC, filtered and concentrated *in vacuo*, purified by column chromatography. Compound **S13** was obtained with $\alpha:\beta = 5:1$. Then compound **S13** was dissolved in DCM/HFIP (1.5 mL: 1.5 mL). TES (380 μ L) and 0.2M HCl/HFIP (600 μ L) were added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material (30min). Then the mixture was diluted with DCM and the reaction quenched with saturated NaHCO₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **17** (240 mg, 47% yield over two steps) was obtained as colorless syrup. [α]_D²⁰ +83.4 (c=1, CHCl₃). IR (neat, cm⁻¹) ν 697, 735, 1029, 1047, 1120, 1454, 2105 (N₃), 2920, 2974, 3476. ¹H-NMR (CDCl₃, 400 MHz) δ 7.40-7.20 (m, 10 H, aromatic *H*), 4.97 (d, *J* = 3.6 Hz, 1 H, H-1a), 4.88 (d, *J* = 11.2 Hz, 1 H, CHH), 4.78 (d, *J* = 11.2 Hz, 1 H, CHH), 4.57 (d, *J* = 12.0 Hz, 1 H, CHH), 4.50 (d, *J* = 12.0 Hz, 1 H, CHH), 3.93-3.82 (m, 3 H, H-3a, H-5a, H-1°), 3.73-3.61 (m, 3 H, H-4a, H-6a), 3.18 (dd, 1 H, *J*₁ = 10.0 Hz, *J*₂ = 3.6 Hz, H-2a), 2.76 (bs, 1 H, OH), 1.23, (d, *J* = 8.4 Hz, 3 H, CH₃), 1.21 (d, *J* = 8.4 Hz, 3 H, CH₃). ¹³C-APT (CDCl₃, 100 MHz) δ 138.20, 137.80 (aromatic C), 128.54, 128.39, 128.00, 127.90, 127.72, 127.59 (aromatic CH), 96.37 (C-1a), 79.64 (C-3a), 74.85, 73.56 (CH₂), 72.06 (C-4a), 70.83 (C-1°), 70.12 (C-5a), 69.65 (C-6a), 62.51 (C-2a), 23.23 (CH₃), 21.48 (CH₃). HR-MS: Calculated for C₂₃H₂₉O₅N₃ [M+NH₄]⁺: 445.24455, found: 445.24441.

Synthesis of acceptor 18



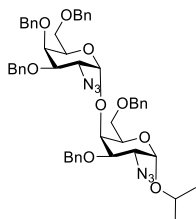
Donor **15** (2.77 g, 4.6 mmol) and isopropanol were dissolved in DCM (40 mL), cooled to 0 °C and TfOH (40 μ L) was added. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the donor. The reaction was quenched with Et₃N after completed checking by TLC, filtered and concentrated *in vacuo*. Compound **S14** was obtained with full α -selectivity. Then compound **S14** was dissolved in THF (20 mL). HF-pyridine (1 mL) was added to the solution. After TLC-analysis showed complete consumption of the starting material, the reaction was quenched with saturated

NaHCO₃. The mixture was diluted with ethyl acetate, washed with H₂O and brine, dried with anhydrous MgSO₄, filtered, concentrated *in vacuo*, purified by column chromatography. Compound **S14** (1.45 g) was obtained with 94% yield over two steps. Then compound **S14** (665 mg, 1.97 mmol), K₂CO₃ (293 mg), KI (327 mg), and borinic acid-catalyzed (44 mg) were mixed in CH₃CN (20 mL), and then BnBr was added in the solution. The reaction was stirred at 60 °C until TLC-analysis showed complete conversion of the starting material. The reaction was quenched with H₂O after completed checking by TLC, filtered and concentrated *in vacuo*, purified by column chromatography. Compound **17** (745 mg, 80% yield) was obtained as colorless syrup. $[\alpha]_D^{20} +102.7$ (c=1, CHCl₃). IR (neat, cm⁻¹) ν 698, 737, 1052, 1454, 2108 (N₃), 2892, 2926. 2972. ¹H-NMR (CDCl₃, 400 MHz) δ 7.42-7.27 (m, 10 H, aromatic *H*), 5.02 (d, *J* = 3.6 Hz, 1 H, H-1a), 4.71 (bs, 2 H, PhCH₂), 4.58 (bs, 2 H, PhCH₂), 4.15 (t, *J* = 1.6 Hz, 1 H, H-4a), 4.01 (bt, 1 H, H-5a), 3.95-3.89 (m, 2 H, H-3a, H-1^o), 3.76 (dd, 1 H, *J*₁ = 10.0 Hz, *J*₂ = 6.0 Hz, H-6a), 3.70-3.62 (m, 2 H, H-6a, H-2a), 2.60 (bs, 1 H, OH), 1.23 (d, 3 H, *J* = 10.4 Hz, CH₃), 1.21 (d, 3 H, *J* = 10.4 Hz, CH₃). ¹³C-APT (CDCl₃, 100 MHz) δ 138.03, 137.45 (aromatic C), 128.76, 128.55, 128.29, 128.12, 127.87, 127.77 (aromatic CH), 96.68 (C-1a), 76.14 (C-3a), 73.77, 71.96 (CH₂), 70.90 (C-1^o), 69.58 (C-6a), 68.73 (C-5a), 66.79 (C-4a), 59.02 (C-2a), 23.34 (CH₃), 21.63 (CH₃). HR-MS: Calculated for C₂₃H₂₉O₅N₃ [M+NH₄]⁺: 445.24455, found: 445.24455.



Synthesis of disaccharide **20**: The reaction was carried out according to the standard procedure A. A mixture of donor **13** (146 mg, 0.22 mmol), acceptor **16** (50 mg, 0.11 mmol) (donors and acceptors co-evaporated with toluene three times), MPF (216 μ L) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 °C, after which TfOH (19 μ L) was added. After 30 min, the reaction was stirred at -10 °C until TLC-analysis showed complete conversion of the acceptor. The

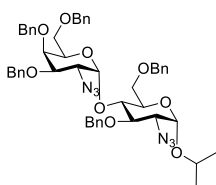
reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **20** (86 mg, 88%, α : β = 10:1) was obtained as a colorless syrup. IR (neat, cm⁻¹) ν 697, 736, 1027, 1046, 1093, 1127, 1150, 1259, 1359, 1454, 2105 (N₃), 2869, 2923. ¹H-NMR (CDCl₃, 400 MHz) δ 7.40-7.05 (m, 25 H, aromatic *H*), 4.99 (bt, 2 H, H-1a and H-1b), 4.90-4.76 (m, 3 H, 3 CHH), 4.69 (d, *J* = 10.8 Hz, 1 H, CHH), 4.63 (d, *J* = 10.8 Hz, 1 H, CHH), 4.59-4.53 (m, 2 H, 2 CHH), 4.39 (bt, 2 H, 2 CHH), 4.31 (d, *J* = 2.4 Hz, 1 H), 4.13-3.49 (m, 13 H), 3.39-3.29 (m, 2 H), 3.22 (dd, *J*₁ = 12.4 Hz, *J*₂ = 2.0 Hz, 1 H), 2.96 (dd, *J*₁ = 10.8 Hz, *J*₂ = 2.0 Hz, 1 H), 4.48 (d, *J*₁ = 10.8 Hz, *J*₂ = 1.6 Hz, 1 H). ¹³C-APT (CDCl₃, 100 MHz) δ 138.05, 137.75, 137.654, 137.49 (aromatic C), 128.62, 128.51, 128.42, 128.35, 128.18, 128.07, 128.06, 127.88, 127.82, 127.78, 127.75, 127.70, 127.22 (aromatic CH), 98.92 (C-1), 98.53 (C-1), 80.15, 78.12, 75.58, 75.42, 74.91, 73.66, 73.34, 73.28, 72.00, 70.94, 69.60, 67.33, 67.26, 67.02, 64.03, 59.36, 50.71. HR-MS: Calculated for C₄₉H₅₃O₉N₉ [M+NH₄]⁺: 929.43045, found: 929.43039.



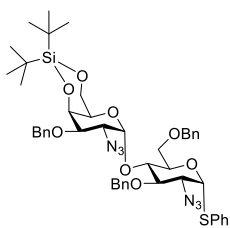
Synthesis of disaccharide **21**: The reaction was carried out according to the standard procedure A. A mixture of donor **14** (77 mg, 0.12 mmol), acceptor **17** (34 mg, 0.08 mmol) (donors and acceptors co-evaporated with toluene three times), MPF (156 μ L) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 °C, after which TfOH (8 μ L) was added. After 30 min, the reaction was stirred at -10 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N,

filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **21** (62

mg, 88% yield, $\alpha:\beta = 8:1$) was obtained as a colorless syrup. $[\alpha]_D^{20} +85.8$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 736, 986, 1037, 1117, 1209, 1261, 1454, 2106 (N_3), 2870, 2925. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.41-7.19 (m, 25 H, aromatic H), 5.64 (d, $J = 3.6$ Hz, 1 H, H-1a), 5.03 (d, $J = 3.6$ Hz, 1 H, H-1b), 4.96 (d, $J = 10.0$ Hz, 1 H, CHH), 4.91 (d, $J = 10.0$ Hz, 1 H, CHH), 4.81 (d, $J = 11.2$ Hz, 1 H, CHH), 4.67 (d, $J = 11.2$ Hz, 1 H, CHH), 4.61 (d, $J = 11.2$ Hz, 1 H, CHH), 4.56 (d, $J = 12.4$ Hz, 1 H, CHH), 4.48 (d, $J = 11.2$ Hz, 1 H, CHH), 4.44 (d, $J = 12.4$ Hz, 1 H, CHH), 4.29 (d, $J = 11.6$ Hz, 1 H, CHH), 4.22 (d, $J = 11.6$ Hz, 1 H, CHH), 4.07 (dd, $J = 8.0, 10.0$ Hz, 1 H, H-3b), 3.98-3.78 (m, 7 H), 3.72-3.63 (m, 2 H, H-6), 3.48-3.37 (m, 2 H, H-6), 3.29 (dd, $J = 3.6, 10.0$ Hz, 1H, H-2b), 1.28 (d, $J = 6.4$ Hz, 1 H, CH_3), 1.24 (d, $J = 6.4$ Hz, 1 H, CH_3). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 138.44, 138.24, 137.89, 137.60 (aromatic C), 128.62, 128.57, 128.50, 128.42, 128.37, 128.33, 128.03, 127.92, 127.89, 127.85, 127.81, 127.54, 127.45 (aromatic CH), 98.04 (C-1a), 96.16 (C-1b), 80.78 (C-3b), 77.58 (C-3a), 74.89, 74.48 (PhCH_2), 73.94 (C-2a), 73.57, 73.18 (PhCH_2), 72.94 (C-4b), 72.16 (PhCH_2), 71.08 (C-4a), 70.18 (C-5b), 70.07 (C-5a), 69.51 (C-6), 68.52 (C-6), 63.63 (C-2b), 59.75 (C-1 $^\circ$), 23.38 (CH_3), 21.65 (CH_3). HR-MS: Calculated for $\text{C}_{50}\text{H}_{56}\text{O}_9\text{N}_6$ $[\text{M}+\text{NH}_4]^+$: 902.44470, found: 902.44482.

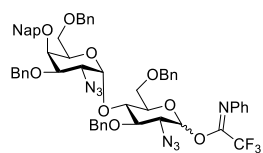


Synthesis of disaccharide **22**: The reaction was carried out according to the standard procedure A. A mixture of donor **14** (77 mg, 0.12 mmol), acceptor **18** (34 mg, 0.08 mmol) (donors and acceptors co-evaporated with toluene three times), MPF (156 μL) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78°C , after which TfOH (8 μL) was added. After 30 min, the reaction was stirred at -10°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion ($\text{DCM}:\text{MeOH} = 1:1$). Compound **22** (56 mg, 80% yield, $\alpha:\beta = 4:1$) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 737, 1050, 1097, 1122, 1258, 1454, 2108 (N_3), 2869, 2928. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.43-7.12 (m, 25 H, aromatic H), 5.05 (d, $J = 3.6$ Hz, 1 H, H-1a), 4.98 (d, $J = 3.6$ Hz, 1 H, H-1b), 4.88 (d, $J = 12.0$ Hz, 1 H, CHH), 4.80 (d, $J = 10.8$ Hz, 1 H, CHH), 4.72 (d, $J = 11.2$ Hz, 1 H, CHH), 4.63 (d, $J = 11.2$ Hz, 1 H, CHH), 4.54 (bd, 3 H, 3 CHH), 4.47 (d, $J = 10.8$ Hz, 1 H, CHH), 4.36 (dd, $J = 5.2, 9.2$ Hz, 1 H, H-5a), 4.28 (d, $J = 2.8$ Hz, 1 H, H-4a), 4.10 (bs, 1 H, H-4b), 4.03-3.85 (m, 8 H, H-6 $_{\text{b}}$, H-5b, H-3b, H-3a, H-2b, H-2a, H-1 $^\circ$), 3.60 (dd, $J = 3.6, 11.2$ Hz, 1H, H-2a), 3.56-3.49 (m, 2 H, H-6 $_{\text{b}}$, H-6 $_{\text{a}}$), 3.14-3.09 (m, 2 H, H-6 $_{\text{a}}$), 1.20 (d, $J = 6.0$ Hz, 1 H, CH_3), 1.19 (d, $J = 6.0$ Hz, 1 H, CH_3). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 138.65, 137.99, 137.70, 137.61 (aromatic C), 128.64, 128.58, 128.55, 128.38, 128.32, 128.16, 128.12, 128.09, 128.01, 127.90, 127.87, 127.75, 127.74, 127.64, 127.25 (aromatic CH), 98.24 (C-1b), 96.84 (C-1a), 77.35 (C-3b), 75.94 (C-3a), 75.03, 73.67, 73.22 (PhCH_2), 73.04 (C-4b), 72.86 (C-4a), 71.91, 71.87 (PhCH_2), 71.01 (C-1 $^\circ$), 69.37 (C-5b), 69.20 (C-5a), 67.74 (C-6a), 67.18 (C-6b), 60.35 (C-2b), 59.51 (C-2a), 23.36 (CH_3), 21.68 (CH_3). HR-MS: Calculated for $\text{C}_{50}\text{H}_{56}\text{O}_9\text{N}_6$ $[\text{M}+\text{NH}_4]^+$: 902.44470, found: 902.44467.



