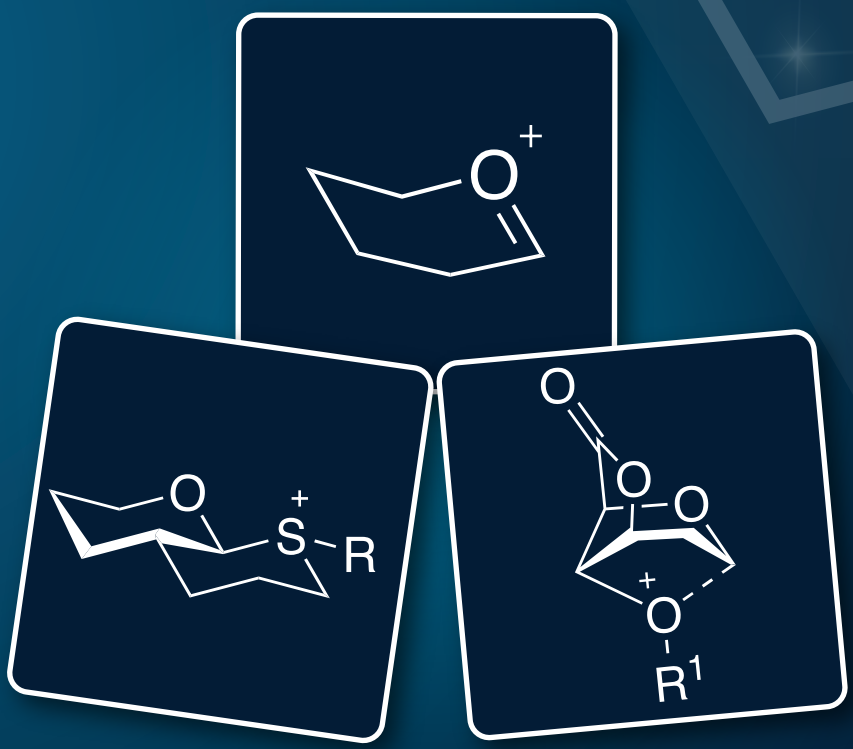
SELECTIVE 1,2-*CIS* GLYCOSYLATIONS EMPLOYING STEREODIRECTING GROUPS



RENS A. MENSINK

SELECTIVE 1,2-*CIS* GLYCOSYLATIONS EMPLOYING STEREODIRECTING GROUPS

Proefschrift

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List of Abbreviations

α	alpha
β	beta
δ	chemical shift
Ac	acetyl
ACB	2-(allylcarboxy)benzyl
Alloc	allyloxycarbonyl
aq	aqueous
BAIB	bis(acetoxy)iodobenzene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bz	benzoyl
C	chair
c	concentration
cat	catalytic
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]-undec-7-ene
DCB	dichlorobenzyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DIPEA	*N*,*N*-di-*iso*-propylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMB	dimethoxybenzene
DMF	*N*,*N*-dimethylformamide
DMP	2,6-dimethoxyphenyl
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
eq	molecular equivalents
Et	ethyl
Fmoc	fluorenylmethyloxycarbonyl
gal	galactose
glc	glucose
GPI	glycosylphosphatidylinositol
H	halfchair
h	hours
HMBC	heteronuclear multiple bond correlation
HOESY	heteronuclear Overhauser effect spectroscopy
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
J	coupling constant
Lev	levulinoyl
LHMDS	lithiumbis(trimethylsilyl)amide
m	multiplet
man	mannose
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MS	molecular sieves
NAP	2-naphthylmethyl
NGP	neighboring group participation
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Nu	nucleophile
p	*para*
PCB	*para*-chlorobenzyl
PCNB	*para*-cyanobenzyl
Ph	phenyl
*p*Ka	acid dissociation constant
PMP	*para*-methoxyphenyl
ppm	parts per million
Py	pyridine
q	quartet
RGP	remote group participation
rt	room temperature
s	singlet
sat	saturated
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
SPE	solid phase extraction

SPOS	solid phase oligosaccharide synthesis
t	triplet
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMB	trimethoxybenzene
TMP	2,4,6-trimethoxyphenyl
TMS	tetramethylsilane
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
Tol	*para*-toluene
Ts	*para*-toluenesulfonyl
TTBP	2,4,6-tri-*tert*-butylpyrimidine
v	volume
VT	variable temperature
wt	weight
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1

Advances in Stereoselective 1,2-*cis* Glycosylation using C-2 Auxiliaries

Part of this chapter has been published as a review:
R.A. Mensink, T.J. Boltje, *Chem. Eur. J.* **2017**, *23*, 17637-17653.

Abstract: The control of stereoselectivity in a glycosylation reaction remains one of the most challenging aspects of oligosaccharide synthesis. Especially the synthesis of 1,2-*cis*-glycosides is challenging and generally applicable methodology to prepare this linkage is needed to standardize oligosaccharide synthesis. This introductory chapter highlights the recent development of an elegant strategy employing a C-2 auxiliary to control the anomeric stereoselectivity in glycosylations. The various auxiliaries developed to date, their compatibility with protecting groups and monosaccharide types as well as mechanistic aspects are summarized. Furthermore, the application, advantages and limitations of C-2 auxiliaries in oligosaccharide synthesis are discussed.

1.0 – Introduction

The three major classes of macromolecules in biological systems comprise DNA, proteins and carbohydrates (also called glycans or saccharides).[1] Information encoded in DNA is transcribed and translated to direct protein synthesis. Hence, with the elucidation of the human genome came the expectation that all biological processes could be understood. However, our genetic blueprint proved insufficient to account for the origin of all biological processes. Other information-rich molecules that are not under direct genetic control must therefore play a major role.[2] Carbohydrates are a very important class of molecules in this respect and hence there is a growing appreciation that glycosylation dramatically increases protein complexity and function.[3] Similar to genomics for DNA and proteomics for proteins, "glycomics" is the study that seeks to identify and understand the structure and function of specific carbohydrate patterns in biological processes and the launch of the human glycome project is imminent.[3] A major obstacle in relating carbohydrate structure to function is the lack of pure and structurally well-defined carbohydrates and glycoconjugates. Because these compounds are difficult to isolate from natural sources, well-defined oligosaccharides can often only be obtained by chemical- or enzymatic synthesis.[4]

1.1 – Oligosaccharide and glycosidic linkage structure

Oligosaccharides are complex structures since they are often highly branched and the monomeric constituents (monosaccharides) are connected by glycosidic bonds which exist as either equatorial or axial diastereoisomers, called anomers. The anomeric stereochemistry is usually defined relative to the C-2 substituent (X), which can be axial (manno-type) or equatorial (gluco-type), as 1,2-*cis* or 1,2-*trans,* giving rise to four possibilities (Figure 1a). The anomeric configuration can also be defined as *α*-anomers (1,2-*cis*-D-glucotype and 1,2-*trans*-D-mannotype) or *β*-anomers (1,2-*cis*-D-mannotype and 1,2-*trans*-D-glucotype). In addition, the C-2 substituent is most frequently an alcohol, amine or hydrogen. The structural differences in the C-2 substituent and its relative orientation with respect to the anomeric substituent may seem subtle, but can have major implications for the biological function. For example, amylose and cellulose are anomeric diastereoisomers of 1,4-linked glucose polymers, and while amylose is a food source and can be enzymatically converted into glucose, cellulose on the other hand forms very strong fibers and is a structural component of wood (Figure 1b). With the importance of anomeric selectivity in mind, the main challenge in carbohydrate synthesis is the regioselective and stereoselective introduction of glycosidic bonds.[4-5] Similar to other stereoselective reactions, the induction of diastereoselectivity during a glycosylation event can be achieved by the use of a chiral catalyst, neighboring group participation (NGP) and creating facial selectivity using remote chiral centers.[4-5] Since most of these methods rely on the relative stereochemistry of neighboring and remote stereocenters, methods that are effective for glucose are not necessarily applicable to galactose or mannose and *vice versa*. A generally applicable

glycosylation methodology is needed to make oligosaccharide synthesis routine work, similar to peptide and oligonucleotide synthesis.[6]

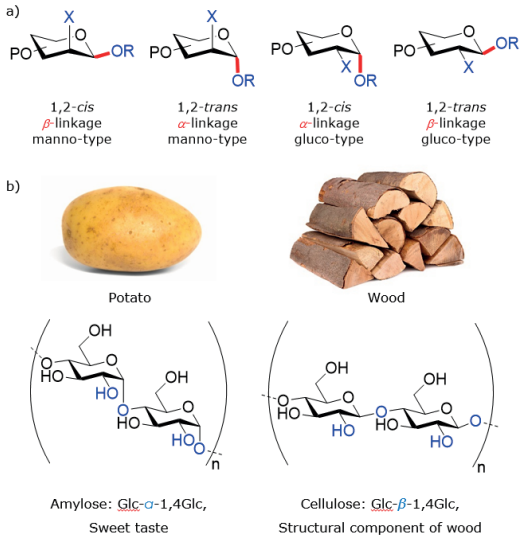
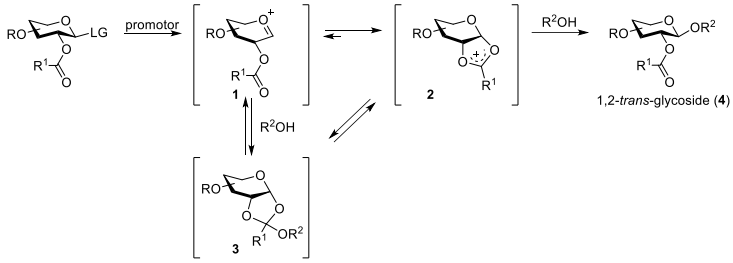


Figure 1: Structures of anomeric linkages. **a**) Four different kinds of linkages found in nature; **b**) The anomeric configuration has a profound influence on the molecular structure, properties and biological function. For example, anomeric diastereoisomers amylose and cellulose have a different biological role as the first is a food source and the latter a structural component of wood.

Ever since the groundbreaking report of the first stereoselective 1,2-*trans* glycosylation by Koenigs and Knorr,[7] general methods to prepare 1,2-*trans* glycosides are available and exploit neighboring group participation of a C-2-acyl group (Scheme 1).[5] When a glycosyl donor carrying an anomeric leaving group is activated to form intermediate oxocarbenium ion **1**, this intermediate is rapidly trapped by the neighboring group to form intermediate **2**, which can only be formed as a 1,2-*cis* fused ring system. A glycosyl acceptor (R^2OH) can only attack **2** at the anomeric center from the *β*-face leading to the stereoselective formation of 1,2-*trans* glycoside **4**. The glycosyl acceptor can also add directly to the dioxolenium ion (**2**) leading to the formation of orthoester **3**. The orthoester is not stable under acidic conditions and will rearrange to the desired 1,2-*trans* glycoside.[8] Numerous 2-*O*-acyl protecting groups have been developed to reduce orthoester formation and/or incorporate a latent nucleophile to enable selective removal in the presence of other esters. For example, the bulky pivaloyl ester (trimethyl acetyl ester) can be used to suppress orthoester formation due to steric shielding of the dioxolenium ion.[9]



Scheme 1: C-2 acyl participation reliably affords 1,2-*trans* glycosides (**4**)

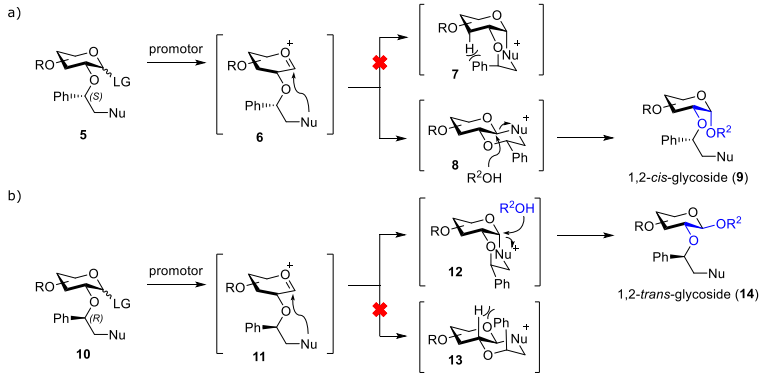
In general, the use of a 2-*O*-acyl functionality to synthesize 1,2-*trans* glycosides is very reliable, highly stereoselective and in the case of gluco-type donors, *β*-linked products will be obtained, whereas manno-type donors will give *α*-linked products. Furthermore, this strategy is also applicable to the synthesis of 2-deoxy-2-amino-glycosides using amine-protecting groups that can perform NGP. However, care needs to be taken when using an *N*-acetyl group for NGP as the corresponding glycosyl oxazoline is a commonly formed byproduct, but can be avoided by using lewis acid catalysis.[10] Alternatively, other amine protecting groups that can perform NGP such as phthalimido, tetrachlorophthalimido, trichloroacetyl, allyloxycarbonyl, and 2,2,2-trichloroethyloxycarbonyl can be used.[11]

In contrast, the introduction of 1,2-*cis* glycosidic linkages is much more challenging and requires glycosyl donors having a non-assisting functionality at C-2.[6] In general, these glycosylations are less selective and require optimization to achieve acceptable anomeric ratios. Recent advances in anomeric control have led to new methodologies to synthesize 1,2-*cis* linkages of monosaccharides such as glucose, galactose, mannose,[12] glucosamine,[13] galactosamine[14] and furanose sugars[15]. Although excellent, these methods are stereoselective *via* different mechanisms ranging from solvent effects,[16] directed aglycon delivery,[17] steric shielding,[14] S_N2-like displacement of a *quasi*-stable intermediate,[12] stabilization of an oxocarbenium ion conformation[15, 18] and post glycosylation anomerization.[6, 19] Out of these methods, the directed aglycon delivery methodology, using a tether between the glycosyl donor and glycosyl acceptor to control anomeric selectivity is applicable to both gluco- and manno-type sugars.[17b, 17c] However, the installation of a tether is additional work and the glycosylation yields can be moderate. This methodology therefore still lacks the applicability and reliability of NGP to prepare 1,2-*cis* glycosides.

The next sections review the development of a methodology that employs a C-2 chiral auxiliary to achieve 1,2-*cis* glycosylation. Similar to the use of NGP to prepare 1,2-*trans* glycosides, this methodology has the potential to become a generally applicable method for 1,2-*cis* glycoside synthesis. Combined, these complementary methods would enable the stereoselective synthesis of the most frequently found linkage types in nature and thereby advance the glycomics effort.[6]

1.2 – Chiral auxiliaries for glucose and galactose

The overall approach to achieve 1,2-*cis* stereoselectivity using C-2 chiral auxiliaries is depicted in Scheme 2a.[20] The chiral auxiliary is designed to trap the oxocarbenium ion from the *β*-face thereby blocking it and displacement of this intermediate should then result in the formation of 1,2-*cis*-glycosides. To achieve this, a nucleophilic group is situated to form a six membered ring system upon participation, which either results in a *cis*- (**7**) or *trans*-decalin (**8**) system. It was envisioned that a chiral substituent could be used to favor the formation of the *cis*- or *trans*-decalin system leading to 1,2-*trans* or 1,2-*cis* glycosides, respectively. In case of an *S*-configured auxiliary, formation of *cis*-decaling intermediate **7** results in axial placement of the chiral substituent which in turn leads to an unfavorable 1,4-diaxial steric interaction. In contrast, formation of *trans*-decalin intermediate **8** leads to a more favorable equatorial substitution and is hence preferred. In addition, *trans*-decalin system **8** will have less *gauche* interactions than *cis*-decalin system **7**. Therefore, the *S*-configuration is expected to favor 1,2-*cis*-glycoside formation by selectively forming *trans*-decalin intermediate **8**. Similarly, the *R*-configured auxiliary was expected to favor 1,2-*trans* glycoside formation, since the *cis*-decalin intermediate (**12**) leads to equatorial placement of the phenyl substituent and prevents the 1,3-diaxial steric interaction that the *trans*-decalin (**13**) experiences (Scheme 2b).



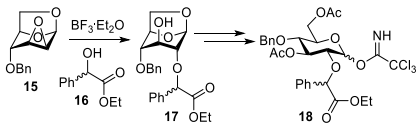
Scheme 2: A chiral **a**) *S*-configured auxiliary affords 1,2-*cis* glycosides (**9**) *via* a *trans*-configured decalin **8**; **b**) *R*-configured auxiliary affords 1,2-*trans* glycosides (**14**) *via cis*-configured decalin **12**.

1.2.1 – 1st generation chiral auxiliaries

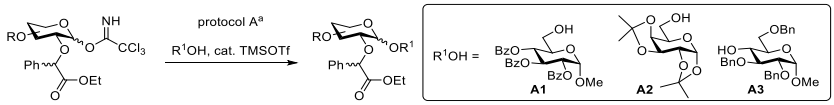
The first generation of chiral auxiliaries employed an (*S*)-ethoxycarbonylbenzyl moiety containing an ethyl ester as the nucleophilic head group since esters are proven to perform NGP. The C-2 ethoxycarbonylbenzyl moiety was installed by reaction of ethylmandelate (**16**) with Cerny epoxide **15**[21] and boron trifluoride (Table 1a).

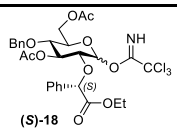
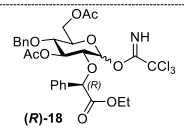
Table 1: Glycosylation with 1st generation auxiliaries.

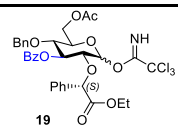
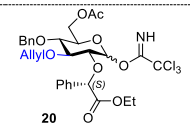
a)



b)



entry	donor	R^1OH	α / β	yield (%)
1		**A1**	18/1	94
2		**A2**	12/1	92
3	**(*S*)-18**	**A3**	20/1	89
4		**A1**	1/1	89
5		**A2**	1/3	88
6	**(*R*)-18**	**A3**	1/5	91

entry	donor	R^1OH	α / β	yield (%)
7		**A2**	>20/1	93
8	**19**	**A3**	7/1	88
9		**A2**	4/1	95
10	**20**	**A3**	1/3	87

a) Introduction of the ethoxycarbonylbenzyl moiety; **b**) Glycosylation results. [a] protocol A: donor (1 eq), R^1OH (1.2 eq), DCM, -78°C, then TMSOTf (0.4 eq), -78 °C – 0 °C.

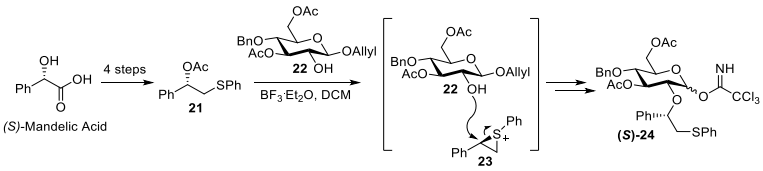
Subsequent acetolysis of the 1,6-anhydro-bridge was carried out, followed by conversion into the trichloroacetimidate donors (*S*)-**18** and (*R*)-**18**. Both the *R* and *S* isomer were prepared following this route and the resulting glycosyl imidates were evaluated as glycosyl donors (Table 1b). As expected, the use of the *S*-configured auxiliary led to the selective formation of 1,2-*cis* glycosides with an *α/β* selectivity ranging from 20/1 to 12/1 depending on the nature of glycosyl acceptor (Table 1b, entries 1-3), whereas the use of the *R*-auxiliary led to the predominate formation of 1,2-*trans*-glycosides (Table 1b, entries 4-6) albeit with lower selectivity (*α/β* between 1/5 and 1/1 depending on the glycosyl acceptor). These results demonstrated that the chirality of the auxiliary is an important determinant of the anomeric selectivity. The protecting group pattern of the glycosyl donor was investigated in a subsequent study and found to be an important determinant of the stereoselectivity.[22] For example, replacement of the C-3 acetyl with a benzoyl protecting group maintained *α*-selectivity, yet substitution by an allyl ether diminished the *α*-selectivity considerably, *α/β* 4:1 (Table 1b, entries 7-8 and 9-10, resp.). The lack of absolute stereoselectivity was attributed to glycosylation *via* the oxocarbenium ion. Hence, it was hypothesized that increasing the nucleophilicity of the participating functionality and reducing the flexibility of rotatable bonds in the auxiliary would speed-up neighboring group participation and improve stereoselectivity.

1.2.2 – 2nd generation chiral auxiliaries

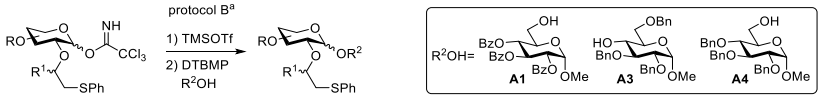
A second generation of chiral auxiliaries was designed to address these issues, employing a thiophenyl ether as the nucleophilic group.[23] The (*S*)-(phenylthiomethyl) benzyl moiety could be stereoselectively introduced by reaction of sugar alcohol **22** with (*S*)-(phenylthiomethyl)benzyl acetate **21** in the presence of $BF_3{\cdot}OEt_2$ (Table 2a).[24] These reactions proceed *via* anchimeric assistance of the thiophenyl group to form episulfonium intermediate **23**. Since double inversion occurs in this process, the stereochemistry of **21** is retained overall. This modification significantly improved 1,2-*cis* stereoselectivities and provided exclusively 1,2-*cis*-glycosides (Table 2b). In general, glycosylations using the (*S*)-(phenylthiomethyl) benzyl moiety were observed to be slower than normal indicating the presence of a *quasi*-stable, slow-reacting intermediate.

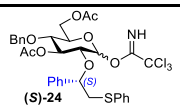
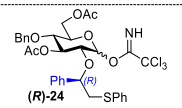
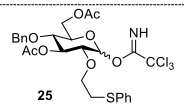
Table 2: Synthesis and glycosylation with 2nd generation auxiliaries

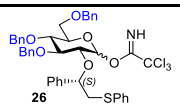
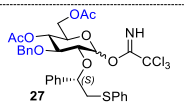
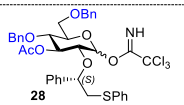
a)



b)



entry	donor	R^2OH	α / β	yield (%)
1		**A1**	1/0	93
2		**A3**	1/0	85
3	**(*S*)-24**	**A4**	1/0	95
4	 **(*R*)-24**	**A4**	1/1	88
5	 **25**	**A4**	8/1	86

entry	donor	R^2OH	α / β	yield (%)
6		**A1**	2/1	83
7	**26**	**A3**	1/1	75
8		**A1**	10/1	82
9	**27**	**A3**	1/0	74
10		**A1**	1/0	86
11	**28**	**A3**	1/0	77

a) Synthesis for the introduction of the C-2 chiral thioether auxiliary; **b)** Chiral auxiliaries designed to form *cis*- or *trans*-decalin sulfonium intermediates (entries 1–5) and protecting group variations (entries 6–11). [a] Protocol B: donor (1 eq), DCM, -78 °C, then TMSOTf (1 eq), -78 °C – 0 °C, then -78 °C, DTBMP (2 eq) and R^2OH (1.2-1.5 eq).

Low temperature NMR experiments showed the selective formation of a *β*-linked sulfonium ion intermediate. Again, the stereoselectivity was strongly dependent on the stereochemistry of the auxiliary. As expected, the (*S*)-auxiliary was 1,2-*cis* selective whilst the (*R*)-auxiliary was non-selective (Table 2b, entries 1-3 and 4, resp.). Interestingly, an auxiliary lacking the chiral substituent was less selective than the (*S*)-(phenylthiomethyl) benzyl moiety, yet still gave a respectable *α*-selectivity (Table 2b, entry 5). Since the 1,2-*cis*-decalin system experiences more unfavorable *gauche* interactions than the 1,2-*trans*-decalin system, 1,2-*cis*-glycosides are still formed predominantly even though no chiral substituent is present (*vide infra*). As in the case of the 1st generation auxiliaries (*vide supra*), the stereoselectivity was also strongly dependent on the type and distribution of protecting groups on the glycosyl donor (Table 2b, entries 6-11).[25] For example, glycosylations of glucosyl donor (*S*)**-24**, protected with acetyl esters at C-3, and C-6, gave the corresponding glucosides as only the *α*-anomer. However, similar glycosylations with glucosyl donor **26**, protected with benzyl ethers gave no or very poor anomeric selectivity (Table 2b, entries 1-3 vs 6-7). To investigate this result, extensive NMR analysis on benzyl protected donor **26** (Figure 2b) was performed to establish the presence or absence of the important *β*-sulfonium ion. After activation of the imidate leaving group, low temperature NMR clearly showed the *β*-sulfonium ion had formed on the basis of the H-1 chemical shift and coupling constant (Figure 2c) and the correlation of C-1 and H-8_{eq} in the HMBC spectrum (Figure 2d).[25]

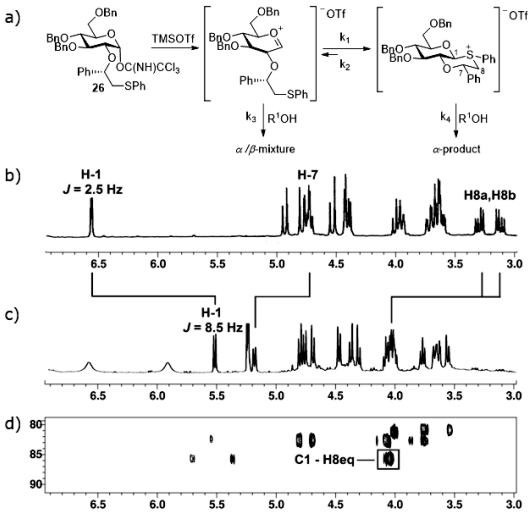
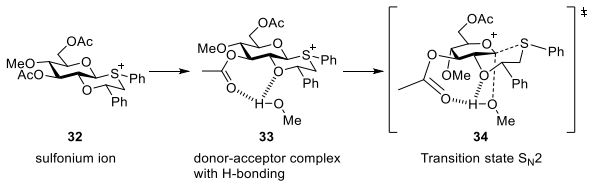


Figure 2: ^{1}H and ^{13}C NMR detection of the *β*-sulfonium ion intermediate. **a**) Curtin-Hammett principle; **b**) ^{1}H NMR spectrum of glucosyl donor **26** in CD_2Cl_2; **c**) ^{1}H NMR spectrum of **26** after addition of TMSOTf at (-20 °C); **d**) ^{1}H-^{13}C HMBC spectrum of the *β*-sulfonium ion at -20 °C. A cross-peak was observed between C-1 and H8-eq.

No other species were detected and hence the *β*-substituted sulfonium ion is the main reaction intermediate. It is, however, not the only reactive intermediate as addition of an alcohol resulted in the formation of a mixture of anomers. This observation was rationalized by the classical Curtin-Hammett principle in which the glycosylation takes place *via* the much more reactive oxocarbenium ion when the rates of interconversion (k_1 and k_2) are faster than that of glycosylation (k_4) (Figure 2a). More strongly electron-withdrawing groups such as the acetyl esters are expected to disfavor oxocarbenium ion formation and hence glycosylations takes place by an S_N2 like displacement of the *β*-anomeric sulfonium ion leading to the formation of *α*-glycosides. On the other hand, glycosylations with donors having electron-donating benzyl protecting groups, involve an equilibrium between the corresponding sulfonium and oxocarbenium ions.[26] Glycosylations then take place mainly through the latter intermediate thereby diminishing the *α*-selectivity. In order to establish how many, what type and at which position electron-withdrawing protecting groups are needed to ensure *α*-selectivity, a number of differentially protected glycosyl donors (**26**-**28**, Table 2b, entries 6-11) were synthesized and tested. From the glycosylations it is clear that one acetyl ester is sufficient to ensure stereoselective glycosylation when present at the C-3 position.[25]

To investigate this effect, DFT calculations were performed that simulated the S_N1 and S_N2 pathways and the role the C-3 acetyl plays in both (Scheme 3).[27] These calculations showed that the C-3 acyl group destabilizes the oxocarbenium ion in the S_N1 pathway thereby promoting the S_N2 pathway, as was postulated in earlier reports.[22, 25] However, the calculated energy difference between the S_N1 and S_N2 pathway is too small to exclude one or the other. Furthermore, DFT studies revealed that in both the S_N1 and S_N2 pathway, the acceptor can engage in dual hydrogen bonding with the C-3 ester functionality and the C-2 oxygen (**33**) thereby directing the approach from the *α*-face (**34**).

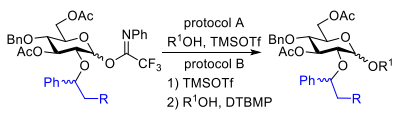


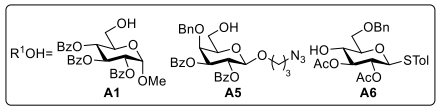
Scheme 3: Reaction intermediates according to DFT calculations of S_N2 transition state involving donor-acceptor hydrogen bonding.

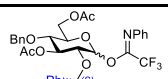
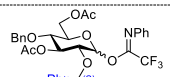
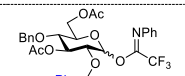
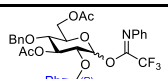
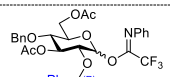
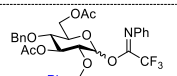
To further investigate if the observed intermediate sulfonium ion is a reactive intermediate or merely a resting state, the nature of the nucleophilic group was varied (Table 3).[27] Three auxiliary variants were prepared, containing either a thiophenyl ether (**29**), phenyl ether (**30**) or benzyl (**31**) moiety. The *R* and *S* configured auxiliaries were prepared giving rise to six variants in total. From the glycosylation results it is clear that the thiophenyl ether auxiliary

performs best and the phenyl ether auxiliary only performs slightly worse. The benzyl auxiliary cannot stabilize the oxocarbenium ion and hence glycosylation through this intermediate is expected in a less selective manner. In some cases however, benzyl auxiliary containing donor **31** performed quite well, but the same is true for a donor protected with a C-2 benzyl (data not shown, α/β = 15:1 with acceptor **A6**).[27] Changing the *S*-configuration to the *R*-configuration had the largest effect on the auxiliaries that are expected to perform neighboring group participation (thiophenyl ether (**29**) and phenyl ether (**30**) auxiliary) suggesting a role of the sulfonium/oxonium ion in the reaction pathway.

Table 3: Auxiliaries with various terminal groups, CH_2, O, S, and chirality





entry	donor	prot-ocol[a]	R^1OH	α / β	yield (%)
1		B	**A1**	1/0	93
2		B	**A5**	1/0	63
3	***(S)*-29**	B	**A6**	1/0	56
4		A	**A1**	1/0	100
5		A	**A5**	12/1	87
6	***(S)*-30**	A	**A6**	15/1	33
7		A	**A1**	1/0	100
8		A	**A5**	2/1	100
9	***(R)*-31**	A	**A6**	15/1	44
10		B	**A1**	3/1	88
11		B	**A5**	3/1	70
12	***(R)*-29**	B	**A6**	6/1	48
13		A	**A1**	4/1	81
14		A	**A5**	2/1	92
15	***(R)*-30**	A	**A6**	7/1	53
16		A	**A1**	10/1	83
17		A	**A5**	1.5/1	62
18	***(S)*-31**	A	**A6**	20/1	48

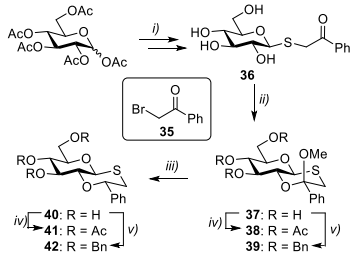
[a] protocol A: donor (1 eq), R^1OH (1.5 eq), DCM, -70 °C, then TMSOTf (1 eq), -70 °C – -40 °C; protocol B: donor (1 eq), DCM, -70 °C, then TMSOTf (1 eq), -70 °C – -20 °C, then -70 °C, DTBMP (2 eq) and R^1OH (1.5 eq), -70 °C – rt.

In case of the *R*-auxiliary, the existence of the expected *α*-sulfonium ion was confirmed by NMR even though the main products of these donors were *α*-glycosides. This result emphasizes that the observed intermediate is not necessarily a reactive intermediate. In case of (*S*)-**29**, it is much more challenging to establish whether the intermediate sulfonium ion is a reactive intermediate since the observed *α*-product could either be formed by S_N2 displacement or highly selective alternate pathways or a combination of both. The hallmark of an S_N2 reaction is the overall second order reaction kinetics, first order in both reagents. Hence, reaction rates were measured at different concentrations of glycosyl acceptor to establish the reaction kinetics. The observed initial rates of reaction could be fitted to a second order rate equation and hence these results therefore support an S_N2 displacement mechanism for glycosylation. Together with the results from the DFT calculations it was concluded that glycosylation occurs *via* a bimolecular mechanism in an S_N2-like fashion.[27]

In addition to participation of chiral auxiliaries from the C-2 position, the participation from the C-6 position has also been studied to prepare *α*-2-deoxy sugars.[28] Indeed the use of the C-6 auxiliary led to the stereoselective formation of *α*-2-deoxy-glycosides albeit with lower selectivity compared to the C-2 participation examples mentioned above.

1.2.3 - Oxathiane glycosyl donors

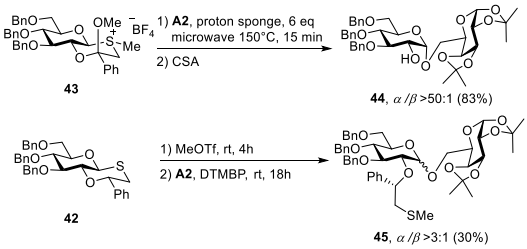
Another route towards *trans*-decalin sulfonium ions *via* an integrated oxathiane stereodirecting group was developed by Turnbull *et al.* to reduce the synthetic effort needed for the implementation of an *α*-directing moiety into the glycosyl donor (Scheme 4).[29] It was envisioned that the thioglycoside moiety could be activated by alkylation or arylation to provide a sulfonium ion intermediate for subsequent glycosylation (Scheme 5 and 6). The oxathiane precursor **36** was synthesized from glucose pentaacetate by conversion into the *β*-thiol, addition to 2-bromoacetophenone **35** and finally deacetylation (Scheme 4).[29] Reaction of **36** in acidic MeOH resulted in regio- and stereoselective cyclization to provide methyl ketal **37**, in which the smaller methoxy group is in the axial position, where it also benefits from stabilization of the anomeric effect. Hence this method obviates the need for elaborate protecting group strategies to isolate the C-2 alcohol for incorporation of the chiral auxiliary. Additionally, since the formation of the methyl ketal is stereoselective, achiral starting materials can be used to construct a chiral auxiliary.



Scheme 4: Synthesis of oxathianes. Reagents and conditions: *i*) a) thiourea, $BF_3.OEt_2$, MeCN; b) **35**, Et_3N; c) NaOMe, MeOH; *ii*) TsOH, MeOH; *iii*) TMSOTf, Et_3SiH, DCE; *iv*) Ac_2O, pyr; *v*) NaH, BnBr, DMF.

Furthermore, the methyl ketal could be reduced in a stereoselective manner to provide oxathiane **40**. Another advantage of the oxathiane donors is their stability during protecting group manipulations and the remaining triol could be protected with various protecting groups.[29-30] The activation of oxathiane donor **39** was investigated by methylation using trimethyloxonium tetrafluoroborate affording **43**, which proved to be highly stable and could even be crystalized from hot ethanol.[31] The crystal structure revealed that the axial methoxy group stabilized the cation, thus making it less reactive. Glycosylation of sulfonium **43** with **A2**

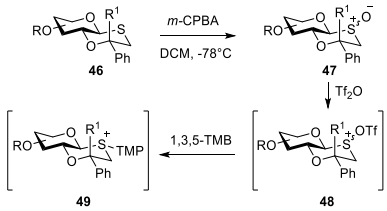
was achieved in a microwave reactor at 150°C and subsequent acidic cleavage of the auxiliary afforded *α*-disaccharide **44** with an *α*/*β* ratio of >50:1 (83%, Scheme 5).



Scheme 5: *α*-selective glycosylations of surprisingly stable activated oxathiane **43** and in-situ activation of donor **42**.

Sulfonium ion **42,** which lacks the axial methoxy group, should be less stable and hence should glycosylate with more ease. Indeed, activation of **42** with methyl triflate, followed by glycosylation with **A2** at room temperature proceeded smoothly, albeit with a significant decrease in stereoselectivity (*α*/*β* 3:1) and yield. The loss in yield was caused by competing *S*-methyl transfer from the donor salt to the newly formed *S*-methyl sulfide in the C-2 auxiliary. The loss of stereoselectivity highlights the importance of the methyl ketal.

The alkyl sulfonium ions proved to be stereoselective, yet quite unreactive and hence aryl sulfonium ions were investigated to improve the reactivity.[29-31] Arylation of oxathiane donors can be achieved by reaction with benzyne,[32] but the most efficient method made use of an electrophilic aromatic substitution of the sulfoxide derivative.[29-31] *m*-CPBA was used to oxidize oxathiane **46** to afford the corresponding sulfoxide glycosyl donor **47** (Scheme 6).



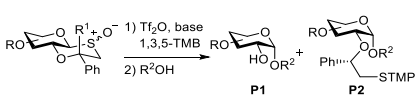
Scheme 6: Oxathiane glycosylation mechanism.