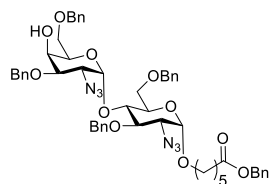
Synthesis of disaccharide **23**: Donor **15** (5 g, 8.2 mmol) and acceptor **19** (3.32 g, 6.95 mmol) (donors and acceptors co-evaporated with toluene three times) were dissolved in DCM (65 mL), cooled to 0°C and TfOH (60 μL) was added. The reaction was stirred at 0°C until TLC-analysis showed complete conversion of the donor. The reaction was quenched with Et_3N after completed checking by TLC, filtered and concentrated *in vacuo*. Compound **23** was obtained with full α -selectivity. Compound **23** (4.36g, 70% yield) was obtained as a

colorless syrup. $[\alpha]_D^{20} +153.3$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 651, 698, 738, 797, 826, 984, 1043, 1066, 1100, 1171, 1364, 1473, 2107 (N_3), 2859, 2933. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.53-7.51 (m, 2 H, aromatic H), 7.44-7.22 (m, 18 H, aromatic H), 5.64 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.59 (d, $J = 5.2$ Hz, 1 H, H-1a), 5.00 (d, $J = 10.4$ Hz, 1 H, CHH), 4.91 (d, $J = 10.4$ Hz, 1 H, CHH), 4.73 (d, $J = 11.6$ Hz, 1 H, CHH), 4.63 (d, $J = 11.6$ Hz, 1 H, CHH), 4.43-4.37 (m, 4 H, 2 CHH , H-4b, H-5a), 3.96-3.77 (m, 6 H, H-2a, H-2b, H-3a, H-4a, H-6), 3.72-3.64 (m, 2 H, H-3b, H-6a), 3.53 (dd, $J_1 = 2.0$ Hz, $J_2 = 10.8$ Hz, 1 H, H-6b), 3.42 (s, 1 H, H-5b), 1.03 (s, 9 H, 3 CH_3), 0.97 (s, 9 H, 3 CH_3). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 137.91, 137.78, 137.42, 133.48 (aromatic C), 132.14, 129.17, 128.62, 128.58, 128.51, 128.48, 128.00, 127.98, 127.79, 127.54 (aromatic CH), 97.66 (C-1b), 87.10 (C-1a), 82.33 (C-3a), 75.54 (C-3b), 74.99, 73.33 (PhCH_2), 72.81 (c-4a), 71.27 (c-5a), 70.45 (PhCH_2), 69.55 (C-4b), 68.89 (C-6), 67.97 (C-5b), 66.89 (C-6), 64.61 (C-2a), 58.14 (C-2b), 27.66 (3 CH_3), 27.28 (3 CH_3), 23.40, 20.73. HR-MS: Calculated for $\text{C}_{47}\text{H}_{58}\text{N}_6\text{O}_8\text{SSi}$ $[\text{M}+\text{NH}_4]^+$: 912.41444, found: 912.41409.



N-phenyl trifluoroacetimidate disaccharide donor **26**: Compound **30** (4.15 g, 4.21 mmol) was dissolved in acetone: H_2O (10:1, 44 mL). *N*-Iodosuccinimide (NIS) (2.0 g, 8.8 mmol) was added in one portion and the reaction was stirred at room temperature for 2 hours. The solution was diluted with DCM and the reaction was quenched with saturated

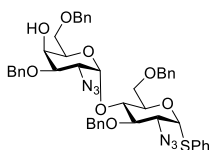
aqueous $\text{Na}_2\text{S}_2\text{O}_3$. Then the organic layer was washed with water and brine. The organic layer was dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*, and the product purified by column chromatography (pentane : ethyl acetate (EA) = 3:1). The lactol **31** was obtained as colourless syrup. Next, the lactol was dissolved in acetone (40 mL). Cs_2CO_3 (1.9 g) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (960 μL) were added to the solution respectively. The reaction was stirred overnight, then quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by column chromatography (pentane:EA = 40:1-20:1). Compound **26** (3.7 g, 83% over two steps) was obtained as yellow syrup. IR (neat, cm^{-1}) ν 695, 734, 818, 1027, 1116, 1209, 1312, 1454, 1489, 1497, 1717, 2107, 2870, 2918. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 7.80-7.09 (m, aromatic H), 6.81 (bt, 1 H), 5.65 (dd, 1 H), 5.01-4.87 (m), 4.68-4.54 (m), 4.45-4.42 (m), 4.33-4.18 (m), 4.03-3.41 (m). $^{13}\text{C-APT}$ (CDCl_3 , 125 MHz) δ 143.37, 143.22, 138.20, 138.18, 137.78, 137.58, 137.55, 137.53, 135.58, 133.26, 133.16 (aromatic C), 128.91, 128.67, 128.53, 128.52, 128.44, 128.43, 128.28, 128.08, 128.05, 128.00, 127.97, 127.92, 127.84, 127.81, 127.69, 127.66, 127.65, 127.55, 127.20, 127.17, 124.67, 124.56 (aromatic CH), 119.41 (C-1), 98.34 (C-1), 98.19 (C-1), 83.55, 80.97, 77.55, 77.25, 75.51, 75.18, 75.16, 74.94, 74.89, 73.64, 73.60, 73.29, 73.21, 73.11, 73.02, 72.76, 72.69, 72.30, 72.16, 70.42, 70.34, 68.97, 68.52, 65.80, 63.65, 59.74, 59.64. HR-MS: Calculated for $\text{C}_{59}\text{H}_{56}\text{F}_3\text{N}_7\text{O}_9$ $[\text{M}-[\text{O}(\text{C}=\text{NPh})\text{CF}_3]+\text{OH}+\text{Na}]^+$: 910.41340, found: 910.41374.



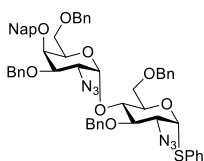
Synthesis of disaccharide acceptor **27**: The compound **33** (865 mg, 1.0 mmol) was dissolved in CH_3CN (10 mL). Then BnBr (182 μL), boronic acid-catalyzed (22 mg), K_2CO_3 (148 mg), KI (166 mg), were added in the mixture. The reaction stirred at 60°C until TLC-analysis indicated full consumption of the starting material (24 h). Then the mixture was diluted with ethyl acetate and the reaction quenched with saturated

NaHCO_3 . The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **27** (910 mg, 94%) was obtained as a colorless syrup. $[\alpha]_D^{20} +66.6$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 736, 1040, 1096, 1259, 1455, 1734 ($\text{C}=\text{O}$), 2106 (N_3), 2869, 2928. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.40-7.21 (m, 25 H, aromatic H), 5.64 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.11 (s, 1

H, PhCH₂), 4.96 (d, $J = 10.4$ Hz, 1 H, CHH), 4.91 (d, $J = 3.6$ Hz, 1 H, H-1a), 4.88 (d, $J = 10.4$ Hz, 1 H, CHH), 4.63 (bs, 2 H, 2 CHH), 4.55 (d, $J = 12.0$ Hz, 1 H, CHH), 4.45 (d, $J = 12.0$ Hz, 1 H, CHH), 4.47-4.36 (m, 3 H, 3 CHH), 4.07-4.03 (m, 2 H, H-3a, H-5a), 3.91-3.44 (m, 12 H), 3.32 (dd, $J_1 = 11.2$ Hz, $J_2 = 3.6$ Hz, 1 H, H-2a), 2.65 (s, 1 H, OH), 2.38 (t, $J = 7.6$ Hz, 2H, H-5°), 1.73-1.63 (m, 4 H, H-2°, H-4°), 1.47-1.39 (m, 2 H, H-3°). ¹³C-APT (CDCl₃, 100 MHz) δ 173.54 (C=O), 138.32, 137.81, 137.27, 136.14 (aromatic C), 129.07, 128.72, 128.65, 128.54, 128.50, 128.39, 128.28, 128.01, 127.89, 127.82, 127.63, 127.56, 127.32 (aromatic CH), 97.92 (C-1b), 97.68 (C-1a), 80.79 (C-3a), 76.25 (C-3b), 74.46 (PhCH₂), 73.94 (C-4a), 73.76, 73.28, 71.68 (PhCH₂), 70.10 (C-4b), 69.52, 69.44 (C-6), 69.16 (C-5b), 68.20 (C-1°), 66.44 (C-5a), 66.23 (PhCH₂), 63.74 (C-2a), 58.88 (C-2b), 34.24 (C-5°), 29.13 (C-2°), 25.74 (C-3°), 24.76 (C-4°). HR-MS: Calculated for C₅₃H₆₀N₆O₁₁ [M+NH₄]⁺: 974.46583, found: 974.46660.

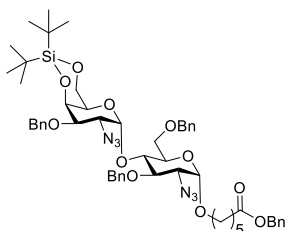


Synthesis of disaccharide **29**: Compound **23** (4.1 g, 4.6 mmol) was dissolved in THF (40 mL) in a round flask. Then HF-pyridine (1.2 mL) was added in the solution. The reaction stirred until TLC-analysis indicated full consumption of the starting material (30 min). Then the mixture was diluted with DCM and the reaction quenched with saturated NaHCO₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude compound **28** was dissolved in CH₃CN (47 mL). Then BnBr (880 μ L), borinic acid-catalyzed (110 mg), K₂CO₃ (710 mg), KI (800 mg) were added in the mixture. The reaction stirred at 60 °C until TLC-analysis indicated full consumption of the starting material (24 h). Then the mixture was diluted with ethyl acetate and the reaction quenched with saturated NaHCO₃. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **29** (3.6 g, 94% yield with two steps) was obtained as a colorless syrup. $[\alpha]_D^{20} +11.7$ (c=1, CHCl₃). IR (neat, cm⁻¹) ν 697, 737, 1029, 1046, 1077, 1266, 2106 (N₃), 2870, 2919, 3493. ¹H-NMR (CDCl₃, 400 MHz) δ 7.54-7.51 (m, 2 H, aromatic H), 7.41-7.23 (m, 23 H, aromatic H), 5.61 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.60 (d, $J = 5.2$ Hz, 1 H, H-1a), 5.00 (d, $J = 10.4$ Hz, 1 H, CHH), 4.94 (d, $J = 10.4$ Hz, 1 H, CHH), 4.66 (s, 2 H, PhCH₂), 4.50-4.37 (m, 3 H, 2 CHH, 5a), 4.08 (s, 1 H, H-4b), 3.97-3.91 (m, 2 H, H-2b, H-4a), 3.85-3.37 (m, 5 H), 3.66 (dd, $J_1 = 2.4$ Hz, $J_2 = 10.8$ Hz, 1 H, H-6_b), 3.59 (dd, $J_1 = 5.6$ Hz, $J_2 = 9.6$ Hz, 1 H), 3.51 (dd, $J_1 = 5.6$ Hz, $J_2 = 9.6$ Hz, 1 H), 2.63 (s, 1 H, OH). ¹³C-APT (CDCl₃, 100 MHz) δ 138.26, 137.83, 137.64, 137.24, 133.50 (aromatic C), 132.29, 128.77, 128.63, 128.53, 128.39, 128.34, 128.08, 127.97, 127.91, 127.86, 127.85, 127.63, 127.55 (aromatic CH), 98.17 (C-1b), 87.10 (C-1a), 82.14 (C-3a), 76.29 (C-3b), 75.14 (PhCH₂), 74.36 (c-4a), 73.78, 73.19, 71.77 (PhCH₂), 71.29 (c-5a), 69.52 (C-6), 69.40 (C-6), 69.30 (C-5b), 66.47 (C-4b), 64.75 (C-2b), 58.96 (C-2a). HR-MS: Calculated for C₄₆H₄₈N₆O₈S [M+NH₄]⁺: 862.35926, found: 862.35895.



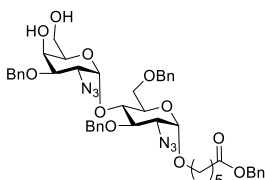
Synthesis of thio-disaccharide **30**: The compound **29** (3.83 g, 4.53 mmol) was dissolved in DMF (10 mL). Then NaH (544 mg) and NapBr (1.5 g) were added in the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material (2 h). Then the mixture was diluted with ethyl acetate and the reaction quenched with ice water. The organic phase was washed with water and brine, dried with anhydrous MgSO₄, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **30** (4.15 g, 93% yield) was obtained as a colorless syrup. $[\alpha]_D^{20} +208.6$ (c=1, CHCl₃). IR (neat, cm⁻¹) ν 697, 737, 1028, 1049, 1093, 1123, 1362, 1454, 2106 (N₃), 2870, 2914. ¹H-NMR (CDCl₃, 400 MHz) δ 7.80-7.11 (m, 32 H, aromatic H), 5.64 (d, $J = 3.6$ Hz, 1 H,

H-1b), 5.59 (d, $J = 5.2$ Hz, 1 H, H-1a), 5.01-4.89 (m, 3 H, 3 CHH), 4.70-4.62 (m, 3 H, 3 CHH), 4.50 (d, $J = 12.0$ Hz, 1 H, CHH), 4.44-4.40 (m, 2 H, CHH, 5b), 4.27 (d, $J = 11.6$ Hz, 1 H, CHH), 4.17 (d, $J = 11.6$ Hz, 1 H, CHH), 4.04 (s, 1 H, H-4b), 3.97-3.81 (m, 6 H, H-2a, H-2b, H-3a, H-3b, H-4a, H-5a), 3.77-3.65 (m, 2 H, H-6), 3.51-3.40 (m, 2 H, H-6). ^{13}C -APT (CDCl_3 , 100 MHz) δ 138.31, 137.79, 137.60, 137.58, 135.58, 133.56, 133.24, 133.15 (aromatic C), 133.28, 129.18, 128.67, 128.64, 128.50, 128.37, 128.27, 128.07, 127.99, 127.97, 127.93, 127.80, 127.56, 127.44, 127.20, 126.49, 126.21, 126.09 (aromatic CH), 98.34 (C-1b), 87.13 (C-1a), 82.24 (C-3a), 77.52 (C-3b), 75.20, 74.91 (PhCH_2), 74.11 (c-4a), 73.58, 73.11 (PhCH_2), 72.77 (C-4b), 72.27 (PhCH_2), 71.28 (C-5b), 70.36 (C-5a), 69.42 (C-6), 68.56 (C-6), 64.80 (C-2a), 69.75 (C-2b). HR-MS: Calculated for $\text{C}_{57}\text{H}_{56}\text{N}_6\text{O}_8\text{S} [\text{M}+\text{NH}_4]^+$: 1002.42186, found: 1002.42125.



Synthesis of disaccharide **32**: Donor **15** (1.09 g) and acceptor **7** (790 mg) (donors and acceptors co-evaporated with toluene three times) were dissolved in DCM (12 mL), cooled to 0 °C and TfOH (12 μL) was added. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the donor. The reaction was quenched with Et_3N after completed checking by TLC, filtered and concentrated *in vacuo*. Compound **32** (1.24 g, 92% yield) was obtained with full α -selectivity as a colorless

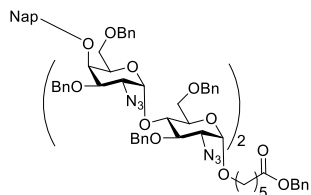
syrup. $[\alpha]_{\text{D}}^{20} +95.9$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 651, 698, 737, 765, 797, 826, 984, 1004, 1040, 1130, 1144, 1171, 1455, 1474, 1735 (C=O), 2106 (N_3), 2860, 2933. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.44-7.24 (m, 20 H, aromatic H), 5.67 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.12 (s, 1 H, PhCH_2), 4.96 (d, $J = 10.4$ Hz, 1 H, CHH), 4.92 (d, $J = 3.6$ Hz, 1 H, H-1a), 4.86 (d, $J = 10.4$ Hz, 1 H, CHH), 4.71 (d, $J = 11.6$ Hz, 1 H, CHH), 4.61 (d, $J = 11.6$ Hz, 1 H, CHH), 4.48 (s, 2 H, PhCH_2), 4.36 (d, $J = 2.0$ Hz, 1 H, H-4b), 4.06 (dd, $J_1 = 10$ Hz, $J_2 = 8.4$ Hz, 1 H, H-3a), 3.91-3.78 (m, 4 H), 3.74-3.45 (m, 6 H), 3.34-3.30 (m, 2 H, H-2a, H-1 $^\circ$), 2.39 (t, $J = 7.6$ Hz, 2H, H-5 $^\circ$), 1.74-1.64 (m, 4 H, H-2 $^\circ$, H-4 $^\circ$), 1.48-1.42 (m, 2 H, H-3 $^\circ$), 1.03 (s, 9 H, 3 CH_3), 0.95 (s, 9 H, 3 CH_3). ^{13}C -APT (CDCl_3 , 100 MHz) δ 173.54 (C=O), 138.03, 137.85, 137.67, 136.15 (aromatic C), 128.66, 128.56, 128.30, 128.02, 127.96, 127.92, 127.86, 127.60 (aromatic CH), 97.77 (C-1b), 97.47 (C-1a), 80.97 (C-3a), 75.51 (C-3b), 74.25, 73.52 (PhCH_2), 72.43 (c-4a), 70.45 (PhCH_2), 70.11 (c-5a), 69.57 (C-4b), 69.10 (C-6), 68.25 (C-1 $^\circ$), 67.90 (C-5b), 66.92 (C-6), 66.25 (PhCH_2), 63.61 (C-2a), 58.13 (C-2b), 34.25 (C-5 $^\circ$), 29.15 (C-2 $^\circ$), 27.70 (3 CH_3), 27.31 (3 CH_3), 25.76 (C-3 $^\circ$), 24.76 (C-4 $^\circ$), 23.44, 20.75. HR-MS: Calculated for $\text{C}_{54}\text{H}_{70}\text{N}_6\text{O}_{11}\text{Si} [\text{M}+\text{NH}_4]^+$: 1024.52101, found: 1024.52157.



Synthesis of disaccharide **33**: Compound **32** (1.16 g, 1.15 mmol) was dissolved in THF (11 mL) in a round flask. Then HF-pyridine (300 μL) was added in the solution. The reaction stirred until TLC-analysis indicated full consumption of the starting material (30 min). Then the mixture was diluted with DCM and the reaction quenched with saturated NaHCO_3 . The organic phase was washed with water and brine, dried with

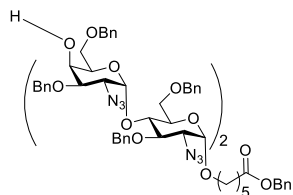
anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude compound **28** was dissolved in CH_3CN . The product was purified by silica gel column chromatography. Compound **33** (910 mg, 91% yield) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +80.6$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 698, 738, 1040, 1145, 1262, 1354, 1455, 1733 (C=O), 2106 (N_3), 2872, 2932, 3461. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.38-7.25 (m, 20 H, aromatic H), 5.65 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.12 (s, 1 H, PhCH_2), 4.97 (d, $J = 10.4$ Hz, 1 H, CHH), 4.92 (d, $J = 3.6$ Hz, 1 H, H-1a), 4.88 (d, $J = 10.4$ Hz, 1 H, CHH), 4.67-4.54 (m, 4 H, 4 CHH), 4.05 (dd, $J_1 = 10.0$ Hz, $J_2 = 8.4$ Hz, 1 H, H-3a), 3.91-3.80 (m, 2 H, H-4a, H-5), 3.74-3.57 (m, 8 H), 3.51-

3.44 (m, 1 H, H-1°), 3.31 (dd, $J_1 = 10.0$ Hz, $J_2 = 3.6$ Hz, 1 H, H-2a), 2.65 (s, 1 H, OH), 2.39 (t, $J = 7.6$ Hz, 2H, H-5°), 2.29 (s, 1 H, OH), 1.74-1.64 (m, 4 H, H-2°, H-4°), 1.47-1.40 (m, 2 H, H-3°). ^{13}C -APT (CDCl_3 , 100 MHz) δ 173.58 (C=O), 138.10, 137.79, 137.10, 136.12 (aromatic C), 128.81, 128.66, 128.57, 128.53, 128.42, 128.31, 128.29, 128.06, 127.88, 127.80, 127.75 (aromatic CH), 97.85 (C-1b), 97.70 (C-1a), 80.77 (C-3a), 76.13 (C-3b), 74.48 (PhCH₂), 73.81 (c-4a), 73.69 (PhCH₂), 71.89 (PhCH₂), 70.28 (c-5b), 70.21 (C-5a), 69.06 (C-6), 68.27 (C-1°), 67.20 (C-4b), 66.27 (PhCH₂), 63.78 (C-2a), 62.93 (C-6), 58.83 (C-2b), 34.26 (C-5°), 29.15 (C-2°), 25.75 (C-3°), 24.76 (C-4°). HR-MS: Calculated for $\text{C}_{46}\text{H}_{54}\text{N}_6\text{O}_{11}$ $[\text{M}+\text{NH}_4]^+$: 884.41888, found: 884.41942.



Synthesis of tetrasaccharide **34**: The reaction was carried out according to the standard procedure A. A mixture of donor **26** (520 mg, 0.49 mmol), acceptor **27** (238 mg, 0.25 mmol) (donors and acceptors co-evaporated with toluene three times), MPF (490 μL) in dry DCM (1 mL) were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78°C , after which

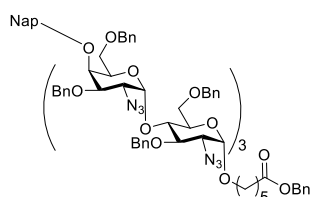
TfOH (40 μL) was added. After 30 min, the reaction was stirred at -10°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **34** (280 mg, 89%, $\alpha:\beta = 10:1$) was obtained as a colorless syrup. IR (neat, cm^{-1}) ν 697, 736, 1028, 1096, 1258, 1319, 1356, 1454, 1497, 1731 (C=O), 2105 (N_3), 2868, 2925. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.77-7.69 (m, 3 H, aromatic H), 7.60 (bs, 1 H, aromatic H), 7.42-7.17 (m, 48 H, aromatic H), 5.73 (d, $J = 3.6$ Hz, 1 H, H-1d), 5.65 (d, $J = 3.6$ Hz, 1 H, H-1b), 5.10 (s, 1 H, PhCH₂), 4.96-4.90 (m, 7 H), 4.74-4.48 (m, 7 H), 4.36-3.61 (m, 22 H), 3.51-3.26 (m, 6 H), 3.20 (d, $J = 10.0$ Hz, 1 H), 3.03 (d, $J = 10.0$ Hz, 1 H), 2.36 (t, $J = 7.6$ Hz, 2H, H-5°), 1.71-1.61 (m, 4 H, H-2°, H-4°), 1.45-1.37 (m, 2 H, H-3°). ^{13}C -APT (CDCl_3 , 100 MHz) δ 173.38 (C=O), 138.42, 138.22, 137.70, 137.68, 137.58, 137.54, 137.47, 136.07, 135.61, 133.14, 133.01 (aromatic C), 128.56, 128.50, 128.40, 128.38, 128.35, 128.27, 128.25, 128.18, 128.11, 128.07, 128.00, 127.92, 127.88, 127.86, 127.78, 127.76, 127.66, 127.59, 127.41, 127.30, 127.08, 127.01, 126.39, 126.02, 125.90 (aromatic CH), 98.74 (C-1), 98.14 (C-1), 97.75 (C-1), 97.65 (C-1), 80.97 (C-3), 80.65 (C-3), 76.82 (C-3), 75.11 (C-3), 74.86, 74.53, 74.42 (CH₂), 73.47 (C-4), 73.45, 73.32 (CH₂), 73.18 (C-4), 72.86 (C-4), 72.82 (C-4), 72.77, 72.24, 71.66 (CH₂), 70.58 (C-5), 70.07 (C-5), 69.87 (C-5), 69.83 (C-5), 69.20, 68.38, 68.12, 67.87, 66.80, 66.11 (CH₂), 64.70 (C-2), 63.70 (C-2), 59.54 (C-2), 59.41 (C-2), 34.13 (C-5°), 29.04 (C-2°), 25.64 (C-3°), 24.65 (C-4°). HR-MS: Calculated for $\text{C}_{104}\text{H}_{110}\text{N}_{12}\text{O}_{19}$ $[\text{M}+\text{NH}_4]^+$: 1848.83484, found: 1848.83541.



Synthesis of tetrasaccharide acceptor **35**: The reaction was carried out according to the standard procedure C. Compound **34** (700 mg, 0.38 mmol) was dissolved in DCM:HFIP (1:1, 0.1 M). TES (304 μL , 1.91 mmol) and 0.2M HCl/HFIP (1.9 mL) were added to the mixture. The reaction stirred until TLC-analysis indicated full consumption of the starting material (15min). Then the mixture was diluted with

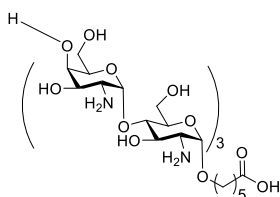
DCM and the reaction quenched with saturated NaHCO_3 . The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **35** (297mg, 73% yield) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +106.7$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 696, 737, 1040, 1100, 1261, 1454, 1735 (C=O), 2106 (N_3), 2869, 2926. ^1H -NMR (CDCl_3 , 500 MHz) δ 7.42-7.17 (m, 45 H, aromatic H), 5.71 (d, $J = 3.5$ Hz, 1 H, H-1d), 5.65 (d, $J = 3.5$ Hz, 1 H, H-1b), 5.10 (s, 1 H, PhCH₂), 4.95-4.89 (m, 6 H, H-

1a, H-1c, 4 CHH), 4.72 (d, $J = 12.0$ Hz, 1 H, CHH), 4.68 (s, 2 H, 2 CHH), 4.57-4.48 (m, 3 H), 4.36-4.17 (m, 7 H), 4.09-3.58 (m, 17 H), 3.51-3.30 (m, 3 H), 3.36-3.30 (m, 3 H), 3.91-3.44 (m, 12 H), 3.17 (dd, $J_1 = 11.5$ Hz, $J_2 = 2.5$ Hz, 1 H), 3.02 (dd, $J_1 = 11.5$ Hz, $J_2 = 2.5$ Hz, 1 H), 2.66 (s, 1 H, OH), 2.37 (t, $J = 7.5$ Hz, 2H, H-5°), 1.71-1.63 (m, 4 H, H-2°, H-4°), 1.45-1.39 (m, 2 H, H-3°). ^{13}C -APT (CDCl_3 , 125 MHz) δ 173.54 (C=O), 138.46, 138.32, 137.84, 137.70, 137.68, 137.56, 137.44, 136.17 (aromatic C), 128.77, 128.67, 128.61, 128.60, 128.48, 128.30, 128.22, 128.18, 128.04, 127.93, 127.89, 127.86, 127.81, 127.72, 127.69, 127.51, 127.48, 127.34, 127.19 (aromatic CH), 98.75 (C-1), 98.06 (C-1), 97.87 (C-1), 97.76 (C-1), 80.92 (C-3), 80.75 (C-3), 76.11 (C-3), 75.75 (C-3), 74.54, 74.46, 73.68 (CH_2), 73.58 (C-4), 73.56, 73.44 (CH_2), 73.14 (2 C-4), 73.07 71.82, 71.75 (CH_2), 70.66 (C-4), 70.18 (C-5), 69.94 (C-5), 69.30, 69.14 (CH_2), 68.80 (C-5), 68.51, 68.25, 68.90 (CH_2), 66.52 (C-5), 66.25 (PhCH_2), 64.71 (C-2), 63.82 (C-2), 59.64 (C-2), 58.75 (C-2), 34.27 (C-5°), 29.15 (C-2°), 25.75 (C-3°), 24.77 (C-4°). HR-MS: Calculated for $\text{C}_{93}\text{H}_{102}\text{N}_{12}\text{O}_{19}$ $[\text{M}+\text{NH}_4]^+$: 1708.77224, found: 1708.77299.