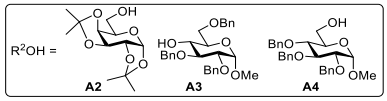
Activation with Tf_2O in the presence of 1,3,5-trimethoxybenzene (TMB) gave rise to arylated sulfonium ion **49** *via* electrophilic aromatic substitution of triflate **48**.[33] This process required the use of highly electronrich aromatic compounds such as TMB and 1,3-dimethoxybenzene (DMB). The thereby formed aryl sulfonium ions proved to be much more reactive than their alkyl counterparts and also very stereoselective. In contrast to earlier auxiliaries, the methyl ketal oxathiane donors showed almost complete *α*-selectivity irrespective of the protecting group

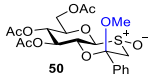
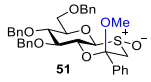
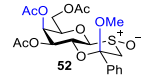
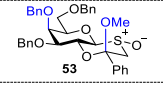
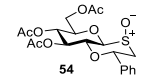
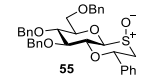
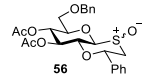
pattern on the glycosyl donor (Table 4, entries 1-4). Furthermore, the stereoselectivity was excellent when galactose was used as a glycosyl donor (Table 4, entries 5-6).[29]

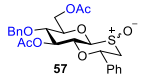
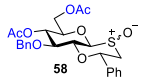
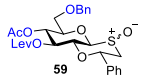
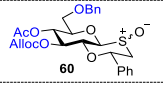
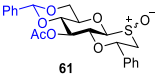
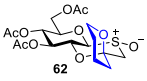
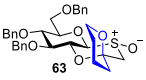
The only drawback of the methyl ketal donors is that the acyclic methyl ketal formed after glycosylation proved to be labile, leading to the release of methanol which subsequently acted as a competing nucleophile. Additionally, the workup procedure resulted in further loss of the ketal functionality, thus the auxiliary was removed completely with $BF_3.OEt_2$ in methanol prior to workup. To address this issue the more stable ether oxathiane donors **54** and **55** were investigated.[30-32]

Table 4: Glycosylations of various oxathiane donors.





entry	donor	Prot-ocol[a]	R^1OH	*α* / *β* yield (%) P1	*α* / *β* yield (%) P2
1	 **50**	C	**A2**	>50/1 85	-
2		C	**A4**	>50/1 44	-
3	 **51**	C	**A2**	>50/1 89	-
4		C	**A4**	>50/1 72	-
5	 **52**	C	**A2**	>50/1 79	-
6	 **53**	C	**A2**	>50/1 78	-
7	 **54**	D	**A2**	-	7/1 61
8		D	**A4**	-	16/1 71
9	 **55**	D	**A2**	-	5/1 67
10		D	**A4**	-	5/1 62
11	 **56**	E	**A2**	-	1/0 94
12		E	**A4**	-	>25/1 67

entry	donor	Prot-ocol[a]	R^1OH	*α* / *β* yield (%) P2
13	 **57**	E	**A2**	1/0 84
14		E	**A3**	>15/1 59
15	 **58**	E	**A2**	1/0 98
16		E	**A3**	7/1 46
17	 **59**	E	**A2**	>15/1 85
18		E	**A3**	>15/1 64
19	 **60**	E	**A2**	1/0 67
20	 **61**	E[b]	**A2**	13/1 69
21	 **62**	F	**A2**	13/1 60
22	 **63**	F	**A2**	12/1 58

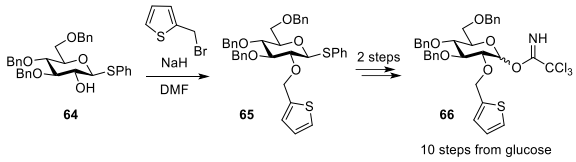
[a] *protocol C:* donor (1 eq), DIPEA (1.2 eq), Tf_2O (1.1 eq), 1,3,5-trimethoxybenzene (2.2 eq), DCE, -30 – -10 °C, then DIPEA (6eq) and R^1OH (2.5 eq) then heated at 50 °C for 18h; *protocol D:* donor (1 eq), DTBMP (2.5 eq), Tf_2O (1.1 eq), 1,3,5-trimethoxybenzene (2.2 eq), DCM, -60 – -10 °C, then R^1OH (1.2-2.5 eq) warmed to rt; *protocol E:* donor (1 eq), DTBMP (2 eq), Tf_2O (1.1 eq), 1,3,5-trimethoxybenzene (1.5 eq), DCM, -10 °C, then cooled to -40 °C and R^1OH (0.8 eq) -40 °C – rt. *protocol F:* donor (1 eq), DIPEA (1.2 eq), Tf_2O (1.1 eq), 1,3,5-trimethoxybenzene (1.1 eq) in DCM -30°C – rt, [b]preactivation -60°C – -10°C, then **A2**, -10°C – rt, 12 days. TMP = 2,4,6-trimethoxyphenyl.

These donors proved to be more stable and provided disaccharides in higher yields. However, the stereoselectivity was reduced compared to the methyl ketal donors again highlighting the importance of this functionality. Whilst the methyl ketal donors provided good stereoselectivity in either acetylated (**50**) or benzylated (**51**) form, the ether variants (**54** and **55**) proved much more sensitive to the protecting group pattern on the donor.[30-31] This was further investigated by the synthesis and glycosylation of differentially protected oxathiane donors **56**-**61** (Table 4, entries 11-20). In general, the use of electron-withdrawing groups, especially at C-3, proved to be important to maintain *α*-selectivity which is in good agreement with aforementioned results. Additionally, temperature might also play an important role in the glycosylations as protocol D adds the acceptors at -10°C, whereas protocol E adds the acceptors at -40°C and the stereoselectivity is much higher in the latter protocol The mechanism of glycosylation of oxathiane donors was also investigated *in silico* using DFT calculations to establish the role of the sulfonium ion in the reaction pathway.[31] The S_N1 and S_N2 pathways of both ketal and ether sulfonium functionalities were investigated, but neither was in full agreement with the experimental results. It is however clear that the sulfonium ion does probably not react solely *via* an S_N2 mechanism on which basis these glycosyl donors were designed.

From the experimental results it was clear that the methyl ketal was vital for excellent stereoselectivity, but proved unstable after glycosylation. With this in mind, Turnbull *et al.* set out to improve the ketal stability by introducing a spiroketal (**62** and **63**).[34] This auxiliary conserves the cyclic nature even after it is displaced by the glycosyl acceptor, hence is more stable and cannot release a competing nucleophile. The spiroketal oxathianes **62** and **63** were prepared starting from a dihydropyran precursor using a similar strategy as used for the methyl ketals. Activation was achieved by oxidation to the sulfoxide and reaction with TMB followed by glycosylation. The reactions proceeded well with a lower acceptor concentration as intended since no competing nucleophile was released. The isolation of the disaccharides again proved to be more convenient after acidic removal of the ketal auxiliary. The glycosylation results reveal a loss of stereoselectivity with the spiroketal, *α*/*β* 13:1 (Table 4, entry 21, acetylated donor) and *α*/*β* 12:1 (Table 4, entry 22, benzylated donor) compared to their methyl ketal counterparts (*α*/*β* > 50:1, Table 4, entries 1 and 3) suggesting that the structure of the ketal is important for the stereoselectivity. It was noted that the glycosylation reaction was sluggish and tuning of the reactivity of the sulfonium ion by modifying the aryl structure was investigated. It was envisioned that the use of less electronrich DMB would lead to a less stabilized and therefore more reactive sulfonium ion. A competition experiment between oxathiane **62** activated with TMB or DMB showed that the DMB was indeed ~1.5 times more reactive. However, the increase in reactivity led to a decrease in selectivity in case of spiroketal donor **62** which is consistent with earlier findings.

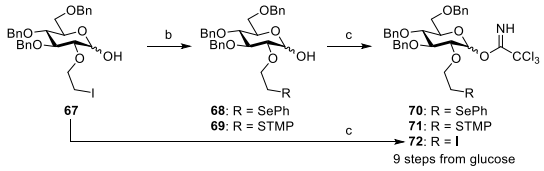
1.3 – Achiral auxiliaries for glucosides and galactosides

The observation made by Boons *et al.* that the achiral version of their auxiliary still provided mainly 1,2-*cis*-products (*α*/*β* 8:1, Table 2b, entry 5) inspired researchers to investigate the use of achiral auxiliaries as they are simpler to synthesize and do not require chiral starting materials. Fairbanks *et al.* investigated the role of the nucleophilic group in such achiral auxiliaries and variants containing a thiophene,[35] iodo and selenophenyl[36] or 2,4,6-trimethoxythiophenyl group (Scheme 7 and 8).[37] Alkylation of the C-2 position in **64** with 2-bromomethyl thiophene under standard conditions gave intermediate **65** which could be converted into glycosyl imidate **66** (Scheme 7).[35]



Scheme 7: Synthesis of thiophene donor **66**.

The installation of the 2-(iodo)-ethyl-, 2-(selenophenyl)-ethyl- and 2-(2,4,6-trimethoxythiophenyl)-ethyl ethers proved more challenging than expected. The best route relied on the 2-iodo-ethyl precursor **67** which was prepared by the conversion of a C-2 allyl ether *via* ozonolysis, reduction and subsequent iodination of the alcohol (Scheme 8).[36] Conversion of this intermediate into the glycosyl imidate afforded the 2-(iodo)-ethyl auxiliary donor **72**. Nucleophilic displacement of the iodide using phenyl selenol or 2,4,6-trimethoxythiophenol afforded hemiacetals **68** and **69** and subsequent imidation gave glycosyl donors **70** and **71**.[36-37] Using this chemistry, a number of differentially protected glycosyl donors were prepared.



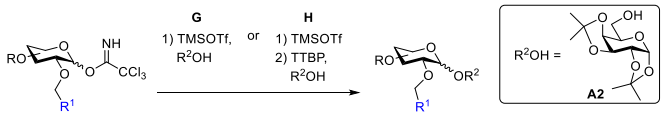
Scheme 8: Synthesis of selenium, sulfur and iodide donors **70**, **71** and **72**, resp. Reagents and conditions: a) PhSeH or 2,4,6-trimethoxybenzenethiol, DIPEA, DMF; *b*) Cl_3CCN, DBU, DCM, 0ºC.

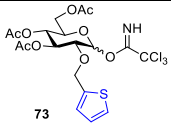
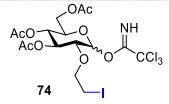
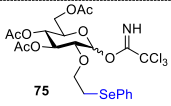
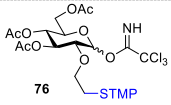
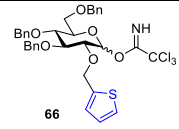
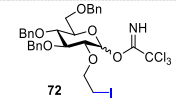
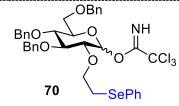
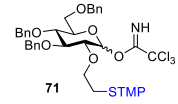
1.3.1 – Glycosylation results

The glycosylation results of glycosyl donors carrying achiral auxiliaries are summarized in Table 5. The stereoselectivity with the thiophene based auxiliary was poor to moderate depending on

the type of protecting groups used.[35] Acetylated donor **73** was unselective (*α*/*β* 1:1), whereas the benzylated counterpart (**66**) was much more stereoselective (*α*/*β* 9:1). In the latter case, the stereoselectivity was also strongly dependent on the type of glycosyl acceptor (up to *α*/*β* 30:1 for benzylidene protected mannose acceptors).[35a] In the case of both the acetyl and benzyl protected donor, low temperature NMR studies showed the presence of distorted *β*-configured sulfonium intermediates.[35b] From the glycosylation results it is clear however, that these intermediates are probably not reactive intermediates. In a subsequent study, the use of a 2-(iodo)-ethyl or 2-(selenophenyl)-ethyl ether as a participating group was explored.[36] Very poor selectivity was observed in both cases with again the benzylated glycosyl donors performing better than their acetylated counterparts (Table 5, entries 2-3 vs 6-7).This result is the reverse of what would be expected based on the findings in earlier studies that show that electron-withdrawing groups on the glycosyl donor perform better than electron-donating ones.[25] Again low temperature NMR experiments were performed to detect reaction intermediates. In the case of the 2-(iodo)-ethyl auxiliary no iodonium ion could be detected for acetylated donor **74** or benzylated donor **72**. Hence, it is clear that this group does not participate in the reaction.

Table 5: Glycosylation results of donors carrying achiral auxiliaries.



entry	donor	protocol[a]	R^2OH	*α* / *β*	yield (%)
1	 **73**	G	**A2**	1/1	89
2	 **74**	G	**A2**	1/2	76
3	 **75**	G	**A2**	2/3	75
4	 **76**	H	**A2**	5/1	63
5	 **66**	G	**A2**	9/1	84
6	 **72**	G	**A2**	4/1	75
7	 **70**	G	**A2**	5/1	80
8	 **71**	H	**A2**	1/0	69

[a] *protocol G:* donor (1 eq) and **A2** (2 eq) in DCM at -40°C (thiophene) or -78°C (I, SePh); *protocol H:* donor (1 eq) in DCM, -78°C, TMSOTf (1 eq), -78°C – 0°C, then -78°C, **A2** (1.5 eq) and TTBP (2eq) then -78°C – rt. TTBP = 2,4,6-tri-*tert*-butylpyrimidine.

In the case of the 2-(selenophenyl)-ethyl auxiliary, a selenium ion was only detected in the case of acetylated donor **75**. However, the stereoselectivity of donor **75** is lower than the benzylated counterpart (**70**) which does not show selenium ion formation in the VT-NMR studies. Hence in this case it is also unlikely that the observed stereoselectivity is a result of neighboring group participation.

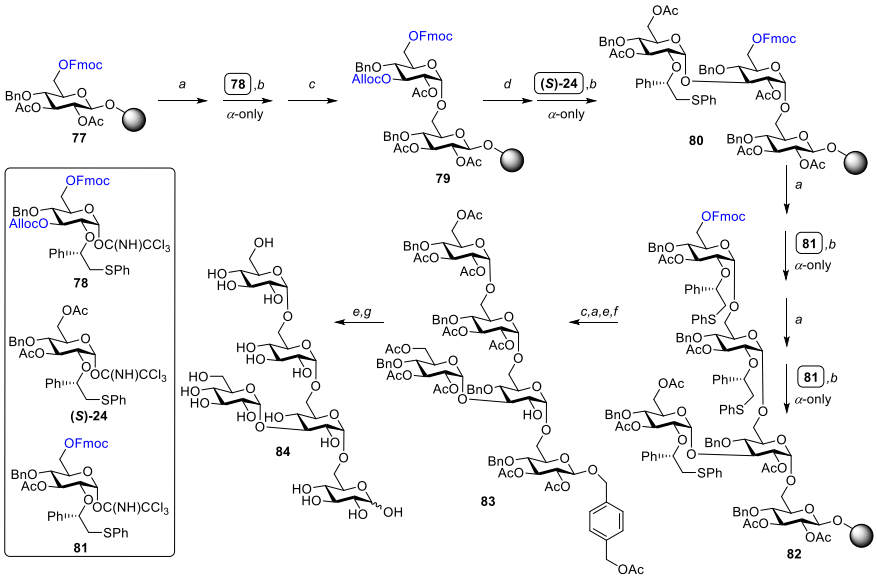
As a result, more electronrich participating groups were explored next. Inspired by the work of Turnbull *et al.* the 2,4,6-trimethoxythiophenyl participating group was explored.[37] This auxiliary showed much improved stereoselectivities with the acetylated donor (**76**) being moderately selective (α/β, 5:1) and benzylated donor **71** being fully α-selective for a range of glycosyl acceptors. This surprising result was rationalized by NMR experiments which showed the formation of a β-sulfonium ion in case of benzylated donor **71**, but not in the case of acetylated counterpart **76**. This result is surprising considering that similar chiral systems were much less selective.[25] The use of achiral auxiliaries has potential as evidenced by the use of the 2-(2,4,6-trimethoxythiophenyl)-ethyl auxiliary (**71**) which was highly stereoselective. However, the synthesis of glycosyl donors containing such auxiliaries is still quite lengthy and does not offset the benefit of not having to use chiral starting materials.

1.4 – Application to complex oligosaccharide synthesis

The true scope and limitations of synthetic methodologies are best established by their application in total syntheses. As can be seen in the previous sections, the protecting groups on the glycosyl donor and its relative stereochemistry as well as the structure of the auxiliary have a profound influence on the stereoselectivity. Application to total synthesis has revealed other aspects to keep in mind when using chiral auxiliaries such as protecting group compatibility, auxiliary removal, sterics and its potential with respect to solid phase synthesis. To date, three total syntheses of oligosaccharides using chiral auxiliaries have been reported.[30, 38] Absolute stereocontrol is especially important to enable solid phase oligosaccharide synthesis. Solid-phase oligosaccharide synthesis (SPOS) offers the promise of increasing the speed of oligosaccharide assembly, primarily by eliminating intermediate purification steps and by automation.[39] Since no intermediate purification is undertaken, intractable mixtures of compounds will be formed if the glycosylations are not fully stereoselective. Not surprisingly, only a few examples of SPOS of oligosaccharides containing 1,2-*cis*-glycosides have been reported.[40] These rely on tedious separation of the anomers by high-performance liquid chromatography or the preparation of a 1,2-*cis*-linked disaccharide in solution, which after purification to remove the unwanted 1,2-*trans*-anomer, can be used in solid-phase synthesis. Thus, a major stumbling block in SPOS is the inability to reliably introduce 1,2-*cis*-glycosides with complete stereoselectivity.

1.4.1 – Synthesis of pentasaccharide found in *Aconitum carmichaeli*

The use of chiral auxiliaries to address this issue was explored in the synthesis of a branched *α*-linked pentasaccharide found in *Aconitum carmichaeli* that has the potential to be developed as an adjuvant.[41] The polysaccharide is composed of an *α*(1,6)-linked glucosyl backbone, branched with an *α*(1,3)-linked glucoside moiety. Such *α*-glucans are considerably challenging to synthesize on solid support due to the multitude of 1,2-*cis*-linkages and their branched structure. Pentasaccharide **84** from *Aconitum carmichaeli* was prepared from monosaccharide building blocks **78**, **(S)-24** and **81** (Scheme 9).[38a] By using orthogonal Alloc and Fmoc protecting groups, branching could be achieved. The Fmoc protecting group of **77** was removed by treatment with piperidine/DMF and coupled with auxiliary-containing glucosyl donor **78** to install the first 1,2-*cis* linkage. The couplings were performed by the addition of preformed sulfonium ion to the acceptor. Double couplings were performed to achieve full conversion. The Alloc function could be removed by treatment with $Pd(PPh_3)_4$ in a mixture of THF and AcOH to give the corresponding disaccharide acceptor. However, this acceptor could not be coupled with preactivated **(*S*)-24**. It was hypothesized that the C3′ hydroxyl is sterically shielded by the neighboring (*S*)-(phenylthiomethyl)benzyl ether.

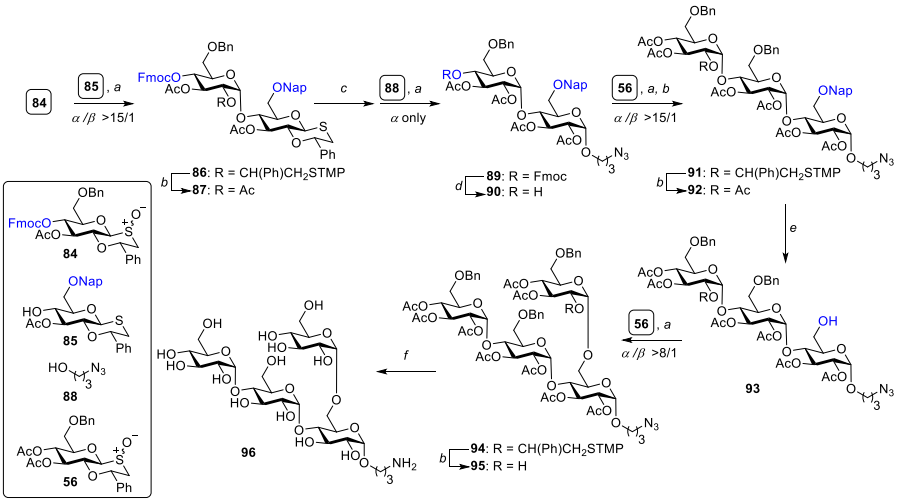


Scheme 9: Solid phase synthesis of branched pentaglucoside **84**. Reagents and conditions: *a)* 10% v/v piperidine in DMF, 5 min, rt. *b)* **78**, **(*S*)-24** or **81**, TMSOTf, DCM, MS4Å, 15 min, -40°C then added to acceptor, DTBMP, DCM, MS4Å, 16h -40°C → rt, double coupling. *c)* $BF_3{\cdot}Et_2O$, Ac_2O/DCM 1/2 v/v, 16h, 0°C. *d)* 40 mol% $Pd(PPh_3)_4$, THF/AcOH 10/1 v/v, 16h, rt. *e)* NaOMe, MeOH/DCM 1/1, 16h, rt. *f)* Ac_2O, pyr 1/3 v/v; *g)* 20 wt% $Pd(OH)_2$/C, H_2, EtOH/H_2O 1/1 v/v, 16h, rt, 87%.

Thus, the auxiliary was converted into an acetyl ester by treatment with acetic anhydride in the presence of $BF_3{\cdot}OEt_2$ affording **79**. The Alloc was removed under standard conditions and coupling with pre-activated **(*S*)-24** was now successful to yield resin-bound trisaccharide **80**. A sequence of Fmoc removals and couplings with donor **81** gave rise to the complete protected pentasaccharide **82**. The C-2 auxiliaries were removed on-resin under aforementioned conditions and the product was cleaved using NaOMe/MeOH affording pentasaccharide **83**. Reacetylation was performed to aid purification and NMR analysis. No anomeric isomers of the completed product were detected which was obtained in an overall yield of 25% (90% per step, 13 on-resin steps). Finally, target compound **84** was prepared by removal of the acetyl esters, using standard conditions followed by hydrogenolysis of the benzyl ethers using $Pd(OH)_2/C$ (20 wt%) and H_2 gas. The total synthesis of pentasaccharide **84** was the first example of a stereoselective solid-supported synthesis of an oligosaccharide having multiple 1,2-*cis*-glycosidic linkages. A particularly interesting feature was that a relatively small excess (2.0 equiv) of glycosyl donor was required to drive the glycosylations to completion. It is likely that the intermediate sulfonium ion is sufficiently stable to diffuse into the polymer support for glycosylation of the resin-bound sugar hydroxyls. However, a limitation of the C-2 auxiliary is that it may block the neighboring C-3 hydroxyl from reacting and hence requiring auxiliary removal prior to glycosylation at this site.

1.4.2 – Synthesis of a tetrasaccharide found in *Pseudallescheria boydii*

Similar *α*-glucans have also been isolated from various microbial sources such as *Pseudallescheria boydii*, producing a polysaccharide that is essential for conidial phagocytosis by macrophages and induction of innate immune responses in a TLR2-dependent manner. Tetrasaccharide **134** isolated from *Pseudallescheria boydii* was synthesized using oxathiane donors and a bi-directional approach.[30] Tetrasaccharide **96** contains an *α*(1,4)-linked backbone and *α*(1,6)-branching which could be prepared from monosaccharides building blocks **56**, **84**, **85** and **88** (Scheme 10). It was envisioned that oxathiane **85** could serve as a latent-active glycosyl donor.[42] Hence, disaccharide **86** was prepared by coupling of preactivated **84** to glycosyl acceptor **85** with excellent selectivity. Activation of this disaccharide required oxidation to the sulfoxide and hence the C-2 auxiliary was removed to prevent oxidation at this site using 10% TFA in DCM, followed by acetylation (**87**). Next, oxidation of the oxathiane with *m*-CPBA enabled sulfonium ion synthesis and coupling with amino spacer **88** with excellent selectivity (**89**, *α*-only). Fmoc removal allowed for *α*(1,4)-extension at the non-reducing end using preactivated **56** to afford trisaccharide **91** in good yield and excellent selectivity. Again, the auxiliary was removed prior to further extension to afford **92**. Installation of the *α*(1,6)-branch was achieved after removal of the 2-methylnaphthyl ether (**93**) and coupling with preactivated **56** afforded tetrasaccharide **94**. The *α*-selectivity was moderate (*α*/*β* 8:1), but could be improved by the use of a different oxathiane sulfoxide donor.



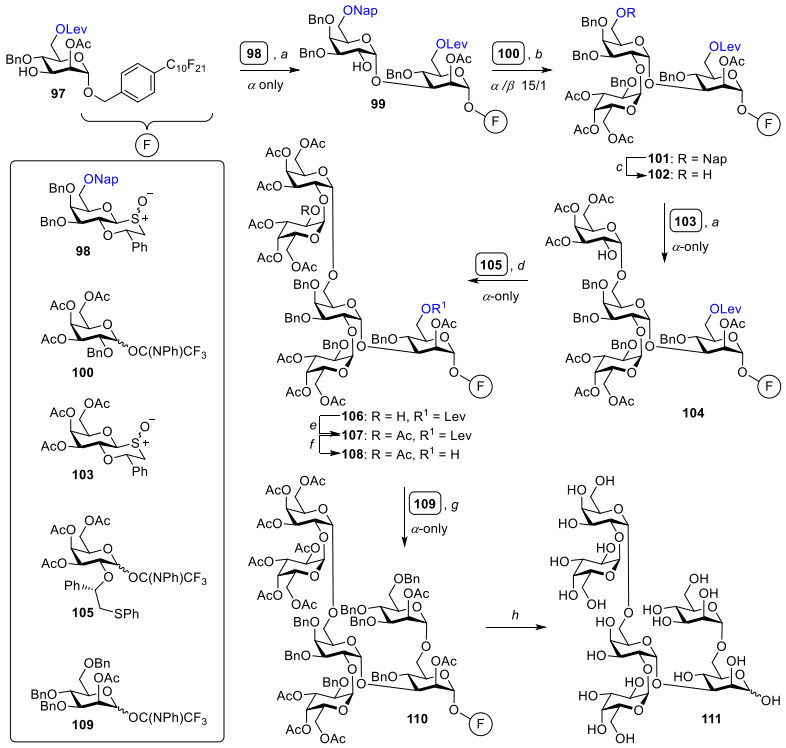
Scheme 10: Synthesis of branched tetraglucoside **96**. Reagents and conditions: *a)* 1,3,5-trimethoxybenzene, Tf_2O, DTBMP, then **85**, **88**, **90** or **93**; *b)* 10% TFA, DCM, then Ac_2O, Pyr. *c) m*-CPBA, DCM *d)* 20% NMP in DMF *e)* DDQ, H_2O, DCM *f)* NaOMe, MeOH, then H_2, $Pd(OH)_2/C$, ^tBuOH, H_2O, AcOH.

Final deprotection afforded tetrasaccharide **96**. The use of oxathiane donors is very attractive since the oxathiane is stable during protecting group manipulations, can serve as a glycosyl acceptor and can be activated by oxidation to the corresponding sulfoxide which can be used as a glycosyl donor. A major drawback is that prior to oxidation of the oxathiane, the removal of C-2 auxiliaries is required to prevent oxidation at this position. Also, the oxathiane donors used in this study are less selective than the second generation Boons auxiliaries used on solid support.

1.4.3 – Synthesis of a hexasaccharide found in *Trypanosoma brucei*

Both the oxathiane donor and donor bearing a C-2 (*S*)-phenylthiomethylbenzyl ether were employed for the synthesis of oligosaccharide **111** found on the glycosylphosphatidylinositol (GPI) anchor of *Trypanosoma brucei* which is a parasite that causes sleeping sickness in humans and similar diseases in domestic animals (Scheme 11).[38b, 43] Hexasaccharide **111** consists of four galactose and two mannose monomers all linked *via* *α*-glycosidic bonds. The synthesis was carried out using a light fluorous tag (F) at the reducing end. This tag allows glycosylation to take place in solution, but facilitates purification by fluorous solid phase extraction (F-SPE) obviating the need for chromatography and is even amendable to automation.[44] The synthesis was rehearsed and optimized using traditional solution phase chemistry and the optimized procedure was next used to enable rapid synthesis using F-SPE. Each glycosylation was performed twice, in order to ensure complete conversion of the glycosyl acceptor. The synthesis started with the addition of preactivated oxathiane donor **98**, to *α*-glucoside **97** bearing the

fluorous tag, forming the disaccharide as the *α*(1,3)-linkage only. Removal of the auxiliary with 10% TFA in DCM afforded acceptor **99**. Addition of preactivated oxathiane donor **103** to **99** did not result in product formation and using an excess of donor **103** resulted in a disappointing 25% yield of the corresponding *α*-1,2-linked trisaccharide. This problem was overcome by implementation of the more reactive C-2 benzyl protected donor **100**, activated by triflic acid, forming trisaccharide **101** with *α*/*β* 15:1. In order to avoid overoxidation, careful oxidative deprotection of the Nap ether was achieved using a small excess of DDQ in H_2O, affording alcohol **102**. Addition of preactivated donor **103** and subsequent acidic deprotection of the C-2 auxiliary afforded tetrasaccharide **104** as only the *α*-anomer. Formation of pentasaccharide **106** by employing preactivated oxathiane donor **103**, surprisingly resulted in a disappointing yield of 20%. Addition of tetrasaccharide **104** to preactivated **105**, followed by acidic removal of the auxiliary resulted in pentasaccharide **106** as only the *α*-anomer in 76% yield. Acetylation and subsequent removal of the Lev ester using hydrazinium acetate yielded acceptor **108**.

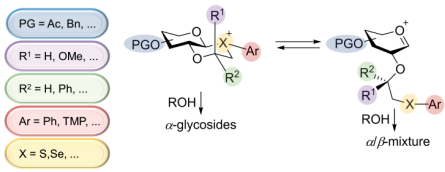


Scheme 11: Synthesis of *Trypanosoma brucei* GPI oligosaccharide **111**. Reagents and conditions: *a)* **98** or **103**, 1,3,5-trimethoxybenzene, Tf_2O, DTBMP, then **97** or **102**. then 10% TFA, DCM; *b)* TfOH, DCM; *c)* DDQ, H_2O, DCM; *d)* **105**, TfOH, then **104**, DTBMP, then 10% TFA, DCM; *e)* Ac_2O, Pyr., DMAP; *f*) $NH_2NH_2{\cdot}AcOH$, pyr.; *g*) **109**, TMSOTf, **146**, DCM; *h*) H_2, Pd/C, MeOH, AcOH, then NaOMe, MeOH.

As discussed earlier, acyl participation in manno-type glycosylations reliably affords *α*-linked products and thus TMSOTf mediated glycosylation of mannoside **109** with acceptor **108** cleanly afforded hexasaccharide **110**. Hydrogenation of the benzyl ethers and subsequent deacetylation afforded target hexasaccharide **111**. The overall yield of the solution phase synthesis was 9%, whereas the fluorous-assisted solid phase synthesis afforded hexasaccharide **111** in 17% overall yield corresponding to an impressive 85% yield per reaction step. Additionally, the authors needed only six days to complete the synthesis, which can probably be sped up further by using automated fluorous-supported synthesis. The synthesis of this hexasaccharide highlights the progress made in the stereoselective synthesis of *α*-glycosides, but also shows one of its weaknesses. Combination of the bulky C-2 sulfonium intermediate with an unreactive acceptor (i.e. alcohol on C-2), affords poor to no glycosylation.

1.5 – Summary and outlook

The use of C-2 chiral auxiliaries for the stereoselective synthesis of 1,2-*cis*-glycosides holds considerable potential to become a general method to prepare this class of molecules. In most cases neighboring group participation of the C-2 auxiliary during glycosylation leads to the formation of a *trans*-decalin intermediate that can be displaced to form 1,2-*cis*-glycosides. Whether the observed *trans*-decalin intermediate is a reactive species or merely a resting state seems to be strongly dependent on the structure of the auxiliary and the protecting groups on the glycosyl donor (Scheme 12). In general, electron-withdrawing protecting groups perform better than electron-donating protecting groups yet more work is needed to establish the exact mechanism of sulfonium ion displacement. Auxiliaries containing a thioether as the nucleophilic group to produce sulfonium ion intermediates perform better than variants containing an ester, ether, seleno ether or iodo group. Furthermore, the structure of the C-2 auxiliary is another major factor that determines the stereoselectivity and auxiliaries carrying a chiral group tend to drastically improve 1,2-*cis* stereoselectivity. Given the fact that chiral auxiliaries are relatively expensive and an elaborate synthesis is required for their introduction, it would therefore be interesting to investigate achiral auxiliaries that potentially speed up the essential ring closing step. This could be done by making use of the *gem*-dimethyl effect (Chapter 2).



Scheme 12: Factors that influence the reactivity of sulfonium ions in glycosylations.

Excellent 1,2-*cis*-selectivity was obtained in most cases, but especially sterically hindered glycosyl acceptors proved difficult to glycosylate. In these cases, more conventional glycosyl donors carrying a non-participation functionality proved to be more efficient. In conclusion, chiral auxiliaries to prepare 1,2-*cis*-glycosides is a promising technology which, combined with the well-established use of C-2 acyl participation to prepare 1,2-*trans*-glycosides, will provide access to the major linkage types found in natural oligosaccharides.

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2

A Study on Stereoselective Glycosylation *via* Sulfonium Ion Intermediates

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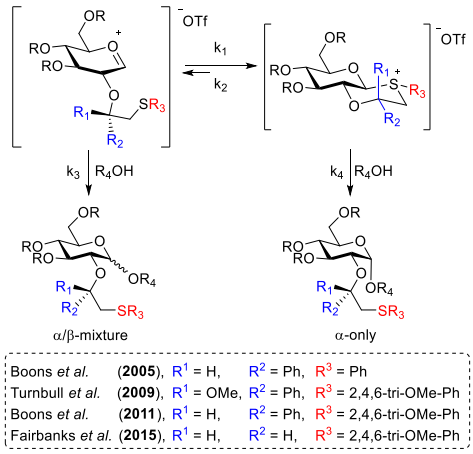
Abstract: The stereoselective synthesis of 1,2-*cis*-linkages can be achieved by an S_N2-like displacement of glycosylation intermediates such as glycosyl triflates and sulfonium ions, provided that they exhibit the right balance between stability and reactivity. This chapter describes the use of an achiral auxiliary that can perform neighboring group participation to afford glycosyl sulfonium ions, aided by the Thorpe-Ingold effect. We investigated the glycosylation properties of the sulfonium ions and used variable temperature NMR studies to investigate their role in the glycosylation mechanism. The influence of the structure of the auxiliary, the protecting groups and stereochemistry of the glycosyl donor were investigated and led to the identification of a highly *α*-selective galactose donor.

2.1 – Introduction

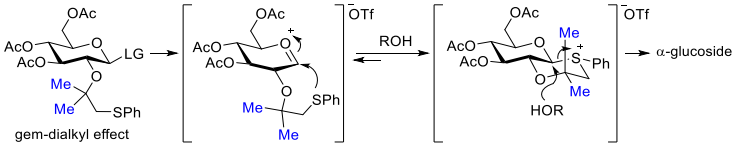
The main challenge of chemical oligosaccharide synthesis is the stereoselective synthesis of glycosidic bonds.[1] In general, 1,2-*trans* glycosides can be synthesized by exploiting neighboring group participation of a C-2 acyl group. The introduction of 1,2-*cis* glycosidic linkages is much more challenging and requires glycosyl donors having a non-assisting functionality at C-2.[2] In general, these glycosylations are less selective and require optimization to achieve acceptable anomeric ratios. Recent advances in anomeric control have led to new methodologies to synthesize 1,2-*cis* linkages of monosaccharides such as glucose, galactose, mannose,[3] glucosamine,[4] galactosamine[5] and furanose sugars.[6] Although excellent, these methods are stereoselective *via* different mechanisms ranging from solvent effects[7], directed aglycon delivery,[8] steric shielding,[5] S_N2-like displacement of a *quasi*-stable intermediate,[3a] stabilization of an oxocarbenium ion conformation[6, 9] and post glycosylation anomerization.[10] Arguably, the development of a methodology that provides stereoselective 1,2-*cis* glycosylation using a generally applicable principle is more desirable as it allows for the use of standardized monosaccharide building blocks. In this respect, the formation of sulfonium ions holds considerable potential.[11] In particular, the use of C-2 auxiliaries to attain highly selective 1,2-*cis* glycosylations *via* neighboring group participation allows for careful tuning of donor reactivity and stereoselectivity. First reported by Boons *et al.*, C-2 chiral auxiliaries such as the (*S*)-(phenylthiomethyl)benzyl ether can be employed for the stereoselective introduction of 1,2-*cis* glycosides such as *α*-glucosides and *α*-galactosides.[12] Neighboring group participation by the chiral auxiliary leads to a *quasi*-stable anomeric sulfonium ion (Scheme 1), which due to steric and electronic factors, is formed as a *trans*-decalin ring system. Subsequent S_N2-like displacement of the sulfonium ion then leads to the stereoselective formation of *α*-glycosides.[13]



Scheme 1: Selected examples of modifications on the C-2 auxiliary group capable of forming a *cis* directing sulfonium intermediate.

Although this methodology is highly stereoselective in many cases,[14] the stereoselectivity depends on the protecting groups on the glycosyl donor[14b, 14e] and the structure of the auxiliary[15] (Scheme 1). Since the intermediate *α*-sulfonium ion is in rapid equilibrium with the oxocarbenium ion, its formation alone is not a guarantee for *α*-selective glycosylation since it may not be a reactive intermediate in the glycosylation mechanism.[3b, 15b, 15d]

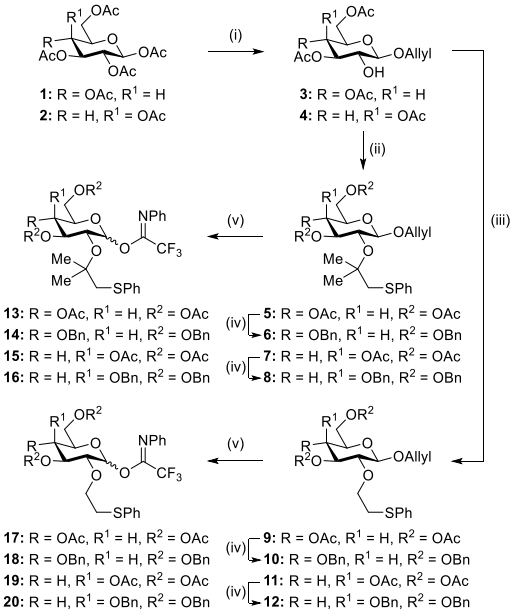
This chapter reports a study aimed at simplifying the auxiliary by using an achiral participating group, which also benefits from the *gem*-dimethyl or Thorpe-Ingold effect in an effort to improve the *α*-selectivity by increasing the speed of the formation of the intermediate *α*-sulfonium ion (Scheme 2).[16] Cyclization of the C-2 participating group is needed to form the sulfonium ion intermediate and this process can be accelerated by the Thorpe-Ingold effect. In addition, we investigated the effects of the protecting groups on, and the stereochemistry of, the glycosyl donor (glucose and galactose) as well as two auxiliaries to evaluate the contribution of the Thorpe-Ingold effect. To this end, we prepared eight different glycosyl donors **13**-**20** (Scheme 2).



Scheme 2: A new auxiliary based on the Thorpe-Ingold effect.

2.2 – Donor synthesis

Glycosyl donors **13**-**20** were prepare in 4-6 steps starting from peracetylated glucose or galactose (Scheme 3). Regioselective C-2 deprotection and anomeric allylation of peracetylated precursors afforded **3**-**4** according to a reported procedure.[17] At this stage, the participating group was installed. In the case of the *gem*-dimethyl auxiliary, **3** and **4** were reacted with $HO(CH_3)_2CCH_2SPh$ and $BF_3{\cdot}Et_2O$ to afford **5** and **7** in 46% and 52% yield, respectively.[18] The moderate yield is a result of the reaction reaching equilibrium and unreacted material can be recovered. Derivatives **9** and **11**, carrying an unsubstituted auxiliary, were prepared to compare the effect of *gem*-dimethyl substitution of the auxiliary group. The aforementioned condensation of **3**-**4** and the alcohol precursor ($HO(CH_2)_2SPh$) using $BF_3{\cdot}Et_2O$ proved unproductive. This was overcome by employing the corresponding bromide ($Br(CH_2)_2SPh$), silver perchlorate and silver carbonate, even though low yields of **9** and **11** (19-37%) were obtained. Despite the low yield, this route was preferred over the multistep route described by Fairbanks *et al.*[15d] To probe the influence of the protecting groups on the glycosylation, in addition to acetylated donors **5**, **7**, **9** and **11**, benzylated donors **6**, **8**, **10** and **12** were prepared *via* deacetylation, followed by benzylation, in good overall yields. Finally, the anomeric imidate leaving group was installed to afford glycosyl donors **13**-**20**.