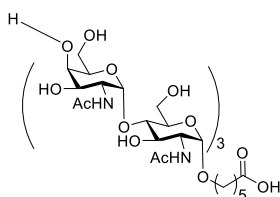


Synthesis of hexasaccharide **36**: The reaction was carried out according to the standard procedure A. A mixture of donor **26** (540 mg, 0.5 mmol), acceptor **35** (360 mg, 0.21 mmol) (donors and acceptors co-evaporated with toluene three times), MPF (400 μL) in dry DCM (1 mL) were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78°C , after which TfOH (44 μL) was added. After 30 min, the reaction was stirred at -10°C until

TLC-analysis showed complete conversion of the acceptor (48 h). The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by size exclusion (DCM:MeOH = 1:1). Compound **36** (500 mg, 91%, $\alpha:\beta = 10:1$) was obtained as a colorless syrup. $[\alpha]_{\text{D}}^{20} +123.0$ ($c=1$, CHCl_3). IR (neat, cm^{-1}) ν 697, 736, 1039, 1099, 1261, 1319, 1359, 1454, 1734 (C=O), 2106 (N_3), 2870, 2926. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.77-7.69 (m, 3 H, aromatic H), 7.60 (bs, 1 H, aromatic H), 7.44-7.07 (m, 68 H, aromatic H), 5.73 (d, $J = 3.6$ Hz, 1 H, H-1), 5.71 (d, $J = 3.2$ Hz, 1 H, H-1), 5.65 (d, $J = 3.6$ Hz, 1 H, H-1), 5.09 (s, 1 H, PhCH_2), 4.96-4.91 (m, 9 H), 4.77-4.65 (m, 5 H), 4.58-4.48 (m, 4 H), 4.33-3.62 (m, 37 H), 3.52-3.16 (m, 10 H), 3.05 (d, $J = 10.0$ Hz, 1 H), 2.99 (d, $J = 10.0$ Hz, 1 H), 2.36 (t, $J = 7.6$ Hz, 2H, H-5°), 1.71-1.61 (m, 4 H, H-2°, H-4°), 1.45-1.37 (m, 2 H, H-3°). ^{13}C -APT (CDCl_3 , 100 MHz) δ 173.40 (C=O), 138.46, 138.38, 138.22, 137.70, 137.66, 137.61, 137.59, 137.57, 137.49, 137.45, 136.07, 135.66, 133.15, 133.02 (aromatic C), 128.56, 128.52, 128.49, 128.48, 128.45, 128.39, 128.36, 128.28, 128.19, 128.10, 128.05, 128.01, 127.98, 127.94, 127.90, 127.86, 127.82, 127.78, 127.77, 127.72, 127.67, 127.60, 127.42, 127.35, 127.31, 127.12, 127.11, 127.03, 127.00 126.40, 126.02, 125.90 (aromatic CH), 98.78 (C-1), 98.69 (C-1), 98.09 (C-1), 97.89 (C-1), 97.78 (C-1), 97.65 (C-1), 80.98 (C-3), 80.80 (C-3), 80.67 (C-3), 76.93 (C-3), 76.10 (C-3), 75.67 (C-3), 74.88, 74.50, 74.40, 73.45, 73.33 (CH_2), 73.26 (C-4), 73.22 (C-4), 72.95 (CH_2), 72.83 (C-4), 72.80 (CH_2), 72.72 (C-4), 72.22, 71.88, 71.70 (CH_2), 70.62 (C-5), 70.52 (C-5), 70.08 (C-5), 69.85 (C-5), 69.80 (C-5), 69.60 (C-5), 69.21, 68.34, 68.13, 67.85, 66.82, 66.48, 66.12 (CH_2), 64.70 (2 C-2), 63.71 (C-2), 59.52 (C-2), 59.47 (C-2), 59.37 (C-2), 34.15 (C-5°), 29.05 (C-2°), 25.65 (C-3°), 24.66 (C-4°).



Synthesis of hexasaccharide **24**: Compound **36** (20 mg, 0.0054 mmol) was dissolved in THF/H₂O/*tert*-BuOH (2 mL/2 mL/1 mL) before a catalytic amount of Pd(OH)₂/C was added. The reaction mixture was stirred for 3 days under a H₂ atmosphere, filtered and concentrated *in vacuo*. A white powder **2** was obtained, which was purified by gel filtration (HW-40, 0.15M NH₄OAc in H₂O) to yield **1** (2 mg, 76%). ¹H-NMR (CDCl₃, 500 MHz) δ 5.40-5.35 (m, 3 H, 3 H-1), 4.85-4.81 (m, 3 H, 3 H-1), 4.13-4.06 (m, 2 H), 3.97-3.50 (m, 35 H), 3.41-3.37 (m, 1 H), 3.15-3.08 (m, 2 H), 2.81 (dd, 2 H), 2.72-2.70 (m, 2 H), 2.06 (t, 2 H), 1.55-1.43 (m, 5 H), 1.29-1.23 (m, 2 H). ¹³C-APT (CDCl₃, 125 MHz) δ 99.56 (C-1), 99.50 (C-1), 99.45 (C-1), 99.22 (2 C-1), 97.44 (C-1), 76.85, 76.66, 76.56, 76.27, 73.74, 73.33, 72.37, 72.32, 71.93, 71.14, 71.03, 70.51, 69.16, 68.81, 68.36, 68.29, 61.19, 60.57, 60.36, 55.30, 55.29, 54.60, 51.11, 51.05, 50.95, 37.48, 28.34, 25.56, 25.43. HR-MS: Calculated for C₄₂H₇₈N₆O₂₇ [M+2H⁺]²: 550.25302; found: 550.25247.



Synthesis of hexasaccharide **25**: Compound **24** was dissolved in H₂O. Then Ac₂O and NaHCO₃ were added in the solution. The reaction mixture was stirred for 3 days until TLC-analysis showed complete conversion of the acceptor. ¹H-NMR (CDCl₃, 500 MHz) δ 5.36-5.34 (m, 4 H, 4 H-1), 5.27 (d, *J* = 4.0 Hz, 1 H, H-1), 4.79 (bt, 2 H, 2 H-1), 4.73 (d, *J* = 3.0 Hz, 1 H, H-1), 4.21-4.06 (m, 5 H), 3.97-3.57 (m, 37 H), 3.40-3.35 (m, 1 H), 2.24 (bt, 2 H), 1.97-1.91 (m, 18 H, 6 CH₃), 1.80-1.74 (m, 2 H), 1.54-1.46 (m, 4 H), 1.32-1.26 (m, 2 H). ¹³C-APT (CDCl₃, 125 MHz) δ 180.21, 174.70, 174.69, 174.63, 174.54, 174.46 (6 C=O), 98.22, 98.15, 96.62 (6 C-1), 77.37, 77.23, 76.10, 75.69, 75.41, 72.45, 72.40, 71.84, 71.66, 71.28, 71.15, 70.74, 70.70, 70.39, 68.45, 68.07, 67.86, 67.58, 66.92, 61.61, 60.66, 60.31, 60.04, 54.44, 54.15, 49.93, 34.64, 28.16, 25.03, 24.38, 22.07 (CH₃), 22.03 (CH₃), 22.02 (CH₃), 21.92 (CH₃), 21.88 (2 CH₃). HR-MS: Calculated for C₅₄H₉₀O₃₃N₆ [M+2H⁺]²: 676.28472; found: 676.28489.

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- [13] To shed light on the mode of action of MPF a low temperature NMR experiment was conducted to study the formed reactive intermediates upon activation of donor **13**. Diagnostic signals were observed for the anomeric protons

corresponding to the α/β -imidinium ions

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Chapter 7

Summary and Future Prospects

Summary

The stereoselective synthesis of glycosidic bonds is a very challenge task and there is no general solution for the construction of demanding glycosidic bonds, such as 1,2-*cis* linkages and linkages of 2-deoxy sugars.^[1] It is tremendously difficult to design a general glycosylation strategy that can accommodate the varying reactivity of different donor-acceptor glycoside combinations and ensures a fully stereoselective glycosylation process. The introduction of nucleophilic additives to modulate the glycosylation reaction has been an important step forwards in this direction, as this opens the way to match donor and acceptor reactivity.^[2] It may enable a glycosylation strategy that employs a single donor type, devoid of any stereodirecting protecting groups and is under full control of the used reagents.^[3]

To this end, this Thesis describes a strategy to synthesize 1,2-*cis*-oligosaccharides modulated by

additives, such as dimethylformamide (DMF), triphenylphosphine oxide ($\text{Ph}_3\text{P}=\text{O}$) and *N*-methyl(phenyl)formamide (MPF), using building blocks that carry solely benzyl type protecting groups and are therefore of uniform reactivity. These three additives were used for different classes of donor-acceptor combinations. The additive DMF was mainly used to modulate glycosylations of per-benzylated glucosyl donors and secondary alcohol acceptors. The TMSI- $\text{Ph}_3\text{P}=\text{O}$ condition was used to glycosylate the more reactive primary alcohol acceptors. The MPF additive, which forms less stable anomeric imidinium ion intermediates than DMF, was used for donors that are somewhat less reactive, such as those in the 2-azido-2-deoxy series.

Chapter 1 provides an overview of the development of additive mediated glycosylations. Several additives (DMF, phosphine oxides, tetraalkyl ammonium halides) have been well studied on a broad scope of substrates and in a number of applications in oligosaccharide syntheses. Mechanistic studies have provided proof that the intermediate adducts of the additive and glycosyl donor play a key role in the glycosylation mechanism. Notwithstanding the initial successes described in Chapter 1, there still is a great demand to develop new additives and strategies using these reactivity modulators for the selective construction of glycosidic bonds and use assembly of complex and branched oligosaccharides.

Chapter 2 describes an additive controlled glycosylation strategy to assemble branched α -glucans (see Figure 1).^[3a] The synthetic strategy builds on the use of DMF and TMSI- $\text{Ph}_3\text{P}=\text{O}$ controlled glycosylation reactions and the use of one single benzyl type protecting group (Bn, PMB, Nap). To illustrate the applicability of the strategy, a linear α -(1,4)-hexasaccharide and a branched α -glucan from *Mycobacterium tuberculosis* were assembled (Figure 1). Encouraged by these results, a linear α -(1,3)-glucan from the pathogenic fungus *Aspergillus fumigatus* was assembled in a fully stereoselective manner as described in **Chapter 3**.^[3b]

Chapter 4 further explores the methodology for the synthesis of α -(1,2)-glucans. It was observed that DMF-mediated glycosylations proceeded with excellent stereoselectivity to forge α -(1,2)-glucosyl linkages of short oligosaccharides, but the construction of longer kojiligosaccharides was confronted with erosion of stereoselectivity, indicating a limitation of the methodology. Likely, the secondary structure of the larger oligosaccharide acceptors led to the decrease in stereoselectivity. A kojitetrasaccharide and a D-Alanine containing kojibiose glycerol phosphate teichoic acid building block to enable the assembly of *Enterococcus faecalis* LTAs, were synthesized (see Figure 1).

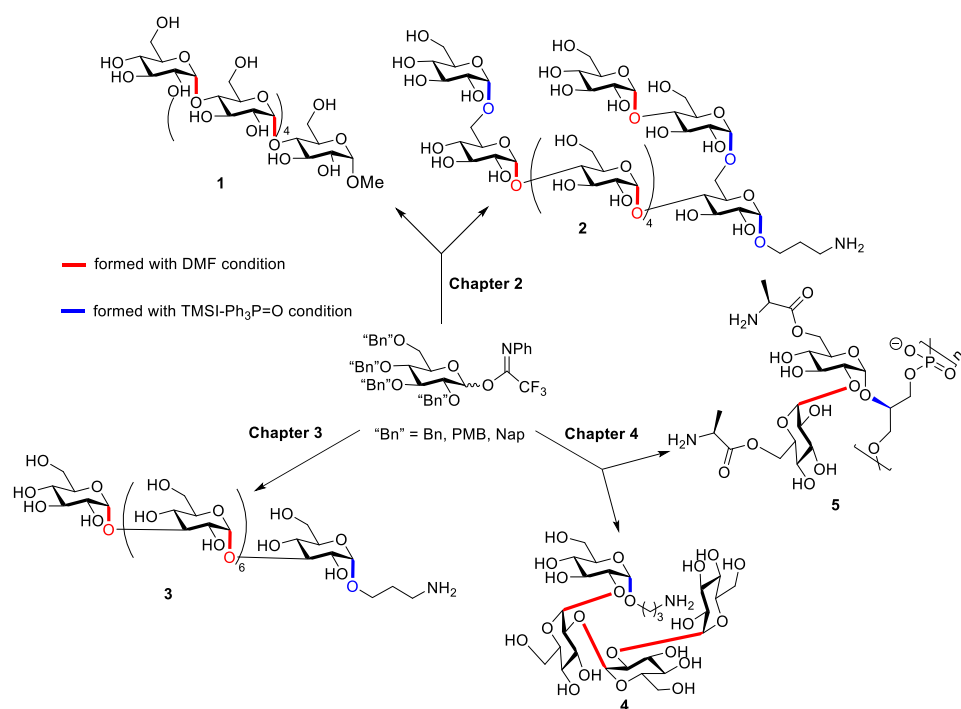


Figure 1. Target molecules assembled in Chapters 2, 3 and 4.

After the successful formation of α -glucosides, the formation of α -galactosides received attention in **Chapter 5** (see Figure 2). The stereoselective construction of the α -(1,4)-galactosides proved especially challenging. After screening different additives, the combination of TMSI- $\text{Ph}_3\text{P}=\text{O}$ at higher temperature proved effective to construct the challenging galactose- α -(1,4)-galactose linkage. It was also shown that the TMSI- $\text{Ph}_3\text{P}=\text{O}$ conditions can be applied to a wider substrate scope.

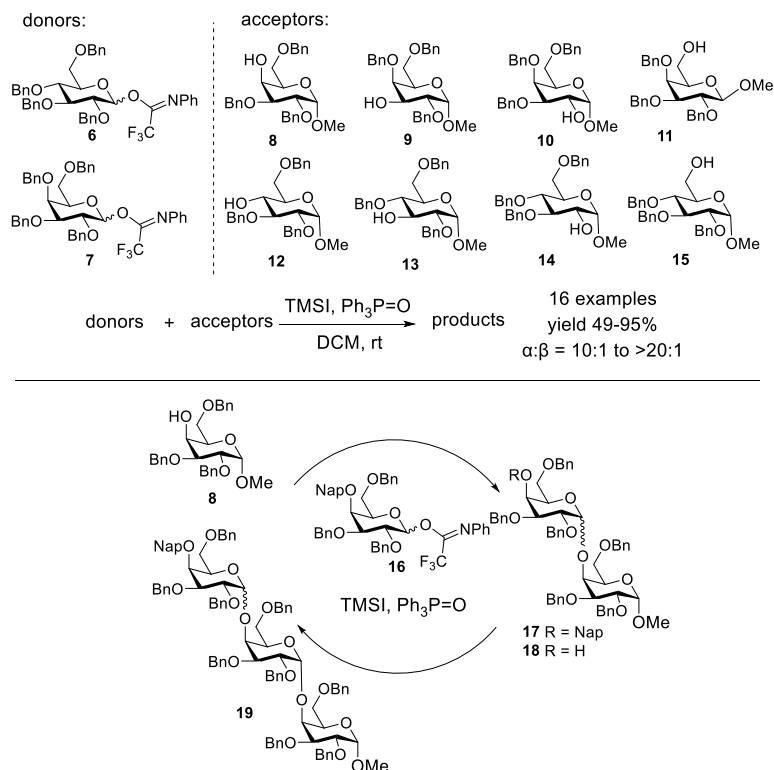


Figure 2. Glycosylations using the TMSI- $\text{Ph}_3\text{P=O}$ conditions developed in Chapter 5.

A new additive, MPF, was introduced in **Chapter 6** (Figure 3) for the glycosylation 2-azido-2-deoxy building blocks, which are less reactive than their 2-*O*-benzyl counterparts. A linear α -(1,4)-glucosamine tetrasaccharide was assembled to prove the utility of MPF. Next, a linear Pel hexasaccharide was assembled using a [2+2+2] strategy modulated by MPF. The used [galactosazide- α -(1,4)-glucosazide] disaccharide building blocks were synthesized using a 4,6-*O*-DTBS protected galactosyl azide donor.

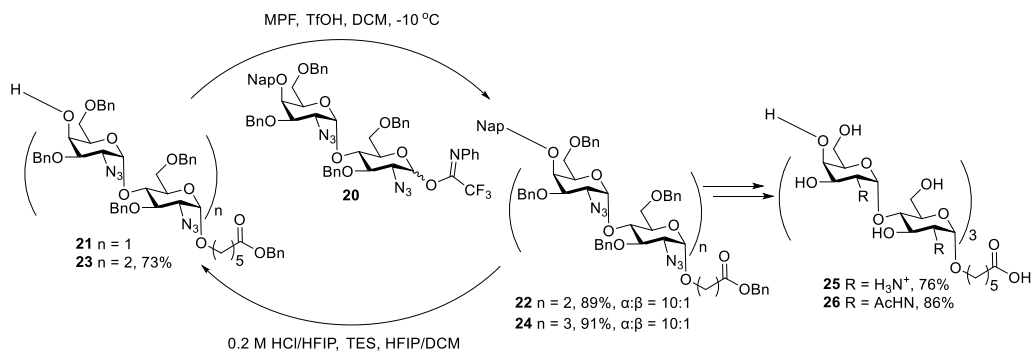
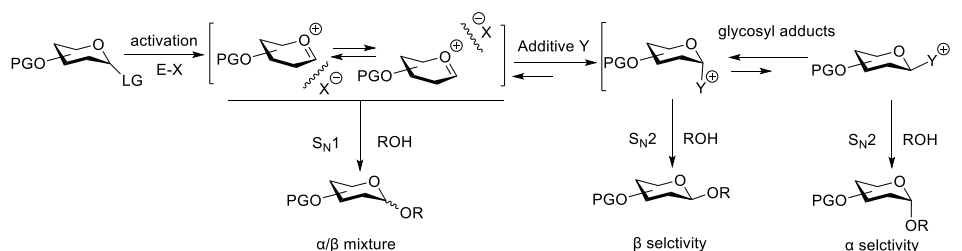


Figure 3. Assembly of Pel fragment.

Future Prospects

In additive-controlled glycosylation reactions, it has been shown that the intermediate adducts of the activated glycosyl donors and additives play a key role in the glycosylation mechanism and the reactivity of the glycosyl adducts is all important for the outcome of the glycosylation reactions.^[4] The proposed mechanism for additive controlled glycosylations is depicted in Scheme 1. In this mechanism, the pool of reactive intermediates, initially formed by activation of the parent donor, is trapped by the nucleophilic additive to provide a mixture of α - and β -linked covalent additive-glycosyl donor species. Of these the more reactive β -adduct is displaced more rapidly which can lead to an overall α -selective glycosylation reaction. Judicious tuning of the reactivity of the reactive adducts is important to enable the stereoselective generation the α -linked products. Although spectroscopic evidence has been forwarded for the existence of the covalent additive-glycosyl donor adducts, detailed kinetic studies underpinning the reaction mechanism are missing to date.



Scheme 1. The proposed reaction mechanism of additive controlled glycosylation reactions.

To determine where the reaction mechanism lies along the S_N2 - S_N1 continuum and how it shifts with changing donor structure and variation of the additive, kinetic isotope effects (KIE) can be studied. This technique has recently been used for a selection of glycosylation reactions, including the β -mannosylations and α -glucosylations developed by Crich and co-workers using benzyldiene protected donors,^[1c] the organocatalyzed glycosylations of Jacobsen^[5] and the anionic glycosylation reactions of Bennett and co-workers^[6]. The evaluation of KIEs (both primary $^{12}\text{C}/^{13}\text{C}$ and secondary $^1\text{H}/^2\text{H}$ effects) in a systematic series of glycosylations in which either the reactivity of the donor, acceptor or additive is gradually changed will provide insight into the origin of the stereoselectivity (or lack thereof) in these glycosylation reactions. This will be instructive in the future development of rationally designed additive controlled glycosylation reactions.

Table 1 shows how the stereoselectivity of a per-*O*-benzylated glucosyl donor developed with gradually changing nucleophilicity of the acceptor (decreasing going from ethanol to monofluoroethanol to difluoroethanol to trifluoroethanol) for DMF-mediated and TMSI- $\text{Ph}_3\text{P}=\text{O}$ promoted glycosylations. The intermediate glycosyl adduct formed from TMSI- $\text{Ph}_3\text{P}=\text{O}$ is less

reactive than that formed under DMF-modulation. In line with the results described above, the less reactive TMSI-Ph₃P=O conditions always gave a higher α -selectivity than the DMF-mediated conditions but at the expense of a lower yield. The α -selectivity is increasing for both sets of glycosylations from ethanol to trifluoroethanol (entry 1-4, Table 1). This clearly shows the influence of the reactivity of the substrates on the outcome of these glycosylations. Using this set of acceptors to measure KIEs and establish whether and how fast the mechanism changes with changing nucleophilicity will underpin the limitation and substrate scope for the studied additives.

Table 1. The influence of acceptor reactivity in glycosylations of per-*O*-benzylated glucosyl donor.

Entry	ROH	Product	Yield %		$\alpha:\beta$	
			a	b	a	b
1	ethanol	27	quant	quant	2.7:1	4:1
2		28	61	42	3.5:1	5.5:1
3		29	75	73	6.7:1	15:1
4		30	62	80	13:1	18:1
5		31	94	61	>20:1	>20:1

In Chapter 6, a new additive, MPF, is preselected for condensations of 2-azido-2-deoxy glucosyl donors. Although this additive was successfully used to assemble an oligo glucosamine and Pel oligosaccharide, Table 2 shows that the substrate scope of this method is quite narrow. The selectivity is significantly better for the C4-OH azidoglucose acceptor **33** and galactose acceptor **35** than their C3-OH counterparts **34** and **36** (entry 1-2 and 3-4, Table 2). A similar trend is revealed for the C4-OH and C3-OH glucose and galactose acceptors (**11** and **12** and **8** and **9**, respectively). Likely this is the result of the reactivity of the MPF imidinium ion, which is too reactive for the C3-OH acceptors, which are more reactive than their C4-OH counterparts. For the more reactive acceptors the less reactive *N*-formylmorpholine (NMF) introduced by Mong and co-workers can be explored.^[7] A systematic study in which these additives and DMF are compared side-by-side will inform on the scope and limitations of these additives. It will also be of interest to map how the stereoselectivity of these systems changes with varying protecting group pattern. The use of acyl groups is commonplace to ensure the formation of 1,2-*trans*-

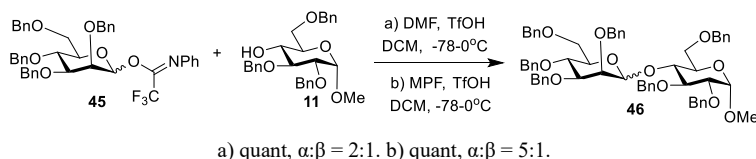
linkages. The electron-withdrawing capacity of these groups will have an effect on the reactivity of neighboring alcohol groups.

Table 2. Glycosylation of 2-azido donor **32** under MPF conditions.

Reaction scheme: Donor **32** (a 2-azido-3,4,6-tri-O-benzyl-α-D-glucopyranoside derivative) reacts with ROH in the presence of MPF, TfOH in DCM at -78-0°C to yield a glycoside product where the azido group is replaced by an OR group.

Entry	ROH	product	yield	α:β
1	33	37	90%	16:1
2	34	38	78%	8:1
3	35	39	57%	5:1
4	36	40	63%,	2:1
5	11	41	97%	10:1
6	12	42	92%	3:1
7	8	43	99%	5:1
8	9	44	99%	1.2:1

The synthesis of β-mannosides is an extremely challenging task because of the axially oriented substituent at the C2 of the donor. Several successful attempts have been reported to form β-mannosides, including Crich's benzylidene mannose system^[8], Demchenko's hydrogen bond guided β-mannosylation strategy,^[9] the use of mannuronic acids, and intramolecular aglycon delivery (IAD) systems. An additive controlled glycosylation would offer an even more direct way to construct these challenging linkages. The synthesis of 1,2-*cis*-mannosides is completely different to 1,2-*cis*-glucosides because an equatorial β-glycosidic bond needs to be formed instead of an axial α-bond. The glycosylation of per-benzyl mannosyl donor **45** was explored using both DMF and MPF mediated conditions. As shown in Scheme 2, the selectivity of both systems is poor, with the less reactive DMF system performing better than the more reactive MPF one. Therefore, new additives need be found from the "toolbox" by further studying of the relationship of the reactivity of the additives and the stereochemistry of this glycosylation reaction.



Scheme 2. Explorative glycosylations of mannosyl donor **45**.

Finally, the scope of the additives, described in this Thesis, should be explored further using various other donor glycosides, including deoxy systems (which can be found on the reactivity side of the spectrum) and glycuronic acids (on the low reactivity side of the spectrum). Relevant examples include fucosylations, rhamnosylations and xylosylations but also C2-deoxy systems such as found in various medically relevant bacterial glycosides and glycoconjugates (*e.g.* doxorubicin, aclarubicin and digitoxin).

Experimental Section

General experimental procedures

All reagents were of commercial grade and used as received. All moisture sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ (25 g/L) and $(\text{NH}_4)_4\text{Ce}(\text{SO}_4)_4 \cdot 2\text{H}_2\text{O}$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at $\sim 150^\circ\text{C}$. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20. ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in CDCl_3 or D_2O . Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard (^1H NMR in CDCl_3) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. NMR peak assignments were made using COSY and HSQC experiments, where applicable Clean TOCSY, HMBC and GATED experiments were used to further elucidate the structure. The anomeric product ratios were analyzed through integration of proton NMR signals and HPLC. HPLC analysis was performed over chiralpak AD column (0.46cm Φ ×25cm) and eluted with hexane/isopropanol (95/5) mixture at a 1 mL/min flow rate and UV 254nm detector.

Standard procedure

Procedure A for the glycosylation of secondary alcohols:

A mixture of donor (1.0 eq), acceptor (0.7 eq) (donors and acceptors co-evaporated with toluene three times), DMF (16 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78°C , after which TfOH (1.0 eq) was added. After 30 min, the reaction was stirred at 0 or -10°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Procedure B for the glycosylation of primary alcohols:

A mixture of donor (1.0 eq), acceptor (0.7 eq) (donors and acceptors co-evaporated with toluene three times), $\text{Ph}_3\text{P}=\text{O}$ (6

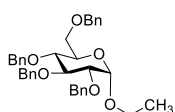
eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. Then TMSI (1.0 eq) was added slowly in the mixture. The reaction was stirred at room temperature until TLC-analysis indicated the reaction to be complete. The solution was diluted and the reaction quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$. The organic phase was washed with water and brine, dried with anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Procedure C for the glycosylation of secondary alcohols:

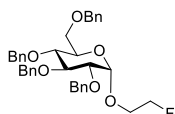
A mixture of donor (1.0 eq), acceptor (0.7 eq) (donors and acceptors co-evaporated with toluene three times), MPF (16 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78°C , after which TfOH (1.0 eq) was added. After 30 min, the reaction was stirred at 0 or -10°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The products were purified by size exclusion.

Experimental Procedures and Characterization Data of Products

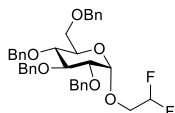
For the synthesis procedure and data of known compounds **6**, **31**, **32**, **33**, **35** see previous Chapter 2 and 6 and **27**^[10], **44**^[11], **46**^[12] see references.