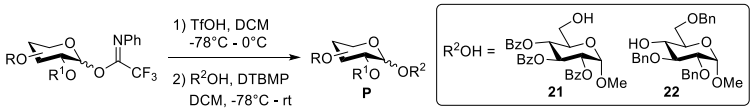


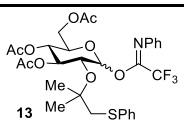
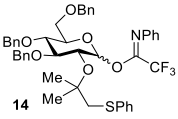
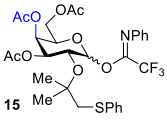
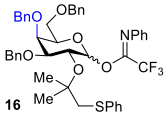
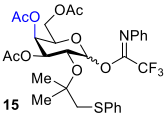
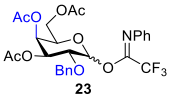
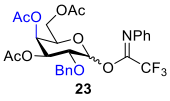
Scheme 3: Synthesis of glycosyl donors **13**-**20**. Reagents and conditions: (i) allyl alcohol, $BF_3.OEt_2$, DCM, 0°C, 1h; **3**, 27%; **4**, 40%; (ii) $HO(CH_3)_2CCH_2SPh$, $BF_3.OEt_2$, DCM, 0°C, 30 min; **5**, 47% ;**7**, 52%; (iii) $Br(CH_2)_2SPh$, $AgClO_4$, Ag_2CO_3, toluene, 4Å MS 60°C; **9**, 19%; **11**, 37%; (iv) (a) K_2CO_3, MeOH (b) NaH, BnBr, DMF, 0°C; **6**, 89%; **8**, 80%; **10**, 84%; **12**, 59%; (v) (a) $Pd(PPh_3)_4$, DCM/AcOH (10:1) (b) $ClC(NPh)CF_3$, DBU, DCM, 0°C; **13**, 88%; **14**, 89%; **15**, 96%; **16**, 71%; **17**, 75%; **18**, 61%; **19**, 60%; **20**, 69%.

2.3 – Glycosylation results

Next, glycosyl donors **13**-**16** were evaluated in the stereoselective glycosylations with glycosyl acceptor **21** (Table 1). Donors **13**-**16**, carrying the *gem*-dimethyl substituted auxiliary were activated at -78 °C using TfOH and allowed to warm to 0°C. Next, after cooling to -78 °C, acceptor **21** and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) were added and the mixture was allowed to warm to rt. Both the benzyl- and acetyl-protected glucosyl donors **13** and **14** showed disappointing stereoselectivity with *α/β* ratios of 2/1 and 3/1, respectively (Table 1, entries 1-2). In contrast, galactosyl donors **15** and **16** proved to be more selective with *α/β* ratios of 19/1 and 4/1, respectively (Table 1, entries 3-4). In each case the acetylated donor was more selective than the benzylated counterpart and the galacto-type sugar was more selective than the gluco-type. Most notably, donor **15** proved to be very selective (19/1) and could also be used to stereoselectively glycosylate secondary acceptor **22**, affording disaccharide **28** with an *α/β* ratio of 16/1 (Table 1, entry 5). To assess the influence of the participating group on the stereoselectivity, two glycosylations were performed with C-2 benzyl-protected galactosyl donor **23**, thus carrying no participating group at C-2 (Table 1, entries 6 and 7).

Table 1: Glycosylations results of donors **13-16** and **23**



entry	donor	R²OH	P	α / β[a]	yield (%)[b]
1	 **13**	**21**	**24**	3/1	87
2	 **14**	**21**	**25**	3/2 2/1[c]	82 78[c]
3	 **15**	**21**	**26**	19/1 24/1[c]	91 38[c]
4	 **16**	**21**	**27**	4/1	50
5	 **15**	**22**	**28**	16/1	63
6	 **23**	**21**	**29**	5/1	93
7	 **23**	**22**	**30**	6/1	66

[a] Ratios were determined by integration of key NMR signals of the crude reaction mixture, [b] Isolated yield, [c] Acceptor **21** was added at rt.

In this case the *α*-selectivity was much lower (~5/1) illustrating the importance of the auxiliary. These results indicate the importance of a variety of reaction parameters on the stereoselectivity. Glycosylation intermediates such as glycosyl sulfonium ions and triflates can be responsible for stereoselectivity via an S_N2-like displacement.[3a, 13-14, 19] However, the presence of such an intermediate does not necessarily mean it is a (main) factor that determines the stereoselectivity.[14b, 15b, 15d] The trend we observed that the armed benzylated donors (**14**, **16**, **18** and **20**) are less selective than their disarmed acetylated counterparts (**13**, **15**, **17** and **19**) is in line with earlier findings reported by Boons *et al.*[14b] The loss of stereoselectivity was attributed to increased stabilization of the oxocarbenium ion and non-selective glycosylation *via* this intermediate.

2.4 – Mechanistic studies

To understand the differences in stereoselectivity, we performed variable temperature NMR experiments to identify reaction intermediates.[20] Glucosyl donors **13** (Figure 1) and **14** (Figure 2) were activated in CD_2Cl_2 at -78 °C with TfOH. Next ^{1}H, ^{1}H-TOCSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC spectra were recorded at -78 °C, -20 °C and at -20 °C again after the sample was allowed to warm up to rt outside the probe. After activation at -78 °C, both a downfield shift of the H-8 protons and a strong C1-H8 correlation in the HMBC spectra confirmed the formation of a cyclic sulfonium ion. Further analysis showed two sulfonium ion anomers had formed. Somewhat surprisingly, the *α*-sulfonium ion was identified as a major species at low temperature and had adopted a $^1C_4$ conformation as was concluded from TOCSY spectra with coupling constants below 5 Hz, consistant with protons in an equatorial-equatorial conformation. The samples were slowly heated (to -40 °C, -20 °C and rt) and additional spectra were recorded. Glycosyl triflates were not detected according to ^{1}H-^{19}F HOESY experiments and for both **13** and **14** the kinetic product, the *α*-sulfonium ion, was formed after rapid cyclization of the auxiliary. In both cases, anomerization to the more stable *β*-sulfonium ion occurs as the temperature increases and is faster for armed donor **14**. The presence of an *α/β* mixture of sulfonium ions may explain the poor glycosylation selectivity of **13** (*α/β* = 3/1) and **14** (*α/β* = 3/2). Critically, reducing the temperature did not result in the reformation of the *α*-sulfonium ion, thus equilibration between the *α*- and *β*-sulfonium ion is slow and the Curtin-Hammett principle may be excluded between these intermediates. However, the oxocarbenium intermediate may also be an important intermediate in these glycosylation reactions and should therefore not be excluded.

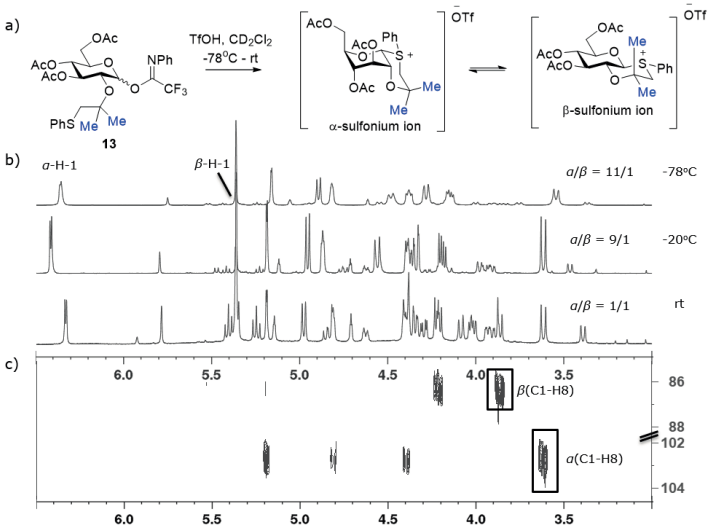


Figure 1: VT-NMR analysis of glycosylation intermediates of donors **13** and **14.** a) Activation of **13** leads to *α*- and *β*-sulfonium intermediates, b) Temperature dependant ^{1}H NMR study, c) ^{1}H-^{13}C HMBC correlation of C1-H8.

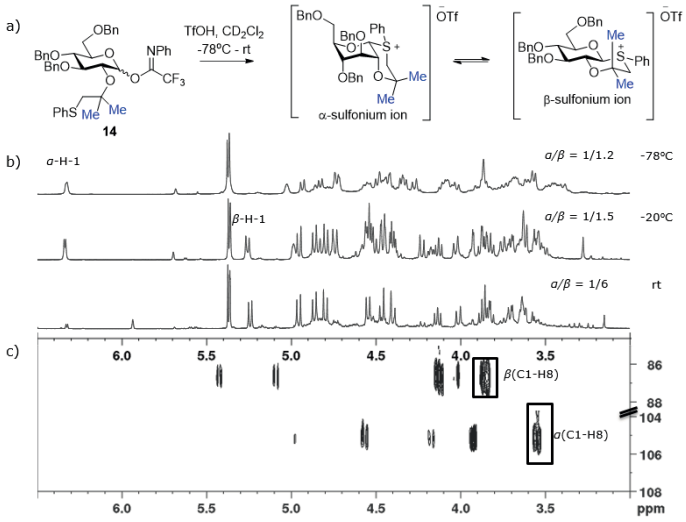


Figure 2: a) Activation of **14** leads to *α*- and β-sulfonium intermediates, b) Temperature dependant ^{1}H NMR study, c) ^{1}H-^{13}C HMBC correlation of C1-H8.

To test this hypothesis, NMR studies of highly selective galactosyl donor **15** were performed, which gave a 19/1 *α/β* ratio. Hence, if glycosylation takes place via the *β*-sulfonium ion, it would be expected to be the major intermediate. However, activation of **15** with triflic acid in CD_2Cl_2 at -20 °C afforded mainly the *α*-sulfonium ion δ(H-1)/δ(C-1) 6.53/101.2 ppm (Figure 3). Again, the *α*-sulfonium ion had adopted the $^{1}C_4$ conformation and converted into the more stable *β*-sulfonium ion as the temperature was increased. On the basis of these results it seems unlikely that the *α*-selectivity of galactosyl donor **15** is a result of an S_N2 reaction with the *β*-sulfonium ion, unless the glycosylation starts taking place at a temperature at which conversion of the *α*-sulfonium ion to the *β*-sulfonium ion is complete. To observe the temperature at which glycosylation takes place, another VT-NMR experiment was performed in which glycosyl acceptor **21** was added and the sample was gradually warmed (Figure 4). NMR analysis revealed the slow conversion of *α*-sulfonium ion to *β*-sulfonium ion δ(H-1)/δ(C-1) 5.63/86.7 ppm occured between -40°C and 0°C and was followed by glycosylation at approximately 0°C. The observation that conversion to the *β*-sulfonium ion required relatively high temperatures and was followed by glycosylation, led us to investigate the effect of temperature on the stereoselectivity. Donors **14** and **15** were activated at low temperature and allowed to warm to room temperature to maximize the formation of *β*-sulfonium ion. Next, acceptor was added at this temperature (Table 1, entries 2^{c}-3^{c}). However, even though VT-studies showed an improvement in the ratio of *β*-sulfonium ion intermediate present, only a marginal improvement in the stereoselectivity was observed.

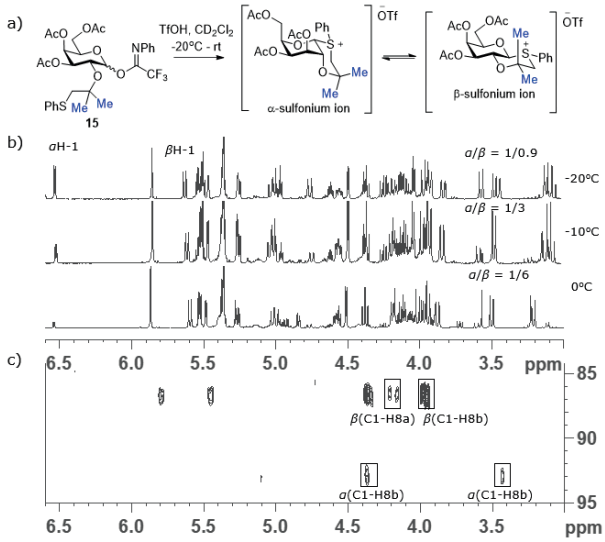


Figure 3: VT-NMR analysis of glycosylation intermediates of donor **15**. a) Activation of **15** leads to *α*- and *β*-sulfonium intermediates; b) Temperature dependant ^{1}H NMR study; c) ^{1}H-^{13}C HMBC correlation of C1-H8.

This led us to conclude that for glucosyl donors **13** and **14**, the sulfonium ion is likely a resting state and glycosylation takes place *via* the oxocarbenium ion pathway in a non-selective manner. In case of galactosyl donor **15**, it is difficult to determine the reason for the highly *α*-selective glycosylation. NMR experiments indicate temperature dependent conversion of the *α*-sulfonium ion to the *β*-sulfonium ion followed by stereoselective glycosylation indicating that S_N2-like displacement may be responsible for the observed *α*-selectivity. The difference in selectivity between sulfonium ions derived from **13** and **15** may be explained by the fact that galactose is more reactive than glucose which is expected to affect the balance between the sulfonium ion and oxocarbenium ion.[21] This difference in reactivity is also reflected in the anomerization of the *α*-sulfonium ion to the *β*-sulfonium ion, which is almost complete for **15** at 0°C whereas a 1/1 mixture is still present at room temperature for **13**. However, the *α*-selectivity could also be the result of a more selective alternative pathway. The possibility of remote neighboring group participation by the C-4 acetyl is often invoked to explain the formation of *α*-galactosides.[22] Computational experiments support this possibility, yet efforts to trap the intermediate have failed.[23] Recently, Yu *et al.* reported the isolation of a glucose-1,2,4-orthoester byproduct formed during a glycosylation which indicated that remote participation from the C-4 position is possible.[24]

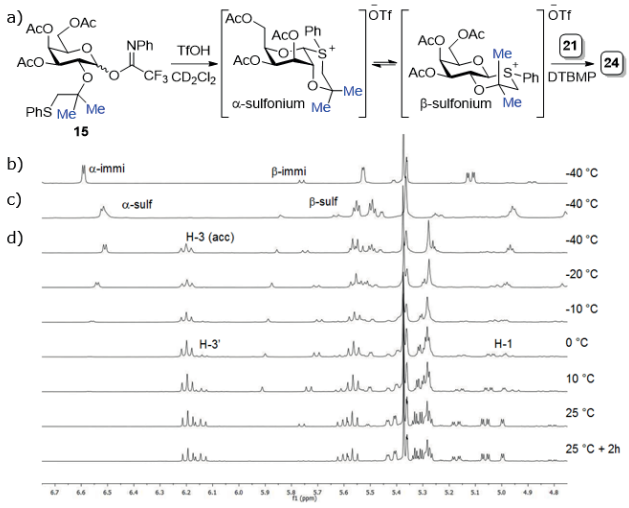
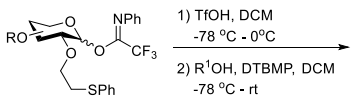


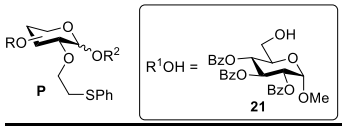
Figure 4: VT-NMR analysis of glycosylation intermediates of donor **15**. a) Activation of **15** leads to *α*- and *β*-sulfonium intermediates; b) **15** pre-activation; c) post-activation; d) temperature dependent glycosylation with **21**.

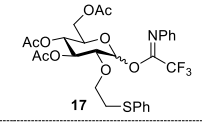
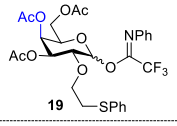
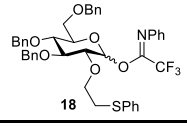
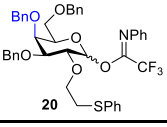
2.5 – Synthesis of control compounds

In addition to the protecting group type and donor stereochemistry we evaluated the influence of the structure of the auxiliary and thus the Thorpe-Ingold effect using glycosyl donors **17**-**20**. These donors lack the *gem*-dimethyl substituent and are expected to be more in equilibrium with the oxocarbenium ion intermediate. The aforementioned glycosylation protocol was used to glycosylate **21** (See Table 2, entries 1-4).

Table 2: Glycosylation results of donors **17**-**20**





entry	donor	P	*α*/*β*[a]	yield[b] (%)	entry	donor	P	*α*/*β*[a]	yield[b] (%)
1		**31**	1/1	75	3		**33**	10/1	81
2		**32**	3/2	73	4		**34**	4/1	71

[a] Ratios were determined by integration of key NMR signals of the crude reaction mixture
[b] Isolated yield.

These donors were less selective than **13**-**16**, but did show a similar trend. Again, the acetylated glycosyl donors were more selective than their benzylated counterparts and the galactosyl donors were more selective than the glucosyl donors.

2.6 – Mechanistic study of control compounds

In order to explain the high *α*-selectivity of donor **19** (Table 2, entry 3), an additional VT-NMR study was performed to identify reaction intermediates (see Figure 5). At -78°C both anomeric sulfonium ions were formed with the *α*-sulfonium ion as a mixture of conformers. Warming the mixture resulted in formation of the $^4C_1$ *α*-sulfonium and also the formation of a fourth unidentified species.

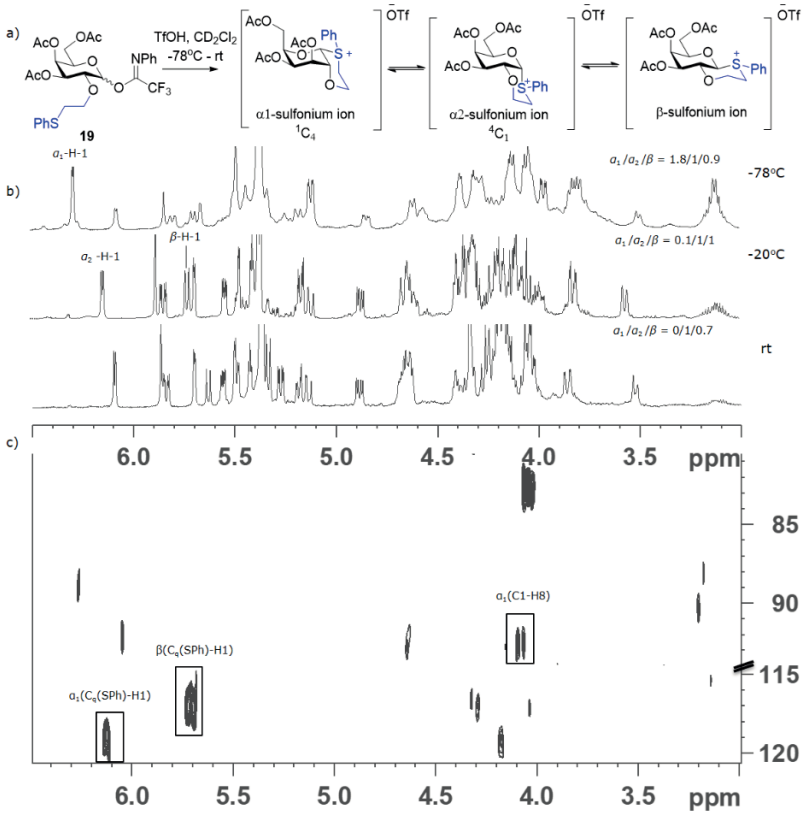
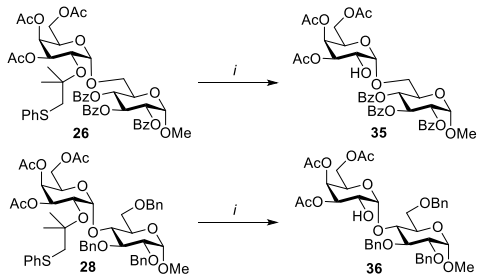


Figure 5: a) VT-NMR analysis of glycosylation intermediates of **19**; b) Sulfonium ion species observed after activation of **19**; c) ^{1}H-^{13}C HMBC spectrum of the sulfonium ion intermediates.

This suggests that in the absence of the *gem*-dimethyl substituents, the $^{1}C_{4}$ *α*-sulfonium ion is less stable and converts to the $^{4}C_{1}$ *α*-sulfonium ion conformer instead of direct conversion to the *β*-sulfonium ion. In addition, even after warming to room temperature, the anomerization towards the *β*-sulfonium ion is incomplete in contrast to donor **15**. Eventhough donor **19** showed good *α*-selectivity, the selectivity was lower than that of donor **15** which carried a *gem*-dimethyl auxiliary. Due to the *gem*-dimethyl effect we expect the sulfonium ion to form rapidly, which may explain this result. By comparing the results of acetylated galactose donors **15**, **19** and **23** the influence of the C-2 substituent becomes clear. The C-2 benzyl derivative is the least selective (*α/β* = 5/1), as expected, followed by the unsubstituted auxiliary (*α/β* = 10/1) and finally the *gem*-dimethyl-auxiliary (*α/β* = 19/1).

2.7 – Auxiliary deprotection

Finally, we explored the removal of the auxiliary on disaccharides **26** and **28**. Using a mixture of TFA and dichloromethane, the C-2 alcohols were produced in good yield (Scheme 4). These mild conditions are compatible with ester and ether protecting groups.



Scheme 4: Removal of the auxiliary. Reagents and conditions: (*i*) TFA/DCM, **26**; 85%, **28**; 54%

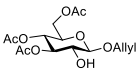
2.8 – Conclusion

It is clear that formation of a *β*-sulfonium ion intermediate alone is not sufficient to guarantee *α*-selective glycosylation since the sulfonium ion may just serve as resting state. Conversely, in case of galactosyl donor **15**, it is difficult to determine the reason for the highly *α*-selective glycosylation. NMR experiments indicate temperature dependent conversion of the *α*-sulfonium ion to the *β*-sulfonium ion followed by stereoselective glycosylation indicating that S_N2-like displacement may be responsible for the observed *α*-selectivity. However, the *α*-selectivity could also be the result of a more selective alternative pathway e.g. remote group participation. Even though chiral auxiliaries are more selective in most cases, galactosyl donor **15** is an attractive alternative since it is easily prepared in 5 steps and highly *α*-selective.

2.9 – Experimental

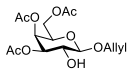
General remarks: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz or on a Bruker Avance III 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS). NMR data is presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet and/or multiple resonances), coupling constant in hertz (Hz), integration, assignment. All NMR signals were assigned on the basis of ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, HMBC and TOCSY experiments. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage Max (MS) mass spectrometer. High resolution mass spectra were recorded on an JEOL AccuTOF CS JMS-T100CS (HRMS) mass spectrometer. Automatic flash column chromatography was performed by using a Biotage Isolera Spektra One, using SNAP cartridges (Biotage, 30-100 µm, 60 Å), 10-50 g. TLC-analysis was conducted on Silicagel F_{254} (Merck KGaA) with detection by UV-absorption (254 nm) where applicable and by spraying with either a 10% sulphuric acid in methanol stain, a potassium permanganate stain or a cerium molybdate followed by charring at ~300°C. MeCN, DCM, Et_2O, THF and toluene were freshly distilled and anhydrous DMF purchased from Sigma Aldrich was used. Molecular sieves (4Å) were flame activated under vacuum prior to use. All reactions requiring an inert atmosphere were either under an argon or nitrogen atmosphere using flame-dried flasks.

Allyl 3,4,6-tri-*O*-acetyl-*α/β*-D-glucopyranoside (3)



Same procedure as **4**, but *β*-D-glucose pentaacetate (5.00 g, 12.81mmol) was used instead. Product was isolated as a mixture of anomers: *β*-anomer (27%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 – 5.88 (m, 1H), 5.37 – 5.30 (m, 1H), 5.29 – 5.23 (m, 1H), 5.13 (t, *J* = 9.5 Hz, 1H, *H-3*), 5.04 (t, *J* = 9.7 Hz, 1H, *H-4*), 4.42 (d, *J* = 7.8 Hz, 1H, *H-1*), 4.28 (dd, *J* = 12.3, 4.9 Hz, 1H, *H-6*), 4.19 – 4.05 (m, 1H, *H-6*), 3.68 (ddd, *J* = 9.8, 4.9, 2.4 Hz, 1H, *H-5*), 3.61 (dd, *J* = 9.4, 7.8 Hz, 1H, *H-2*), 2.43 (br, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.74, 170.71, 169.67, 133.29, 118.53, 101.63, 74.42, 72.15, 71.87, 70.60, 68.42, 62.10, 20.83, 20.77, 20.66. HR ESI-TOF MS (*m/z*) calcd for $C_{15}H_{22}O_9$ $[M + Na]^+$ 369.1186, found 369.1166.

Allyl 3,4,6-tri-*O*-acetyl-*β*-D-galactopyranoside (4)



To a mixture of *β*-D-galactose pentaacetate (5.00 g, 12.81 mmol) and dry allyl alcohol (3.48 mL, 51.20 mmol) in anhydrous DCM (50 mL), was added $BF_3.Et_2O$ (2.44 mL, 19.21 mmol) under a nitrogen atmosphere at 0 °C. The solution was stirred at 0 °C for 1 h, then at room temperature overnight, then poured into ice-water and extracted with EtOAc. The organic phases were combined, dried with $MgSO_4$, filtered, concentrated under reduced pressure and purified *via* silica flash column chromatography to afford **4** (1.77 g, 40%). NMR was consistent with literature values.[17] HRMS (*m/z*) calcd for $C_{15}H_{22}O_9$ $[M + Na]^+$ 369.1162, found 369.1170.

General method A

A mixture of **3** or **4** (1 eq), 2-methyl-1-(phenylthio)propan-2-ol (1.5 eq) and 4 Å MS in DCM (0.1 M) was cooled to 0 °C. $BF_3.OEt_2$ (1.5 eq) was added and the reaction was quenched with Et_3N after 1h, after which the MS were filtered off. The solution was extracted with a sat. $NaHCO_3$ solution (2x) and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica flash column chromatography (0-40% EA/Hept) afforded the pure products.

General method B

Compound **3** or **4** (1.8 g, 5.2 mmol) were dissolved in dry toluene (35 mL) at room temperature. 2-bromo ethyl phenyl sulfide (1.57 ml, 10.4 mmol), molecular sieves (5 g), Ag_2CO_3 (3.6 g, 13.0 mmol) and $AgClO_4$ (1.6 g, 7.8 mmol) were added. The reaction mixture was heated to 55 °C and allowed to react protected from light for 5 days. After reaching room temperature, the precipitate was filtrated through celite and rinsed with toluene. Toluene was evaporated *in vacuo*, and the residue was purified by flash column chromatography (ethyl acetate : heptane 10-50%) to afford the pure product, 17-38%.

General method C

Acetylated precursor **5**,**7**,**9** or **11** was dissolved in MeOH and K_2CO_3 (0.3 eq) was added. The solution was left to stir until no starting material was observed *via* TLC. After filtration, the volatiles were removed *in vacuo*. The residue was dissolved in DMF, cooled to 0 °C and NaH (5eq) (60% in mineral oil) was added in portions. BnBr was added and the mixture was left to warm to RT overnight. The mixture was quenched with MeOH and the volatiles were removed *in vacuo*. The residue was dissolved in EtOAc and washed with sat. $NaHCO_3$ and brine (x2), dried with $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified using flash column chromatography (0-40% EtOAC-Heptane) affording the pure product.

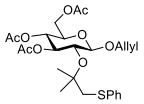
General method D

Allyl glycoside (**5**-**12**) (1 eq) was dissolved in a mixture of DCM and AcOH (10:1) and $Pd(PPh_3)_4$ (0.3 eq) was added. The mixture was left to stir for 1h after which the volatiles were removed *in vacuo*. The residue was purified using flash column chromatography (0-20% EtOAc – Heptane), affording the pure product. The anomeric alcohol was dissolved in dry DCM (0.1 molar) and cooled to 0 °C under inert conditions. 1,8-Diazabicyclo[5.4.0]undeC-7-ene (1,5 eq) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (1.1 eq) were added and left to stir for 2h. The volatiles were removed *in vacuo* and the residue was purified using flash column chromatography (10-50% EtOAc – Heptane) affording the pure products.

General method E

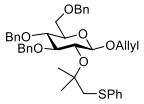
Glycosyl imidate (2 eq, (**13**-**20**)) was dissolved in dry DCM under inert conditions and 4Å MS were added. The mixture was cooled to -78 °C and triflic acid (2 eq) was added. When the starting material had been completely consumed, a precooled mixture of acceptor **21** (1eq) or **22** (1eq), 4Å MS and 2,6-di-*tert*-butyl-4-methylpyridine (4 eq) in dry DCM was added and the mixture was left to warm to RT overnight. The suspension was filtered, diluted in DCM and extracted with a sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified using silica flash column chromatography (10-50% EtOAc – heptane, v/v) affording the pure products.

Allyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α*/*β*-D-glucopyranoside (5)



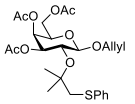
3 (560 mg, 1.62 mmol) *via* protocol **A** afforded **5** (47%). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.35-7.23 (m, 4H), 7.17-7.13 (m, 1H), 5.98-5.89 (m, 1H), 5.29 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H), 5.20 (ddd, *J* = 10.4, 2.6, 1.2 Hz, 1H), 5.07 (t, *J* = 9.3 Hz, 1H, *H-3*), 4.99 (t, *J* = 9.7 Hz, 1H, *H-4*), 4.37-4.32 (m, 1H), 4.34 (d, *J* = 7.5 Hz, 1H, *H-1*), 4.27 (dd, *J* = 12.2, 4.9 Hz, 1H, *H-6*), 4.11 (dt, *J* = 9.7 Hz, 1H), 4.10 (dd, *J* = 12.1, 2.1 Hz, 1H, *H-6*), 3.66 (dd, *J* = 9.0, 7.6 Hz, 1H, *H-2*), 3.65-3.62 (m, 1H, *H-5*), 3.09 (d, *J* = 12.6 Hz, 1H), 3.05 (d, *J* = 12.6 Hz, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.70, 169.90 (x2), 169.76(x2), 137.87, 133.56, 128.99, 128.76, 125.67, 118.11, 102.03 (C-*1*), 78.24, 74.39 (C-*3*), 72.61 (C-*2*), 71.45 (C-*5*), 70.99, 68.93 (C-*4*), 62.20 (C-*6*), 46.55, 26.44, 25.93, 21.01, 20.76, 20.67. **HRMS** (*m*/*z*) calcd for $C_{25}H_{34}O_9S$ [M + Na]$^+$ 533.1821, found 533.1832.

Allyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α*/*β*-D-glucopyranoside (6)



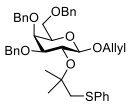
5 (0.71 mg, 1.38 mmol) *via* protocol **C** afforded **6** (807 mg, 89 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 17H), 7.15 – 7.07 (m, 3H), 5.96 (dddd, *J* = 17.2, 10.4, 6.3, 5.4 Hz, 1H), 5.28 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.84 (d, *J* = 11.1 Hz, 1H), 4.77 (d, *J* = 10.8 Hz, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.51 (d, *J* = 10.8 Hz, 1H), 4.37 (ddt, *J* = 12.5, 5.5, 1.5 Hz, 1H), 4.28 (d, *J* = 7.4 Hz, 1H, *H-1*), 4.09 (ddt, *J* = 12.5, 6.3, 1.3 Hz, 1H), 3.72 (dd, *J* = 10.7, 2.1 Hz, 1H, *H-6*), 3.66 (dd, *J* = 10.7, 4.8 Hz, 1H, *H-6'*), 3.59 (t, *J* = 8.9 Hz, 1H, *H-2*), 3.58 (t, *J* = 8.9 Hz, 1H, *H-4*), 3.48 (t, 9.0 Hz, 1H, *H-3*), 3.44 (ddd, *J* = 9.8, 4.8, 2.1 Hz, 1H, *H-5*), 3.19 (d, *J* = 12.5 Hz, 1H), 3.10 (d, *J* = 12.5 Hz, 1H), 1.34 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.55, 138.15, 138.11, 138.00, 134.10, 128.72 (x2), 128.66 (x2), 128.35 (x2), 128.34 (x2), 128.32 (x2), 127.91 (x2), 127.79 (x2), 127.72, 127.60, 127.38, 127.34 (x2), 125.38, 117.54, 102.26, 84.94, 78.41, 78.00, 75.82, 74.92, 74.79, 74.77, 73.47, 70.68, 68.92, 46.33, 26.72, 26.15. **HRMS** (*m*/*z*) calcd for $C_{40}H_{46}O_6S$ [M + Na]$^+$ 677.2913, found 677.2905.

Allyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*β*-D-galactopyranoside (7)



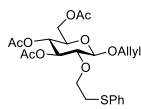
4 (0.79 g, 3.33 mmol) *via* protocol **A** afforded **7** (52%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 4H), 7.14 (ddt, *J* = 7.9, 6.8, 1.3 Hz, 1H), 5.95 (dddd, *J* = 17.3, 10.4, 6.3, 5.5 Hz, 1H), 5.37 (dd, *J* = 3.4, 1.2 Hz, 1H, *H-4*), 5.30 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.83 (dd, *J* = 9.9, 3.4 Hz, 1H, *H-3*), 4.37 (ddt, *J* = 12.5, 5.6, 1.4 Hz, 1H), 4.33 (d, *J* = 7.6 Hz, 1H), 4.17 (dd, *J* = 11.2, 6.6 Hz, 1H), 4.14-4.09 (m, 1H), 4.10 (dd, *J* = 11.3, 7.0 Hz, 1H), 3.85 (dd, *J* = 6.8, 1.2 Hz, 1H, *H2*), 3.83 (dd, J = 9.7, 7.7 Hz, 1H, *H-5*) 3.11 (d, *J* = 12.6 Hz, 1H), 3.07 (d, *J* = 12.6 Hz, 1H), 2.13 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.41, 170.22, 169.91, 137.97, 133.60, 128.81 (x2), 128.74 (x2), 125.60, 118.07, 102.35, 77.95, 72.64, 71.09, 70.32, 69.68, 67.68, 61.40, 46.59, 26.26, 26.21, 20.84, 20.71, 20.69. **HRMS** (*m/z*) calcd for $C_{25}H_{34}O_9S$ [M + Na]$^+$ 533.1821, found 533.1835.

Allyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*β*-D-galactopyranoside (8)



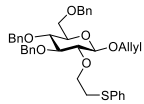
7 (0.75 g, 1.47 mmol) *via* protocol **C** afforded **8** (0.77 g, 80%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.17 (m, 19H), 7.13 – 7.08 (m, 1H), 5.93 (dddd, *J* = 17.3, 10.4, 6.3, 5.4 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.13 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.89 (d, *J* = 11.6 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.8 Hz, 1H), 4.35 (ddt, *J* = 12.5, 5.4, 1.5 Hz, 1H), 4.24 (d, *J* = 7.6 Hz, 1H, *H-1*), 4.05 (ddt, *J* = 12.5, 6.3, 1.4 Hz, 1H), 3.97 (dd, *J* = 9.6, 7.5 Hz, 1H, *H-2*), 3.87 (dd, *J* = 2.7, 1.1 Hz, 1H, *H-4*), 3.58 (d, *J* = 6.3 Hz, 2H, *H-6*), 3.55 – 3.48 (m, 1H, *H-5*), 3.35 (dd, *J* = 9.6, 2.7 Hz, 1H, *H-3*), 3.18 (d, *J* = 12.5 Hz, 1H), 3.14 (d, *J* = 12.5 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (126 MHz, CDCl3) δ 138.68, 138.31, 138.28, 137.94, 134.24, 128.64 (x2), 128.54 (x2), 128.41 (x2), 128.36 (x2), 128.23 (x2), 128.12 (x2), 127.85 (x2), 127.76, 127.58 (x2), 127.54, 127.48, 125.25, 117.32, 102.52, 82.53, 77.95, 74.47, 73.62, 73.55, 73.37, 73.11, 71.92, 70.57, 68.94, 46.12, 26.56, 26.26. **HRMS** (*m/z*) calcd for $C_{40}H_{46}O_6S$ [M + Na]$^+$ 677.2913, found 677.2906.

Allyl 3,4,6-tri-*O*-acetyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-glucopyranoside (9)



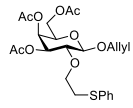
3 (1.80 g, 5.20 mmol) *via* protocol **B** afforded **9** (0.48 g, 19%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 8H), 7.23 – 7.16 (m, 2H), 5.96 – 5.84 (m, 2H), 5.41 (t, *J* = 9.7 Hz, 1H), 5.36 – 5.31 (m, 1H), 5.29 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.25 – 5.18 (m, 2H), 5.12 (t, *J* = 9.5 Hz, 1H), 5.02 – 4.97 (m, 2H), 4.44 (d, *J* = 7.8 Hz, 1H), 4.36 (ddt, *J* = 12.8, 5.2, 1.5 Hz, 1H), 4.27 (ddd, *J* = 12.3, 4.7, 3.0 Hz, 2H), 4.20 (ddt, *J* = 12.9, 5.2, 1.5 Hz, 1H), 4.15 – 3.97 (m, 5H), 3.79 – 3.61 (m, 4H), 3.52 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.31 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.08 – 3.01 (m, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.67, 170.63, 170.18, 170.02, 169.84, 169.69, 135.92, 135.60, 133.41, 133.20, 129.52, 129.27, 129.01, 128.95, 126.37, 126.16, 118.53, 117.84, 101.98, 95.44, 79.82, 78.08, 73.74, 71.75, 71.54, 71.26, 70.53, 69.95, 68.72, 68.65, 68.58, 67.35, 62.07, 61.99, 52.97, 33.41, 20.86, 20.74, 20.73, 20.66, 20.65. **HRMS** (*m/z*) calcd for $C_{23}H_{30}O_9S$ [M + Na]$^+$ 505.1508, found 505.1508.

Allyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-glucopyranoside (10)



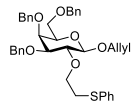
9 (0.74 g, 0.97 mmol) *via* protocol **C** afforded **10** (0.51 g, 84%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 17H), 7.21 – 7.10 (m, 3H), 5.97 – 5.84 (m, 1H), 5.29 (ddq, *J* = 17.4, 14.7, 1.6 Hz, 1H), 5.22 – 5.11 (m, 1H), 4.99 (d, *J* = 3.6 Hz, 1H), 4.94 (dd, *J* = 10.9, 5.1 Hz, 1H), 4.84 – 4.76 (m, 2H), 4.68 – 4.44 (m, 3H), 4.40 – 4.32 (m, 2H), 4.22 – 4.13 (m, 1H), 4.13 – 4.03 (m, 2H), 3.94 (t, *J* = 9.3 Hz, 1H), 3.91 – 3.62 (m, 4H), 3.60 – 3.52 (m, 1H), 3.49 – 3.40 (m, 1H), 3.31 – 3.25 (m, 1H), 3.15 – 3.08 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.83, 138.59, 138.21, 138.16, 138.09, 137.96, 134.00, 133.70, 129.46, 129.38, 129.07, 128.99, 128.93, 128.90, 128.42, 128.40, 128.38, 128.36, 128.33, 128.30, 128.00, 127.96, 127.95, 127.91, 127.89, 127.88, 127.79, 127.76, 127.73, 127.70, 127.65, 127.63, 127.61, 127.57, 126.25, 125.97, 118.31, 117.30, 102.30 (*β*-C-1), 95.43 (*α*-C-1), 84.58, 82.88, 81.85, 81.17, 77.79, 77.64, 75.79, 75.68, 75.11, 75.01, 73.47, 71.28, 70.29, 69.92, 68.91, 68.42, 68.19, 33.48, 33.44. **HRMS** (*m/z*) calcd for $C_{38}H_{42}O_6S$ [M + Na]$^+$ 649.2600, found 649.2590.

Allyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-(phenylthio)ethyl)-*α/β*-D-galactopyranoside (11)



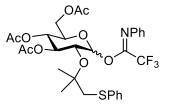
4 (100 mg, 0.29 mmol) *via* protocol **B** afforded **11** (52 mg, 37%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 4H), 7.20 – 7.16 (m, 1H), 5.90 (dddd, *J* = 17.2, 10.5, 6.0, 5.3 Hz, 1H), 5.35 (dd, *J* = 3.4, 0.9 Hz, 1H, *H-4*), 5.30 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.20 (ddd, *J* = 10.5, 2.7, 1.3 Hz, 1H), 4.92 (dd, *J* = 10.2, 3.5 Hz, 1H, *H-3*), 4.43 (d, *J* = 7.7 Hz, 1H, *H-1*), 4.38 (ddt, *J* = 12.8, 5.3, 1.5 Hz, 1H), 4.18 – 4.06 (m, 3H, *H-6, H-6*), 4.00 (ddd, *J* = 10.3, 7.3, 6.1 Hz, 1H), 3.83 (td, *J* = 6.8, 1.0 Hz, 1H, *H-5*), 3.76 (tdd, *J* = 10.1, 7.2, 4.7 Hz, 1H), 3.49 (dd, *J* = 10.2, 7.7 Hz, 1H, *H-2*), 3.12 – 3.01 (m, 2H), 2.13 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.36, 170.13, 170.04, 136.10, 133.47, 129.05 (x2), 128.89 (x2), 126.02, 117.78, 102.30, 77.09, 72.09, 71.48, 70.57, 70.39, 67.34, 61.33, 33.33, 20.71, 20.67, 20.65. **HRMS** (*m/z*) calcd for $C_{23}H_{30}O_9S$ [M + Na]$^+$ 505.1508, found 505.1515.

Allyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-galactopyranoside (12)



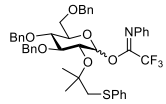
11 (0.47 g, 0.97 mmol) *via* protocol **B** afforded **12** (0.37 g, 59%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 1H), 7.57 – 7.52 (m, 1H), 7.50 – 7.44 (m, 1H), 7.41 – 7.13 (m, 17H), 5.96 – 5.86 (m, 1H), 5.60 (d, *J* = 4.3 Hz, 1H), 5.57 (d, *J* = 4.3 Hz, 1H), 5.53 – 5.47 (m, 1H), 5.38 – 5.32 (m, 1H), 5.29 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.21 – 5.15 (m, 1H), 4.99 (d, *J* = 3.5 Hz, 1H), 4.93 (d, *J* = 4.7 Hz, 1H), 4.91 (d, *J* = 4.8 Hz, 1H), 4.82 (d, *J* = 2.2 Hz, 1H), 4.79 (d, *J* = 2.7 Hz, 1H), 4.70 (d, *J* = 3.3 Hz, 1H), 4.68 (d, *J* = 3.6 Hz, 1H), 4.63 – 4.36 (m, 12H), 4.23 – 3.76 (m, 13H), 3.70 – 3.52 (m, 4H), 3.17 – 3.06 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.79, 138.64, 138.40, 138.13, 137.99, 137.90, 133.91, 132.15, 132.07, 131.96, 131.94, 129.31, 128.93, 128.56, 128.55, 128.47, 128.45, 128.40, 128.39, 128.29, 128.24, 128.21, 128.04, 128.01, 127.98, 127.96, 127.87, 127.86, 127.75, 127.72, 127.67, 127.64, 127.58, 127.55, 127.52, 127.49, 127.43, 126.08, 118.09, 104.27, 103.68, 100.66, 97.64, 96.08, 85.53, 81.38, 79.85, 78.84, 78.77, 77.84, 77.59, 77.49, 75.13, 74.81, 74.41, 73.46, 73.21, 72.88, 72.84, 72.74, 72.64, 72.44, 71.56, 71.46, 71.40, 71.36, 70.14, 69.55, 69.43, 68.97, 68.24, 68.22, 68.15, 33.35. **HRMS** (*m/z*) calcd for $C_{38}H_{42}O_6S$ [M + Na]$^+$ 649.2600, found 649.2582

***N*-phenyl-2,2,2-trifluoroacetimidate 3,4,6-tri-*O*-acetyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α/β*-D-gluco-pyranoside (13)**: **5** (310 mg, 0.66 mmol) *via* protocol **D** afforded **13** (0.39 g, 88%). **^{1}H NMR** (500 MHz, $CDCl_3$)



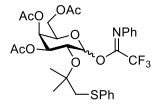
δ 7.37 – 7.09 (m, 8H), 6.81 (d, *J* = 7.5 Hz, 2H), 6.54 (br, 1H, *H-1*), 5.37 (t, *J* = 9.7 Hz, 1H, *H-3*), 5.12 (t, *J* = 9.9 Hz, 1H, *H-4*), 4.33 (dd, *J* = 12.3, 3.7 Hz, 1H, *H-6*), 4.21 – 4.08 (m, 2H, *H-2*, *H-6*), 3.93 (d, *J* = 7.0 Hz, 1H, *H-5*), 3.08 (d, *J* = 12.9 Hz, 1H), 3.02 (d, *J* = 12.9 Hz, 1H), 2.11 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.55, 169.78, 169.73, 143.29, 137.31, 129.23 (x2), 128.87 (x2), 128.78 (x2), 125.99 (x2), 124.36, 119.37, 77.91, 71.15, 69.80, 69.59, 68.04, 61.52, 46.43, 25.52, 25.25, 20.92, 20.72, 20.65.

***N*-phenyl-2,2,2-trifluoroacetimidate 3,4,6-tri-*O*-benzyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α/β*-D-gluco-pyranoside (14): 6** (0.71 g, 1.38 mmol) *via* protocol **D** afforded **14** (0.81 g, 89%). **^{1}H NMR** (500 MHz, $CDCl_3$)



δ 7.47 – 7.01 (m, 21H), 6.88 – 6.75 (m, 4H), 6.52 (br, 1H, *α-H-1*), 5.55 (br, 1H, *β-H-1*), 5.01 – 4.77 (m, 3H), 4.76 – 4.37 (m, 9H), 4.22 – 3.49 (m, 9H), 3.46 – 3.29 (m, 1H), 3.19 – 3.01 (m, 2H), 1.40 – 1.25 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.64, 138.58, 138.49, 138.45, 138.40, 137.99, 137.93, 137.88, 137.81, 137.78, 137.76, 128.92, 128.91, 128.78, 128.76, 128.69, 128.66, 128.59, 128.41, 128.38, 128.36, 128.34, 128.26, 128.24, 128.12, 127.98, 127.88, 127.85, 127.78, 127.76, 127.68, 127.65, 127.64, 127.60, 127.48, 127.45, 125.69, 125.57, 125.52, 124.01, 119.30, 82.04, 78.27, 77.61, 77.09, 75.80, 75.30, 75.05, 75.00, 74.65, 74.33, 73.53, 73.47, 73.44, 73.38, 73.32, 73.13, 72.98, 72.18, 70.33, 68.73, 68.41, 68.28, 68.00, 46.65, 45.95, 26.16, 25.99, 25.84, 24.85.

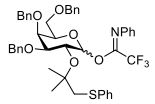
***N*-phenyl-2,2,2-trifluoroacetimidate 3,4,6-tri-*O*-acetyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α/β*-D-galacto-pyranoside (15)**: **7** (296 mg, 0.63 mmol) *via* protocol **D** afforded **15** (96 %). **^{1}H NMR**



(500 MHz, $CDCl_3$) δ 7.40 – 6.94 (m, 8H), 6.83 (d, *J* = 7.6 Hz, 2H), 6.54 (br, 1H, *H-1*), 5.54 (d, *J* = 3.1 Hz, 1H, *H-4*), 5.20 (dd, *J* = 10.5, 3.3 Hz, 1H, *H-3*), 4.36 (s, 1H, *H-2*), 4.21 – 4.08 (m, 3H, *H-5, H-6, H-6*), 3.09 (d, *J* = 12.9 Hz, 1H), 3.04 (d, *J* = 12.9 Hz, 1H), 2.16 (s, 3H), 2.06 (s, 3H),

2.02 (s, 3H), 1.32 (s, 4H), 1.31 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.36, 169.95, 169.76, 137.39, 129.10 (x2), 128.87 (x2), 128.82, 128.78 (x2), 128.75, 125.96, 124.30, 119.41, 119.11, 77.75, 68.88, 68.70, 68.04, 65.99, 61.35, 46.24, 25.73, 25.13, 20.77, 20.68, 20.64.

***N*-phenyl-2,2,2-trifluoroacetimidate 3,4,6-tri-*O*-benzyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α/β*-D-galacto-pyranoside (16)**: **8** (0.69 g, 1.13 mmol) *via* protocol **D** afforded **16** (0.63g 71%). **^{1}H NMR** (500 MHz, $CDCl_3$)



δ 7.91 (s, 1H), 7.58 – 7.52 (m, 2H), 7.44 – 7.17 (m, 18H), 7.17 – 7.03 (m, 2H), 6.85 – 6.72 (m, 2H), 5.55 (br, 1H, *β-H-1*), 4.88 (d, *J* = 11.5 Hz, 1H), 4.73 – 4.65 (m, 2H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 4.22 – 4.12 (m, 1H), 3.94 – 3.88 (m, 1H), 3.68 – 3.58 (m, 2H), 3.39 (s, 1H), 3.15 (d, *J* = 12.6 Hz, 1H), 3.11 (d, *J* = 12.7 Hz, 1H), 1.35 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.63, 138.39, 137.98, 137.87, 137.76, 135.01, 129.33, 128.92, 128.90, 128.69, 128.59, 128.41, 128.37, 128.34, 128.24, 128.12, 127.88, 127.76, 127.68, 127.65, 127.64, 126.34, 125.52, 124.02, 120.45, 119.29, 96.90 (C-1), 82.02, 78.26, 74.64, 74.34, 73.43, 73.32, 73.12, 70.33, 68.29, 46.64, 26.15, 25.83.

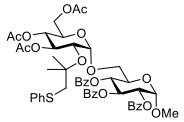
***N*-phenyl-2,2,2-trifluoroacetimidate 3,4,6-tri-*O*-acetyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-glucopyranoside (17)**: **9** (0.47mg, 0.97 mmol) *via* protocol **D** afforded **17** (0.45 g, 75%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.07 (m, 15H), 6.88 – 6.75 (m, 3H), 6.57 (br, 1H,□*α-H-1*), 5.64 (br, 1H, *β-H-1*) 5.42 (t, *J* = 9.7 Hz, 1H), 5.22 – 5.00 (m, 2H), 4.28 (td, *J* = 13.5, 13.1, 4.2 Hz, 2H), 4.21 – 4.04 (m, 3H), 3.96 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.89 – 3.80 (m, 1H), 3.76 (dt, *J* = 10.2, 6.9 Hz, 1H), 3.73 – 3.64 (m, 2H), 3.61 – 3.51 (m, 1H), 3.06 (t, *J* = 6.6 Hz, 4H), 2.09 (s, 3H), 2.06 (s, 2H), 2.05 (s, 2H), 2.04 (s, 4H), 2.04 (s, 1H), 2.02 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.54, 170.51, 169.98, 169.96, 169.71, 169.61, 143.16, 143.04, 135.59, 135.44, 129.62, 129.56, 129.05, 129.02, 128.83, 128.79, 126.48, 126.42, 124.54, 119.30, 119.13, 78.77, 77.31, 73.61, 72.43, 71.59, 71.37, 70.61, 69.98, 67.91, 67.77, 61.50, 33.51, 20.83, 20.80, 20.69, 20.68, 20.62, 20.60.

***N*-phenyl-2,2,2-trifluoroacetimidate 3,4,6-tri-*O*-benzyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-glucopyranoside (18): 10** (0.47 g, 0.75 mmol) *via* protocol **D** afforded **18** (0.35 g, 61%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 6.99 (m, 23H), 6.92 – 6.69 (m, 2H), 6.56 (br, 1H), 5.56 (br, 1H), 4.99 – 4.89 (m, 1H), 4.86 – 4.75 (m, 2H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.55 – 4.47 (m, 2H), 4.02 – 3.84 (m, 2H), 3.82 – 3.40 (m, 5H), 3.13 – 3.05 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.28, 137.86, 129.41, 129.30, 128.98, 128.93, 128.75, 128.68, 128.43, 128.40, 128.35, 127.99, 127.91, 127.83, 127.76, 127.73, 127.68, 127.65, 126.26, 126.17, 124.27, 119.30, 84.26, 81.55, 80.35, 75.74, 75.71, 75.52, 75.32, 75.04, 73.48, 73.38, 73.06, 71.60, 70.35, 67.94, 33.53.

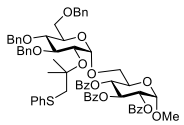
***N*-phenyl-2,2,2-trifluoroacetimidate 3,4,6-tri-*O*-acetyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-galactopyranoside (19)**: **11** (0.20 g, 0.41 mmol) *via* protocol **D** afforded **19** (0.15 g, 60%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.09 (m, 16H), 6.88 – 6.76 (m, 4H), 6.59 (br, 1H, *α-H-1*), 5.65 (s, 1H), 5.51 (s, 1H), 5.37 (s, 1H), 5.27 (dd, *J* = 10.6, 3.2 Hz, 1H), 4.96 (s, 1H), 4.33 (s, 1H), 4.17 – 4.04 (m, 4H), 4.00 – 3.66 (m, 6H), 3.14 – 3.02 (m, 4H), 2.16 (s, 3H), 2.14 (s, 3H), 2.06 (s, 3H), 2.01 (s, 6H), 2.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.33, 170.28, 170.02, 169.92, 169.88, 169.86, 129.42, 129.28, 129.01, 128.99, 128.82, 128.78, 126.37, 126.28, 124.49, 124.43, 119.34, 119.11, 76.03, 73.76, 72.08, 71.78, 71.50, 70.63, 69.21, 68.98, 67.70, 67.01, 61.36, 60.99, 33.40, 20.75, 20.69, 20.66, 20.64, 20.61.

***N*-phenyl-2,2,2-trifluoroacetimidate 3,4,6-tri-*O*-benzyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-galactopyranoside (20)**: **12** (0.25 g, 0.40 mmol) *via* protocol **D** afforded **20** (0.21 g, 69%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.05 (m, 23H), 6.79 (d, *J* = 7.9 Hz, 2H), 5.57 (s, 1H), 4.91 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 11.8 Hz, 1H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 3.97 (t, *J* = 6.9 Hz, 2H), 3.92 – 3.80 (m, 3H), 3.64 – 3.42 (m, 3H), 3.12 (td, *J* = 6.9, 3.8 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.48, 138.30, 138.08, 137.69, 136.06, 129.11 (x2), 128.90 (x2), 128.62(x2), 128.45(x2), 128.42, 128.39 (x2), 128.26(x2), 128.21(x2), 127.90(x2),

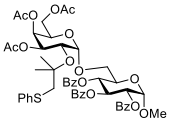
127.80, 127.74, 127.68, 127.56 (x2), 126.02, 124.12, 119.30, 81.64, 78.66, 74.72, 74.34, 73.46, 73.13, 73.02, 71.73, 68.07, 33.42.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α/β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (24): **13** (106 mg, 0.17 mmol) *via* protocol **E** afforded **24** as an anomeric mixture, 3:1 (*α/β*) (137 mg, 87%). 

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.81 (m, 7H), 7.55 – 7.10 (m, 18H), 6.16 (t, *J* = 9.7 Hz, 1H), 5.42 (t, *J* = 9.9 Hz, 1H), 5.36 (t, *J* = 9.6 Hz, 1H), 5.27 – 5.19 (m, 2H, *α-H-1*), 5.14 (d, *J* = 3.6 Hz, 1H, *β-H-1*), 5.04 (t, *J* = 9.2 Hz, 1H), 4.99 (t, *J* = 9.7 Hz, 1H), 4.93 (t, *J* = 9.7 Hz, 1H), 4.89 (d, *J* = 3.4 Hz, 1H, *α-H-1*`), 4.42 – 4.31 (m, 2H, *α-H-1*`), 4.28 – 4.16 (m, 2H), 4.11 – 4.03 (m, 1H), 3.98 (ddd, *J* = 11.1, 7.4, 2.3 Hz, 1H), 3.88 (dd, *J* = 10.7, 7.9 Hz, 1H), 3.79 (dd, *J* = 11.1, 7.7 Hz, 1H), 3.70 (ddd, *J* = 13.7, 10.4, 2.6 Hz, 2H), 3.66 – 3.59 (m, 1H), 3.51 (s, 3H), 3.44 (s, 3H), 3.14 (d, *J* = 12.7 Hz, 1H), 3.07 (d, *J* = 12.8 Hz, 1H), 3.04 (d, *J* = 12.9 Hz, 1H), 2.98 (d, *J* = 12.8 Hz, 1H), 2.12 (s, 3H), 2.02 (s, 6H), 2.01 (s, 3H), 2.00 (s, 3H), 1.94 (s, 3H), 1.26 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.71, 170.62, 169.91, 169.86, 169.81, 169.77, 165.82, 165.76, 165.71, 165.44, 137.78, 137.40, 133.51, 133.47, 133.34, 133.05, 129.92, 129.89, 129.85, 129.82, 129.63, 129.60, 129.19, 129.15, 129.10, 129.02, 129.00, 128.81, 128.80, 128.73, 128.46, 128.44, 128.39, 128.24, 125.82, 125.76, 103.05 (*α*-C-*1*`), 98.82 (*α*-C-*1'*), 96.87 (*α*-C-*1*), 96.61 (*β*-C-*1*), 78.39, 77.28, 74.32, 72.50, 72.20, 71.96, 71.40, 71.17, 70.59, 70.42, 70.24, 70.01, 69.71, 69.29, 68.96, 68.87, 68.80, 68.75, 67.50, 67.34, 62.25, 62.08, 55.88, 55.66, 46.39, 46.18, 26.16, 25.96, 25.84, 25.69, 20.99, 20.80, 20.69, 20.66, 20.55. **HRMS** (*m/z*) calcd for $C_{50}H_{54}O_{17}S$ [M + Na]$^+$ 981.2979, found 981.2986.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α/β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (25): **14** (100 mg) *via* protocol **E** afforded **25** as an anomeric mixture, (*α/β*), (95 mg, 82%). Product was isolated as an anomeric mixture 3:2 (*α*:β) 

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.82 (m, 6H), 7.55 – 7.05 (m, 33H), 6.16 (td, *J* = 9.9, 2.6 Hz, 1H), 5.48 (dt, *J* = 48.4, 9.9 Hz, 1H), 5.28 – 5.20 (m, 1H), 5.18 (d, *J* = 3.6 Hz, 1H, *H-1'*), 5.15 (d, *J* = 3.5 Hz, 1H, *H-1'*), 4.93 (dd, *J* = 11.2, 7.1 Hz, 1H), 4.89 (d, *J* = 3.3 Hz, 1H *α-H-1*), 4.81 (dd, *J* = 11.1, 6.7 Hz, 1H), 4.73 (dd, *J* = 14.1, 11.0 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 9.9 Hz, 1H), 4.41 – 4.34 (m, 2H), 4.27 (d, *J* = 7.4 Hz, 1H. *β-H-1*), 4.02 (dd, *J* = 10.9, 2.1 Hz, 1H), 3.93 – 3.81 (m, 2H), 3.79 – 3.73 (m, 1H), 3.71 – 3.60 (m, 2H), 3.63 – 3.51 (m, 2H), 3.45 (s, 3H), 3.43 (s, 3H), 3.25 (d, *J* = 12.6 Hz, 1H), 3.12 (t, *J* = 11.8 Hz, 1H), 3.01 (d, *J* = 12.7 Hz, 1H) 1.36 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.28 – 1.24 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.80, 165.76, 165.72, 165.42, 165.25, 138.83, 138.55, 138.06, 138.01, 137.99, 137.88, 137.66, 133.31, 133.28, 133.27, 132.98, 129.89, 129.88, 129.84, 129.63, 129.61, 129.24, 129.22, 129.06, 128.95, 128.91, 128.82, 128.75, 128.68, 128.36, 128.35, 128.31, 128.30, 128.29, 128.23, 128.21, 128.18, 127.96, 127.85, 127.74, 127.68, 127.64, 127.55, 127.51, 127.38, 127.33, 127.30, 127.28, 125.60, 125.45, 103.30 (*β*-C-*1*), 99.65 (*α*-C-*1*), 96.78(*α*-C-*1'*), 96.68 (*α*-C-*1'*), 84.79, 81.04, 78.15, 78.10, 77.80, 77.10, 75.73, 75.61, 74.82, 74.80, 74.73, 74.68, 73.44, 73.40, 73.20, 72.24, 72.06, 70.62, 70.40, 70.21, 70.03, 69.63, 69.09, 68.90, 68.87, 68.59, 68.26, 67.20, 55.80, 55.66, 46.20, 46.01, 26.38, 26.31, 26.24, 25.63. **HRMS** (*m/z*) calcd for $C_{65}H_{66}O_{14}S$ [M + Na]$^+$ 1125.4071, found 1025.4086.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α/β*-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (26): **15** (109 mg, 0.17 mmol) *via* protocol **E** afforded **26** as an anomeric mixture, 19:1 (*α/β* (75 mg, 91%). 

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.91 (m, 4H), 7.88 – 7.82 (m, 2H), 7.54 – 7.45 (m, 2H), 7.43 – 7.11 (m, 12H), 6.16 (t, *J* = 9.8 Hz, 1H), 5.51 – 5.43 (m, 2H, *H-4 & H-4'*), 5.26 (dd, *J* = 10.2, 3.7 Hz, 1H, *H-2'*), 5.22 (dd, *J* = 10.5, 3.2 Hz, 1H, *H-3*), 5.21 (d, *J* = 3.6 Hz, 1H, *H-1'*), 4.93 (d, *J* = 3.4 Hz, 1H, *H-1*), 4.43 – 4.38 (m, 1H, *H-5*), 4.36 (ddd, *J* = 9.8, 7.4, 1.6 Hz, 1H, *H-5'*), 4.12 (dd, *J* = 11.3, 5.8 Hz, 1H, *H-6*), 4.01 (d, *J* = 7.2 Hz, 1H, *H-2*), 3.99 (dd, *J* = 10.5, 3.5 Hz, 1H, *H-6*), 3.89 (dd, *J* = 10.9, 7.4 Hz, 1H, *H-6'*), 3.72 (dd, *J* = 10.9, 1.7 Hz, 1H, *H-6'*), 3.49 (s, 3H), 3.08 (d, *J* = 12.8 Hz, 1H), 3.02 (d, *J* = 12.8 Hz, 1H), 2.13 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.28 (s, 3H), 1.28 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.50, 170.09, 169.75, 165.78, 165.71, 165.39, 137.53, 133.41, 133.30, 133.01, 129.90 (x2), 129.82 (x2), 129.61 (x2), 129.18, 129.03, 128.91 (x2), 128.79 (x2), 128.41

(x2), 128.36 (x2), 128.21 (x2), 125.77, 99.50, 96.68, 77.15, 72.10, 70.47, 69.69, 69.03, 68.75, 68.62, 67.39, 67.11, 66.44, 62.02, 55.65, 46.08, 25.97, 25.55, 20.81, 20.70, 20.64. **HRMS** (*m/z*) calcd for $C_{50}H_{54}O_{17}S$ [M + Na]$^+$ 981.2979, found 981.2983.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α/β*-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (27): **20** (50 mg, 0.13 mmol) *via* protocol **E** afforded **27** as an anomeric mixture, 4:1 (*α/β*) (31 mg, 50%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 – 7.84 (m, 6H), 7.55 – 7.06 (m, 29H), 6.14 (t, *J* = 9.8 Hz, 1H), 5.52 (t, *J* = 9.9 Hz, 1H), 5.24 (dd, *J* = 10.3, 3.7 Hz, 1H), 5.13 (d, *J* = 3.7 Hz, 1H, *α-H-1*), 4.92 (d, *J* = 11.3 Hz, 1H), 4.86 (d, *J* = 3.3 Hz, 1H, *α-H-1'*), 4.80 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.38 – 4.31 (m, 2H), 4.15 (dd, *J* = 10.1, 3.5 Hz, 1H), 4.04 (t, *J* = 6.6 Hz, 1H), 3.96 – 3.91 (m, 1H), 3.87 (dd, *J* = 11.4, 7.0 Hz, 1H), 3.79 (dd, *J* = 10.1, 2.7 Hz, 1H), 3.74 (dd, *J* = 11.3, 2.1 Hz, 1H), 3.51 – 3.42 (m, 2H), 3.40 (s, 1H), 3.38 (s, 3H), 3.17 (d, *J* = 12.7 Hz, 1H), 3.04 (d, *J* = 12.7 Hz, 1H), 1.32 (s, 4H), 1.31 (s, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.77, 138.93, 138.77, 138.08, 133.28, 129.92, 129.87, 129.82, 129.64, 129.29, 129.13, 128.99, 128.75, 128.73, 128.38, 128.35, 128.34, 128.24, 128.23, 128.16, 127.75, 127.75, 127.61, 127.57, 127.57, 127.52, 127.37, 127.28, 125.47, 100.25 *(α-C-1')*, 96.72 *(α-C-1)*, 77.56, 77.16, 75.66, 74.86, 73.28, 73.23, 72.17, 70.67, 69.85, 69.66, 69.31, 68.83, 68.64, 67.45, 55.56, 45.65, 26.35, 25.56. **HRMS** (*m/z*) calcd for $C_{65}H_{66}O_{14}S$ [M + Na]$^+$ 1125.4071, found 1025.4084.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-methyl-1-(phenylthio)propanyl)-*α/β*-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranoside (28): **15** (100 mg, 0.16 mmol) *via* protocol **E** afforded **28** as an anomeric mixture, 16:1 (*α/β*) (90 mg, 63%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.19 (m, 19H), 7.15 – 7.10 (m, 1H), 5.50 (d, *J* = 3.3 Hz, 1H, *α-H-1*), 5.38 (dd, *J* = 3.3, 1.6 Hz, 1H), 5.18 (dd, *J* = 10.6, 3.2 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 3.5 Hz, 1H, *α-H-1'*), 4.57 (s, 2H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.23 (ddd, *J* = 7.7, 6.3, 1.6 Hz, 1H), 4.06 – 4.03 (m, 2H), 4.00 (dd, *J* = 10.9, 7.4 Hz, 1H), 3.91 (ddd, *J* = 11.0, 3.3, 1.8 Hz, 2H), 3.86 (dd, *J* = 10.9, 6.3 Hz, 1H), 3.76 – 3.71 (m, 1H), 3.62 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.60 – 3.56 (m, 1H), 3.35 (s, 3H), 2.95 (s, 2H), 2.11 (s, 3H), 1.99 (s, 3H), 1.90 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.23, 170.11, 169.79, 139.12, 137.94, 137.93, 137.74, 128.89, 128.72, 128.44, 128.39, 128.32, 128.27, 128.13, 128.11, 127.97, 127.88, 127.58, 127.54, 127.35, 126.91, 126.58, 125.63, 97.95 (*α-C-1*), 97.67 (*α-C-1'*), 81.18, 80.01, 77.51, 73.75, 73.47, 73.21, 72.64, 69.42, 68.89, 68.65, 68.27, 67.22, 66.52, 61.38, 55.22, 55.20, 46.06, 25.82, 24.88, 20.86, 20.67, 20.58. **HRMS** (*m/z*) calcd for $C_{50}H_{60}O_{14}S$ [M + Na]$^+$ 939.3601, found 939.3611.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-*α/β*-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (29): 23 (40 mg, 0.07 mmol) *via* protocol E afforded **29** as an anomeric mixture, 5:1 (*α/β*), (29 mg, 93%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 – 7.91 (m, 4H), 7.89 – 7.82 (m, 2H), 7.60 – 7.48 (m, 2H), 7.45 – 6.98 (m, 14H), 6.20 – 6.12 (m, 1H), 5.52 – 5.41 (m, 2H), 5.35 (ddd, *J* = 10.3, 6.9, 3.4 Hz, 1H), 5.27 – 5.20 (m, 2H, *α-H-1`*), 4.82 (d, *J* = 3.5 Hz, 1H, *α-H-1*), 4.71 (d, *J* = 12.4 Hz, 1H), 4.57 (d, *J* = 12.3 Hz, 1H), 4.40 – 4.29 (m, 2H), 4.12 – 4.05 (m, 1H), 3.96 (dd, *J* = 11.3, 7.2 Hz, 1H), 3.88 – 3.80 (m, 2H), 3.55 (dd, *J* = 10.8, 2.0 Hz, 1H), 3.49 (s, 2H), 3.47 – 3.45 (m, 1H), 2.10 (s, 2H), 2.01 (s, 2H), 1.98 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.46, 170.12, 169.93, 165.77, 165.73, 165.34, 138.11, 133.49, 133.32, 133.05, 129.92, 129.89, 129.87, 129.64, 129.17, 129.04, 128.84, 128.46, 128.43, 128.38, 128.37, 128.28, 128.24, 127.85, 127.69, 97.27 (*α-C-1`*), 96.71 (*α-C-1*), 73.68, 73.13, 72.09, 70.41, 69.62, 69.43, 68.69, 68.50, 66.66, 66.43, 62.02, 55.57, 20.79, 20.68, 20.65. **HRMS** (*m/z*) calcd for $C_{47}H_{48}O_{17}$ [M + Na]$^+$ 907.2789, found 907.2805.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-*α/β*-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranoside (30): **23** (94 mg, 0.17 mmol) *via* protocol E afforded **30** as an anomeric mixture, 6:1 (*α/β*) (46 mg, 66%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (dt, *J* = 7.5, 1.2 Hz, 2H), 7.37 – 7.19 (m, 16H), 7.16 – 7.11 (m, 2H), 7.05 – 7.01 (m, 2H), 6.41 (d, *J* = 3.6 Hz, 0H), 5.77 (d, *J* = 3.7 Hz, 1H), 5.36 (dd, *J* = 3.5, 1.9 Hz, 2H), 5.31 (dd, *J* = 3.3, 1.4 Hz, 1H), 5.28 – 5.21 (m, 4H), 5.00 (d, *J* = 11.7 Hz, 1H), 4.82 (d, *J* = 16.0 Hz, 2H), 4.77 – 4.72 (m, 2H), 4.71 – 4.53 (m, 6H), 4.45 (s, 2H), 4.42 (dd, *J* = 9.7, 5.9 Hz, 2H), 4.30 (dd, *J* = 11.4, 7.2 Hz, 2H), 4.12 – 4.02 (m, 4H), 3.97 – 3.91 (m, 2H), 3.90 – 3.84 (m, 2H), 3.83 – 3.75 (m, 3H), 3.67 (dd, *J* = 11.0, 1.9 Hz, 1H), 3.57 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.39 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.94 (s, 3H), 1.91 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.54, 170.35, 170.18, 170.14, 169.93, 139.09, 138.06, 137.87, 137.77, 134.89, 130.46, 128.53, 128.44, 128.39, 128.27, 128.25, 128.23, 128.17, 128.14, 128.10, 128.06, 128.04, 127.97, 127.95, 127.91, 127.75, 127.67, 127.65, 127.60, 127.52, 127.48, 127.35, 127.04, 126.54, 126.27, 124.21, 97.64, 97.29, 81.76, 80.19, 74.17, 73.37, 73.25, 73.14, 69.55, 69.36, 69.13, 69.04, 68.94, 68.63, 68.34, 68.00, 66.60, 66.43, 62.82, 61.72, 61.55, 55.24, 20.91, 20.77, 20.67. **HRMS** (*m/z*) calcd for $C_{47}H_{54}O_{14}$ $[M + Na]^+$ 865.3411, found 865.3424.

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (31): 17 (100 mg, 0.16 mmol) *via* protocol **E** afforded **31** as an anomeric mixture, 1:1 (*α/β*), (57 mg, 75%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 – 7.92 (m, 5H), 7.89 – 7.83 (m, 2H), 7.57 – 7.48 (m, 2H), 7.46 – 7.12 (m, 21H), 6.36 (d, *J* = 3.6 Hz, 1H), 6.16 (t, *J* = 9.5 Hz, 1H), 5.58 (d, *J* = 8.2 Hz, 1H), 5.50 – 5.34 (m, 3H), 5.28 – 5.20 (m, 2H), 5.02 – 4.93 (m, 3H), 4.85 (d, *J* = 3.5 Hz, 1H), 4.46 (d, *J* = 7.8 Hz, 1H), 4.36 (ddd, *J* = 9.9, 7.5, 1.9 Hz, 1H), 4.32 – 4.17 (m, 4H), 4.06 (ddt, *J* = 11.5, 9.2, 2.2 Hz, 2H), 3.89 (dd, *J* = 10.8, 7.6 Hz, 1H), 3.82 – 3.59 (m, 6H), 3.51 (s, 4H), 3.43 (s, 2H), 3.09 – 2.99 (m, 5H), 2.09 (d, *J* = 0.5 Hz, 5H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.64, 170.61, 169.98, 169.95, 169.86, 169.82, 165.80, 165.70, 165.35, 135.59, 133.52, 133.35, 133.07, 129.91, 129.87, 129.80, 129.63, 129.60, 129.52, 129.50, 129.44, 129.22, 129.13, 129.03, 129.01, 128.98, 128.97, 128.93, 128.70, 128.46, 128.39, 128.24, 126.38, 126.36, 126.31, 126.13, 126.10, 104.14, 103.39, 97.79, 96.83, 96.65, 96.45, 93.41, 89.15, 79.81, 79.71, 78.64, 78.24, 78.10, 73.91, 73.70, 73.62, 72.43, 72.13, 71.91, 71.75, 71.60, 71.54, 71.51, 71.41, 71.36, 71.29, 71.14, 70.35, 70.24, 70.15, 69.67, 69.62, 68.75, 68.60, 68.56, 68.53, 68.51, 67.96, 67.88, 67.44, 67.12, 66.75, 62.00, 61.97, 61.56, 57.36, 55.63, 55.61, 55.48, 33.44, 33.41, 33.40, 33.38, 20.97, 20.86, 20.84, 20.74, 20.72, 20.68, 20.66, 20.64, 20.62, 20.60. **HRMS** (*m/z*) calcd for $C_{48}H_{50}O_{17}S$ $[M + Na]^+$ 953.2666, found 953.2643.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (32): 18 (100 mg, 0.13 mmol) *via* protocol **E** afforded **32** as an anomeric mixture, 3:2 (*α/β*) (51mg, 73%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.83 (m, 6H), 7.54 – 7.08 (m, 29H), 6.14 (t, *J* = 9.9 Hz, 1H), 5.52 (dd, *J* = 10.3, 9.5 Hz, 1H), 5.24 (dd, *J* = 10.2, 3.7 Hz, 1H), 5.17 (d, *J* = 3.7 Hz, 1H, *α-H-1'*), 4.92 (d, *J* = 3.5 Hz, 1H, *α-H-1*), 4.86 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 11.1 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.44 (d, *J* = 11.1 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.32 (ddd, *J* = 9.8, 6.8, 2.2 Hz, 1H), 3.92 – 3.84 (m, 3H), 3.82 – 3.75 (m, 2H), 3.70 – 3.60 (m, 3H), 3.53 (dd, *J* = 10.7, 2.1 Hz, 1H), 3.45 – 3.41 (m, 4H), 3.14 – 3.02 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.82, 165.76, 165.24, 138.77, 138.50, 137.92, 135.80, 133.33, 133.02, 129.92, 129.90, 129.64, 129.37, 129.23, 129.05, 128.92, 128.39, 128.37, 128.35, 128.32, 128.24, 128.22, 127.89, 127.62, 127.59, 127.48, 127.46, 126.14, 96.97 (*α*-C-*1*), 96.71 (*α*-C-*1'*), 81.42, 80.96, 77.50, 75.42, 74.76, 73.39, 72.18, 70.56, 70.31, 69.93, 68.52, 68.20, 66.68, 55.61, 33.38. **HRMS** (*m/z*) calcd for $C_{63}H_{62}O_{14}S$ $[M + Na]^+$ 1097.3758, found 1097.3740.