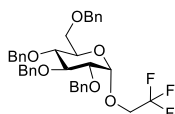
Synthesis of **27**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **6** (70 mg, 0.1 mmol, 0.1 M in DCM), ethanol (11 μL , 0.2 mmol), DMF (124 μL) and TfOH (10 μL , 0.1 mmol). The reaction was stirred at -78 - 0°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **27** (quant, $\alpha:\beta = 2.7:1$) was obtained as a colorless syrup. Under condition B, using **6** (80 mg, 0.11 mmol, 0.1 M in DCM), ethanol (13 μL , 0.22 mmol), $\text{Ph}_3\text{P}=\text{O}$ (185 mg, 0.66 mmol) and TMSI (15 μL , 0.11 mmol). The product was purified by silica gel column chromatography. Compound **27** (quant, $\alpha:\beta > 4:1$) was obtained as a colorless syrup.



Synthesis of **28**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **6** (70 mg, 0.1 mmol, 0.1 M in DCM), 2-fluoroethanol (11 μL , 0.2 mmol), DMF (124 μL) and TfOH (10 μL , 0.1 mmol). The reaction was stirred at -78 - 0°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **28** (35 mg, 61% yield, $\alpha:\beta = 3.5:1$) was obtained as a colorless syrup. Under condition B, using **6** (80 mg, 0.11 mmol, 0.1 M in DCM), 2-fluoroethanol (13 μL , 0.22 mmol), $\text{Ph}_3\text{P}=\text{O}$ (185 mg, 0.66 mmol) and TMSI (15 μL , 0.11 mmol). The product was purified by silica gel column chromatography. Compound **28** (27 mg, 42% yield, $\alpha:\beta > 5.5:1$) was obtained as a colorless syrup. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.37-7.11 (m, 20 H, a aromatic H), 5.00 (d, $J = 10.8$ Hz, 1 H, CHH), 4.84-4.77 (m, 4 H), 4.67-4.59 (m, 3 H), 4.55-4.50 (m, 1 H), 4.48-4.44 (m, 2 H), 4.00 (t, $J = 9.6$ Hz, 1 H), 3.90-3.56 (m, 7 H). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 138.95, 138.32, 137.99 (aromatic C), 128.60, 128.53, 128.50, 128.27, 128.08, 128.06, 128.05, 127.84, 127.73 (aromatic CH), 97.47, 83.50, 82.08, 81.81, 80.00, 77.68, 75.90, 75.23, 73.58, 73.42, 70.31, 68.48, 67.08 (d, FCH₂).

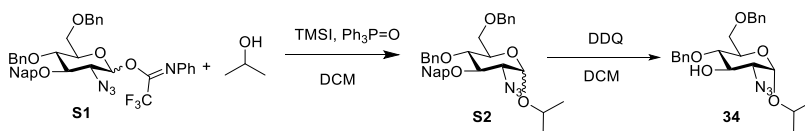


Synthesis of **29**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **6** (70 mg, 0.1 mmol, 0.1 M in DCM), 2-difluoroethanol (11 μ L, 0.2 mmol), DMF (124 μ L) and TfOH (10 μ L, 0.1 mmol). The reaction was stirred at $-78-0^{\circ}\text{C}$ until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **29** (45 mg, 75% yield, $\alpha:\beta = 6.7:1$) was obtained as a colorless syrup. Under condition B, using **6** (80 mg, 0.11 mmol, 0.1 M in DCM), 2-difluoroethanol (13 μ L, 0.22 mmol), $\text{Ph}_3\text{P}=\text{O}$ (185 mg, 0.66 mmol) and TMSI (15 μ L, 0.11 mmol). The product was purified by silica gel column chromatography. Compound **29** (50 mg, 73 % yield, $\alpha:\beta > 15:1$) was obtained as a colorless syrup. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.34-7.11 (m, 20 H, aromatic *H*), 6.10-5.81 (m, 1 H, F_2CH), 4.98 (d, $J = 10.8$ Hz, 1 H, *CHH*), 4.84-4.75 (m, 4 H), 4.64-4.58 (m, 2 H), 4.48-4.44 (m, 2 H), 3.96 (t, $J = 9.2$ Hz, 1 H), 3.80-3.56 (m, 7 H). ^{13}C -APT (CDCl_3 , 100 MHz) δ 138.80, 138.17, 138.14, 137.85 (aromatic C), 128.64, 128.53, 128.51, 128.24, 128.16, 128.03, 127.88, 127.76 (aromatic CH), 114.19 (t, F_2CH), 98.09, 81.85, 79.86, 77.46, 75.91, 75.26, 73.61, 73.59, 70.71, 68.31, 67.29 (t, F_2CHCH_2).



Synthesis of **30**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **6** (70 mg, 0.1 mmol, 0.1 M in DCM), 2-trifluoroethanol (11 μ L, 0.2 mmol), DMF (124 μ L) and TfOH (10 μ L, 0.1 mmol). The reaction was stirred at $-78-0^{\circ}\text{C}$ until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **30** (38 mg, 62% yield, $\alpha:\beta = 13:1$) was obtained as a colorless syrup. Under condition B, using **6** (80 mg, 0.11 mmol, 0.1 M in DCM), 2-trifluoroethanol (13 μ L, 0.11 mmol), $\text{Ph}_3\text{P}=\text{O}$ (185 mg, 0.66 mmol) and TMSI (15 μ L, 0.11 mmol). The product was purified by silica gel column chromatography. Compound **30** (56 mg, 80% yield, $\alpha:\beta > 18:1$) was obtained as a colorless syrup. ^1H -NMR (CDCl_3 , 400 MHz) δ 7.36-7.11 (m, 20 H, aromatic *H*), 4.98 (d, $J = 10.8$ Hz, 1 H, *CHH*), 4.84-4.77 (m, 4 H), 4.64-4.58 (m, 2 H), 4.48-4.44 (m, 2 H), 3.98 (t, $J = 9.2$ Hz, 1 H), 3.91-3.85 (m, 2 H), 3.77-3.57 (m, 5 H). ^{13}C -APT (CDCl_3 , 100 MHz) δ 138.81, 138.15, 137.83 (aromatic C), 128.61, 128.52, 128.20, 128.11, 128.05, 128.04, 127.90, 127.76 (aromatic CH), 123.76 (q, F_2CH), 97.92, 81.68, 79.76, 75.90, 75.29, 73.61, 73.45, 71.00, 68.21, 64.80 (q, F_2CHCH_2).

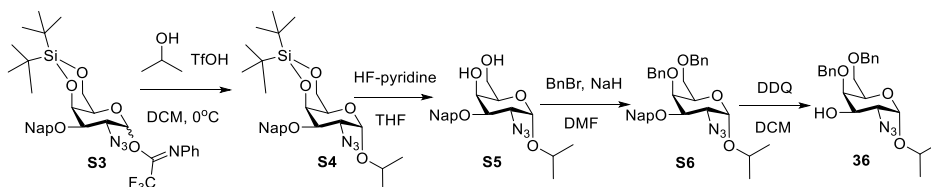
Synthesis of **34**



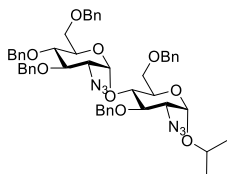
Donor **S1** (1200 mg, 1.7 mmol), isopropanol (265 μ L, 3.4 mmol) and $\text{Ph}_3\text{P}=\text{O}$ (2.8 g) were dissolved in DCM, and TMSI (250 μ L, 1.7 mmol) was added at room temperature. The reaction was stirred at rt until TLC-analysis showed complete conversion of the donor. The reaction was quenched with Et_3N after completed checking by TLC, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **S2** was obtained with $\alpha:\beta = 5:1$. Next compound **S2** (700 mg, 1.2 mmol) was dissolved in DCM (0.1 M), and then DDQ (300 mg) was added in the solution. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material. The reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ after completed checking by TLC, filtered and concentrated *in vacuo*, purified by column chromatography. Compound **34** (660 g, 80% yield) was obtained as colorless syrup. ^1H -NMR (CDCl_3 ,

400 MHz) δ 7.36-7.21 (m, 10 H, aromatic *H*), 5.02 (d, J = 3.6 Hz, 1 H, H-1a), 4.71 (d, J = 11.2 Hz, 1 H, *CHH*), 4.66 (d, J = 12.0 Hz, 1 H, *CHH*), 4.56 (d, J = 11.2 Hz, 1 H, *CHH*), 4.50 (d, J = 12.0 Hz, 1 H, *CHH*), 4.10 (t, J = 10.4 Hz, 1 H, H-3a), 3.93-3.84 (m, 2 H, H-5a, H-1°), 3.78 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 3.6 Hz, H-6a_a), 3.65 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 3.6 Hz, H-6a_b), 3.58 (t, 1 H, J_1 = 10.4 Hz, J_2 = 3.6 Hz, H-4a), 3.13 (dd, 1 H, J_1 = 10.4 Hz, J_2 = 3.6 Hz, H-2a), 2.63 (bs, 1 H, *OH*), 1.21 (d, J = 8.4 Hz, 3 H, *CH*₃), 1.20 (d, J = 8.4 Hz, 3 H, *CH*₃). ¹³C-APT (CDCl₃, 100 MHz) δ 138.12, 137.84 (aromatic C), 128.65, 128.47, 128.06, 128.03, 127.86 (aromatic CH), 96.41 (C-1a), 78.52 (C-4a), 74.98, 73.62 (CH₂), 71.75 (C-3a), 71.00 (C-1°), 70.32 (C-5a), 68.39 (C-6a), 62.78 (C-2a), 23.29 (CH₃), 21.59 (CH₃).

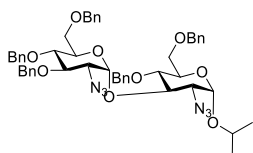
Synthesis of **36**



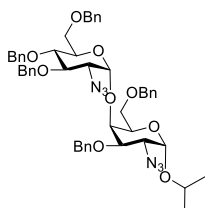
Donor **S3** (855 mg, 1.3 mmol) and isopropanol (150 mg, 2.5 mmol) were dissolved in DCM, cooled to 0 °C and TfOH (11.5 μ L, 0.13 mmol) was added. The reaction was stirred at 0 °C until TLC-analysis showed complete conversion of the donor. The reaction was quenched with Et₃N after completed checking by TLC, filtered and concentrated *in vacuo*. Compound **S4** (500 mg, 73%) was obtained with full α -selectivity. Then compound **S4** (500 mg, 0.95 mmol) was dissolved in THF. HF-pyridine (10 eq) was added to the solution. After TLC-analysis showed complete consumption of the starting material, the reaction was quenched with saturated NaHCO₃. The mixture was diluted with ethyl acetate, washed with H₂O and brine, dried with anhydrous MgSO₄, filtered, concentrated *in vacuo*. Crude compound **S5** was dissolved in DMF, and then BnBr (1.5 eq) and NaH (5 eq) were added in the solution. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material. The reaction was quenched with ice water after completed checking by TLC, filtered and concentrated *in vacuo*, purified by column chromatography. Compound **S6** (442 mg, 82% yield over two steps) was obtained as colorless syrup. Next compound **S6** (442 mg, 0.78 mmol) was dissolved in DCM, and then DDQ was added in the solution. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material. The reaction was quenched with saturated Na₂S₂O₃ after completed checking by TLC, filtered and concentrated *in vacuo*, purified by column chromatography. Compound **36** (266 mg, 80%) was obtained as colorless syrup. ¹H-NMR (CDCl₃, 400 MHz) δ 7.43-7.24 (m, 10 H, aromatic *H*), 5.02 (d, J = 3.6 Hz, 1 H, H-1a), 4.90 (d, J = 11.6 Hz, 1 H, *CHH*), 4.73 (s, 2 H, PhCH₂), 4.56 (d, J = 11.6 Hz, 1 H, *CHH*), 4.00-3.97 (m, 2 H, H-3a, H-4a), 3.91-3.85 (m, 2 H, H-5a, H-1°), 3.80 (dd, 1 H, J_1 = 10.0 Hz, J_2 = 3.6 Hz, H-2a), 3.74-3.70 (m, 1 H, H-6a_a), 3.56-3.51 (m, 1 H, H-6a_b), 2.07 (bs, 1 H, *OH*), 1.21-1.18 (bt, 6 H, 2 CH₃). ¹³C-APT (CDCl₃, 100 MHz) δ 137.95, 137.52 (aromatic C), 128.53, 128.44, 128.33, 127.97, 127.94, 127.81 (aromatic CH), 96.61 (C-1a), 77.39 (C-3a), 74.49 (CH₂), 73.41 (C-4a), 72.39 (CH₂), 70.74 (C-5a), 70.63 (C-1°), 62.07 (C-6a), 59.61 (C-2a), 23.20 (CH₃), 21.44 (CH₃). HR-MS: Calculated for C₂₃H₂₉O₅N₃ [M+NH₄]⁺: 445.24455, found: 445.24422.



Synthesis of 37: The reaction was carried out according to the standard procedure C. Using **32** (78 mg, 0.12 mmol), **33** (35 mg, 0.08 mmol, 0.1 M in DCM), MPF (156 μ L, 1.27 mmol) and TfOH (10 μ L, 0.11 mmol). The reaction was stirred at -78°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **37** (65 mg, 90% yield, $\alpha:\beta = 16:1$) was obtained as a colorless syrup. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.40-7.10 (m, 25 H, aromatic *H*), 5.67 (d, $J = 4.0$ Hz, 1 H, H-1), 5.05 (d, $J = 3.6$ Hz, 1 H, H-1), 5.00 (d, $J = 10.4$ Hz, 1 H, *CHH*), 4.90-4.86 (m, 3 H), 4.74 (d, $J = 10.8$ Hz, 1 H, *CHH*), 4.55-4.43 (m, 4 H), 4.23 (d, $J = 12.0$ Hz, 1 H, *CHH*), 4.12-4.08 (m, 1 H), 4.07-3.85 (m, 4 H), 3.79 (dd, 1 H, $J_1 = 10.8$ Hz, $J_2 = 3.6$ Hz), 3.70-3.62 (m, 3 H), 3.52 (bd, 1 H), 3.36-3.29 (m, 3 H), 1.28-1.24 (m, 6 H, 2 CH_3). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 138.24, 138.11, 137.96, 137.93, 137.81 (aromatic C), 128.57, 128.55, 128.48, 128.45, 128.41, 128.09, 127.97, 127.92, 127.90, 127.83, 127.74, 127.62, 127.37 (aromatic CH), 97.71 (C-1), 96.20 (C-1), 80.79, 80.48, 78.10, 75.56, 75.04, 73.38, 73.60, 73.53, 73.46, 71.56, 71.11, 70.12, 69.15, 67.91, 63.59, 63.53, 23.37 (CH_3), 21.65 (CH_3). HR-MS: Calculated for $\text{C}_{50}\text{H}_{56}\text{N}_6\text{O}_9$ $[\text{M}+\text{H}]^+$: 885.41815, found: 885.41775.

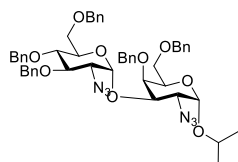


Synthesis of 38: The reaction was carried out according to the standard procedure C. Using **32** (77 mg, 0.12 mmol), **34** (33 mg, 0.08 mmol, 0.1 M in DCM), DMF (156 μ L, 1.27 mmol) and TfOH (10 μ L, 0.11 mmol). The reaction was stirred at -78°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **38** (53 mg, 78% yield, $\alpha:\beta = 8:1$) was obtained as a colorless syrup. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.38-7.14 (m, 25 H, aromatic *H*), 5.55 (d, $J = 3.6$ Hz, 1 H, H-1), 5.05 (d, $J = 4.0$ Hz, 1 H, H-1), 5.00 (d, $J = 10.4$ Hz, 1 H, *CHH*), 4.98 (d, $J = 10.8$ Hz, 1 H, *CHH*), 4.94-4.86 (m, 2 H), 4.79 (d, $J = 10.8$ Hz, 1 H, *CHH*), 4.69-4.65 (m, 2 H), 4.55-4.42 (m, 4 H), 4.22-4.13 (m, 2 H), 4.05-4.00 (m, 1 H), 3.97-3.74 (m, 7 H), 3.66 (dd, 1 H, $J_1 = 10.8$ Hz, $J_2 = 2.0$ Hz), 3.40 (dd, 1 H, $J_1 = 10.4$ Hz, $J_2 = 4.0$ Hz), 3.02 (dd, 1 H, $J_1 = 10.4$ Hz, $J_2 = 3.6$ Hz), 1.24-1.22 (m, 6 H, 2 CH_3). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 138.24, 138.07, 138.02, 138.68 (aromatic C), 128.55, 128.52, 128.49, 128.46, 128.15, 128.12, 128.08, 127.96, 127.92, 127.83, 127.81, 127.78, 127.44 (aromatic CH), 98.77 (C-1), 96.72 (C-1), 80.15, 79.22, 78.28, 75.80, 75.52, 75.02, 74.10, 73.74, 73.73, 71.66, 71.23, 70.37, 68.36, 68.22, 63.54, 61.32, 23.38 (CH_3), 21.61 (CH_3). HR-MS: Calculated for $\text{C}_{50}\text{H}_{56}\text{N}_6\text{O}_9$ $[\text{M}+\text{H}]^+$: 885.41815, found: 885.41742.



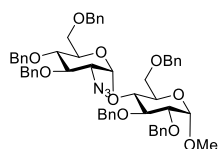
Synthesis of 39: The reaction was carried out according to the standard procedure C. Using **32** (77 mg, 0.12 mmol), **35** (34 mg, 0.08 mmol, 0.1 M in DCM), DMF (156 μ L, 1.27 mmol) and TfOH (10 μ L, 0.11 mmol). The reaction was stirred at -78°C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N , filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **39** (40 mg, 57% yield, $\alpha:\beta = 5:1$) was obtained as a colorless syrup. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.40-7.04 (m, 25 H, aromatic *H*), 5.06 (d, $J = 3.6$ Hz, 1 H, H-1), 4.99 (d, $J = 4.0$ Hz, 1 H, H-1), 4.90-4.50 (m, 8 H), 4.42-4.30 (m, 3 H), 4.12-3.86 (m, 7 H), 3.37 (dd, 1 H, $J_1 = 10.8$ Hz, $J_2 = 2.0$ Hz), 3.20 (dd, 1 H, $J_1 = 10.4$ Hz, $J_2 = 4.0$ Hz), 2.94 (dd, 1 H, $J_1 = 10.8$ Hz, $J_2 = 2.0$ Hz), 1.22-1.20 (m, 6 H, 2 CH_3). $^{13}\text{C-APT}$ (CDCl_3 , 100 MHz) δ 138.13, 138.11, 137.92, 137.82, 137.60 (aromatic C), 128.81, 128.65, 128.55, 128.51, 128.45, 128.40, 128.38, 128.20, 128.17, 128.12, 127.91, 127.85,

127.80, 127.78, 127.67, 127.18 (aromatic CH), 98.91 (C-1), 96.83 (C-1), 80.31, 78.18, 75.82, 75.49, 74.94, 73.71, 73.52, 73.36, 71.97, 71.06, 70.91, 69.18, 67.38, 67.08, 64.15, 59.48, 23.37 (CH₃), 21.70 (CH₃). HR-MS: Calculated for C₅₀H₅₆N₆O₉ [M+H]⁺: 885.41815, found: 885.41783.



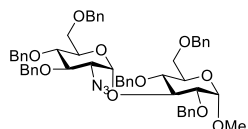
Synthesis of **40**: The reaction was carried out according to the standard procedure C. Using **32** (77 mg, 0.12 mmol), **36** (33 mg, 0.08 mmol, 0.1 M in DCM), DMF (156 μ L, 1.27 mmol) and TfOH (10 μ L, 0.11 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The products were purified by size exclusion.

Compound **40** (44 mg, 63% yield, $\alpha:\beta = 2:1$) was obtained as a colorless syrup. ¹H-NMR (CDCl₃, 400 MHz) δ 7.38-7.10 (m, 25 H, aromatic H), 5.18 (d, $J = 3.6$ Hz, 1 H, H-1), 5.07-5.04 (m, 2 H), 4.84-4.75 (m, 3 H), 4.66 (d, $J = 12.0$ Hz, 1 H, CHH), 4.60-4.43 (m, 5 H), 4.17-4.02 (m), 3.95-3.78 (m), 3.73-3.47 (m), 1.21-1.19 (m, 6 H, 2 CH₃). ¹³C-APT (CDCl₃, 100 MHz) δ 138.71, 138.21, 138.02, 137.94, 137.92 (aromatic C), 128.56, 128.53, 128.50, 128.42, 128.22, 128.05, 127.93, 127.86, 127.80, 127.74 (aromatic CH), 96.69 (C-1), 96.54 (C-1), 80.58, 78.24, 75.62, 75.37, 75.19, 75.07, 74.96, 73.81, 73.62, 73.56, 71.62, 70.73, 69.48, 68.51, 68.19, 63.98, 59.09, 23.35 (CH₃), 21.54 (CH₃). HR-MS: Calculated for C₅₀H₅₆N₆O₉ [M+H]⁺: 885.41815, found: 885.41763.



Synthesis of **41**: The reaction was carried out according to the standard procedure C. Using **32** (63 mg, 0.1 mmol), **11** (30 mg, 0.06 mmol, 0.1 M in DCM), MPF (127 μ L, 1.0 mmol) and TfOH (10 μ L, 0.1 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **41** (60 mg,

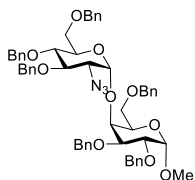
97% yield, $\alpha:\beta = 10:1$) was obtained as a colorless syrup. ¹H-NMR (CDCl₃, 400 MHz) δ 7.36-7.09 (m, 30 H, aromatic H), 5.74 (d, $J = 4.0$ Hz, 1 H, H-1), 5.11 (d, $J = 10.8$ Hz, 1 H, 1 CHH), 4.87-4.84 (m, 3 H), 4.77-4.73 (m, 2 H), 4.64-4.60 (m, 2 H), 4.50-4.43 (m, 4 H), 4.24 (d, $J = 12.4$ Hz, 1 H, CHH), 4.08 (t, $J = 9.2$ Hz, 1 H, CHH), 3.94-3.63 (m, 8 H), 3.58 (dd, 1 H, $J_1 = 9.2$ Hz, $J_2 = 3.6$ Hz), 3.51 (dd, 1 H, $J_1 = 10.8$ Hz, $J_2 = 2.0$ Hz), 3.38 (s, 3 H, OCH₃), 3.33-3.27 (m, 2 H). ¹³C-APT (CDCl₃, 100 MHz) δ 138.77, 138.26, 138.18, 138.08, 138.05, 137.87 (aromatic C), 128.62, 128.57, 128.46, 128.42, 128.31, 128.12, 127.94, 127.88, 127.83, 127.69, 127.61, 127.58, 127.37 (aromatic CH), 97.87 (C-1), 97.83 (C-1), 82.12, 80.59, 80.25, 78.17, 75.47, 75.14, 75.05, 73.64, 73.43, 73.32, 71.50, 69.57, 69.37, 67.92, 63.41, 55.43 (CH₃). HR-MS: Calculated for C₅₅H₅₉N₃O₁₀ [M+NH₄]⁺: 939.45387, found: 939.45366.



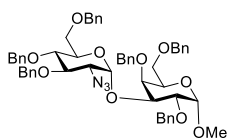
Synthesis of **42**: The reaction was carried out according to the standard procedure C. Using **32** (63 mg, 0.1 mmol), **12** (30 mg, 0.06 mmol, 0.1 M in DCM), MPF (127 μ L, 1.0 mmol) and TfOH (10 μ L, 0.1 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N,

filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **42** (55 mg, 92% yield, $\alpha:\beta = 3:1$) was obtained as a colorless syrup. ¹H-NMR (CDCl₃, 400 MHz) δ 7.36-7.09 (m, 30 H, aromatic H), 5.74 (d, $J = 4.0$ Hz, 1 H, H-1), 5.11 (d, $J = 10.8$ Hz, 1 H, 1 CHH), 4.87-4.84 (m, 3 H), 4.77-4.73 (m, 2 H), 4.64-4.60 (m, 2 H), 4.50-4.43 (m, 4 H), 4.24 (d, $J = 12.4$ Hz, 1 H, CHH), 4.08 (t, $J = 9.2$ Hz, 1 H, CHH), 3.94-3.63 (m, 8 H), 3.58 (dd, 1 H, $J_1 = 9.2$ Hz, $J_2 = 3.6$ Hz), 3.51 (dd, 1 H, $J_1 = 10.8$ Hz, $J_2 = 2.0$ Hz), 3.38 (s, 3 H, OCH₃), 3.33-3.27 (m, 2 H). ¹³C-APT (CDCl₃, 100

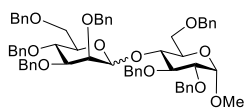
MHz,) δ 138.77, 138.26, 138.18, 138.08, 138.05, 137.87 (aromatic C), 128.62, 128.57, 128.46, 128.42, 128.31, 128.12, 127.94, 127.88, 127.83, 127.69, 127.61, 127.58, 127.37 (aromatic CH), 97.87 (C-1), 97.83 (C-1), 82.12, 80.59, 80.25, 78.17, 75.47, 75.14, 75.05, 73.64, 73.43, 73.32, 71.50, 69.57, 69.37, 67.92, 63.41, 55.43 (CH₃). HR-MS: Calculated for C₅₅H₅₉N₃O₁₀ [M+NH₄]⁺: 939.45387, found: 939.45374.



Synthesis of 43: The reaction was carried out according to the standard procedure C. Using **32** (63 mg, 0.1 mmol), **8** (30 mg, 0.06 mmol, 0.1 M in DCM), MPF (127 μ L, 1.0 mmol) and TfOH (10 μ L, 0.1 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **43** (61 mg, 99% yield, α : β = 5:1) was obtained as a colorless syrup. ¹H-NMR (CDCl₃, 400 MHz) δ 7.38-7.11 (m, 30 H, aromatic H), 4.94 (d, J = 3.6 Hz, 1 H, H-1), 4.88-4.68 (m, 9 H), 4.56-4.41 (m, 4 H), 4.25-4.15 (m, 3 H), 3.93-3.83 (m, 5 H), 3.78-3.73 (m, 1 H), 3.57-3.51 (m, 1 H), 3.38-3.34 (m, 4 H), 3.28 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 2.0 Hz), 3.02 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 2.0 Hz). ¹³C-APT (CDCl₃, 100 MHz,) δ 138.79, 138.44, 138.26, 138.20, 137.96, 137.67 (aromatic C), 128.61, 128.57, 128.47, 128.45, 128.40, 128.18, 128.13, 128.10, 127.91, 127.86, 127.80, 127.77, 127.59, 127.54 (aromatic CH), 98.71 (C-1), 98.61 (C-1), 80.53, 78.24, 77.39, 75.48, 75.32, 74.98, 74.89, 73.69, 73.43, 73.28, 70.79, 68.96, 67.52, 67.36, 64.19, 55.51 (CH₃). HR-MS: Calculated for C₅₅H₅₉N₃O₁₀ [M+NH₄]⁺: 939.45387, found: 939.45353.



Synthesis of 44: The reaction was carried out according to the standard procedure C. Using **32** (63 mg, 0.1 mmol), **9** (30 mg, 0.06 mmol, 0.1 M in DCM), MPF (127 μ L, 1.0 mmol) and TfOH (10 μ L, 0.1 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **44** (61 mg, 99% yield, α : β = 1.2:1) was obtained as a colorless syrup. HR-MS: Calculated for C₅₅H₅₉N₃O₁₀ [M+NH₄]⁺: 939.45387, found: 939.45379.



Synthesis of 46: The reaction was carried out according to the standard procedure A and C. Under condition A, using **45** (106 mg, 0.15 mmol, 0.1 M in DCM), **9** (45 mg, 0.1 mmol), DMF (189 μ L, 2.4 mmol) and TfOH (13 μ L, 1.59 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **46** (67 mg, quent, α : β = 2:1) was obtained as a colorless syrup. Under condition C, using **45** (106 mg, 0.15 mmol, 0.1 M in DCM), **9** (45 mg, 0.1 mmol), MPFF (189 μ L, 2.4 mmol) and TfOH (13 μ L, 1.59 mmol). The reaction was stirred at -78-0 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et₃N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **46** (67 mg, quent, α : β = 5:1) was obtained as a colorless syrup.