Mehtyl 3,4,6-tri-*O*-acetyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (33): 19 (90 mg, 0.15 mmol) *via* protocol **E** afforded **33** as an anomeric mixture, 10:1 (*α/β*) (55mg, 81%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 – 7.93 (m, 4H), 7.87 – 7.82 (m, 2H), 7.55 – 7.49 (m, 2H), 7.45 – 7.21 (m, 11H), 7.18 – 7.12 (m, 1H), 6.16 (dd, *J* = 10.2, 9.5 Hz, 1H), 5.48 (dd, *J* = 10.4, 9.5 Hz, 1H), 5.43 (dd, *J* = 3.4, 1.3 Hz, 1H), 5.29 (dd, *J* = 10.6, 3.4 Hz, 1H), 5.25 (dd, *J* = 10.2, 3.7 Hz, 1H), 5.21 (d, *J* = 3.7 Hz, 1H, *α-H-1'*), 4.99 (d, *J* = 3.5 Hz, 1H,□*α-H-1*), 4.41 – 4.30 (m, 2H), 4.10 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.97 (dd, *J* = 11.3, 7.2 Hz, 1H), 3.89 (dd, *J* = 10.9, 7.3 Hz, 1H), 3.81 – 3.71 (m, 3H), 3.67 (dd, *J* = 10.9, 2.0 Hz, 1H), 3.49 (s, 3H), 3.07 (ddd, *J* = 7.4, 6.5, 1.8 Hz, 2H), 2.12 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.48, 170.11, 169.87, 165.78, 165.72, 165.36, 135.79, 133.50, 133.34, 133.06, 129.92, 129.91, 129.87, 129.63, 129.28, 129.15, 129.01, 128.93, 128.78, 128.46, 128.39, 128.25, 126.21, 126.00, 97.19 (*α*-C-*1*), 96.73 (*α*-C-*1'*), 74.63, 72.05, 70.39, 70.16, 69.63, 69.41, 68.62, 68.50, 66.70, 66.51, 62.00, 55.62, 33.31, 20.80, 20.70, 20.68. **HRMS** (*m/z*) calcd for $C_{48}H_{50}O_{17}S$ $[M + Na]^+$ 953.2666, found 953.2650.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-(phenylthio)ethyl)-*α/β*-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (34): 20 (50 mg, 0.07 mmol) *via* protocol **E** afforded **34** as an anomeric mixture, 16:1 (*α/β*) (25 mg, 71%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 – 7.79 (m, 6H), 7.58 – 7.05 (m, 29H), 6.12 (t, *J* = 9.8 Hz, 1H), 5.52 (t, *J* = 9.9 Hz, 1H), 5.25 (dd, *J* = 10.3, 3.7 Hz, 1H), 5.12 (d, *J* = 3.7 Hz, 1H, *β-H-1'*), 4.97 – 4.84 (m, 2H, *β-H-1*), 4.82 – 4.65 (m, 3H), 4.64 – 4.49 (m, 2H), 4.47 – 4.23 (m, 5H), 4.05 – 3.72 (m, 6H), 3.72 – 3.40 (m, 5H), 3.35 (s, 2H), 3.21 – 2.98 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.76, 165.32, 138.69, 138.04, 133.33, 133.01, 129.92, 129.82, 129.63, 129.23, 128.87, 128.82, 128.37, 128.36, 128.34, 128.31, 128.29, 128.28, 128.23, 128.22, 128.19, 128.16, 128.12, 128.09, 128.05, 127.87, 127.83, 127.73, 127.66, 127.59, 127.54, 127.52, 127.51, 127.47, 127.43, 127.38, 127.35, 125.99, 97.68 (*α*-C-*1*), 96.73 (*α*-C-*1'*), 78.16, 74.96, 74.78, 73.22, 72.75, 72.08, 70.63, 70.07, 69.58, 69.26, 68.60, 68.39, 66.64, 55.44, 33.25. **HRMS** (*m/z*) calcd for $C_{63}H_{62}O_{14}S$ $[M + Na]^+$ 1097.3758, found 1097.3790.

Methyl 3,4,6-tri-*O*-acetyl-*α/β*-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (35):

26 (65 mg, 0.07 mmol) was dissolved in 2 ml dry DCM under inert conditions and 0.2 ml TFA was added. The mixture was left to stir for 1 h, after which the volatiles were removed. Silica flash column chromatography (40-80% EtOAC-heptane) afforded **35** as an anomeric mixture 19:1 (*α/β*) (46 mg, 85%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 4H), 7.89 – 7.83 (m, 2H), 7.56 – 7.49 (m, 2H), 7.45 – 7.36 (m, 5H), 7.32 – 7.25 (m, 2H), 6.16 (t, *J* = 9.5 Hz, 1H), 5.65 (t, *J* = 9.9 Hz, 1H), 5.42 (dd, *J* = 3.4, 1.2 Hz, 1H), 5.26 (d, *J* = 9.5 Hz, 2H, *β-H-1'*), 5.19 – 5.13 (m, 2H, *β-H-1*), 4.31 – 4.23 (m, 2H), 4.05 (dd, *J* = 11.3, 5.9 Hz, 1H), 4.01 (dd, *J* = 11.3, 7.1 Hz, 1H), 3.93 (dd, *J* = 11.7, 4.9 Hz, 1H), 3.80 (dd, *J* = 11.8, 2.0 Hz, 1H), 3.48 (s, 3H), 2.55 (d, *J* = 10.9 Hz, 1H), 2.14 (s, 3H), 2.08 (s, 3H), 1.95 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.66, 170.41, 170.16, 165.76, 165.38, 133.62, 133.38, 133.13, 129.93, 129.88, 129.67, 129.04, 128.96, 128.66, 128.50, 128.40, 128.27, 98.559 (*α*-C-*1'*), 97.06 (*α*-C-*1*), 72.11, 70.66, 70.31, 68.96, 68.63, 68.32, 67.20, 66.95, 65.59, 61.95, 55.79, 20.88, 20.65, 20.59. **HRMS** (*m/z*) calcd for $C_{40}H_{42}O_{17}$ $[M + Na]^+$ 817.2320, found 817.2334.

Methyl 3,4,6-tri-*O*-acetyl-*α/β*-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranoside (36):

28 (25 mg, 0.03 mmol) was dissolved in 2 ml dry DCM under inert conditions and 0.2 ml TFA was added. The mixture was left to stir for 1 h, after which the volatiles were removed. Silica flash column chromatography (40-80% EtOAC-heptane) afforded **36** as an anomeric mixture 16:1 (*α/β*) (11 mg, 54%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 15H), 5.35 (dd, *J* = 3.3, 1.3 Hz, 1H), 5.22 (d, *J* = 3.6 Hz, 1H), 5.11 (d, *J* = 10.7 Hz, 1H), 5.05 (dd, *J* = 10.6, 3.2 Hz, 1H), 4.73 (d, *J* = 10.8 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.64 – 4.49 (m, 4H), 4.24 (td, *J* = 6.6, 1.4 Hz, 1H), 4.04 – 3.95 (m, 3H), 3.93 – 3.80 (m, 3H), 3.72 – 3.65 (m, 2H), 3.60 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.54 (d, *J* = 11.7 Hz, 1H), 3.38 (s, 3H), 2.09 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.63, 170.32, 170.14, 137.78, 137.53, 137.32, 128.55, 128.34, 128.30, 128.24, 128.18, 128.13, 127.80, 127.64, 127.61, 101.50, 97.82, 80.43,

80.11, 78.13, 75.58, 73.28, 73.13, 70.57, 70.09, 68.17, 68.09, 67.82, 67.56, 61.93, 55.42, 29.68, 20.83, 20.68, 20.61. **HRMS** (*m/z*) calcd for $C_{40}H_{48}O_{14}$ [M + Na]$^+$ 775.2942, found 775.2943.

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3

A Novel Synthetic Route to Universal Stereoselective Glycosylations

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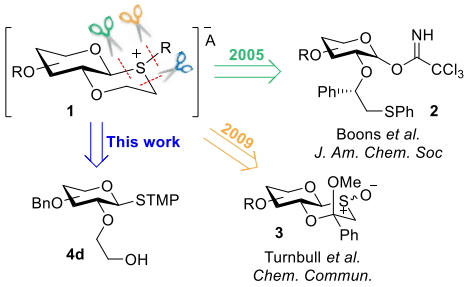
Abstract: To date, a general and reliable glycosylation procedure for *α*-glucosides remains elusive. In this respect, the application of neighboring group participation (NGP) of C-2 chiral auxiliaries has greatly improved the *α*-selectivity, but the synthetic effort is extensive. This chapter reports a novel four-step synthesis to produce either an *α*-, or *β*-directing donor using a C-2 stereo-directing group. In addition, an important factor to obtain good stereoselectivity is the protecting groups on glycosyl donors. Benzylic protecting groups tend to diminish *α*-selectivity and investigation of the negative inductive effect of substituted benzyl protecting groups on the stereoselectivity revealed that the 2,4-dichlorobenzyl protecting group provided much improved *α*-selectivity.

3.1 – Introduction

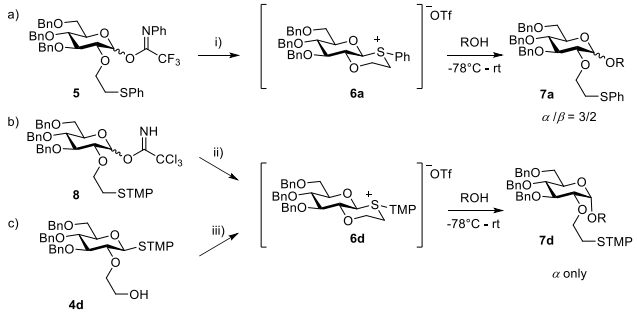
The main challenge of chemical oligosaccharide synthesis is the stereoselective synthesis of the glycosidic bond.[1] A unified methodology that allows for a late stage introduction of a stereo-directing group (1,2-*trans* and 1,2-*cis* linkages) would enable the use of standardized monosaccharide building blocks. Unfortunately, this generally applicable methodology is still missing. 1,2-*trans* Glycosides can be synthesized by exploiting neighboring group participation of a C-2 acyl group, whereas previous research summarized in Chapter 1[2] and Chapter 2[3], exemplify that the stereoselective synthesis of 1,2-*cis* glycosidic linkages can be accomplished using a *β*-sulfonium intermediate. The use of a C-2 acyl group to provide 1,2-*trans* linkages is very stereoselective and applicable to manno- and gluco-type sugars. In contrast, the use of *β*-sulfonium ions to prepare 1,2-*cis*-linkages does not always ensure good stereoselectivity. Critical determinants in this respect are the structure of the auxiliary and the protecting groups on the glycosyl donor. Furthermore, the introduction of the (chiral) auxiliary is quite laborious and takes place at an early stage in the building block synthesis using current methodology. In theory, the *β*-sulfonium ion intermediate can be prepared by making three disconnections, two of which have been explored (Scheme 1). In 2005, Boons *et al.* pioneered the formation of the *β*-sulfonium ion intermediate (**1**) by using a 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether participating group and an anomeric imidate leaving group (**2**, Scheme 1).[1a, 4]



Scheme 1: Retrosyntheses of the *β*-sulfonium ion.

Turnbull *et al.* subsequently reported the synthesis of a prearranged bicyclic oxathiane intermediate (**3**) that could be activated by oxidation and subsequent electrophilic aromatic substitution to afford *β*-sulfonium ion intermediate **1**.[5] The third, so far unexplored disconnection is the bond between the sulfur and the auxiliary skeleton. This disconnection would yield a thioglycoside precursor which is a frequently used anomeric protecting/leaving group and would allow for late stage introduction of the C-2 auxiliary. The use of an ethylene glycol derived auxiliary was explored because it is the simplest achiral auxiliary that could yield a *β*-sulfonium ion. Furthermore, Fairbanks *et al.* reported full *α*-selectivity using a very similar armed 3,4,6-tribenzylated donor (**8**) utilizing an achiral auxiliary carrying a 2,4,6-

trimethoxythiophenyl (STMP) moiety (Scheme 2b).[6] This result was intriguing since we only obtained an *α*/*β* ratio of 3/2 using donor **4d** which only differs in the thiophenyl moiety (Scheme 2a). Hence, we set out to explore the possibility to generate **6d** from precursor **4d** by triflation which would greatly streamline donor synthesis. In addition, we systematically investigated the contribution of the thiophenyl moiety as this was the only difference between our donor (**4d**) and the one reported by Fairbanks *et al.* (**8**). To this end, we prepared a series of thioglycoside precursors with increasingly electron-donating thiophenyl moieties, *id est* 4-methoxyphenyl (PMP), 2,6-dimethoxyphenyl (DMP) and 2,4,6-trimethoxyphenyl (TMP).

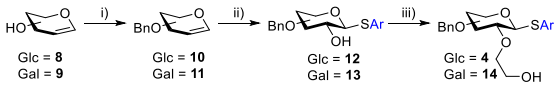


Scheme 2: Syntheses of the *β*-sulfonium ion *via* **a)** This manuscript, Chapter 2; **b)** Fairbanks' donor; **c)** this study. Reagents and conditions: *i)* 1) TfOH, DCM, -78°C – 0°C, 2) ROH, DTBMP, DCM, -78°C – rt; *ii)* 1) TMSOTf (1 eq), DCM, -78°C to 0°C, 2) ROH (1.2 eq), TTBP (2 eq) -78°C to rt, 16h; *iii)* 1) Tf_2O (1.5 eq), DTBMP (4 eq), DCM, -40°C to 0°C, 30 min, 2) ROH (1.2 eq), -78°C to rt, 16h. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, TTBP = 2,4,6-tri-*tert*-butylpyrimidine.

3.2 – Donor synthesis I

To prepare a series of glycosyl donors, we used a simple and efficient three step synthesis starting from commercially available *D*-glucal (**8**). Introduction of the benzyl protecting groups was achieved using standard conditions to provide glucal **10** in an excellent 98% yield. Next, a combination of $NaHCO_3$, H_2O, oxone and acetone was used to generate dimethyldioxirane (Murray's reagent) *in situ* and epoxidation of **10** resulted in a 1,2-*cis* configured epoxide.[7] Notably, the reaction had to remain basic and hence solid $NaHCO_3$ was added occasionally to keep the reaction going. After a simple work-up, consisting of extraction of the water layer with DCM and concentration of the combined organic layers *in vacuo*, the epoxide was opened with $ZnCl_2$ and the appropriate thiophenyl to provide **12a-d**. In most cases this procedure led to the formation of an anomeric mixture from which the desired *β*-anomer could be separated by silicagel flash column chromatography. Next, a 2-(2-bromoethoxy)tetrahydro-*2H*-pyran auxiliary was installed on the C-2 position, which after subsequent deprotection with *p*TsOH in methanol afforded glucosyl donors **4a-d** (Table 1, entries 1-4). Having observed improved selectivity with the galacto-type donors in Chapter 2[3], we decided to also include this C-4 epimer of glucose in our study.

Table 1: Donor Syntheses I



entry	type	Ar	yield (%) i)	yield (%) ii)	yield (%) iii)	entry	type	Ar	yield (%) i)	yield (%) ii)	yield (%) iii)
1	glc	Ph	**10** (98)	**12a** (37)	**4a** (81)	5	gal	Ph	**11** (87)	**13a** (64)	**14a** (20)
2	glc	PMP	-	**12b** (47)	**4b** (70)	6	gal	PMP	-	**13b** (26)	**14b** (69)
3	glc	DMP	-	**12c** (39)	**4c** (81)	7	gal	DMP	-	**13c** (55)	**14c** (66)
4	glc	TMP	-	**12d** (76)	**4d** (83)	8	gal	TMP	-	**13d** (59)	**14d** (41)

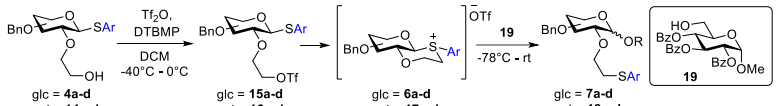
Reagents and conditions: *i)* 1) BnBr, NaH, DMF, 0°C; *ii)* 1) acetone, DCM, aq. $NaHCO_3$, oxone, 2) corresponding thiol, $ZnCl_2$, DCM, -78°C; *iii)* 1) NaH, DMF, $Br(CH_2)_2OTHP$, 0°C, 2) *p*-TsOH, MeOH. glc = glucose-type; gal = galactose-type; PMP = *p*-methoxyphenyl; DMP = 2,6-dimethoxyphenyl; TMP = 2,4,6-trimethoxyphenyl.

In this case, the donor synthesis started out from commercially available *D*-galactal (**9**) and followed the same steps mentioned above, affording galactose donors **14a-d** (Table 1, entries 5-8). It is worth noting that after opening of the epoxide with $ZnCl_2$ and the appropriate thiol, separation of the galacto-type anomers was rather tedious.

3.3 – Glycosylation results I

Glycosylation of donors **4a-d** and **14a-d**, was achieved by activation with Tf_2O in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at -40°C. After thin layer chromatography (TLC) indicated complete consumption of the starting material, the temperature was raised to 0°C which initiated the formation of *β*-sulfonium ions **6a-d**. Next, the mixture was cooled to -78°C and acceptor **19** was added. Slowly raising the temperature to room temperature (rt) overnight afforded the corresponding glycosides, **7a-d** and **18a-d** (Table 2, entries 1-4 and 5-8, resp.).

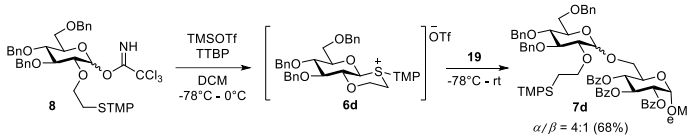
Table 2: Glycosylation results I



entry	donor	type	Ar	yield (%)[a]	*α* / *β*[b]	entry	donor	type	Ar	yield (%)[a]	*α* / *β*[b]
1	**4a**	glc	Ph	71	2.5/1	5	**14a**	gal	Ph	55	3/1
2	**4b**	glc	PMP	62	2.5/1	6	**14b**	gal	PMP	36	3/1
3	**4c**	glc	DMP	83	3.5/1	7	**14c**	gal	DMP	37	6/1
4	**4d**	glc	TMP	76	4/1	8	**14d**	gal	TMP	59	7/1

[a] isolated yield; [b] anomeric ratios were determined *via* key integrals in ^{1}H-NMR and/or ^{13}C spectra of the crude reaction mixtures. glc = glucose; gal = galactose; PMP = *p*-methoxyphenyl; DMP = 2,6-dimethoxyphenyl; TMP = 2,4,6-trimethoxyphenyl.

In both the glucose and galactose series, disscharide product formed with moderate to good yield indicating that triflation of the C-2 glycol substituent indeed led to thioglycoside alkylation and subsequent glycosylation. Furthermore, the expected trend that a more electronrich aromatic thiophenyl group provides better *α*-selectivity was indeed observed. However the stereoselectivity of donor **4d** was far from the reported exclusive *α*-selectivity (Table 2, entry 4, *α/β* = 4/1).[6] As the used donors and corresponding activation method in both methodologies are different, we synthesized donor **8** and exactly followed the reported glycosylation procedure. The ratio was determined by NMR analysis of the crude reaction mixture and in our hands the reaction again provided an *α/β* ratio of 4/1, highlighting that the activation method was not responsible for the discrepancy between the result we obtained and that reported by Fairbanks *et al.* (*α/β* = 1/0).



Scheme 3: Glycosylation of donor **8** on our laboratory resulted in an *α/β* mixture of 4/1, as opposed to *α*-only in Fairbanks' laboratory (*α/β* = 1:0).

These results led us to investigate the reaction intermediates *via* variable temperature (VT) NMR studies. Donor **4d** and DTBMP were dissolved in CD_2Cl_2 and cooled to -78°C (Figure 1a). Triflic anhydride was added (Figure 2b) after which ^{19}F NMR revealed the formation of a new compound (intermediate alkyl triflate **15d**). Additionally, TLC analysis indicated the complete consumption of starting material and formation of a more apolar compound, which is an important observation as **4d** could also serve as a glycosyl acceptor if it were not fully consumed. Temperature was then slowly raised to -20°C and the peak indicating the formation of **15d** in the ^{19}F spectrum disappeared again. ^{1}H-NMR revealed the formation of a new compound, as a significant downfield shift of H-1 from 4.30 (d, *J* = 10.1 Hz) to 5.48 (d, *J* = 9.5 Hz) ppm in combination with a downfield shift of the H-8 protons from 3.22 ppm for both protons to 3.54 and 4.56 ppm for H_{ax} and H_{eq} indicated the formation of *β*-sulfonium **6d** (Figure 1c). After 30 minutes, another measurement showed the formation of a single new compound (Figure 1d). An ^{1}H-^{13}C-HMBC spectrum showed a $^{3}J_{C1,H8}$ correlation at 81.54 and 3.54 ppm (Figure 1e), which can only exist when a sulfonium ion is formed. These results represent the same intermediate as the one found by Fairbanks *et al.* and both suggest *β*-sulfonium **6d** as the major intermediate species after activation. However, from the experimental result it is clear that **6d** may not be a reactive intermediate which reacts *via* an S_N2-like displacement, as an *α/β* ration of 4/1 is obtained after glycosylation. The above results also show that the triflation of the ethylene glycol auxiliary can lead to highly pure *β*-sulfonium ion intermediates which represents a new methodology for thioglycoside activation.

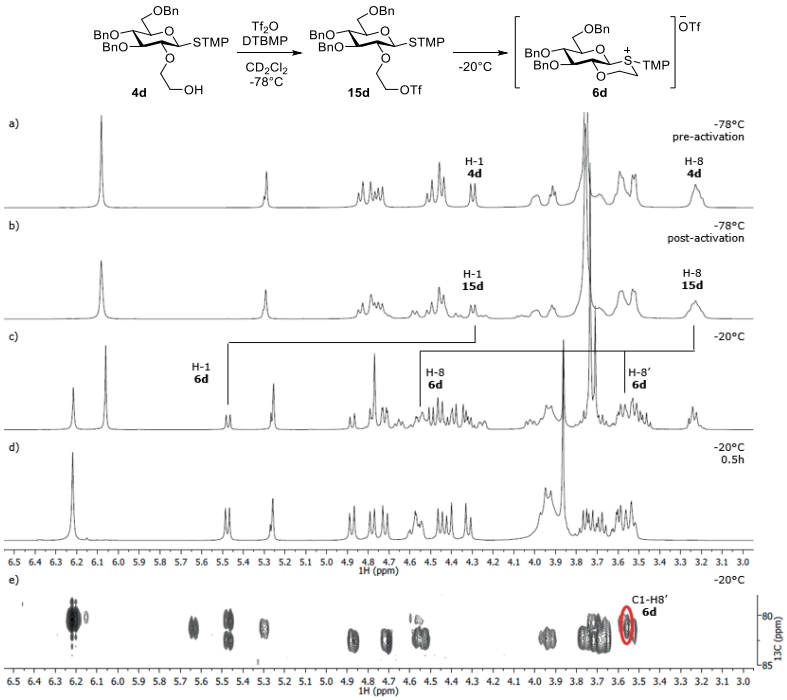


Figure 1: VT-NMR study of donor **4d**. *a)* pre-activation at -80°C; *b)* post-activation at -80°C (**15d**); *c) i*ncreasing temperature to -20°C shows the formation of **6d**; *d)* 30 minutes later only **6d** remains*; e)* HMBC shows C1-H8 correlation indicating ring closure.

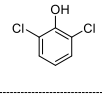
To improve the stereoselectivity of *β*-sulfonium ion mediated glycosylations, electron-withdrawing protecting groups on the glycosyl donor can be used (see chapter 1). Electron-withdrawing protecting groups on glycosyl donors are assumed to destabilize the oxocarbenium ion and therefore, as the sulfonium intermediate is further away from the withdrawing substituents this intermediate should be better stabilized and subsequent S_N2-like displacement of this intermediate stereoselectively results in *α*-glycosides.[8]

Hence, we set to explore the influence of the inductive effect of the *O*-3, *O*-4 and *O*-6 protecting groups. To minimize the contribution of other mechanism such as remote participation we excluded ester protecting groups and instead used increasingly electron-withdrawing benzyl ethers. Jensen and coworkers investigated the reactivity for various para substituted benzylated donors and found that reactivity follows the trend OMe > H > Cl > CN. Glycosylation of the respective para substituted benzyl donors afforded a similar trend for the *α*/*β* ratio where the *α*-selectivity increases with the associated strength of the positive inductive effect, 1/5 > 1/3 > 1/1 = 1/1 (OMe > H > Cl > CN, resp.).[9] These results suggest an inductive influence of the *p*-substituents and we sought to investigate this further.

3.4 – Donor synthesis II

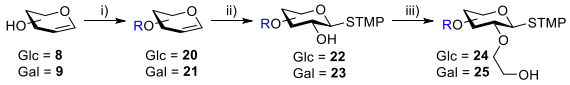
In order to be able to estimate the contribution of the of the electron-withdrawing substituents, we compared the acid dissociation constant (pK_a) values of the corresponding substituted phenol derivatives, which follow the trend that Jensen and co-workers observed.[9] In addition to phenol, *p*-chlorophenol and *p*-cyanophenol, we selected 2,4- and 2,6-dichlorophenol as their pK_a values are lower than *p*-cyanophenol and thus suggest better *α*-selectivity (Table 3).[10]

Table 3: Substituted phenol derivatives and related pK_a values.

phenol						
***p*K$_a$**	10.10	9.99	9.41	7.97	7.89	6.79

Thus, four gluco- and galacto-type donors consisting of *p*-chlorobenzyl (PCB), *p*-cyanobenzyl (PCNB), 2,4- and 2,6-dichlorobenzyl (DCB) protecting groups were synthesized (Table 3). The anomeric TMP thioether provided the best selectivity in the previous screening and was therefore selected as anomeric group for this study (Table 2). The same reaction steps as in section 3.2 were followed, which afforded products **24a-c**, and **25a-c** in moderate to good yields. Especially the epoxidation step occasionally provided moderate yields. PCNB donors **24d** and **25d** were obtained from PCB compounds **24a** and **25a** following an elegant procedure based on a method from Seeberger, Buchwald and Plante[11] using $K_4[Fe(CN)_6]\cdot 3H_2O$ as the cyanide donor and 5 mol% ^{t}BuXPhos-Pd-G3 as the metal catalyst.[9] Unfortunately, dichlorinated benzyl ether failed to afford the corresponding dicyanated products under these conditions.

Table 4: Donor syntheses



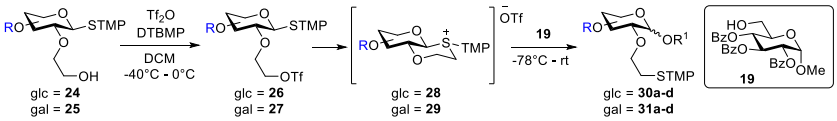
Entry	Type	R	yield (%) i)	ii)	iii)	iv)	Entry	Type	R	yield (%) i)	ii)	iii)	iv)
1	glc	PCB	**20a** (88)	**22a** (61)	**24a** (82)	-	5	gal	PCB	**21a** (90)	**23a** (60)	**25a** (85)	-
2	glc	PCNB	-	-	-	**24d** (88)	6	gal	PCNB	-	-	-	**25d** (93)
3	glc	2,4-DCB	**20b** (90)	**22b** (50)	**24b** (72)	-	7	gal	2,4-DCB	**21b** (46)	**23b** (26)	**25b** (74)	-
4	glc	2,6-DCB	**20c** (89)	**22c** (38)	**24c** (59)	-	8	gal	2,6-DCB	**21c** (92)	**23c** (51)	**25c** (63)	-

Reagents and conditions: *i)* 1) corresponding benzyl halide, NaH, DMF, 0°C; *ii)* 1) acetone, DCM, aq. $NaHCO_3$, oxone, 2) 2,4,6-trimethoxybenzene thiol, $ZnCl_2$, DCM, -78°C; *iii)* 1) NaH, DMF, $Br(CH_2)_2OTHP$, 0°C, 1h, 2) *p*-TsOH, MeOH; *iv)* **24a** or **25a**, $K_4[Fe(CN_6)]\cdot 3H_2O$, ^{t}BuXPhos-Pd-G3 (5 mol%), KOAc, H_2O:dioxane (1:1 v/v), 100°C, 1h. glc = glucose; gal = galactose; PCB = *p*-chlorobenzyl; PCNB = *p*-cyanobenzyl; DCB = dichlorobenzyl; TMP = 2,4,6-trimethoxyphenyl.

3.5 – Glycosylation results II

Glycosylation of donor **24a** containing PCB protecting groups already revealed slightly improved selectivity, *α/β* = 5/1, compared to benzylated donor **4d,** *α/β* = 4/1 (Table 5, entries 1 and 2). Increasing polarization by using the PCNB and 2,4-DCB protecting groups further improved *α*-selectivity up to *α/β* = 9/1 for 2,4-DCB glucose donor **24d** (Table 5, entry 4). Switching one of the chloride substituents from the para to the ortho position resulted in a 33% drop in stereoselectivity (Table 4, entry 5). Hence, 2,6-DCB donor **24c** did not follow the hypothesized trend that a lower *p*K_a affords better *α*-selectivity. This could be the result of the different orientation of the dipoles associated with the electron-withdrawing chlorine substituents or possibly steric factors due to ortho-ortho-substitution on the aromatic ring. With this in mind, it would be very interesting to investigate the contribution of protecting groups at individual positions to gain more insight. Similar studies with ester protecting groups have shown that the *O*-3 position is most important to achieve *α*-glycosides.[8] Interestingly, the galacto-series (donor **25a-d**) again displayed better inherent *α*-selectivity following the same trend as was observed for the gluco-type counterparts. The most selective galactosyl donor (**25b**) afforded disaccharide **31b** with a ratio of 13/1.

Table 5: Glycosylation results

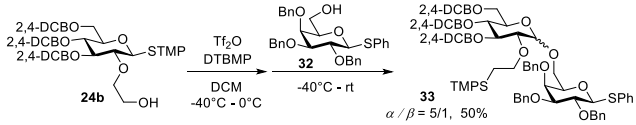


glc = **24** gal = **25** | glc = **26** gal = **27** | glc = **28** gal = **29** | glc = **30a-d** gal = **31a-d** | **19**

entry	donor	type	R	yield (%)[a]	*α* / *β*[b]	entry	donor	type	R	yield (%)[a]	*α* / *β*[b]
1[c]	**4d**	glc	Bn	76	4/1	6[c]	**11d**	gal	Bn	59	7/1
2	**24a**	glc	PCB	75	5/1	7	**25a**	gal	PCB	33	9/1
3	**24d**	glc	PCNB	65	7.5/1	8	**25d**	gal	PCNB	87	12.5/1
4	**24b**	glc	2,4-DCB	81	9/1	9	**25b**	gal	2,4-DCB	68	13/1
5	**24c**	glc	2,6-DCB	84	6/1	10	**25c**	gal	2,6-DCB	70	8.5/1

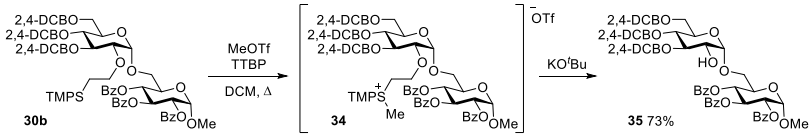
[a] isolated yield; [b] anomeric ratios were determined *via* key integrals in ^{1}H-NMR and/or ^{13}C spectra of the crude reaction mixtures; [c] results adopted from Table 2. glc = glucose; gal = galactose; PCB = *p*-chlorobenzyl; PCNB = *p*-cyanobenzyl; DCB = dichlorobenzyl; TMP = 2,4,6-trimethoxyphenyl.

To further explore the scope of the most successful glucose donor **24b**, we glycosylated glycosyl acceptor **32** as it is protected with an anomeric thioether. Glycosyl building blocks carrying an anomeric thioether group are now regularly used, as they are stable to a wide range of functional group transformations, protecting group manipulations, as well as several activation procedures for glycosylation and, selective coupling is not easy to achieve.[12] We envisioned that preactivation of **24b** with triflic anhydride would yield the intermediate sulfonium ion and subsequent addition of **32** would lead to disaccharide without activation of **32**. Indeed, donor **24b** could be coupled to anomeric thioglycoside **32**, using the Tf_2O activation method resulting in disaccharide **33**, albeit with a lower *α*-selectivity *α/β* = 5/1 (50%, Scheme 4).



Scheme 4: The newly designed activation method allows for orthogonal glycosylation steps.

Another important challenge is the removal of the auxiliary. This can be achieved by activation of the thioether with MeOTf/TTBP in DCM resulting in sulfonium ion **34** and subsequent treatment with KO^{t}Bu to afford the free alcohol at C-2 in 73% (Scheme 5, **35**).[6]

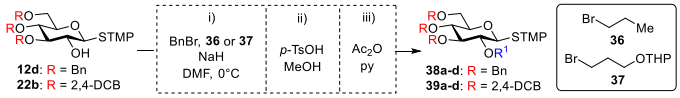


Scheme 5: Treatment of **30b** with MeOTf followed by KO^{t}Bu results in the free C-2 alcohol.

3.6 – Control compounds synthesis

In order to provide evidence that the 2-*O*-(hydroxyethyl) auxiliary is indeed involved in the *α*-selective glycosylation reaction pathway, we introduced a 2-*O*-benzyl as well as a 2-*O*-propyl group which are both non-participating substituents. The chain length of the C-2 auxiliary was also elongated by one more carbon to investigate the effect of ring size. The above substituents were introduced on both the benzyl and the 2,4-DCB protecting group as the first is the standard and the latter gave the highest selectivity in the previous screening.

Table 6: Synthesis of control compounds



entry	donor	R	R^1	method	yield (%)	entry	donor	R	R^1	method	yield (%)
1	**38a**	Bn	Bn	i)	73	5	**39a**	2,4-DCB	Bn	i)	60
2	**38b**	Bn	$(CH_2)_2Me$	i)	86	6	**39b**	2,4-DCB	$(CH_2)_2Me$	i)	84
3	**38c**	Bn	$(CH_2)_3OH$	i) then ii)	62	7	**39c**	2,4-DCB	$(CH_2)_3OH$	i) then ii)	73
4	**38d**	Bn	Ac	iii)	88	8	**39d**	2,4-DCB	Ac	iii)	69

DCB = dichlorobenzyl; TMP = 2,4,6-trimethoxyphenyl.

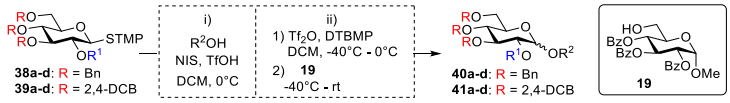
To this end, building blocks containing Bn groups (**12d**) and 2,4-DCB groups (**22b**) were reacted with NaH and the respective alkyl bromide (benzyl bromide, *n*-propyl bromide (**36**), or 2-(3-bromopropoxy)tetrahydro-2H-pyran (**37**)). Subsequent *p*TsOH mediated deprotection of the latter THP ether afforded the desired control donors in 60-86% yield (Table 6, entries 1-3 and 5-7). Fundamentally, in order for this methodology to be a universal procedure for

stereoselective glycosylations, synthesis of *β*-glycosides should also be achieved. This route lends itself perfectly for late stage introduction of the C-2 directing group, and the C-2 alcohol of thioethers **9d** and **19b** could easily be modified with a *β*-directing acyl group by reacting it with acetic anhydride in pyridine, obtaining **35d** and **36d** in 88% and 69% yield, resp. (Table 6, entries 4 and 8).

3.7 – Control compounds results

As donors **38a,b** and **39a,b** do not contain an alcohol which can be triflated to initiate the glycosylation reaction, another activating method had to be used. The NIS/TfOH combination is an excellent method for thioether activation[13] and **38a,b** and **39a,b** were glycosylated accordingly (Table 7, entries 1-2 and 5-6). Benzyl protected donors **38a,b** proved unselective (entries 1-2), whereas the use of 2,4-DCB protecting groups (**39a,b**) did increase the anomeric ratios (entries 5-6). This indicates that the 2,4-DCB protecting group inherently makes the glycosylation reaction more *α*-selective, independent of the C-2 substituent. Combining these results with the results from section 3.5, where we used the model 2-*O*-(2-hydroxyethyl) auxiliary, we can clearly see an increase in *α*-selectivity when an auxiliary is used (Table 5, entry 4, *α*/*β* = 9/1). Glycosylation of donor **38c** and **39c**, bearing a 2-*O*-(3-hydroxypropanyl) auxiliary considerably reduces the anomeric rations for both the Bn and 2,4-DCB protected donors to *α*/*β* = 2/1 and 2.5/1, respectively (Table 7, entries 3 and 7). *Id est*, with the C-2 auxiliary increased by 1 carbon, anomeric control is diminished. This provides evidence that the chair-like conformation of the original donors' *β*-sulfonium ion intermediate is needed to afford improved *α*-selectivity. Finally, glycosylation of donors **38d** and **39d** carrying an C-2 acetyl auxiliary both afforded the *β*-glycoside only, as expected (Table 7, entries 4 and 8). Combined with the improved selectivity of the 2,4-DCB protected carbohydrates, these results bring a universal glycosylation procedure, in which one can choose the stereoselective outcome of this reaction, considerably closer.

Table 7: Glycosylation of control compounds



entry	product	R	R¹	method	yield (%)[a]	*α* / *β*[b]	entry	product	R	R¹	method	yield (%)[a]	*α* / *β*[b]
1	**40a**	Bn	Bn	i)	68	1.4/1	5	**41a**	2,4-DCB	Bn	i)	57	4/1
2	**40b**	Bn	$(CH_2)_2Me$	i)	65	1.2/1	6	**42b**	2,4-DCB	$(CH_2)_2Me$	i)	51	3/1
3	**40c**	Bn	$(CH_2)_3OH$	ii)	71	2/1	7	**43c**	2,4-DCB	$(CH_2)_3OH$	ii)	49	2.5/1
4	**40d**	Bn	Ac	i)	83	<1/20	8	**44d**	2,4-DCB	Ac	i)	60	<1/20

[a] Isolated yield; [b] anomeric ratios were determined *via* key integrals in ^{1}H- and ^{13}C-NMR spectra of the crude reaction mixtures.

3.8 – Conclusions

We have developed a unique activation methodology for the formation of the challenging *α*-glucosidic bond. Donors equipped with electron-deficient 2,4-DCB protecting groups show enhanced *α*-selectivity on themselves which is significantly improved by introduction of the participating 2-*O*-(hydroxyethyl) auxiliary. Especially galacto-type donors reach an *α*/*β* ratio of 13/1, equivalent to 92% *α*-galactosides. With the simple building block synthesis and the possibility for late stage introduction of an *α*-or *β*-directing auxiliary, a universal procedure for the respective stereoselective glycosylations has now come closer than ever.

3.9 – Experimental section

General methods: For general methods please refer to section 2.9.

General procedure A: *D*-glucal or *D*-galactal was dissolved in dry DMF (0.2 M) under inert atmosphere and cooled to 0°C. NaH (8 eq; 60% dispersion in mineral oil) was added and the reaction mixture was stirred for 30 minutes, after which the corresponding benzylating agent (5 eq) was added. The reaction was stirred for 16h at ambient temperature after which it was quenched with MeOH. The mixture was concentrated under reduced pressure and taken up in DCM (100 mL) and water (100 mL). The aqueous layer was extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the crude product.

General procedure B: To a cooled (0°C) solution of a benzylated glycal (2.4 mmol) in DCM (10 mL) were added acetone (1 mL) and sat. aq. $NaHCO_3$ (17 mL). The mixture was stirred vigorously, and a solution of oxone (4.8 mmol) in H_2O (6 mL) was added dropwise over 15 min. The mixture was stirred vigorously at 0°C for 30 min and then at rt until TLC indicated consumption of the starting material. The organic phase was separated and the aqueous phase was extracted with DCM (2x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was dissolved in dry DCM (23 mL). MS (4Å) and the corresponding thiol (3.6 mmol) were added under inert atmosphere. The mixture was cooled to -78°C and stirred for 15 minutes. A 1M solution of $ZnCl_2$ in Et_2O (0.24 mmol) was added and the mixture was stirred overnight while slowly warmed up to rt. The reaction was quenched with TEA and purified with silicagel flash column chromatography to obtain the pure product.

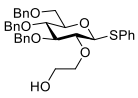
General procedure C: An anomeric thioether with a free 2-OH (**12a-d**, **13a-d**, **22a-c** or **23a-c**) was dissolved in dry DMF (0.1 M) and cooled to 0°C. NaH (4 eq; 60% dispersion in mineral oil) was added and the mixture was stirred at 0°C for 15 min, after which the appropriate auxiliary ($Br(CH_2)_3OTHP$ or **37**) was added (4 eq). The reaction was stirred for 16h at ambient temperature, after which it was quenched with MeOH. The reaction mixture was concentrated under reduced pressure and were taken up in MeOH (25 mL). *p*TsOH was added until a pH of 2 was reached. The reaction was stirred for 4 h and subsequently concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with water (3 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the crude product.

General procedure D: Thioglucosides **12d** or **22b** were dissolved in dry DMF (0.1 M) and cooled to 0°C. NaH (4 eq; 60% dispersion in mineral oil) was added and the mixture was stirred at 0°C for 15 min, after which benzyl- or propyl bromide was added (4 eq). The reaction was stirred for 16h at ambient temperature, after which it was quenched with MeOH. The reaction mixture was concentrated under reduced pressure and the residue was taken up in EtOAc (20 mL). The organic layer was washed with water (3 x 20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure yielding the crude product.

General glycosylation procedure E: the corresponding glycosyl donors (0.50 mg) and DTBMP (4 eq) were dissolved in dry DCM (2 mL). MS (4Å) were added under inert atmosphere and the mixture was stirred at -40°C for 15 min. Tf_2O (1.5 eq) was added and the mixture was allowed to slowly warm up to 0°C and stirred at 0°C for 30 min. When TLC analysis indicated complete consumption of the triflated intermediate, the mixture was cooled down to -78°C and the appropriate acceptor (2 eq) was added. The reaction was left to warm up to rt in 16 hours and was subsequently taken up in EtOAc (20 mL) and filtered. The filtrate was washed with aq. $Na_2S_2O_3$ (20 mL, 10%), brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the crude product.

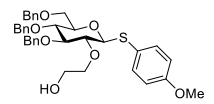
General glycosylation procedure F: One of glycosyl donors **38a,b,d** or **39a,b,d** (0.05 g) and acceptor 37 (2 eq) were dissolved in dry DCM (2 mL). MS (4Å) were added and the mixture was cooled to -5°C. NIS (1.1 eq) and TfOH (0.2 eq) were added and the reaction was stirred for 2h. The reaction was quenched with Et_3N and taken up in EtOAc (20 mL) and filtered. The filtrate was washed with aq $Na_2S_2O_3$ sol (20 mL, 10%), brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the crude product.

Phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-glucopyranoside (4a):



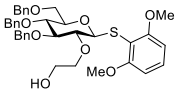
Via general procedure C. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) afforded **4a** (0.12 gr, 81%). **TLC:** (EtOAc/n-heptane, 30/70 v/v): R_f = 0.4; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 2H), 7.38 – 7.15 (m, 17H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.85 (d, *J* = 10.9 Hz, 1H), 4.80 (d, *J* = 10.8 Hz, 1H), 4.64 – 4.56 (m, 2H), 4.57 (d, *J* = 9.8 Hz, 1H (H-1)), 4.54 (d, *J* = 12.0 Hz, 1H), 3.89 (ddd, *J* = 10.7, 5.8, 3.0 Hz, 1H), 3.83 (ddd, *J* = 10.7, 6.0, 3.0 Hz, 1H), 3.78 (dd, *J* = 10.9, 2.0 Hz, 1H, (H-6)), 3.72 (dd, *J* = 10.9, 4.5 Hz, 1H, (H-6)), 3.70 – 3.61 (m, 4H, (H-3, H-4)), 3.50 (ddt, *J* = 6.6, 4.6, 1.9 Hz, 1H, (H-5)), 3.40 – 3.33 (m, 1H, (H-2)), 2.72 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.15, 137.87, 137.83, 133.21, 131.93, 128.92, 128.50, 128.44, 128.33, 127.89, 127.86, 127.84, 127.64, 127.59, 127.57, 87.50 (C-1), 86.62 (C-3), 80.63 (C-2), 79.12 (C-5), 77.94 (C-4), 77.25, 77.00, 76.75, 75.85, 74.99, 74.72, 73.41, 68.82 (C-6), 62.29. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{35}H_{38}O_6S$, 609.2287; found, 609.2275

4-Methoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)-1-thio-β-D-glucopyranoside (4b):



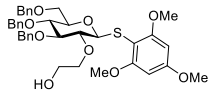
Via general procedure C. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) afforded **4b** (0.13 gr, 70%). **TLC:** (EtOAc/n-heptane, 40/60 v/v): R_f = 0.4; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.9 Hz, 2H), 7.30 – 7.16 (m, 13H), 7.12 (dd, *J* = 7.5, 2.1 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 4.83 (d, *J* = 10.9 Hz, 1H), 4.76 (d, *J* = 10.9 Hz, 1H), 4.72 (d, *J* = 10.9 Hz, 1H), 4.57 – 4.42 (m, 4H), 4.36 (d, *J* = 9.7 Hz, 1H), 3.83 (ddd, *J* = 10.7, 5.4, 3.1 Hz, 1H), 3.76 (ddd, *J* = 10.7, 6.1, 3.1 Hz, 1H), 3.72 – 3.51 (m, 11H, (H-3, H-4, H-6, H-6)), 3.38 (ddd, *J* = 9.5, 4.3, 1.9 Hz, 1H, (H-5)), 3.22 (dd, *J* = 9.7, 8.6 Hz, 1H, (H-2)), 2.72 (s, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.79, 138.24, 137.90, 137.85, 135.18, 128.49, 128.43, 128.32, 127.86, 127.84, 127.63, 127.54, 122.74, 114.41, 87.84 (C-1), 86.64 (C-3), 80.47 (C-2), 79.02 (C-5), 77.96 (C-4), 75.80, 74.97, 74.66, 73.40, 73.26, 68.88 (C-6), 62.29, 55.25; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{36}H_{40}O_7S$, 639.2392; found, 639.2382

2,6-Dimethoxyphenyl 3,4,6-tri-O-benzyl-2-O-(2-hydroxyethyl)-1-thio-β-D-glucopyranoside (4c):



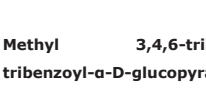
Via general procedure C. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) afforded **4c** (0.16 gr, 81%). **TLC:** (EtOAc/n-heptane, 40/60 v/v): R_f = 0.30; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 14H), 7.17 (dd, *J* = 7.3, 2.2 Hz, 2H), 6.56 (d, *J* = 8.3 Hz, 2H), 4.87 (s, 2H), 4.79 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 10.9 Hz, 1H), 4.53 (d, *J* = 10.0 Hz, 1H (H-1)), 4.49 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.05 (ddd, *J* = 10.9, 5.7, 2.5 Hz, 1H), 3.95 (ddd, *J* = 10.8, 6.7, 2.4 Hz, 1H), 3.84 (m, 7H), 3.75 – 3.67 (m, 2H, (H-6)), 3.66 – 3.59 (m, 2H, (H-3, H-6)), 3.59 – 3.48 (m, 2H, (H-4)), 3.43 – 3.32 (m, 2H, (H-2, H-5)); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.01, 138.35, 138.24, 137.94, 130.43, 128.50, 128.42, 128.26, 127.93, 127.88, 127.82, 127.80, 127.51, 108.57, 104.33, 87.92 (C-1), 87.23 (C-3), 81.74 (C-2), 79.63 (C-5), 78.20 (C-4), 75.75, 74.98, 74.94, 73.58, 69.41 (C-6), 61.87, 56.25; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{37}H_{42}O_8S$, 669.2498; found, 669.2495.

2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-glucopyranoside (4d):



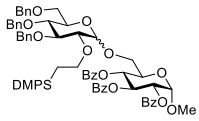
via general procedure C starting from **9d** (0.33 g, 0.52 mmol). The crude product was purified by silicagel flash column chromatography (30% to 60% EtOAc in *n*-heptane) afforded **4d** as a white solid (0.294 g, 83%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.21. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.11 (m, 18H), 6.12 (s, 2H), 4.87 (s, 2H), 4.78 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 10.9 Hz, 1H), 4.48 (s, 2H), 4.38 (d, *J* = 9.9 Hz, 1H, H-1), 4.05 (ddd, *J* = 10.8, 5.6, 2.5 Hz, 1H), 3.94 (ddd, *J* = 10.8, 6.8, 2.5 Hz, 1H), 3.82 (s, 7H), 3.79 (s, 3H), 3.74 – 3.67 (m, 2H, H-6a), 3.64 – 3.58 (m, 3H, H-3, H-6b), 3.49 (t, *J* = 9.4 Hz, 1H, H-4), 3.39 – 3.31 (m, 2H, H-2, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.32, 162.13, 138.40, 138.27, 137.94, 128.49, 128.42, 128.26, 127.95, 127.89, 127.82, 127.80, 127.79, 127.51, 99.96, 91.19, 88.74 (C-1), 87.22 (C-3), 81.60 (C-2), 79.60 (C-5), 78.19 (C-4), 75.75, 74.97, 74.88, 73.64, 69.58 (C-6), 61.85, 56.21, 55.34; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{38}H_{44}O_9S$, 699.2604; found, 699.2583.

Methyl 3,4,6-tribenzyl-2-*O*-(2-benzenethioethyl)-*α/β*-D-glucopyranosyl-(1→6)- 2,3,4-*O*-tribenzoyl-*α*-D-glucopyranoside (7a): *Via* general procedure E and donor **4a** Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **7a** as an anomeric mixture (*α/β* = 2.5/1, 69 mg, 71%). **TLC:** (EtOAc/n-heptane, 40/60 v/v): R_f = 0.5; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 2H), 7.85 (d, *J* = 7.8 Hz, 2H), 7.55 – 7.44 (m, 2H), 7.44 – 7.17 (m, 24H), 7.17 – 7.05 (m, 3H), 6.14 (t, *J* = 9.9 Hz, 1H, (H-3')), 5.53 (t, *J* = 9.9 Hz, 1H, (H-4')), 5.25 (dd, *J* = 10.3, 3.7 Hz, 1H, (H-2')), 5.18 (d, *J* = 3.7 Hz, 1H, (H-1')), 4.92 (d, *J* = 3.5 Hz, 1H, (H-1)), 4.87 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 11.1 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.32 (ddd, *J* = 9.7, 6.6, 2.0 Hz, 1H, (H-5')), 3.93 – 3.83 (m, 3H, (H-6', H-3)), 3.83 – 3.75 (m, 2H, H-5), 3.72 – 3.59 (m, 3H, (H-6', H-4, H-6)), 3.52 (dd, *J* = 10.9, 2.0 Hz, 1H, H-6), 3.48 – 3.39 (m, 4H, (H-2)), 3.17 – 3.00 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.82, 165.78, 165.24, 138.78, 138.49, 137.92, 133.32, 133.02, 129.91, 129.89, 129.86, 129.81, 129.64, 129.38, 129.23, 129.05, 128.91, 128.40, 128.38, 128.36, 128.31, 128.30, 128.23, 128.22, 127.88, 127.86, 127.61, 127.60, 127.47, 126.14, 96.99 (C-1), 96.74 (C-1'), 81.41 (C-3), 80.97 (C-2), 77.52 (C-4), 75.41, 74.76, 73.38, 72.17 (C-2'), 70.59 (C-3'), 70.33 (C-5), 69.92, 69.64 (C-4'), 68.53 (C-5'), 68.23 (C-6), 66.64 (C-6'), 55.61, 33.40. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{63}H_{62}O_{14}S$, 1079.3758; found, 1097.3798



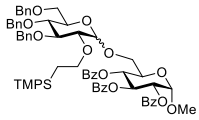
Methyl 3,4,6-tribenzyl-2-*O*-(2-(4-methoxybenzenethio)ethyl)-α-D-glucopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (7b): *Via* general procedure E and donor **4b**. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **7b** as an anomeric mixture (*α/β* = 2.5/1, 76 mg, 62%). **TLC:** (EtOAc/n-heptane, 40/60 v/v): R_f = 0.5; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.7 Hz, 2H), 7.92 (d, *J* = 7.7 Hz, 2H), 7.85 (d, *J* = 7.7 Hz, 2H), 7.49 (dt, *J* = 16.8, 7.4 Hz, 2H), 7.44 – 7.20 (m, 22H), 7.14 – 7.05 (m, 2H), 6.78 (d, *J* = 8.3 Hz, 2H), 6.13 (t, *J* = 9.9 Hz, 1H, (H-3')), 5.53 (t, *J* = 9.9 Hz, 1H, (H-4')), 5.25 (dd, *J* = 10.2, 3.7 Hz, 1H, (H-2')), 5.18 (d, *J* = 3.7 Hz, 1H, (H-1')), 4.92 (d, *J* = 3.5 Hz, 1H, (H-1)), 4.86 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.32 (ddd, *J* = 9.8, 6.8, 2.2 Hz, 1H, (H-5')), 3.92 – 3.81 (m, 3H, (H-6', H-3, H-5)), 3.81 – 3.66 (m, 6H, (H-6')), 3.66 – 3.56 (m, 2H, (H-4, H-6)), 3.52 (dd, *J* = 10.7, 2.0 Hz, 1H, (H-6)), 3.46 – 3.37 (m, 4H, (H-2)), 3.07 – 2.88 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.82, 165.78, 165.25, 159.03, 138.79, 138.51, 137.92, 133.48, 133.31, 133.02, 129.91, 129.89, 129.65, 129.24, 129.07, 128.93, 128.38, 128.36, 128.32, 128.29, 128.24, 128.22, 127.91, 127.87, 127.62, 127.60, 127.46, 125.75, 114.60, 97.05 (C-1), 96.74 (C-1'), 81.41 (C-3), 80.92 (C-2), 77.50 (C-4), 75.41, 74.76, 73.38, 72.18 (C-2'), 70.60 (C-3'), 70.32 (C-5), 70.06, 69.63 (C-4'), 68.54 (C-5'), 68.24 (C-6), 66.63 (C-6'), 55.61, 55.30, 35.38. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{64}H_{64}O_{15}S$, 1127,3864; found, 1127,3879.

Methyl 3,4,6-tribenzyl-2-*O*-(2-(2,6-dimethoxybenzenethio)ethyl)-α-D-glucopyranosyl-(1→6)- 2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (7c): *Via* general procedure E and donor **4c**. Silicagel flash column chromatography



(0% → 40% - EtOAc in *n*-heptane) afforded **7c** (51 mg, 83%) as an α/β mixture. **TLC:** (EtOAc/n-heptane, 40/60 v/v): R_f = 0.4; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.95 (m, 2H), 7.95 – 7.89 (m, 2H), 7.85 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.55 – 7.44 (m, 2H), 7.39 (dt, *J* = 18.0, 7.7 Hz, 3H), 7.35 – 7.17 (m, 20H), 7.11 (dd, *J* = 7.7, 1.9 Hz, 2H), 6.50 (d, *J* = 8.4 Hz, 2H), 6.12 (t, *J* = 9.8 Hz, 1H, (H-3')), 5.49 – 5.41 (m, 1H, (H-4')), 5.23 (dd, *J* = 10.2, 3.7 Hz, 1H, (H-2')), 5.16 (d, *J* = 3.8 Hz, 1H, (H-1')), 4.92 (d, *J* = 3.4 Hz, 1H, (H-1)), 4.84 (d, *J* = 10.9 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.67 (d, *J* = 10.9 Hz, 1H), 4.44 (d, *J* = 11.1 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.33 (ddd, *J* = 9.9, 7.3, 2.1 Hz, 1H, (H-5')), 3.93 – 3.76 (m, 9H, (H-6', H-3, H-5)), 3.72 – 3.63 (m, 4H, (H-6', H-6)), 3.60 (dd, *J* = 10.1, 8.9 Hz, 1H, (H-4)), 3.53 (dd, *J* = 10.7, 2.0 Hz, 1H, (H-6)), 3.50 – 3.36 (m, 4H, (H-2)), 3.01 (dt, *J* = 12.9, 7.3 Hz, 1H), 2.97 – 2.87 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.81, 165.73, 165.31, 161.05, 138.81, 138.60, 137.99, 133.30, 133.00, 129.90, 129.75, 129.63, 129.24, 129.07, 128.87, 128.37, 128.35, 128.30, 128.25, 128.22, 128.19, 127.95, 127.85, 127.59, 127.53, 127.41, 127.40, 109.39, 104.00, 97.05 (C-1), 96.63 (C-1'), 81.45 (C-3), 81.01 (C-2), 77.44 (C-4), 75.34, 74.69, 73.36, 72.19 (C-2'), 70.98, 70.57 (C-3'), 70.28 (C-5), 69.74 (C-4'), 68.41 (C-5'), 68.29 (C-6), 66.81 (C-6'), 56.07, 55.57, 33.37; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{65}H_{66}O_{16}S$, 1157.3969; found, 1157.3954.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-(2,4,6-trimethoxyphenylthio)ethyl)-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (7d): *via* general procedure E starting from glucosyl donor **4d** (48 mg; 0.071 mmol)



and using acceptor **19**. The crude product was purified by silicagel flash column chromatography (10% to 40% EtOAc in *n*-heptane) affording **7d** as an anomeric mixture (63 mg, 76%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.35. **^{1}H NMR ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.92 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.85 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.53 – 7.44 (m, 2H), 7.43 – 7.34 (m, 3H), 7.34 – 7.22 (m, 17H), 7.11 (dd, *J* = 7.7, 1.8 Hz, 2H), 6.11 (m, 3H, (H-3')), 5.45 (dd, *J* = 10.3, 9.5 Hz, 1H, (H-4')), 5.23 (dd, *J* = 10.2, 3.7 Hz, 1H, (H-2')), 5.16 (d, *J* = 3.7 Hz, 1H, (H-1')), 4.93 (d, *J* = 3.4 Hz, 1H, (H-1)), 4.84 (d, *J* = 10.9 Hz, 1H), 4.79 (d, *J* = 11.1 Hz, 1H), 4.66 (d, *J* = 10.9 Hz, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.34 (ddd, *J* = 10.0, 7.4, 2.1 Hz, 1H, (H-5')), 3.92 – 3.86 (m, 2H, (H-6', H-5)), 3.79, m, 10H, (H-3)), 3.72 – 3.58 (m, 5H, (H-6', H-4, H-6)), 3.53 (dd, *J* = 10.7, 2.0 Hz, 1H, (H-6)), 3.44 – 3.36 (m, 4H, (H-2)), 2.91 (ddd, *J* = 12.9, 8.3, 6.5 Hz, 1H), 2.82 (ddd, *J* = 12.9, 8.4, 7.0 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.79, 165.71, 165.30, 162.01, 161.79, 138.81, 138.60, 137.96, 133.28, 132.99, 129.89, 129.61, 129.24, 129.07, 128.85, 128.36, 128.33, 128.29, 128.23, 128.21, 128.17, 127.96, 127.86, 127.58, 127.51, 127.40, 127.38, 100.78, 97.10 (C-1), 96.62 (C-1'), 90.93, 81.45 (C-3), 81.03 (C-2), 77.42 (C-4), 75.34, 74.67, 73.35, 72.18 (C-2'), 70.98, 70.57 (C-3'), 70.26 (C-5), 69.72 (C-4'), 68.40 (C-5'), 68.28 (C-6), 66.81 (C-6'), 56.01, 55.56, 55.32, 33.89; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{66}H_{68}O_{17}S$, 1187.4075; found, 1187.4118.

3,4,6-Tri-*O*-benzyl-*D*-glucal (10):

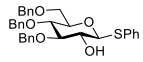
Via general procedure A starting from *D*-glucal (5.13 g, 35.1 mmol) using BnBr as the benzylating agent. The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) affording **7** (13.3 g, 91%). **TLC** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.55. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 15H), 6.42 (dd, *J* = 6.1, 1.3 Hz, 1H, H-1), 4.87 (dd, *J* = 6.2, 2.7 Hz, 1H, H-2), 4.83 (d, *J* = 11.3 Hz, 1H), 4.66 – 4.61 (m, 2H), 4.61 – 4.53 (m, 3H), 4.21 (ddd, *J* = 6.2, 2.7, 1.3 Hz, 1H, H-3), 4.06 (ddd, *J* = 8.3, 5.1, 2.9 Hz, 1H, H-5), 3.86 (dd, *J* = 8.7, 6.2 Hz, 1H, H-4), 3.83 – 3.72 (m, 2H, H-6); **^{13}C NMR:** (126 MHz, $CDCl_3$) δ 144.71 (C-1), 138.32, 138.17, 137.98, 128.47, 128.35, 128.28, 127.89, 127.77, 127.71, 127.63, 99.93 (C-2), 76.74 (C-5), 75.73 (C-3), 74.40 (C-4), 73.75, 73.51, 70.45, 68.52 (C-6).

3,4,6-tri-*O*-benzyl-*β*-D-galactal (11):

Via general procedure A and benzyl bromide. Silicagel flash column chromatography (0% - 30% EtOAc in *n*-heptane) afforded **8** (12.392 g, 87%). **TLC**: (EtOAc/n-heptane,50/50 v/v): R_f = 0.74; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 15H), 6.36 (dd, *J* = 6.2, 1.4 Hz, (H-1)), 4.85 (ddd, *J* = 8.5, 6.6, 4.1 Hz,

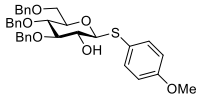
1H, H-2), 4.67 – 4.58 (m, 3H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 4.21 – 4.15 (m, H-3, H-5), 3.96 – 3.92 (m, H-4), 3.78 (dd, *J* = 10.1, 7.2 Hz, H-6a), 3.65 (dd, *J* = 10.2, 5.1 Hz, H-6b). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.21 (C-1), 138.52, 138.39, 138.01, 128.40, 128.34, 128.17, 127.92, 127.71, 127.58, 127.46, 99.99 (C-2), 75.72 (C-5), 73.44, 73.35, 71.30 (H-4), 70.91, 70.77 (C-3), 68.46 (H-6). **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{27}H_{28}O_4$, 439.1885; found, 439.1877.

Phenyl 3,4,6-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (12a):



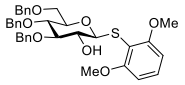
Via general procedure B starting from **10** and thiophenol. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) afforded **12a** (0,30 gr, 37%). **TLC:** (EtOAc/n-heptane, 30/70 v/v): R_f = 0.4; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.52 (m, 2H), 7.37 – 7.16 (m, 18H), 4.91 (d, *J* = 11.2 Hz, 1H), 4.86 – 4.80 (m, 2H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.57 (d, *J* = 10.9 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 9.6 Hz, 1H, (H-1)), 3.79 (dd, *J* = 10.9, 2.0 Hz, 1H, (H-6)), 3.73 (dd, *J* = 11.0, 4.5 Hz, 1H, (H-6)), 3.64 – 3.46 (m, 4H, (H-2, H-3, H-4, H-5)), 2.45 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.40, 138.21, 137.98, 132.81, 131.74, 128.89, 128.45, 128.36, 128.29, 127.99, 127.92, 127.89, 127.74, 127.57, 127.51, 87.96(C-1), 85.88(C-3), 79.34(C-5), 77.27(C-4), 75.27, 75.00, 73.36, 72.53(C-2), 68.92(C-6). **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{33}H_{34}O_5S$, 565.2025; found, 565.2022

4-Methoxyphenyl 3,4,6-tri-O-benzyl-1-thio-β-D-glucopyranoside (12b):



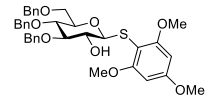
Via general procedure B starting from **10** and 4-methoxythiophenol. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) afforded **12b** (0.12 gr, 47%). **TLC:** (EtOAc/n-heptane, 40/60 v/v): R_f = 0.7; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.8 Hz, 1H), 7.38 – 7.15 (m, 14H), 6.76 (d, *J* = 8.8 Hz, 1H), 4.93 – 4.78 (m, 3H), 4.64 – 4.51 (m, 3H), 4.36 (d, *J* = 9.6 Hz, 1H, (H-1)), 3.80 – 3.72 (m, 5H, (H-6, H-6, OMe)), 3.61 – 3.53 (m, 2H, (H-3, H-4)), 3.50 (ddd, *J* = 7.4, 4.3, 2.1 Hz, 1H, (H-5)), 3.40 (dd, *J* = 9.6, 8.4 Hz, 1H, (H-2)), 2.41 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.15, 138.49, 138.38, 138.08, 136.01, 128.52, 128.43, 128.35, 128.01, 127.98, 127.81, 127.64, 127.56, 121.08, 114.51, 88.03(C-1), 85.90(C-3), 79.43(C-5), 77.36(C-4), 75.34, 75.09, 73.45, 72.28(C-2), 69.03(C-6), 55.32. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{34}H_{36}O_6S$, 595.2130; found, 595.2134

2,6-Dimethoxyphenyl 3,4,6-tri-O-benzyl-1-thio-β-D-glucopyranoside (12c):



Via general procedure B starting from **10** and 2,6-dimethoxythiophenol. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) afforded **12c** (0.44 g, 39%). **TLC:** (EtOAc/n-heptane, 40/60 v/v): R_f = 0.6; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.08 (m, 16H), 6.56 (d, *J* = 8.4 Hz, 2H), 5.04 (d, *J* = 11.1 Hz, 1H), 4.79 (dd, *J* = 11.0, 1.7 Hz, 2H), 4.57 – 4.50 (m, 2H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.29 (d, *J* = 9.6 Hz, 1H, H-1), 3.83 (m, 7H), 3.79 (d, *J* = 2.7 Hz, 2H, (H-6, H-6)), 3.61 (t, *J* = 8.7 Hz, 1H, (H-3)), 3.53 (dd, *J* = 9.7, 8.7 Hz, 1H, (H-4)), 3.46 (dt, *J* = 9.7, 2.7 Hz, 1H, (H-5)), 3.32 (ddd, *J* = 9.5, 8.6, 1.9 Hz, 1H, (H-2)). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.17, 138.83, 138.43, 138.30, 131.56, 128.27, 128.26, 128.20, 127.92, 127.84, 127.65, 127.56, 127.47, 127.40, 105.00, 104.56, 88.43 (C-1), 85.61 (C-3), 79.96 (C-5), 76.88 (C-4), 75.15, 75.02, 73.59, 73.48 (C-2), 69.12 (C-6), 56.39. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{35}H_{38}O_7S$, 625.2236; found, 625.2223

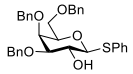
2,4,6-Trimethoxyphenyl 3,4,6-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (12d):



Via general procedure B starting from **10** (1.9 g; 4.54 mmol) and 1,3,5-trimethoxybenzene. The crude product was purified by silicagel flash column chromatography (10% to 40% EtOAc in *n*-heptane) yielding **12d** (0.35 g, 76%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.41. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.13 (m, 15H), 6.11 (s, 2H), 5.04 (d, *J* = 11.0 Hz, 1H), 4.79 (dd, *J* = 11.0, 2.6 Hz, 2H), 4.54 (dd, *J* = 11.2, 7.6 Hz, 2H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.20 (d, *J* = 9.4 Hz, 1H, H-1), 3.84 – 3.77 (m, 11H, H-2, H-6), 3.61 (t, *J* = 8.8 Hz, 1H, H-3), 3.54 (t, *J* = 9.3 Hz, 1H, H-4), 3.46 (ddd, *J* = 9.7, 3.2, 2.0 Hz, 1H, H-5), 3.28 (ddt, *J* = 9.5, 8.7, 2.5 Hz, 1H, H-2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.18, 162.96, 138.95, 138.56, 138.40, 128.30, 128.24, 127.97, 127.89, 127.73, 127.59, 127.49,

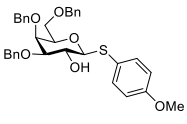
127.45, 96.19, 91.51, 88.48 (C-1), 85.62 (C-3), 80.01 (C-5), 76.93 (C-4), 75.19, 75.07, 73.71, 73.24 (C-2), 73.13, 69.17 (C-6), 56.36, 55.39. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{36}H_{40}O_8S$, 655.2342; found, 655.2339.

Phenyl 3,4,6-tri-*O*-benzyl-1-thio-*β*-D-galactopyranoside (13a):



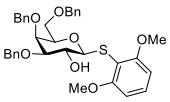
Via general procedure B and thiophenol. Silicagel flash column chromatography (0% 30% - Diethylether in toluene) afforded **13a** (0.57 g, 64%). **TLC**: (EtOAc/n-heptane, 30/70 v/v): R_f = 0,38; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.53 (m, 2H), 7.52 – 7.48 (m, 2H), 7.39 – 7.17 (m, 16H), 5.70 (d, *J* = 5.5 Hz), 4.89 (d, *J* = 11.4 Hz, 2H), 4.75 (dd, *J* = 13.9, 11.7 Hz, 2H), 4.70 – 4.63 (m, 2H), 4.59 - 4.56 (d, *J* = 7.0 Hz, 2H), 4.55 – 4.41 (m, 2H, H-1), 4.01 (t, *J* = 9.4 Hz, H-2), 3.98 (d, *J* = 2.7 Hz, H-4), 3.67 – 3.64 (m, 3H, H-6, H-5), 3.58 (dd, *J* = 9.4, 6.0 Hz, 1H, H-6), 3.47 (dd, *J* = 9.2, 2.8 Hz, H-3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.65, 138.40, 138.01, 137.93, 137.85, 137.77, 134.04, 132.60, 132.20, 132.00, 128.92, 128.83, 128.63, 128.58, 128.55, 128.45, 128.42, 128.31, 128.18, 128.02, 128.01, 127.93, 127.87, 127.84, 127.81, 127.79, 127.77, 127.74, 127.69, 127.57, 127.45, 127.32, 126.99, 88.52 (C-1), 83.23 (C-3), 77.63 (C-5),74.81, 74.41, 73.61, 73.48, 73.22 (C-4), 72.44, 72.35, 69.09 (C-2), 68.70 (C-6); **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{33}H_{34}O_5S$, 565.2024; found, 565.2014.

4-methoxyphenyl 3,4,6-tri-*O*-benzyl-1-thio-*β*-D-galactopyranoside (13b):



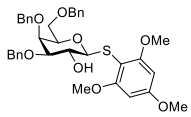
Via general procedure B and 4-methoxythiophenol. Silicagel flash column chromatography (0% - 30% Diethyl ether in toluene) afforded **13b** (0.19 g, 26%). **TLC**: (Diethylether/toluene, 20/80 v/v): R_f = 0,65; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.38 – 7.18 (m, 15H), 6.75 (d, *J* = 8.8 Hz, 2H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.69 (dd, *J* = 11.9 Hz, 2H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.46 (q, *J* = 11.7 Hz, 2H), 4.40 (d, *J* = 9.5 Hz, H-1), 3.95 (d, *J* = 2.6 Hz, H-4), 3.91 (td, *J* = 9.4, 1.5 Hz, H-2), 3.74 (s, 3H), 3.69 – 3.58 (m, H-6a, H-6b, H-5), 3.45 (dd, *J* = 9.3, 2.7 Hz, H-3), 2.45 (d, *J* = 1.8 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.84, 138.73, 138.06, 137.91, 135.33, 128.54, 128.45, 128.14, 127.92, 127.85, 127.83, 127.70, 127.62, 127.38, 122.22, 114.41, 88.85 (C-1), 83.24 (C-3), 77.56 (C-5), 74.30, 73.59, 73.25 (C-4), 72.42, 68.95 (C-2), 68.72 (C-6); **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{34}H_{36}O_6S$, 595.2130; found, 595.2110.

2,6-dimethoxyphenyl 3,4,6-tri-*O*-benzyl-1-thio-*β*-D-galactopyranoside (13c):



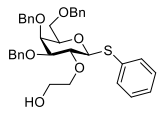
Via general procedure B and 2,6-dimethoxythiophenol. Silicagel flash column chromatography (0% - 30% diethyl ether in toluene) afforded **13c** (0.667 g, 55%). **TLC**: (Diethylether/toluene, 20/80 v/v): R_f = 0,52; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 15H), 7.16 – 7.11 (m, 2H), 6.59 (d, *J* = 8.4 Hz, 1H), 4.89 (d, *J* = 11.7 Hz, 1H), 4.83 (d, *J* = 12.2 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.42 (dd, *J* = 11.7 Hz, 2H), 4.26 (d, *J* = 9.4 Hz, H-1), 3.90 – 3.69 (m, 3H, H-2, H-4), 3.65 – 3.50 (m, H-5, H-6a, H-6b), 3.45 (dd, *J* = 9.4, 2.8 Hz, H-3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.97, 139.11, 138.68, 137.98, 131.26, 128.38, 128.34, 127.99, 127.86, 127.73, 127.53, 127.47, 127.26, 127.05, 104.67, 89.81 (C-1), 82.73 (C-3), 77.61 (C-5), 74.14 (C-4), 74.12, 73.48, 72.74, 70.49 (C-2), 68.51 (C-6), 56.47. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{35}H_{38}O_7S$, 625.2235; found, 625.2228.

2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-benzyl-1-thio-*β*-D-galactopyranoside (13d):



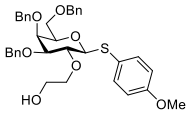
Via general procedure B and 2,4,6-trimethoxythiophenol. Silicagel flash column chromatography (0% - 30% diethyl ether in toluene) afforded **13d** (0.61 g, 59%). **TLC**: (EtOAc/n-heptane, 50/50 v/v): R_f = 0,44; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 - 7.10 (m, 15H), 6.16 (s, 2H), 4.89 (d, J = 11.8 Hz, 1H), 4.84 (d, J = 12.2 Hz, 1H), 4.71 (d, J = 12.2 Hz, 1H), 4.44 (dt, J = 11.5 Hz, 3H), 4.17 (d, J = 9.3 Hz, H-1), 3.87 (d, J = 2.6 Hz, H-4), 3.82 (s, 3H), 3.81 (s, 6H), 3.76 - 3.51 (m, H-2), 3.46 (dd, J = 9.5, 2.8 Hz, H-3, H-5, H-6a, H-6b). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.95, 162.82, 162.29, 139.19, 138.74, 138.01, 128.39, 128.35, 127.98, 127.86, 127.74, 127.55, 127.47, 127.19, 127.04, 97.71, 91.60, 90.63, 89.92 (C-1), 82.68 (C-3), 77.51 (C-5), 74.19 (C-4), 74.06, 73.49, 72.75, 70.20 (C-2), 68.50 (C-6), 56.43, 56.02, 55.43, 55.41. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{36}H_{40}O_8S$, 655.2341; found, 655.2327.

Phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-galactopyranoside (14a):



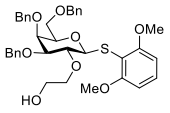
Via general procedure C. Silicagel flash column chromatography (0% - 30% diethyl ether in toluene) afforded **14a** (0.117 g, 20%). **TLC**: (Diethylether/toluene, 50/50 v/v): R_f = 0,61; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 5H), 7.36 – 7.13 (m, 15H), 4.89 (d, *J* = 11.4 Hz, 1H), 4.73 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 9.6 Hz, H-1), 4.45 (q, *J* = 11.7 Hz, 2H), 4.00 (d, *J* = 2.4 Hz, H-4), 3.86 – 3.80 (m, 2H, H-2), 3.68 – 3.58 (m, 2H, H-5, H-6a, H-6b), 3.55 (dd, *J* = 9.3, 2.7 Hz, H-3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 131.42, 129.05, 128.86, 128.60, 128.46, 128.24, 128.07, 127.95, 127.86, 127.84, 127.79, 127.56, 127.24, 125.31, 87.97 (C-1), 83.97 (C-3), 77.28 (C-5), 77.23 (C-2), 75.03, 74.52, 73.62, 72.87 (C-4), 72.17, 68.61 (C-6), 62.27, 60.41. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{35}H_{38}O_6S$, 609.3386; found, 609.2274.

4-methoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-galactopyranoside (14b):



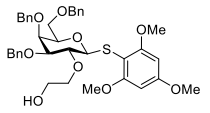
Via general procedure C. Silicagel flash column chromatography (0% - 40% EtOAc in *n*-heptane) afforded **14b** (0.142 gr, 67%). **TLC**: (Diethylether/toluene, 50/50 v/v): R_f = 0,61; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.36 – 7.23 (m, 15H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.49 – 4.40 (m, 2H, H-1), 3.98 (d, *J* = 2.4 Hz, H-4), 3.86 (t, *J* = 4.4 Hz, 2H), 3.74 (s, 3H, H-2), 3.65 (dd, *J* = 10.4, 5.6 Hz, 2H, H-6a, H-6b), 3.59 – 3.51 (m, H-3, H-5), 3.07 (t, *J* = 6.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.55, 138.58, 137.82, 137.40, 134.56, 128.58, 128.44, 128.19, 128.03, 127.93, 127.84, 127.80, 127.73, 127.49, 123.41, 114.39, 88.55 (C-1), 84.02 (C-3), 77.22 (C-5), 77.17 (C-2), 74.99, 74.41, 73.59, 72.84 (C-4), 72.12, 68.63 (C-6), 62.28, 55.25. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{36}H_{40}O_7S$, 639.2392; found, 639.2376.

2,6-dimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-galactopyranoside (14c):



Via general procedure C. Silicagel flash column chromatography (0% - 50% EtOAc in *n*-heptane) afforded **14c** (0.465 gr, 66%). **TLC**: (EtOAc/n-heptane, 30/70 v/v): R_f = 0,35; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.6 Hz, 2H), 7.33 – 7.18 (m, 15H), 6.54 (d, *J* = 8.4 Hz, 1H), 4.88 (d, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 9.8 Hz, H-1), 4.37 (dd, *J* = 11.6 Hz, 2H), 4.06 (ddd, *J* = 11.1, 5.6, 2.3 Hz, 1H), 3.94 (ddd, *J* = 11.2, 6.3, 2.0 Hz, 1H), 3.91 (d, *J* = 2.2 Hz, H-4), 3.82 (s, 3H), 3.79 – 3.73 (m, 1H, H-2), 3.71 – 3.64 (m, 1H), 3.62 – 3.53 (m, H-6a, H-6b), 3.49 (dd, *J* = 9.2, 2.8 Hz, H-3), 3.44 (t, *J* = 6.3 Hz, H-5), 1.67 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.01, 138.67, 137.98, 137.96, 130.23, 128.49, 128.36, 128.17, 127.95, 127.81, 127.73, 127.63, 127.47, 109.26, 104.30, 88.93 (C-1), 84.67 (C-3), 78.32 (C-2), 77.50 (C-5), 75.13, 74.44, 73.52, 73.43 (C-4), 72.31, 69.08 (C-6), 61.81, 56.18. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{37}H_{42}O_8S$, 669.2398; found, 669.2484.