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Chinese Summary

中文总结

本论文围绕课题“添加剂控制的立体选择性合成1,2-顺势寡糖”，总结了博士期间的工作。在本论文中，应用添加剂（*N,N*-二甲基甲酰胺（DMF），三苯基氧化膦（ $\text{Ph}_3\text{P}=\text{O}$ ），*N*-甲基甲酰苯胺（MPF）和具有相似活性的单一芳香基团保护的单糖合成一系列顺式多糖。其中添加剂DMF主要应用于芳香基保护的葡萄糖给体和仲醇受体之间的耦合。添加剂 $\text{Ph}_3\text{P}=\text{O}$ 主要应用于活性更高的伯醇受体。而由于添加剂MPF与给体生成活性较高的中间体，所以其主要应用于活性更低的给体与受体，例如2-叠氮去氧糖。

在**第一章**中，总结了添加剂在糖苷化中的应用和发展。一些添加剂，如 DMF，氧化膦试剂和季铵盐类添加剂，已经被广泛研究并应用于糖苷化反应中调控选择性。许多的机理研究也已经证明添加剂与糖给体形成的中间加成物具有重要的功能。尽管在第一章描述中有许多非常成功的添加剂，但是发展新的添加剂和糖苷化条件仍然十分重要。因为目前仍缺乏具有普适性好且简单高效的添加剂或糖苷化方法，并且对于选择性合成多链寡糖仍非常具有挑战性。

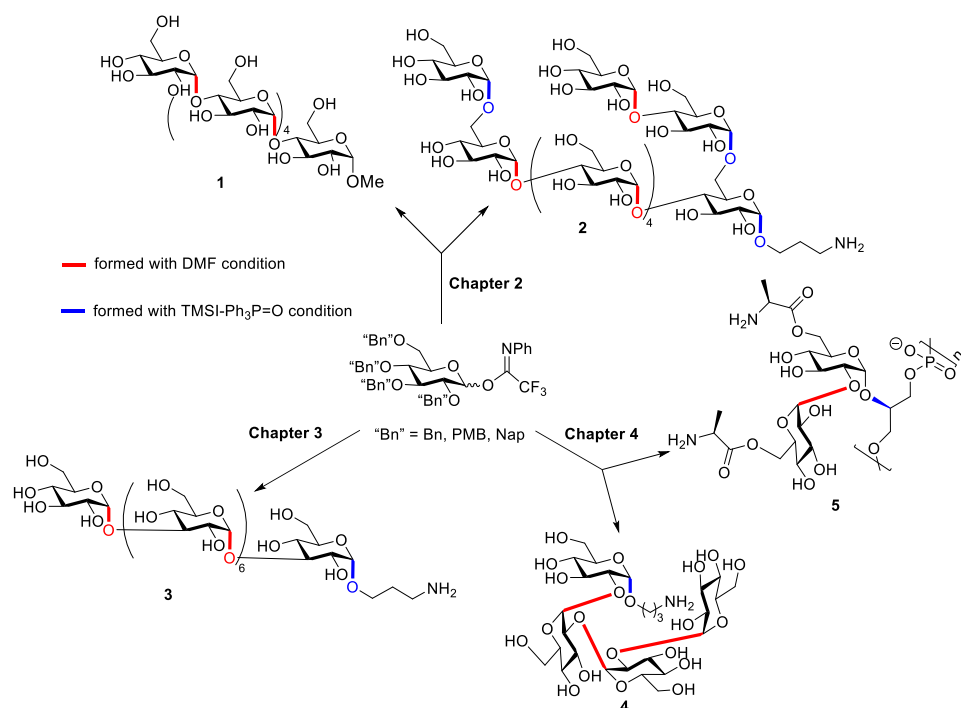


图 1. 第二，三和四章中的目标分子。

第二章描述了添加剂控制下 α -葡萄糖寡糖的合成。结合添加剂 DMF 和 $\text{Ph}_3\text{P}=\text{O}$ ，高效选择性的合成了目标分子，并且使用单一芳香基保护基团（Bn，PMB，Nap）使底物反应活性保持一致。应用该策略，对 α -(1,4)-直链葡萄糖六糖和结核杆菌衍生的支链 α -葡萄糖九糖被进行了高效选择性合成。在第三章中，应用同样的策略，对衍生自病原真菌 *Aspergillus fumigatus* 的 α -(1,3)-直链葡萄糖八糖进行了高效选择性合成。

第四章进一步描述了 α -(1,2)-葡萄糖寡糖的合成。应用 DMF 添加剂，对一个 α -(1,2)-葡萄糖四糖和一个衍生于 *Enterococcus faecalis* LTAs 的含有丙氨酸的 α -(1,2)-葡萄糖二糖进行了选择性合成。研究发现，在 DMF 条件下，合成一些较短的 α -(1,2)-葡萄糖寡糖具有很高的选择性。但是对于较长的 α -(1,2)-葡萄糖寡糖，选择性较差，可能由于较长的 α -(1,2)-葡萄糖寡糖受体空间结构复杂导致位阻增加，降低了反应活性和选择性。

在成功合成葡萄糖寡糖后，第五章转向了顺势半乳糖的合成研究。研究中发现， α -(1,4)-半乳糖苷的合成非常困难。经过筛选，在高温条件下，用添加剂 TMSI- $\text{Ph}_3\text{P}=\text{O}$ 调控合成 α -(1,4)-半乳糖苷能得到较好的选择性。并且此条件具有较好的底物扩展性。

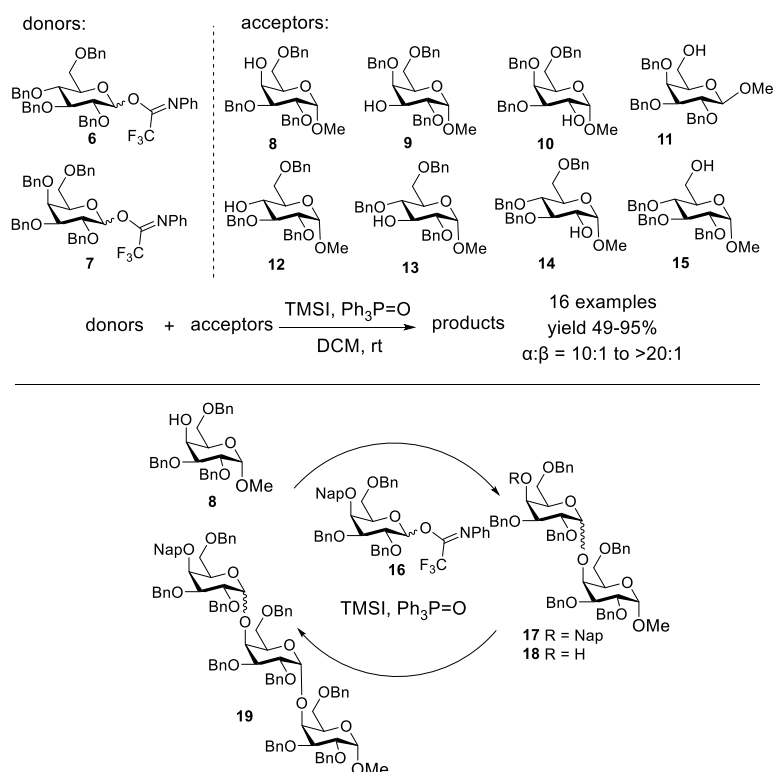


图 2. 用 TMSI- $\text{Ph}_3\text{P}=\text{O}$ 调控糖苷化（第五章）。

第六章描述了一个新的添加剂 *N*-甲基甲酰苯胺（MPF），此添加剂用于合成活性较低的 2-氨基去氧寡糖。在添加剂 MPF 调控下，对一个直链 α -(1,4)-氨基葡萄糖四糖进行了高效

高选择性合成。然后，采用[2+2+2]的合成策略，在添加剂 MPF 调控下对直链 Pel 六糖进行选择合成。

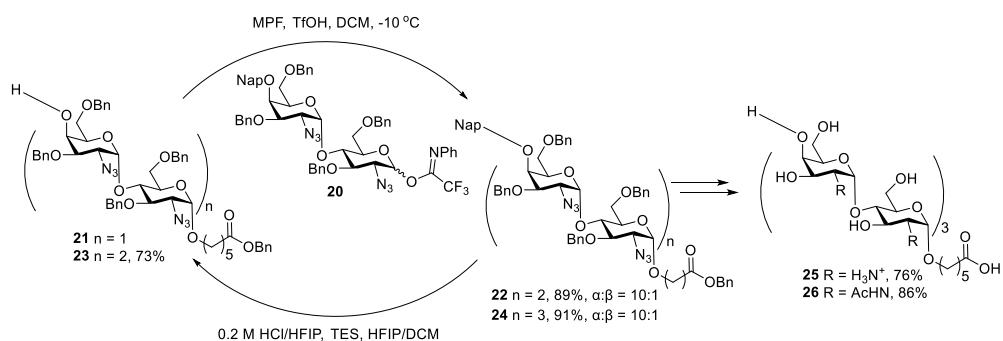


图 3. Pel 六糖分子的合成（第六章）。

第七章对本论文进行了总结和对未来的展望。目前添加剂调控的糖苷化主要应用于 α -糖苷的合成，期望未来发展出新的添加剂并应用于合成 β -糖苷。

List of Publications

Publications based on this Thesis:

1. Reagent Controlled Glycosylations for the Assembly of Well-defined Pel Oligosaccharides.
Liming Wang, Yongzhen Zhang, Herman S. Overkleeft, Gijsbert A. van der Marel, and Jeroen D. C. Codée. **2019**, manuscript in preparation.
2. α -Selective Galactosylation Using TMSI/Ph₃P=O Activation.
Liming Wang, Zhen Wang, Herman S. Overkleeft, Gijsbert A. van der Marel, and Jeroen D. C. Codée. **2019**, manuscript in preparation.
3. Synthesis of Teichoic Acid α -(1,2)-Glucans.
Liming Wang, Francesca Berni, Jacopo Enotarpi, Herman S. Overkleeft, Gijsbert A. van der Marel, and Jeroen D. C. Codée. **2019**, manuscript in preparation.
4. Reagent Controlled Stereoselective Assembly of α -(1,3)-Glucans.
Liming Wang, Herman S. Overkleeft, Gijsbert A. van der Marel, and Jeroen D. C. Codée*, *Eur. J. Org. Chem.* **2019**, 10, 1994-2003.
5. Reagent Controlled Stereoselective Synthesis of α -Glucans.
Liming Wang, Herman S. Overkleeft, Gijsbert A. van der Marel, and Jeroen D. C. Codée*, *J. Am. Chem. Soc.* **2018**, 140, 4632-4638.

Other Publications:

6. General and Efficient One-pot Synthesis of Novel Sugar/Heterocyclic(aryl) 1,2-Diketones from Sugar Terminal Alkynes by Sonogashira/tetra-*n*-butylammonium Permanganate Oxidation.
Fuyi. Zhang*, Xiaopei Wu, **Liming Wang**, Hong Liu, Yufen Zhao, *Carbohydr. Res.* **2015**, 417, 41-51.
7. Novel Regio- and Stereoselective Phosphonyl Radical Addition to Glycals Promoted by Mn(II)-air: Syntheses of 1,2-Dideoxy 2-*C*-diphenylphosphinylglycopyranosides.
Fuyi Zhang*, **Liming Wang**, Cui Zhang, Yufen Zhao, *Chem. Commun.* **2014**, 50, 2046-2048.

8. Synthesis of Substituted Mono- and Diindole C-Nucleoside Analogues from Sugar Terminal Alkynes by Sequential Sonogashira/Heteroannulation Reaction.
Fuyi Zhang*, Delong Mu, **Liming Wang**, Fen Han, Yufen Zhao, *J. Org. Chem.* **2014**, 79, 9490–9499.
9. Novel Syntheses of Aryl Quinoxaline C-nucleoside Analogs by Mild and Efficient three-component sequential reactions.
Fuyi Zhang*, Yuan Xi, Yanhui Lu, **Liming Wang**, Linwei Liu, Jinliang Li, Yufen Zhao, *Chem. Commun.* **2014**, 50, 5771-5773.

Curriculum Vitae

Liming Wang was born on 18th July 1988 in Yuzhou, Henan province, China. After finishing the high school education in Yuzhou, he was enrolled in Henan Normal University in 2008. He obtained his bachelor diploma in 2012 and joined in Zhengzhou University in the same year. In 2015, he received his master diploma after finishing the thesis “Synthesis of C-nucleoside analogues” under the supervision of Prof. Dr. Fuyi Zhang.

He started his PhD study on “Reagent controlled synthesis of 1,2-*cis*-oligosaccharides” under supervision of Dr. Jeroen D. C. Codée and Prof. Dr. Gijsbert A. van der Marel in the bio-organic synthesis group of Leiden University from September 2015 sponsored by Chinese Scholarship Council (CSC). Parts of his work was presented as poster at the annual Dutch chemistry conference “CHAINS” (2016, 2017, 2018). A poster was presented at the 19th European Carbohydrate Symposium 2017 in Barcelona, Spain. A poster was presented at the 29th International Carbohydrate Symposium 2018 in Lisbon, Portugal. And Parts of his work was presented as an oral presentation at the 20th European Carbohydrate Symposium 2019 in Leiden, the Netherland.

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Firstly, I feel deeply gratitude to my supervisor Dr. Jeroen D. C. Codée. I learned so much from you. You are a rigorous scientist and more a teacher. You are knowledgeable and always so patient and careful to guide me. Your trust, support and encouragement give me confidence to face and solve problems in chemistry and life. I am really honored as your PhD student. And I also express my gratitude to my promoter Prof. Dr. Gijsbert A. van der Marel. You are professional and humors. You can always find problems in my work summary and give me suggestions. Both of you are my supervisors forever.

I would like to thank Prof. Dr. Herman S. Overkleeft for his support to my application of PhD. And I would like to thank Nico, Rian, Hans and Bobby for your kind help to purify and analyze my compounds.

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Liming Wang
Leiden, 12/2019