2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-galactopyranoside (14d):



Via general procedure C. Silicagel flash column chromatography (0% - 20% EtOAc in toluene) afforded **14d** (0.162 g, 41%). **TLC**: (EtOAc/n-heptane, 30/70 v/v): R_f = 0,30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.17 (m, 15H), 6.11 (s, 2H), 4.88 (d, *J* = 11.6 Hz, 1H), 4.68 (dd, *J* = 28.1, 11.6 Hz, 2H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.37 (q, *J* = 11.6 Hz, 2H), 4.30 (d, *J* = 9.8 Hz, H-1), 4.06 (ddd, *J* = 11.3, 5.3, 2.6 Hz, 1H), 3.99 – 3.87 (m, 1H, H-4), 3.80 (m, 10H), 3.72 (t, *J* = 9.5 Hz, 1H, H-2), 3.63 – 3.51 (m, H-6a, H-6b), 3.48 (dd, *J* = 9.2, 2.8 Hz, H-3), 3.42 (t, *J* = 6.3 Hz, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.20, 162.15, 138.72, 138.03, 138.02, 128.49, 128.36, 128.16, 127.97, 127.95, 127.80, 127.74, 127.63, 127.45, 100.75, 91.15, 89.80 (C-1), 84.70 (C-3), 78.13 (C-2), 77.43 (C-5), 75.08, 74.39, 73.55, 73.40 (C-4), 72.31, 69.20 (C-6), 61.78, 56.15, 55.35. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{38}H_{44}O_9S$, 699.2603; found, 699.2593.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-(benzenethio)ethyl)-*α/β*-D-galactopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (18a): *Via* general procedure E. Silicagel flash column chromatography (0% - 20% -diethyl ether in toluene) afforded **18a** as an anomeric mixture (61 mg, 55%). **TLC**: (Et_2O/toluene, 30/70 v/v): R_f = 0,50; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 – 7.79 (m, 6H), 7.54 – 7.06 (m, 29H), 6.12 (t, *J* = 9.8 Hz, 1H), 5.52 (t, *J* = 9.9 Hz, 1H), 5.28 – 5.22 (m, 1H), 5.13 (d, *J* = 3.5 Hz, H-1'), 4.94 – 4.86 (m, H, H-1), 4.76 (dd, *J* = 11.9, 3.6 Hz, 1H), 4.68 (d, *J* = 11.9 Hz, 1H), 4.55 (t, *J* = 11.3 Hz, 1H), 4.34 (dt, *J* = 12.0 Hz, 3H), 3.99 (t, *J* = 6.4 Hz, 1H), 3.86 (m, 6H), 3.65 (d, *J* = 11.1 Hz, 1H), 3.52 – 3.39 (m, 2H), 3.36 (m, 3H), 3.11 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.79, 165.34, 138.73, 138.66, 138.07, 133.34, 133.03, 129.94, 129.84, 129.65, 129.29, 129.27, 129.14, 128.99, 128.89, 128.39, 128.36, 128.33, 128.29, 128.25, 128.21, 127.67, 127.61, 127.54, 127.50, 127.45, 97.72 (C-1), 96.77 (C-1'), 78.20, 77.37, 75.02, 74.80, 73.24, 72.79, 72.11, 70.68, 70.10, 69.61, 69.30, 68.64, 68.42, 66.65, 55.47. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{63}H_{62}O_{15}S$, 1113.3707; found, 1113.3652.

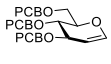
Methyl 3,4,6-tri-O-benzyl-2-*O*-(2-(4-methoxybenzenethio)ethyl)-*α/β*-D-galactopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-*α*-D-glucopyranoside (18b): *Via* general procedure E. Silicagel flash column chromatography (0% - 25% diethyl ether in toluene) afforded **18b** as an anomeric mixture (32 mg, 36%). **TLC**: (Diethylether/toluene, 50/50 v/v): R_f = 0,64; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 – 7.81 (m, 6H), 7.55 – 7.10 (m, 26H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.13 (m, 1H), 5.53 (t, *J* = 9.9 Hz, 1H), 5.24 (td, *J* = 10.2, 3.5 Hz, 2H), 5.13 (d, *J* = 3.5 Hz, H-1'), 4.95 – 4.85 (m, 1H, H-1), 4.76 (m, 1H), 4.67 (m, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.43 – 4.24 (m, 3H), 3.99 (t, *J* = 6.4 Hz, 1H), 3.93 – 3.84 (m, 4H), 3.84 – 3.71 (m, 6H), 3.67 (d, *J* = 10.3 Hz, 2H), 3.45 (m, 2H), 3.38 (m, 3H), 3.00 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.79, 165.35, 158.96, 138.79, 138.69, 138.09, 133.38, 133.33, 133.03, 132.69, 129.94, 129.84, 129.66, 129.30, 129.14, 129.00, 128.40, 128.36, 128.32, 128.26, 128.21, 128.20, 127.68, 127.61, 127.54, 127.49, 127.43, 114.57, 97.77 (C-1), 96.78 (C-1'), 78.21, 77.34, 75.10, 74.80, 73.24, 72.84, 72.12, 70.70, 70.18, 69.60, 69.32, 68.67, 68.44, 66.65, 55.48, 55.31, 35.33. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{64}H_{64}O_{15}S$, 1127.3863; found, 1127.3816.

Methyl 3,4,6-tri-O-benzyl-2-*O*-(2-(2,6-dimethoxybenzenethio)ethyl)-α-D-galactopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (18c): *Via* general procedure E. Silicagel flash column chromatography (0% - 25% diethyl ether in toluene) afforded **18c** as an anomeric mixture (39 mg, 37%). **TLC**: (EtOAc/n-heptane, 50/50 v/v): R_f = 0,68; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.81 (m, 6H), 7.53 – 7.12 (m, 25H), 6.47 (d, *J* = 8.4 Hz, 2H), 6.11 (t, *J* = 9.8 Hz, H-3'), 5.45 (t, *J* = 9.9 Hz, H-4'), 5.23 (dd, *J* = 10.2, 3.6 Hz, H-2'), 5.11 (d, *J* = 3.5 Hz, H-1'), 4.92 (d, *J* = 3.2 Hz, H-1), 4.87 (d, *J* = 11.4 Hz, 1H), 4.74 (d, *J* = 12.1 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.42 – 4.32 (dd, 2H), 4.30 (t, *J* = 9.3 Hz, H-5'), 4.01 (t, *J* = 6.5 Hz, H-5), 3.92 – 3.83 (m, H-2, H-4, H-6a'), 3.83 – 3.62 (m, 8H, H-3, H-6b'), 3.45 (t, *J* = 6.1 Hz, H-6a, H-6b), 3.33 (s, 3H), 3.06 – 2.87 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.77, 165.39, 161.08, 138.86, 138.74, 138.11, 133.31, 133.02, 129.93, 129.86, 129.64, 129.29, 129.15, 128.93, 128.40, 128.37, 128.27, 128.25, 128.20, 128.18, 127.68, 127.61, 127.50, 127.43, 127.35, 103.99, 97.74 (C-1), 96.67 (C-1'), 78.21 (C-3), 77.49 (C-2), 75.17 (C-4), 74.79, 73.23, 72.77, 72.12 (C-2'), 71.18, 70.67 (C-3'), 69.70 (C-4'), 69.22 (C-5), 68.64 (C-6), 68.31 (C-5'), 66.73 (C-6'), 56.07, 55.41, 33.41. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{65}H_{66}O_{16}S$, 1157.3969; found, 1157.3926.

Methyl 3,4,6-tri-O-benzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-α-D-galactopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (18d): *Via* general procedure E. Silicagel flash column chromatography (0% - 30% EtOAc in *n*-heptane) afforded **18d** (45 mg, 59%). **TLC**: (EtOAc/n-heptane, 50/50 v/v): R_f = 0,64; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.80 (m, 6H), 7.54 – 7.21 (m, 24H), 6.14 – 6.01 (m, 2H, H-3'), 5.48 – 5.41 (m, H-4'), 5.23 (dd, *J* = 10.2, 3.7 Hz, H-2'), 5.12 (t, *J* = 3.8 Hz, H-1'), 4.94 (d, *J* = 3.3 Hz, H-1), 4.88 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.43 – 4.27 (m, 2H, H-5'), 4.01 (t, *J* = 6.7 Hz, H-5), 3.91 – 3.77 (m, 3H, H-2, H-3, H-4, H-6'), 3.77 – 3.63 (m,

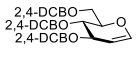
8H, H2-6'), 3.45 (dd, *J* = 6.5, 3.4 Hz, H2-6), 3.32 (s, 3H), 3.02 – 2.71 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.79, 165.76, 165.41, 162.08, 161.77, 138.91, 138.76, 138.14, 133.32, 133.03, 129.95, 129.87, 129.66, 129.31, 129.17, 128.94, 128.41, 128.38, 128.28, 128.26, 128.24, 128.20, 127.69, 127.62, 127.51, 127.45, 127.36, 97.77 (C-1), 96.68 (C-1'), 90.92, 78.23 (C-3), 77.55 (C-2), 75.22 (C-4), 74.80, 73.24, 72.82, 72.14 (C-2'), 71.18, 70.68 (C-3'), 69.71 (C-4'), 69.23 (C-5), 68.66 (C-6), 68.32 (C-5'), 66.74 (C-6'), 56.03, 55.41, 55.35. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{66}H_{68}O_{17}S$, 1187.4074; found, 1187.4038.

3,4,6-Tri-*O*-(4-chlorobenzyl)-*D*-glucal (20a):



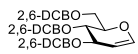
Via general procedure A starting from *D*-glucal (**8**) (2.0 g, 13.7 mmol) using 4-chlorobenzyl chloride (11.0 g, 68 mmol) as the benzylating agent. The crude product was purified by silicagel flash column chromatography (0% to 20% EtOAc in *n*-heptane) yielding **20a** (6.23 g, 88%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.76. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 11H), 7.16 – 7.10 (m, 2H), 6.41 (dd, *J* = 6.1, 1.4 Hz, 1H, H-1), 4.85 (dd, *J* = 6.2, 2.6 Hz, 1H, H-2), 4.75 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 2H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.50 – 4.45 (m, 2H), 4.18 (ddd, *J* = 6.3, 2.6, 1.4 Hz, 1H, H-3), 4.01 (ddd, *J* = 8.8, 4.8, 2.7 Hz, 1H, H-5), 3.81 (dd, *J* = 8.9, 6.3 Hz, 1H, H-4), 3.77 (dd, *J* = 10.7, 4.8 Hz, 1H, H-6a), 3.72 (dd, *J* = 10.8, 2.7 Hz, 1H, H-6b). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.88 (C-1), 136.77, 136.63, 136.43, 133.54, 133.49, 133.46, 129.04, 129.01, 128.96, 128.60, 128.57, 99.73 (C-2), 76.70 (C-5), 76.01 (C-3), 74.45 (C-4), 72.93, 72.73, 69.62, 68.48 (C-6); **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{27}H_{25}Cl_3O_4$, 541.0716; found, 541.0707.

3,4,6-Tri-*O*-(2,4-dichlorobenzyl)-*D*-glucal (20b):



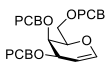
Via general procedure A starting from *D*-glucal (**8**) (1.7 g, 11.6 mmol) using 2,4-dichloro-1-(chloromethyl)benzene as the benzylating agent. The crude product was purified by silicagel flash column chromatography (0% to 20% EtOAc in *n*-heptane) yielding **20b** (6.39 g, 90%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.76. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.26 (m, 9H), 7.25 – 7.15 (m, 3H), 6.45 (dd, *J* = 6.1, 1.4 Hz, 1H, H-1), 4.92 (dd, *J* = 6.2, 2.5 Hz, 1H, H-2), 4.89 (d, *J* = 12.7 Hz, 1H), 4.73 (d, *J* = 12.8 Hz, 1H), 4.71 – 4.66 (m, 1H), 4.63 (d, *J* = 13.4 Hz, 1H), 4.56 (dd, *J* = 13.1, 3.7 Hz, 2H), 4.28 (ddd, *J* = 6.4, 2.6, 1.4 Hz, 1H, H-3), 4.07 (ddd, *J* = 9.1, 4.5, 2.6 Hz, 1H, H-5), 3.95 – 3.87 (m, 2H, H-4, H-6a), 3.82 (dd, *J* = 10.7, 2.7 Hz, 1H, H-6b). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.03 (C-1), 134.53, 134.50, 134.34, 133.94, 133.87, 133.75, 133.36, 133.33, 133.23, 129.95, 129.89, 129.81, 129.69, 129.63, 129.15, 129.07, 129.05, 129.01, 127.18, 127.10, 127.07, 127.03, 99.59 (C-2), 76.69 (C-3), 76.61 (C-5), 74.64 (C-4), 71.03, 70.19, 69.87, 69.31, 68.95 (C-6), 66.97. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{27}H_{22}Cl_6O_4$, 642.9547; found, 642.9545.

3,4,6-Tri-*O*-(2,6-dichlorobenzyl)-*D*-glucal (20c):



Via general procedure A starting from D-glucal (**8**) (1.00 g, 6.84 mmol) using 2-(bromomethyl)-1,3-dichlorobenzene as the benzylating agent. The crude product was purified by silicagel flash column chromatography (0% to 20% EtOAc in *n*-heptane) yielding **20c** (3.80 g, 89%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.71. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 8H, C*H* Ar), 7.22 – 7.12 (m, 4H, C*H* Ar), 6.44 (dd, *J* = 6.1, 1.3 Hz, 1H, H-1), 5.14 (d, *J* = 10.5 Hz, 1H), 4.97 (dd, *J* = 6.2, 2.9 Hz, 1H, H-2), 4.91 – 4.84 (m, 3H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.77 (d, *J* = 10.8 Hz, 1H), 4.30 – 4.25 (m, 1H, H-3), 4.11 (ddd, *J* = 9.1, 5.9, 3.6 Hz, 1H, H-5), 3.87 – 3.77 (m, 3H, H-4, H-6). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.89 (C-1), 137.01, 136.92, 136.85, 133.58, 133.50, 133.36, 129.95, 129.88, 129.77, 128.44, 128.33, 128.30, 99.36 (C-2), 76.32 (C-5), 75.76 (C-3), 74.72 (C-4), 69.46 (C-6), 67.71, 67.55, 66.94, 64.67. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{27}H_{22}Cl_6O_4$, 642.9547; found, 642.9528.

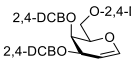
3,4,6-tri-*O*-(4-chlorobenzyl)-*β*-D-galactal (21a):



Via general procedure A and 4-chlorobenzylbromide. Silicagel flash column chromatography (0% - 30% EtOAc in *n*-heptane) afforded **21a** (0.12 gr, 47%). **TLC**: (EtOAc/n-heptane, 30/70 v/v): R_f = 0,37; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (m, 12H), 6.36 (dd, *J* = 6.3, 1.4 Hz, H-1), 4.84 (ddd, *J* = 6.3, 3.0, 1.2 Hz, H-2), 4.79 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.17 (m, H-3, H-5), 3.91 (m, H-4), 3.74 (dd, *J* = 10.1, 7.2 Hz, H-

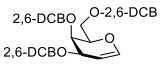
6a), 3.63 (dd, *J* = 10.1, 5.1 Hz, H-6b). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.30 (C-1), 136.84, 136.73, 136.37, 133.54, 133.52, 133.38, 132.57, 129.24, 129.12, 128.69, 128.58, 128.56, 128.50, 99.59 (C-2), 75.46 (C-5), 72.63, 72.54, 71.63 (C-4), 70.78 (C-3), 70.18, 68.22 (C-6); **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{27}H_{25}Cl_3O_4$, 541.0716; found, 541.0709.

3,4,6-tri-O-(2,4-dichlorobenzyl)-*β*-D-galactal (21b):



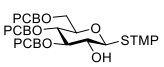
Via general procedure A and 2,4-dichlorobenzylchloride. Silicagel flash column chromatography (0% - 30% EtOAc in *n*-heptane) afforded **21b** (3.88 g, 46%). **TLC**: (EtOAc/n-heptane, 30/70 v/v): R_f = 0,60; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.15 (m, 9H), 6.41 (dd, *J* = 6.2, 1.3 Hz, H-1), 4.93 – 4.87 (m, 1H, H-2), 4.72 (d, *J* = 6.6 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.66 – 4.58 (m, 2H), 4.51 (d, *J* = 13.0 Hz, 1H), 4.32 – 4.26 (m, H-3, H-5), 4.08 – 4.04 (m, H-4), 3.87 – 3.76 (m, H-6a, H-6b). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.43 (C-1), 134.70, 134.65, 134.22, 133.95, 133.76, 133.61, 133.12, 133.02, 130.07, 130.01, 129.56, 129.15, 129.01, 128.90, 127.11, 127.07, 99.52 (C-2), 75.30 (C-5), 72.37 (H-4), 71.64 (C-3), 69.97, 69.86, 68.58 (C-6), 67.77; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{27}H_{22}Cl_6O_4$, 642.9547; found, 642.9545.

3,4,6-tri-O-(2,6-dichlorobenzyl)-*β*-D-galactal (21c):

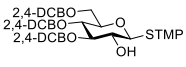


Via general procedure A and 2,6-dichlorobenzylchloride. Silicagel flash column chromatography (0% - 30% EtOAc in *n*-heptane) afforded **21c** (7.80 g, 92%). **TLC**: (EtOAc/n-heptane, 30/70 v/v): R_f = 0,60; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.09 (m, 9H), 6.34 (dd, *J* = 6.2, 1.3 Hz, H-1), 5.13 (d, *J* = 10.6 Hz, 1H), 4.99 – 4.87 (m, 2H, H-2), 4.84 (d, *J* = 10.5 Hz, 1H), 4.78 – 4.69 (m, 2H), 4.27 (m, H-3, H-5), 4.06 – 4.00 (m, H-4), 3.92 – 3.74 (m, H-6a, H-6b). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.11 (C-1), 137.13, 136.99, 136.94, 133.97, 133.79, 133.38, 129.81, 129.77, 128.35, 128.31, 128.30, 99.81 (C-2), 75.67 (C-5), 73.10 (C-4), 72.06 (C-3), 68.67 (C-6), 67.63, 67.57, 66.63. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{27}H_{22}Cl_6O_4$, 642.9547; found, 642.9544.

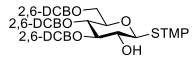
2,4,6-trimethoxyphenyl 3,4,6-Tri-*O*-(4-chlorobenzyl)-1-thio-*β*-D-glucopyranoside (22a): *via* general procedure B starting from **20a** (1.0 g, 1.9 mmol). The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) to afford **22a** as white solid (0.84 g, 61%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.52. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 8H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.11 (s, 2H), 4.99 (d, *J* = 11.4 Hz, 1H), 4.75 – 4.62 (m, 2H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.18 (d, *J* = 9.4 Hz, 1H, H-1), 3.85 (d, *J* = 2.0 Hz, 1H), 3.81 (s, 9H), 3.77 – 3.73 (m, 2H, H-6a, H-6b), 3.56 (t, *J* = 8.7 Hz, 1H, H-3), 3.47 (t, *J* = 9.2 Hz, 1H, H-4), 3.42 (dt, *J* = 9.7, 2.5 Hz, 1H, H-5), 3.26 (td, *J* = 9.1, 2.0 Hz, 1H, H-2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.13, 163.02, 137.32, 136.93, 136.74, 133.34, 133.26, 133.24, 129.20, 129.00, 128.90, 128.42, 128.39, 91.46, 88.41 (C-1), 85.44 (C-3), 79.88 (C-5), 76.74 (C-4), 74.22, 74.05, 73.24 (C-2), 72.90, 69.03 (C-6), 56.33, 55.38; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{36}H_{37}Cl_3O_8S$, 757.1172; found, 757.1148.



2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(2,4-dichlorobenzyl)-1-thio-*β*-D-glucopyranoside (22b): *via* general procedure B starting from **20a** (2.01 g, 3.22 mmol). The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) to afford **22b** as white solid (1.35 g, 50%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.52. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.27 (d, *J* = 2.1 Hz, 1H), 7.25 – 7.23 (m, 2H), 7.18 – 7.13 (m, 3H), 7.09 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.12 (s, 2H), 5.08 (d, *J* = 12.8 Hz, 1H), 4.77 (m, 2H), 4.58 (d, *J* = 12.8 Hz, 1H), 4.52 (d, *J* = 12.9 Hz, 1H), 4.46 (d, *J* = 12.8 Hz, 1H), 4.20 (d, *J* = 9.5 Hz, 1H, H-1), 3.85 (d, *J* = 2.0 Hz, 1H), 3.81 (m, 11H, H-6a, H-6b), 3.62 (t, *J* = 8.7 Hz, 1H, H-3), 3.55 (dd, *J* = 9.7, 8.7 Hz, 1H, H-4), 3.46 (dt, *J* = 9.7, 2.6 Hz, 1H, H-5), 3.27 (ddd, *J* = 9.5, 8.7, 2.0 Hz, 1H, H-2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.17, 163.05, 135.21, 134.74, 134.73, 133.67, 133.63, 133.57, 133.35, 133.21, 132.97, 130.14, 130.03, 129.63, 128.93, 128.85, 126.99, 126.89, 96.05, 91.49, 88.42 (C-1), 85.70 (C-3), 79.39 (C-5) 76.74 (C-4), 73.17 (C-2), 71.22, 71.13, 69.99, 69.62 (C-6), 56.37, 55.42. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{36}H_{34}Cl_6O_8S$, 859.0003; found, 858.9974.

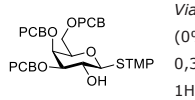


2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(2,6-dichlorobenzyl)-1-thio-*β*-D-glucopyranoside (22c):



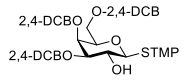
Via general procedure B starting from **20c** (1.98 g; 3.18 mmol). The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) yielding the products **22c** (1.011 g; 1.20 mmol; 38%) and **58b** (0.335 g; 0.399 mmol; 12%). **TLC** (EtOAc/*n*-heptane 20/80 v/v): R_f = 0.48. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.14 (td, *J* = 8.9, 7.5 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.94 (dd, *J* = 8.5, 7.5 Hz, 1H), 6.10 (s, 2H), 5.40 (d, *J* = 10.7 Hz, 1H), 5.06 (d, *J* = 10.7 Hz, 1H), 4.93 (d, *J* = 11.3 Hz, 1H), 4.85 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 10.6 Hz, 1H), 4.55 (d, *J* = 10.5 Hz, 1H), 4.21 (d, *J* = 9.6 Hz, 1H, H-1), 3.83 (d, *J* = 2.2 Hz, 1H), 3.80 (s, 6H), 3.76 (s, 3H), 3.74 (t, *J* = 8.4 Hz, 1H, H-3), 3.71 – 3.68 (m, 2H, H-6), 3.51 (dd, *J* = 9.9, 8.3 Hz, 1H, H-4), 3.43 (ddd, *J* = 9.9, 3.5, 2.4 Hz, 1H, H-5), 3.34 (ddd, *J* = 9.5, 8.5, 2.2 Hz, 1H, H-2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.15, 162.94, 136.91, 136.87, 136.72, 134.51, 134.05, 133.91, 129.53, 129.49, 129.39, 128.29, 128.09, 128.04, 91.34, 88.14 (C-1), 85.99 (C-3), 80.43 (C-5), 76.30 (C-4), 73.21 (C-2), 70.12 (C-6), 68.53, 68.11, 56.25, 55.36; **HRMS** (m/z): $[M+Na]^+$ calcd for $C_{36}H_{34}O_8SCl_6$, 859.0003; found, 859.0004.

2,4,6-trimethoxyphenyl 3,4,6-tri-O-(4-chlorobenzyl)-1-thio-β-D-galactopyranoside (23a):



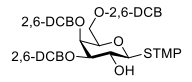
Via general procedure B and 2,4,6-trimethoxythiophenol. Silicagel flash column chromatography (0% - 20% - Et_2O in toluene) afforded **23a** (0.85 g, 60%). **TLC**: (Et_2O/toluene, 20/80 v/v): R_f = 0,39; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 6.98 (m, 12H), 6.17 (s, 2H), 4.82 (d, *J* = 11.9 Hz, 1H), 4.80 (d, *J* = 11.9 Hz, 1H), 4.69 – 4.63 (m, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.39 (d, *J* = 11.9 Hz, 1H), 4.34 (d, *J* = 11.9 Hz, 1H), 4.15 (d, *J* = 9.3 Hz, H-1), 3.86 – 3.78 (m, 9H, H-4), 3.73 – 3.65 (m, H-2), 3.61 – 3.49 (m, H-5, H-6a, H-6b), 3.43 (dd, *J* = 9.4, 2.8 Hz, H-3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.99, 162.89, 137.53, 137.22, 136.36, 133.58, 133.20, 132.73, 129.12, 128.76, 128.57, 128.48, 128.21, 128.13, 97.46, 91.53, 90.60, 89.82 (C-1), 82.58 (C-3), 77.23 (C-5), 74.41 (C-4), 73.17, 72.68, 72.10, 70.25 (C-2), 68.30 (C-6), 56.42, 56.00, 55.40. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{36}H_{37}Cl_3O_8S$, 757.1172; found, 757.1148.

2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(2,4-dichlorobenzyl)-1-thio-*β*-D-galactopyranoside (23b):



Via general procedure B and 2,4,6-trimethoxythiophenol. Silicagel flash column chromatography (0% - 20% - Et_2O in toluene) afforded **23b** (0.70 g, 26%). **TLC**: (Et_2O/toluene, 20/80 v/v): R_f = 0,49; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.00 (m, 9H), 6.19 (s, 2H), 4.92 (d, *J* = 13.3 Hz, 1H), 4.85 (d, *J* = 13.5 Hz, 1H), 4.75 (d, *J* = 13.4 Hz, 1H), 4.54 (d, *J* = 12.7 Hz, 1H), 4.48 (d, *J* = 13.5 Hz, 1H), 4.44 (d, *J* = 12.7 Hz, 1H), 4.20 (d, *J* = 9.0 Hz, H-1), 3.96 (d, *J* = 2.5 Hz, H-4), 3.89 – 3.75 (m, 9H), 3.71 – 3.56 (m, H-2, H-5, H-6a, H-6b), 3.53 (dd, *J* = 9.2, 2.5 Hz, H-3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.15, 162.94, 135.49, 134.99, 134.09, 134.04, 133.76, 133.59, 133.11, 132.96, 131.99, 130.24, 129.83, 129.16, 129.03, 128.94, 128.85, 128.43, 128.22, 127.05, 126.78, 125.29, 97.14, 91.46, 89.54 (C-1), 82.91 (C-3), 76.84 (C-5), 74.76 (C-4), 70.59, 70.07 (C-2), 69.90, 69.65, 68.38 (C-6), 56.44, 55.38. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{36}H_{34}Cl_6O_8S$, 859.0003; found, 859.0024.

2,4,6-trimethoxyphenyl 3,4,6-tri-O-(2,6-dichlorobenzyl)-1-thio-*α/β*-D-galactopyranoside (23c):



Via general procedure B and 2,4,6-trimethoxythiophenol. Silicagel flash column chromatography (0% - 25% - diethyl ether in toluene) afforded **23c** (0.98 g, 51%). **TLC**: (Diethylether/toluene, 20/80 v/v): R_f = 0,52; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.00 (m, 18H), 6.06 (s, 4H), 5.51 (d, *J* = 5.4 Hz, H-1(α)), 5.30 (d, *J* = 9.8 Hz, 1H), 5.21 (d, *J* = 10.6 Hz, 1H), 5.13 (dd, *J* = 13.1, 10.2 Hz, 2H), 4.98 (d, *J* = 10.3 Hz, 1H), 4.90 (d, *J* = 10.6 Hz, 1H), 4.82 (d, *J* = 9.8 Hz, 1H), 4.74 (d, *J* = 10.7 Hz, 1H), 4.71 – 4.66 (m, 3H), 4.63 (d, *J* = 10.1 Hz, 1H), 4.55 (dd, *J* = 8.0, 5.0 Hz, H-5(α)), 4.43 (dt, *J* = 9.7, 4.7 Hz, H-2(α)), 4.23 – 4.17 (m, H-1(β), H-4(α)), 3.91 (d, *J* = 7.7 Hz, H-3(α), H-4(β)), 3.85 – 3.67 (m, 18H, H-2(β), H-6a(α), H-6a(β)), 3.57 (m, H-3(β), H-5(β), H-6b(β)), 3.51 – 3.48 (s, OH(β)), 3.29 (dd, *J* = 8.7, 4.8 Hz, H-6b(α)), 2.89 (d, *J* = 4.6 Hz, OH(α)). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.79, 162.67, 162.63, 162.36, 162.29, 162.14, 137.85, 137.12, 136.96, 136.91, 136.87, 136.86, 136.80, 134.41, 134.21, 134.10, 133.55, 133.45, 133.41, 130.06, 129.94, 129.91, 129.76, 129.65, 129.36, 129.05, 128.45, 128.37, 128.34, 128.24, 128.15, 127.93, 125.32, 105.89, 98.85, 98.25, 91.61, 90.89, 90.63, 89.87 (C-1(β)), 88.20 (C-1(α)), 84.31 (C-3(β)), 81.50 (C-3(α)), 77.94 (C-5(β)),

75.32 (C-4(β)), 74.45 (C-4(α)), 71.10 (C-5(α)), 70.49 (C-2(β)), 69.18 (C-6(β)), 69.11 (C-2(α), 68.90, 68.54, 68.52 (C-6(α)), 68.40, 67.55, 67.47, 67.43, 56.38, 56.01, 55.98, 55.42, 55.34, 55.33. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{36}H_{34}Cl_6O_8S$, 859.0003; found, 859.0031.

2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(4-chlorobenzyl)-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-glucopyranoside (24a): *via* general procedure C starting from **22a** (0.18 g; 0.21 mmol). The crude product was purified by silicagel flash column chromatography (20% to 60% EtOAc in *n*-heptane) affording **24a** as a white solid (0.11 g, 59%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.24. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 9H), 7.18 – 7.13 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.12 (s, 2H), 4.84 (d, *J* = 11.3 Hz, 1H), 4.75 (d, *J* = 11.3 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 9.9 Hz, 1H, H-1), 4.01 (ddd, *J* = 10.7, 5.5, 2.5 Hz, 1H), 3.93 (ddd, *J* = 10.7, 6.8, 2.5 Hz, 1H), 3.82 (s, 6H), 3.80 (s, 3H), 3.74 – 3.68 (m, 1H), 3.67 (dd, *J* = 11.4, 2.0 Hz, 1H, H-6a), 3.63 – 3.51 (m, 2H, H-3, H-6b), 3.45 (t, *J* = 9.4 Hz, 1H, H-4), 3.37 – 3.28 (m, 2H, H-2, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.35, 162.06, 136.78, 136.64, 136.32, 133.56, 133.54, 133.28, 129.14, 128.89, 128.61, 128.54, 128.40, 99.68, 91.15, 88.48 (C-1), 87.04 (C-4), 81.69 (C-2), 79.42 (C-5), 78.05 (C-3), 74.84, 74.73, 73.98, 72.78, 69.39 (C-6), 61.83, 56.18, 55.33; **HRMS** (m/z): $[M+Na]^+$ calcd for $C_{38}H_{41}Cl_3O_9S$, 801.1435; found, 801.1399.

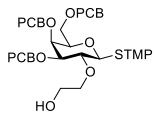
2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(2,4-dichlorobenzyl)-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-glucopyranoside (24b): *via* general procedure C starting from **22b** (0.56 g; 0.67 mmol). The crude product was purified by silicagel flash column chromatography (30% to 60% EtOAc in *n*-heptane) affording **24b** as a white solid (0.45 g, 76%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.35. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 2.1 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.19 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.18 – 7.13 (m, 2H), 7.10 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.12 (s, 2H), 4.92 (d, *J* = 13.1 Hz, 1H), 4.81 (d, *J* = 13.1 Hz, 1H), 4.71 (d, *J* = 12.7 Hz, 1H), 4.59 (d, *J* = 12.7 Hz, 1H), 4.54 (d, *J* = 13.0 Hz, 1H), 4.47 (d, *J* = 13.0 Hz, 1H), 4.41 (d, *J* = 9.9 Hz, 1H, H-1), 4.01 – 3.87 (m, 2H), 3.83 (s, 6H), 3.80 (s, 3H), 3.79 – 3.67 (m, 5H, H-6), 3.64 (t, *J* = 8.8 Hz, 1H, H-3), 3.55 (t, *J* = 9.4 Hz, 1H, H-4), 3.49 (s, 1H), 3.41 – 3.32 (m, 2H, H-2, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.39, 162.09, 134.72, 134.63, 134.28, 133.90, 133.68, 133.35, 133.12, 132.71, 130.12, 129.73, 129.27, 128.98, 128.94, 128.92, 127.11, 127.00, 126.98, 99.74 , 91.18, 88.66 (C-1), 87.24 (C-3), 81.73 (C-2), 79.03 (C-5), 78.10 (C-4), 74.89, 71.66, 71.10, 70.00 (C-6), 61.85, 56.23, 55.35. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{38}H_{38}Cl_6O_9S$, 903.0265; found, 903.0224.

2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(2,6-dichlorobenzyl)-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-glucopyranoside (24c): *via* general procedure C starting from **22c** (0.18 g; 0.21 mmol). The crude product was purified by silicagel flash column chromatography (20% to 60% EtOAc in *n*-heptane) affording **24c** as a white solid (0.11 g, 59%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.27. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.20 (m, 4H), 7.20 – 7.03 (m, 3H), 6.01 (s, 2H), 5.22 – 5.07 (m, 2H), 4.90 (s, 2H), 4.55 – 4.42 (m, 2H), 4.40 (d, *J* = 9.9 Hz, 1H, H-1), 3.96 – 3.82 (m, 2H), 3.78 (m, 7H, H-3), 3.73 – 3.62 (m, 5H, H-6a), 3.59 (dd, *J* = 11.1, 5.6 Hz, 1H), 3.54 – 3.45 (m, 2H, H-4, H-6b), 3.43 – 3.28 (m, 3H, H-2, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.27, 162.07, 136.75, 136.71, 134.38, 133.91, 133.77, 129.86, 129.81, 129.57, 128.38, 128.17, 99.56, 91.06, 88.24 (C-1), 87.88 (C-3), 81.68 (C-2), 79.97 (C-5), 78.40 (C-4), 74.25 (C-7), 70.55 (C-6), 69.54, 68.62, 67.69, 62.04, 56.13, 55.16. **HRMS** (m/z): $[M+Na]^+$ calcd for $C_{38}H_{38}O_9SCl_6$, 903.0265; found, 903.0276.

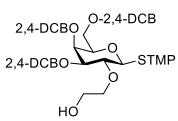
2,4,6-trimethoxyphenyl 3,4,6-tri-O-(4-cyanobenzyl)-2-O-(2-hydroxyethyl)-1-thio-β-D-glucopyranoside (24d): 24a (0.2 mmol), ^{t}BuXPhos-Pd-G3 (0.01 mmol, 5 mol%), ^{t}BuXPhos (0.01 mmol, 5 mol%) and $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.3 mmol) were added to a solution of dioxane (1.3 mL) and 0.05 M KOAc in degassed water (1.3 mL) The mixture was vigorously at 100°C for 4h. The reaction was cooled to rt and diluted with EtOAc (50 mL) and brine (50 mL). The aqueous layer was further extracted with EtOAc (2x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified using silicagel flash column chromatography (0-80%

EtOAc in *n*-heptane to obtain the product **24d** (0.16 g, 93%). **TLC**: (EtOAc/n-heptane, 60/40 v/v): R_f = 0,16. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 – 7.22 (m, 12H), 6.13 (s, 2H), 4.96 (d, *J* = 12.5 Hz, 1H), 4.79 (d, *J* = 12.5 Hz, 1H), 4.74 (d, *J* = 12.5 Hz, 1H), 4.62 (d, *J* = 12.5 Hz, 1H), 4.53 (q, *J* = 12.8 Hz, 2H), 4.45 (d, *J* = 9.9 Hz, H-1), 3.96 (dd, *J* = 5.2, 2.7 Hz, 2H), 3.82 (d, *J* = 6.5 Hz, 9H), 3.69 (m, 1H, H-6a, H-6b), 3.61 (t, *J* = 8.9 Hz, H-3), 3.51 (t, *J* = 9.4 Hz, H-4), 3.41 – 3.33 (m, H-2, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.47, 162.07, 143.77, 143.42, 143.17, 132.29, 132.22, 132.11, 127.81, 127.49, 127.39, 118.74, 118.56, 118.50, 111.64, 111.61, 111.34, 99.42, 91.22, 88.26 (C-1), 87.21 (C-3), 81.88 (C-2), 79.25 (C-5), 78.27 (C-4), 74.92, 74.39, 73.71, 72.70, 69.72 (C-6), 61.87, 56.25, 55.40.δ **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{41}H_{41}N_3O_9S$, 774.2461; found, 774.2465.

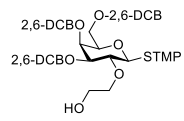
2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(4-chlorobenzyl)-2-*O*-(2-hydroxyethyl)-1-thio-β-D-galactopyranoside (25a): *Via* general procedure C. Silicagel flash column chromatography (0% - 50% Et_2O in toluene) afforded **25a** (0.51 g, 85%). **TLC**: (Et_2O/toluene, 30/70 v/v): R_f = 0,21; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.09 (m, 12H), 6.11 (s, 2H), 4.78 (d, *J* = 11.9 Hz, 1H), 4.63 (m, 2H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.32 – 4.27 (m, 1H, H-1), 4.04 (ddd, *J* = 10.9, 5.6, 2.3 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.81 – 3.72 (m, 10H, H-4), 3.68 (t, *J* = 9.5 Hz, 1H), 3.60 – 3.51 (m, H-6a, H-6b), 3.49 – 3.39 (m, H-3, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.29, 162.14, 137.04, 136.40, 136.39, 133.63, 133.58, 133.22, 129.20, 128.99, 128.77, 128.69, 128.54, 128.33, 100.47, 91.13, 89.75 (C-1), 84.57 (C-3), 78.18 (C-2), 77.19 (C-5), 75.13, 73.77 (C-4), 73.64, 72.72, 71.62, 69.00 (C-6), 61.76, 56.15, 55.36. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{38}H_{41}Cl_3O_9S$, 801.1434; found, 801.1419.



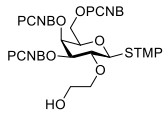
2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(2,4-dichlorobenzyl)-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-galacto-pyranoside (25b): *Via* general procedure C. Silicagel flash column chromatography (0% - 20% Et_2O in toluene) afforded **25b** (0.39 g, 74%). **TLC**: (Et_2O/toluene, 30/70 v/v): R_f = 0,37; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.10 (m, 9), 6.13 (s, 2H), 4.91 (d, *J* = 13.2 Hz, 1H), 4.75 (m, 2H), 4.55 (d, *J* = 13.2 Hz, 1H), 4.51 (d, *J* = 12.6 Hz, 1H), 4.40 (d, *J* = 12.6 Hz, 1H), 4.33 (d, *J* = 9.8 Hz, H-1), 4.05 – 3.99 (m, 1H, H-4), 3.93 – 3.87 (m, 1H), 3.86 – 3.75 (m, 10H), 3.76 – 3.64 (m, 1H, H-6a, H-2), 3.61 (dd, *J* = 9.3, 5.5 Hz, H-6b), 3.58 – 3.50 (m, H-3, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.39, 162.22, 135.04, 134.23, 134.12, 134.04, 133.85, 133.39, 133.20, 132.36, 130.36, 129.76, 129.75, 129.17, 129.13, 129.03, 128.63, 128.22, 127.28, 127.01, 127.00, 125.29, 100.33, 91.13, 89.99 (C-1), 84.92 (C-3), 78.18 (C-2), 76.71 (C-5), 75.20, 74.60 (C-4), 71.11, 69.95, 69.05, 68.91 (C-6), 61.78, 56.17, 55.38. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{38}H_{38}Cl_6O_9S$, 903.0265; found, 903.0303.



2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(2,6-dichlorobenzyl)-2-*O*-(2-hydroxyethyl)-1-thio-*β*-D-galacto-pyranoside (25c): *Via* general procedure C. Silicagel flash column chromatography (0% - 30% Et_2O in toluene) afforded **25c** (1.0061 g, 63%). **TLC**: (Et_2O/toluene, 30/70 v/v): R_f = 0,37; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.05 (m, 9H), 6.05 (s, 2H), 5.31 (d, *J* = 9.5 Hz, 1H), 5.04 – 4.93 (m, 2H), 4.71 (d, *J* = 9.5 Hz, 1H), 4.68 (s, 2H), 4.30 (d, *J* = 9.8 Hz, H-1), 4.15 – 4.07 (m, 1H), 4.04 (d, *J* = 1.8 Hz, 1H), 3.93 – 3.65 (m, 11H, H-2, H-6a), 3.63 (dd, *J* = 10.0, 5.4 Hz, H-6b), 3.56 (dd, *J* = 9.2, 2.4 Hz, H-3), 3.47 (t, *J* = 5.8 Hz, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.23, 162.17, 137.05, 136.81, 136.72, 134.06, 133.58, 133.50, 130.11, 129.90, 129.70, 129.03, 128.46, 128.35, 128.22, 128.12, 125.30, 100.58, 91.06, 89.96 (C-1), 86.15 (C-3), 77.81 (C-5), 77.70 (C-2), 75.00, 74.65 (C-4), 69.98 (C-6), 68.60, 67.65, 67.54, 61.70, 56.24, 56.08, 55.40, 55.27, 38.34. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{38}H_{38}Cl_6O_9S$, 903.0265; found, 903.0278.

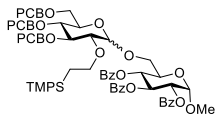


2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(4-cyanobenzyl)- 2-*O*-(2-hydroxyethyl)-1-thio-β-D-galactopyranoside (25d): 25a (0.2 mmol), ^{t}BuXPhos-Pd-G3 (0.01 mmol, 5 mol%), ^{t}BuXPhos (0.01 mmol, 5 mol%) and $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.3 mmol) were added to a solution of dioxane (1.3 mL) and 0.05 M KOAc in degassed water (1.3 mL) The mixture was vigorously at 100°C for 4h. The reaction was cooled to rt and diluted with EtOAc (50 mL) and brine (50 mL). The aqueous layer was further extracted with EtOAc (2x 25 mL). The combined organic layers were dried ($MgSO_4$),



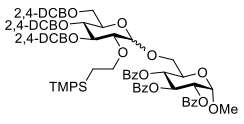
filtered and concentrated under reduced pressure. The residue was purified using silicagel flash column chromatography (0-100% EtOAc in *n*-heptane to obtain the product **25d** (0.16 g, 93%). (0.169 g, 88%).**TLC**: (EtOAc/n-heptane, 60/40 v/v): R_f = 0,08. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 – 7.24 (m, 12H), 6.13 (s, 1H), 4.92 (d, *J* = 12.7 Hz, 1H), 4.79 (s, 2H), 4.57 (d, *J* = 12.7 Hz, 1H), 4.50 (d, *J* = 12.7 Hz, 1H), 4.42 (d, *J* = 12.7 Hz, 1H), 4.35 (d, *J* = 9.8 Hz, H-1), 4.03 (ddd, *J* = 10.7, 5.5, 2.3 Hz, 1H), 3.97 – 3.90 (m, 1H, H-4), 3.82 (m, 10H), 3.75 – 3.58 (m, 1H, H-2, H-6a, H-6b), 3.55 – 3.48 (m, H-3, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.44, 162.15, 143.80, 143.29, 143.22, 132.38, 132.20, 132.09, 127.80, 127.53, 127.41, 118.73, 118.60, 118.55, 111.73, 111.58, 111.32, 100.08, 91.15, 89.70 (C-1), 84.72 (C-3), 78.37 (C-2), 76.94 (C-5), 75.25, 74.84 (C-4), 73.74, 72.53, 71.59, 69.33 (C-6), 61.76, 56.18, 55.41. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{41}H_{41}N_3O_9S$, 774.2461; found, 774.2448.

Methyl 3,4,6-tri-*O*-(4-chlorobenzyl)-2-*O*-(2-(2,4,6-trimethoxyphenylthio)ethyl)-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (30a): *via* general procedure E starting from glucosyl donor **24a**



(67 mg, 0.086 mmol) and using acceptor **19**. The crude product was purified by silicagel flash column chromatography (20% to 60% EtOAc in *n*-heptane) yielding **30a** as an anomeric mixture (*α/β* = 7.5/1, 82 mg, 75%). **TLC** (/toluene 20/80 v/v): R_f = 0.61; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.95 (m, 2H), 7.93 – 7.90 (m, 2H), 7.87 – 7.83 (m, 2H), 7.55 – 7.14 (m, 22H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.16 – 6.07 (m, 3H, H-3'), 5.47 (dd, *J* = 10.3, 9.5 Hz, 1H, H-4'), 5.23 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2'), 5.17 (d, *J* = 3.6 Hz, 1H, H-1'), 4.93 (d, *J* = 3.4 Hz, 1H, H-1), 4.82 (d, *J* = 11.3 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.51 (d, *J* = 12.3 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.34 – 4.29 (m, 1H, H-5'), 4.32 (d, *J* = 12.4 Hz, 1H), 3.91 – 3.74 (m, 12H, H-3, H-5, H-6a'), 3.72 – 3.55 (m, 4H, H-6a, H-6b'), 3.53 (dd, *J* = 10.1, 8.9 Hz, 1H, H-4), 3.48 (dd, *J* = 10.7, 2.1 Hz, 1H, H-6b), 3.42 (s, 3H), 3.38 (dd, *J* = 9.7, 3.5 Hz, 1H, H-2), 2.90 (ddd, *J* = 12.9, 9.0, 5.8 Hz, 1H), 2.81 (ddd, *J* = 13.0, 9.1, 5.9 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.84, 165.73, 165.28, 162.01, 161.83, 137.27, 136.91, 136.34, 133.47, 133.35, 133.20, 133.16, 133.04, 129.90, 129.87, 129.62, 129.21, 129.17, 129.14, 129.02, 128.84, 128.51, 128.48, 128.39, 128.38, 128.37, 128.36, 128.24, 100.79, 96.94 (C-1), 96.68 (C-1'), 90.95, 81.30 (C-3), 81.01 (C-2), 77.32 (C-4), 74.38, 73.73, 72.55, 72.16 (C-2'), 70.83, 70.52 (C-3'), 70.06 (C-5), 69.63 (C-4'), 68.40 (C-5'), 68.25 (C-6), 66.70 (C-6'), 56.05, 55.52, 55.35, 33.96; **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{66}H_{65}Cl_3O_{17}S$, 1289.2906; found, 1289.2888.

Methyl 3,4,6-tri-*O*-(2,4-dichlorobenzyl)-2-*O*-(2-(2,4,6-trimethoxyphenylthio)ethyl)-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (30b): *via* general procedure E starting from glucosyl donor **24b**



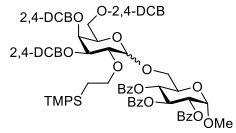
(0.051 g; 0.058 mmol) using acceptor **19**. The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) yielding **24b** as an anomeric mixture (*α/β* = 9/1, 69 mg, 81%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.40. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.95 (m, 2H), 7.94 – 7.89 (m, 2H), 7.88 – 7.83 (m, 2H), 7.54 – 7.45 (m, 2H), 7.45 – 7.27 (m, 12H), 7.25 – 7.08 (m, 6H), 6.14 (t, *J* = 9.8 Hz, 1H, H-3'), 6.09 (s, 2H), 5.48 (dd, *J* = 10.3, 9.5 Hz, 1H, H-4'), 5.24 (dd, *J* = 10.2, 3.7 Hz, 1H, H-2'), 5.19 (d, *J* = 3.7 Hz, 1H, H-1'), 4.96 (d, *J* = 3.4 Hz, 1H, H-1), 4.90 (d, *J* = 12.9 Hz, 1H), 4.76 (d, *J* = 13.1 Hz, 1H), 4.67 (d, *J* = 12.9 Hz, 1H), 4.59 (d, *J* = 13.2 Hz, 1H), 4.52 (d, *J* = 13.1 Hz, 1H), 4.42 (d, *J* = 13.3 Hz, 1H), 4.35 (ddd, *J* = 9.8, 7.2, 2.0 Hz, 1H, H-5'), 3.94 – 3.82 (m, 3H, H-5, H-3, H-6a'), 3.81 (s, 3H), 3.78 (s, 6H), 3.71 (dd, *J* = 10.9, 2.0 Hz, 1H, H-6b'), 3.69 – 3.52 (m, 5H, H-4, H-6), 3.46 (s, 3H), 3.42 (dd, *J* = 9.7, 3.4 Hz, 1H, H-2), 2.84 (dddd, *J* = 40.2, 12.9, 9.2, 5.8 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.86, 165.75, 165.33, 162.00, 161.85, 135.13, 134.88, 134.28, 133.77, 133.47, 133.46, 133.41, 133.38, 133.35, 133.15, 133.08, 132.62, 130.02, 129.93, 129.89, 129.86, 129.65, 129.23, 129.08, 129.04, 129.03, 128.83, 128.81, 128.80, 128.42, 128.40, 128.26, 127.01, 126.87, 126.86, 100.70, 96.94 (C-1), 96.77 (C-1'), 90.95, 81.58 (C-3), 80.97 (C-2), 77.45 (C-4), 72.17 (C-2'), 71.37, 70.96, 70.88, 70.55 (C-3'), 70.01 (C-5), 69.76, 69.62 (C-4'), 68.87 (C-6), 68.46 (C-5'), 66.78 (C-6'), 56.05, 55.58, 55.36, 33.86. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{66}H_{62}Cl_6O_{17}S$, 1391.1737; found, 1391.1701.

Methyl 3,4,6-tri-*O*-(2,6-dichlorobenzyl)-2-*O*-(2-(2,4,6-trimethoxyphenylthio)ethyl)-*α/β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (30c): *via* general procedure E starting from glucosyl donor **24c** (50 mg, 0.057 mmol) and using acceptor **19**. The crude product was purified by silicagel flash column chromatography (0% to 40% Et_2O in toluene) yielding **30c** as an anomeric mixture (*α/β* = 5/1, 66 mg, 84%)**. TLC** (Et_2O/toluene 20/80 v/v): R_f = 0.61 **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (dt, *J* = 8.4, 1.2 Hz, 2H), 7.94 – 7.91 (m, 2H), 7.85 (ddt, *J* = 7.1, 5.2, 1.6 Hz, 3H), 7.54 – 7.04 (m, 40H), 6.16 – 6.10 (m, 2H, H-3'), 6.09 (s, 3H), 5.46 – 5.32 (m, 1H, H-4'), 5.23 (d, *J* = 10.2, 3.7 Hz, 1H, H-2'), 5.14 (d, *J* = 3.7 Hz, 1H, H-1'), 5.09 (d, *J* = 11.4 Hz, 1H), 4.98 – 4.92 (m, 1H), 4.92 – 4.85 (m, 3H, H-1), 4.83 – 4.62 (m, 4H), 4.39 – 4.26 (m, 2H, H-5', *β*-H-1), 3.96 – 3.87 (m, 3H, H-6a', H-3, H-5), 3.87 – 3.77 (m, 13H), 3.74 – 3.68 (m, 1H, H-6a), 3.65 – 3.59 (m, 3H, H-6b', H-6b), 3.58 – 3.53 (m, 2H, H-4), 3.47 (dd, *J* = 10.0, 5.3 Hz, 1H), 3.45 – 3.41 (m, 4H), 3.31 (dd, *J* = 9.6, 3.4 Hz, 1H, H-2), 2.97 – 2.76 (m, 1H), 2.69 (ddd, *J* = 12.9, 9.9, 6.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.80, 165.76, 165.73, 165.38, 165.28, 162.08, 162.03, 161.99, 161.87, 161.80, 161.64, 137.85, 136.97, 136.81, 136.74, 136.71, 136.65, 134.66, 134.60, 134.46, 134.15, 133.97, 133.86, 133.62, 133.52, 133.45, 133.27, 132.98, 129.93, 129.79, 129.68, 129.65, 129.50, 129.45, 129.41, 129.30, 129.18, 129.16, 129.02, 128.87, 128.37, 128.33, 128.26, 128.22, 128.18, 125.29, 104.10, 103.44 (*β*-C-1), 101.56, 100.74, 97.44, 96.64, 96.55 (*α*-C-1), 96.49 (C-1'), 91.00, 90.90, 84.80, 82.69, 82.25, 81.86 (C-3), 81.47, 80.96 (C-2), 78.04 (C-4), 77.86, 77.80, 74.91, 74.58, 72.23 (C-2'), 72.18, 71.66, 70.67 (C-3'), 70.60, 70.55, 70.16 (C-5), 69.86, 69.84 (C-4'), 69.69 (C-6), 69.33, 69.09, 68.92, 68.87, 68.81, 68.61 (C-5'), 68.54, 68.46, 67.71, 67.62, 66.72 (C-6'), 56.10, 56.07, 56.04, 55.66, 55.64, 55.37, 55.35, 55.34, 33.91, 33.65, 33.60. **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{66}H_{62}Cl_6O_{17}S$, 1391.1737; found, 1391.1744.

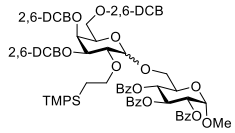
Methyl 3,4,6-tri-O-(4-cyanobenzyl)-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-α-D-glucopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (30d): *Via* general procedure E. Silicagel flash column chromatography (0% - 60% EtOAc in *n*-heptane) afforded **product** (64 mg, 65%). **TLC**: (Et_2O/toluene, 40/60 v/v): R_f = 0,36; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.18 (m, 27H), 6.12 (d, *J* = 12.3 Hz, 2H, H-3'), 5.51 (t, *J* = 9.9 Hz, H-4'), 5.23 (dd, *J* = 10.2, 3.7 Hz, H-2'), 5.19 (d, *J* = 3.6 Hz, H-1'), 5.00 (d, *J* = 12.5 Hz, 1H), 4.97 (d, *J* = 3.4 Hz, H-1), 4.82 (d, *J* = 12.8 Hz, 1H), 4.67 (d, *J* = 12.6 Hz, 1H), 4.56 (d, *J* = 13.6 Hz, 2H), 4.44 (d, *J* = 13.2 Hz, 1H), 4.35 – 4.29 (m, H-5'), 3.95 – 3.84 (m, H-3, H-5, H-6a'), 3.80 (d, *J* = 20.3 Hz, 9H), 3.75 – 3.52 (m, 2H, H-4, H-6b', H-6a, H-6b)), 3.44 (s, H-2), 2.92 – 2.78 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.90, 165.76, 165.30, 162.00, 161.90, 144.24, 143.79, 143.42, 133.45, 133.14, 132.21, 132.14, 132.05, 129.91, 129.84, 129.62, 129.17, 128.96, 128.86, 128.45, 128.41, 128.29, 127.78, 127.61, 127.16, 118.75, 118.67, 118.57, 111.46, 111.41, 111.17, 100.86, 96.82 (C-1'), 96.81 (C-1), 91.03, 81.62 (C-3), 81.03 (C-2), 77.69 (C-4), 74.14, 73.53, 72.40, 72.10 (C-2'), 70.56, 70.48 (C-3'), 69.94 (C-5), 69.53 (C-4'), 69.01 (C-6), 68.45 (C-5'), 66.68 (C-6'), 60.39, 56.08, 55.55, 55.40, 34.18.

Methyl 3,4,6-tri-O-(4-chlorobenzyl)-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-α-D-galactopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (31a): *Via* general procedure E. Silicagel flash column chromatography (0% - 40% EtOAc in *n*-heptane) afforded **31a** (27 mg, 33%). **TLC**: (EtOAc/n-heptane, 60/40 v/v): R_f = 0,75; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 – 7.82 (m, 6H), 7.55 – 7.05 (m, 21H), 6.10 (m, 2H, H-3'), 5.49 (t, *J* = 9.9 Hz, H-4'), 5.23 (dd, *J* = 10.2, 3.7 Hz, H-2'), 5.15 (d, *J* = 3.6 Hz, H-1'), 4.95 (d, *J* = 3.3 Hz, H-1), 4.79 (d, *J* = 11.6 Hz, 1H), 4.74 (d, *J* = 12.1 Hz, 1H), 4.58 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 12.1 Hz, 1H), 4.33 – 4.24 (m, 1H, H-5'), 3.99 (t, *J* = 6.7 Hz, H-5), 3.89 – 3.73 (m, 9H, H-2, H-3, H-4, H-6a'), 3.72 – 3.63 (m, 2H, H-6b'), 3.46 – 3.37 (m, H-6a, H-6b), 2.94 – 2.78 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.82, 165.75, 165.38, 162.06, 161.80, 137.32, 137.07, 136.47, 133.44, 133.35, 133.32, 133.12, 133.05, 129.94, 129.83, 129.64, 129.32, 129.25, 129.09, 129.03, 128.92, 128.88, 128.74, 128.57, 128.43, 128.38, 128.36, 128.26, 128.22, 125.30, 97.68 (C-1), 96.76 (C-1'), 90.93, 78.13 (C-3), 77.55 (C-2), 75.48 (C-4), 73.99, 72.46, 72.22, 72.12 (C-2'), 70.97, 70.60 (C-3'), 69.62 (C-4'), 69.00 (C-5), 68.59 (C-6), 68.29 (C-5'), 66.70 (C-6'), 56.05, 55.41, 55.36, 34.06. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{66}H_{65}Cl_3O_{17}S$, 1289.2905; found, 1289.2852.

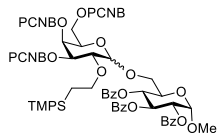
Methyl 3,4,6-tri-O-(2,4-dichlorobenzyl)-2-*O*-(2-(2,4,6-trimethoxythiophenyl)ethyl)-α-D-galactopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (31b): *Via* general procedure E. Silicagel flash column chromatography (0% - 40% EtOAc in *n*-heptane) afforded **31b** as an anomeric mixture (53 mg, 68%). **TLC**: (EtOAc/n-heptane, 50/50 v/v): R_f = 0,50; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 – 7.72 (m, 6H), 7.48 – 6.93 (m, 18H), 6.11 – 5.99 (m, 2H, H-3'), 5.33 (t, *J* = 9.9 Hz, H-4'), 5.16 (dd, *J* = 10.2, 3.7 Hz, H-2'), 5.12 (d, *J* = 9.9 Hz, 1H), 5.04 (d, *J* = 3.6 Hz, H-1'), 4.98 (d, *J* = 10.6 Hz, 1H), 4.81 (s, H-1), 4.72 – 4.49 (m, 4H), 4.31 – 4.20 (m, H-5'), 4.04 (t, *J* = 6.3 Hz, H-5), 3.94 (s, H-4), 3.83 – 3.60 (m, 10H, H-2, H-3, H-6a', H-6b', H-6a), 3.54 (td, *J* = 10.1, 6.0 Hz, 1H), 3.42 (dd, *J* = 9.3, 5.4 Hz, H-6b), 2.91 – 2.64 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.74, 165.71, 165.40, 162.10, 161.77, 137.19, 136.86, 136.78, 134.18, 134.12, 133.49, 133.30, 133.28, 132.99, 129.92, 129.88, 129.86, 129.67, 129.64, 129.53, 129.30, 129.21, 128.87, 128.40, 128.34, 128.24, 128.23, 128.08, 100.94, 97.94 (C-1), 96.65 (C-1'), 90.91, 79.59 (C-3), 77.50 (C-2), 75.89 (C-4), 72.09 (C-2'), 71.63, 70.68 (C-3'), 69.87 (C-4'), 69.56 (C-5), 68.79, 68.71(C-6), 68.46 (C-5'), 68.27, 67.43, 67.24 (C-6'), 56.04, 55.52, 55.35, 33.89. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{66}H_{62}Cl_6O_{17}S$, 1391.1736; found, 1391.1805.



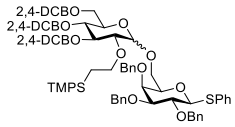
Methyl 3,4,6-tri-O-(2,6-dichlorobenzyl)-2-*O*-(2-(2,4,6-trimethoxybenzenethio) ethyl)-*a*-D-galactopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (31c): *Via* general procedure E. Silicagel flash column chromatography (0% - 40% EtOAc in *n*-heptane) afforded **31c** as an anomeric mixture (55 mg, 70%).**TLC**: (EtOAc/n-heptane, 50/50 v/v): R_f = 0,61; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.79 (m, 6H), 7.54 – 7.10 (m, 18H), 6.12 (t, *J* = 9.8 Hz, H-3'), 6.09 (s, 2H), 5.51 (t, J = 9.80 Hz, H-4'), 5.25 (dd, *J* = 10.2, 3.6 Hz, H-2'), 5.18 (d, *J* = 3.6 Hz, H-1'), 5.00 (s, H-1), 4.91 (d, *J* = 12.9 Hz, 1H), 4.81 (d, *J* = 13.0 Hz, 1H), 4.69 (d, *J* = 13.0 Hz, 1H), 4.58 (d, *J* = 12.9 Hz, 1H), 4.44 (d, *J* = 13.1 Hz, 1H), 4.37 – 4.28 (m, 2H, H-5'), 4.08 (t, *J* = 6.7 Hz, H-5), 3.96 (s, H-4), 3.93 – 3.84 (m, H-2, H-3, H-6a'), 3.79 (m, 9H), 3.73 – 3.62 (m, 2H, H-6b'), 3.60 – 3.44 (m, H-6a, H-6b), 2.96 – 2.76 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.80, 165.77, 165.39, 162.04, 161.80, 135.00, 134.32, 133.77, 133.63, 133.58, 133.37, 133.34, 133.23, 133.18, 133.15, 133.06, 130.18, 129.94, 129.80, 129.67, 129.64, 129.25, 129.10, 129.02, 128.91, 128.88, 128.87, 128.41, 128.36, 128.26, 127.10, 127.05, 126.92, 97.75 (C-1), 96.84 (C-1'), 90.95, 78.58 (C-3), 77.51 (C-2), 76.03 (C-4), 72.10 (C-2'), 71.22, 70.98 (C-6), 70.64 (C-3'), 69.72, 69.65, 69.61 (C-4'), 68.97 (C-5), 68.94, 68.32 (C-5'), 66.84 (C-6'), 56.05, 55.51, 55.36, 34.03. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{66}H_{62}Cl_6O_{17}S$, 1391.1736; found, 1391.1784.



Methyl-3,4,6-tri-O-(4-cyanobenzyl)-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-α-D-galactopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (31d): *Via* general procedure E. Silicagel flash column chromatography (0% - 40% - EtOAc in *n*-heptane) afforded **31d** as an anomeric mixture (86 mg, 87%). **TLC**: (EtOAc/n-heptane, 60/40 v/v): R_f = 0,51; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 – 7.78 (m, 6H), 7.66 – 7.24 (m, 21H), 6.11 (m, 2H, H-3'), 5.54 (t, *J* = 9.9 Hz, H-4'), 5.24 (dd, *J* = 10.2, 3.6 Hz, H-2'), 5.17 (d, *J* = 3.6 Hz, H-1'), 5.02 (d, *J* = 2.9 Hz, H-1), 4.95 (m, 2H), 4.72 (d, *J* = 13.1 Hz, 1H), 4.56 (d, *J* = 12.6 Hz, 1H), 4.44 (d, *J* = 13.1 Hz, 1H), 4.37 (d, *J* = 13.1 Hz, 1H), 4.29 (ddd, *J* = 10.1, 6.1, 2.0 Hz, H-5'), 4.07 (t, *J* = 6.6 Hz, H-5), 3.96 – 3.86 (m, H-2, H-3, H-4, H-6a'), 3.82 (s, 3H), 3.77 (s, 6H), 3.75 – 3.60 (m, 2H, H-6b'), 3.56 – 3.45 (m, H-6a, H-6b). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.87, 165.75, 165.39, 162.04, 161.87, 144.33, 143.93, 143.40, 133.43, 133.42, 133.13, 132.27, 132.14, 132.10, 129.92, 129.78, 129.60, 129.19, 128.99, 128.92, 128.45, 128.40, 128.30, 127.79, 127.47, 127.39, 118.77, 118.70, 111.46, 111.38, 111.20, 100.94, 97.58 (C-1), 96.90 (C-1'), 91.00, 78.50 (C-3), 77.74 (C-2), 76.67 (C-4), 74.03, 72.52, 72.20, 72.03 (C-2'), 70.58, 70.55 (C-3'), 69.51 (C-4'), 69.13 (C-6), 68.89 (C-5), 68.32 (C-5'), 66.70 (C-6'), 56.07, 55.48, 55.41, 34.28. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{69}H_{65}N_3O_{17}S$, 1262.3932; found, 1262.3873.

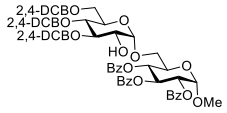


Phenyl 3,4,6-Tri-*O*-(*o*,*p*-dichlorobenzyl)-2-*O*-(2-(2,4,6-trimethoxyphenylthio)ethyl)-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-galactopyranoside (33): *Via* general procedure E starting from

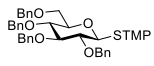


glucosyldonor **24b** (0.044 g; 0.050 mmol) using acceptor **32**. The crude product was purified by silicagel flash column chromatography (10% to 30% EtOAc in *n*-heptane) affording **33** (0.035 g, 50%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.53. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.38 – 6.89 (m, 29H), 6.01 (s, 2H), 4.92 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 13.0 Hz, 1H), 4.82 (d, *J* = 3.6 Hz, 1H, H-1), 4.74 (d, *J* = 10.2 Hz, 1H), 4.70 – 4.60 (m, 6H), 4.60 – 4.51 (m, 3H, H-1'), 4.45 (d, *J* = 13.0 Hz, 1H), 4.32 (d, *J* = 13.2 Hz, 1H), 3.93 – 3.82 (m, 3H, H-2', H-5, H-6a'), 3.81 – 3.77 (m, 2H, H-3, H-4'), 3.77 – 3.70 (m, 2H), 3.68 (s, 6H), 3.67 – 3.60 (m, 3H, H-5', H-6a), 3.60 – 3.49 (m, 5H, H-3', H-4, H-6b, H-7), 3.43 (dd, *J* = 10.0, 4.4 Hz, 1H, H-6b'), 3.35 (dd, *J* = 9.6, 3.6 Hz, 1H, H-2), 2.83 – 2.65 (m, 2H, C-8). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.97, 161.86, 138.53, 138.23, 138.18, 135.22, 134.68, 134.50, 134.19, 133.79, 133.49, 133.39, 132.80, 132.67, 131.26, 130.11, 129.58, 129.33, 129.01, 128.85, 128.77, 128.44, 128.36, 128.33, 128.27, 127.88, 127.77, 127.74, 127.63, 127.60, 126.95, 126.87, 100.69 , 97.11 (C-1), 90.96, 87.96 (C-1'), 84.04 (C-3'), 81.94 (C-3), 81.03 (C-2), 77.71 (C-4), 77.25 (C-2'), 77.17 (C-5), 75.67, 74.35 (C-4'), 74.33, 73.04, 71.47, 71.15 (C-7), 71.11, 69.87 (C-5), 69.81, 68.88 (C-6), 67.89 (C-6'), 56.04, 55.37, 34.06 (C-8). **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{71}H_{70}O_{13}S_2Cl_6$, 1431.2228; found, 1431.2277.

Methyl 3,4,6-Tri-*O*-(*o*,*p*-dichlorobenzyl)-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (35): 30b (36 mg, 0.026 mmol) was dissolved in dry DCM (10 mL). MeOTf (4.6 µL, 0.041 mmol) and TTBP (14 mg, 0.055 mmol) were added and the reaction mixture was refluxed for 4 h at 40°C, after which the mixture was allowed to cool down to rt. KO^{t}Bu (68 mg, 0.041 mmol) was added and the mixture was stirred at rt for 1h, after which the mixture was diluted with DCM (15 mL) and washed with water (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by silicagel flash column chromatography (20% to 40% EtOAc in *n*-heptane) affording **35** (22 mg, 73%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.24. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.96 (m, 2H), 7.96 – 7.90 (m, 2H), 7.90 – 7.84 (m, 2H), 7.56 – 7.27 (m, 15H), 7.23 – 7.09 (m, 4H), 6.15 (t, *J* = 9.9 Hz, 1H, H-3'), 5.67 (t, *J* = 9.9 Hz, 1H, H-4'), 5.28 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2'), 5.23 (d, *J* = 3.7 Hz, 1H, H-1'), 5.08 – 5.03 (m, 1H, H-1), 5.01 (d, *J* = 12.8 Hz, 1H), 4.83 (d, *J* = 12.8 Hz, 1H), 4.80 (d, *J* = 12.9 Hz, 1H), 4.57 (d, *J* = 13.0 Hz, 1H), 4.55 (d, *J* = 13.3 Hz, 1H), 4.41 (d, *J* = 13.3 Hz, 1H), 4.28 (ddd, *J* = 10.3, 4.6, 2.2 Hz, 1H, H-5'), 3.93 (dd, *J* = 11.8, 4.6 Hz, 1H, H-6a'), 3.84 – 3.71 (m, 4H, H-2, H-3, H-5, H-6b'), 3.67 (dd, *J* = 10.7, 3.6 Hz, 1H, H-6a), 3.65 – 3.60 (m, 1H, H-4), 3.54 (dd, *J* = 10.6, 1.9 Hz, 1H, H-6b), 3.47 (s, 3H), 2.65 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.83, 165.80, 165.35, 135.04, 134.73, 134.25, 133.73, 133.64, 133.58, 133.41, 133.22, 133.22, 133.14, 132.86, 130.20, 129.95, 129.85, 129.75, 129.68, 129.47, 129.14, 128.99, 128.98, 128.90, 128.88, 128.81, 128.49, 128.43, 128.29, 127.05 – 126.99 (m), 126.92, 98.55 (C-1), 97.13 (C-1'), 83.45 (C-3), 77.18 (C-4), 73.27 (C-2), 72.12 (C-2'), 71.43, 71.03, 70.49 (C-5), 70.44 (C-3'), 69.73, 69.16 (C-4), 68.88 (C-6), 68.55 (C-5'), 65.57 (C-6'), 55.77. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{55}H_{48}O_{14}Cl_6$, 1165.1073; found, 1165.1048.

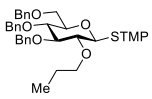


2,4,6-trimethoxyphenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*β*-D-glucopyranoside (38a):



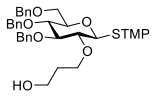
via general procedure D starting from **12d** (98 mg, 0.155 mmol) using BnBr as the benzylation agent. The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) affording **38a** as a white solid (81 mg, 73%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.53. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 2H), 7.38 – 7.14 (m, 19H), 6.10 (s, 2H), 5.15 (d, *J* = 10.3 Hz, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.84 – 4.76 (m, 3H), 4.69 (d, *J* = 9.7 Hz, 1H, H-1), 4.56 (d, *J* = 10.9 Hz, 1H), 4.46 – 4.32 (m, 2H), 3.78 (s, 6H), 3.75 (s, 3H), 3.74 – 3.55 (m, 4H, H-2, H-3, H-6), 3.52 (dd, *J* = 9.8, 8.9 Hz, 1H, H-4), 3.37 (ddd, *J* = 9.8, 5.6, 1.7 Hz, 1H, H-5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.22, 162.04, 138.67, 138.65, 138.60, 138.16, 128.42, 128.39, 128.27, 128.24, 128.21, 127.96, 127.87, 127.86, 127.74, 127.63, 127.60, 127.45, 99.80, 91.24, 86.87 (C-3), 86.78 (C-1), 82.57 (C-2), 79.81 (C-5), 78.16 (C-4), 75.76, 75.21, 74.96, 73.63, 69.62 (C-6), 56.17, 55.29. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{43}H_{46}O_8S$, 745.2811; found, 745.2783.

2,4,6-Trimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-propyl-1-thio-*β*-D-glucopyranoside (38b):



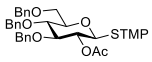
via general procedure D starting from **12d** (99 mg, 0.156 mmol) using propyl bromide as the alkylating agent. The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) yielding **38b** (91 mg, 87%) as a white solid. **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.54. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 19H), 7.21 – 7.12 (m, 4H), 6.10 (s, 2H), 4.94 (d, *J* = 10.9 Hz, 1H), 4.87 – 4.75 (m, 2H), 4.63 (d, *J* = 9.8 Hz, 1H, H-1), 4.53 (d, *J* = 11.0 Hz, 1H), 4.43 – 4.29 (m, 2H), 4.03 – 3.92 (m, 1H), 3.81 (s, 6H), 3.74 (s, 4H), 3.71 (dd, *J* = 11.6, 1.8 Hz, 1H, H-6a), 3.64 – 3.54 (m, 2H, H-3, H-6b), 3.49 – 3.43 (m, 1H, H-4), 3.41 – 3.30 (m, 2H, H-2, H-5), 1.68 (h, *J* = 7.1 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.08, 128.39, 128.35, 128.18, 127.92, 127.83 127.82, 127.68, 127.59, 127.37, 91.23, 86.89 (C-3), 86.31 (C-1), 82.69 (C-2), 79.85 (C-5), 78.07 (C-4), 75.68, 75.00, 74.91, 73.56, 69.61 (C-6), 56.19, 55.24, 23.62, 10.56; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{39}H_{46}O_8S$, 697.2811; found, 697.2786.

2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(benzyl)-2-*O*-(3-hydroxypropyl)-1-thio-*β*-D-glucopyranoside (38c):



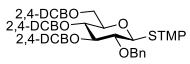
via general procedure C starting from **12d** (124 mg; 0.192 mmol) using $Br(CH_2)_3OTHP$ as the alkylating agent. The crude product was purified by silicagel flash column chromatography (10% to 60% EtOAc in *n*-heptane) yielding **38c** as a white solid (84 mg, 62%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.25. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.08 (m, 15H), 6.11 (s, 2H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.84 (d, *J* = 10.9 Hz, 1H), 4.79 (d, *J* = 10.9 Hz, 1H), 4.57 – 4.52 (m, 2H, H-1), 4.41 (d, *J* = 11.7 Hz, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.07 – 4.00 (m, 2H), 3.97 – 3.89 (m, 1H), 3.83 (s, 6H), 3.76 (s, 3H), 3.70 (dd, *J* = 11.6, 1.7 Hz, 1H, H-6a), 3.62 (t, *J* = 8.9 Hz, 1H, H-3), 3.57 (dd, *J* = 11.6, 5.8 Hz, 1H, H-6b), 3.46 (t, *J* = 9.4 Hz, 1H, H-4), 3.34 (dd, *J* = 10.0, 8.8 Hz, 1H, H-2), 3.32 – 3.28 (m, 1H, H-5), 3.09 (t, *J* = 6.9 Hz, 1H), 1.96 – 1.84 (m, 1H), 1.82 – 1.73 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.29, 162.25, 138.51, 138.48, 138.04, 128.43, 128.35, 128.19, 127.89, 127.84, 127.71, 127.69, 127.44, 98.77, 91.18, 86.98 (C-1), 86.72 (C-3), 82.07 (C-2), 79.76 (C-5), 77.99 (C-4), 75.66, 74.89, 73.64, 71.41, 69.58 (C-6), 60.61, 56.18, 55.27, 32.69.

2,4,6-Trimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-acetyl-1-thio-*β*-D-glucopyranoside (38d):



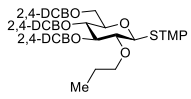
To a solution of **12d** (58 mg, 0.092 mmol) in pyridine (2 ml), was added acetic anhydride (1 mL). The solution was stirred for 4 h at rt before it was concentrated *in vacuo*. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) of the residue afforded **38d** (56 mg, 91%). **TLC:** (EtOAc/n-heptane, 40/60 v/v): R_f = 0.4; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 13H), 7.18 (dd, *J* = 7.5, 2.0 Hz, 2H), 6.09 (s, 2H), 5.04 (dd, *J* = 10.0, 8.7 Hz, 1H, (H-2)), 4.77 (dd, *J* = 11.0, 4.2 Hz, 2H), 4.67 (d, *J* = 11.3 Hz, 1H), 4.57 – 4.54 (m, 2H, (H-1)), 4.48 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 3.77 (d, *J* = 9.6 Hz, 10H, (H-6)), 3.69 – 3.58 (m, 3H, (H-3, H-4, H-6)), 3.41 (ddd, *J* = 9.5, 5.3, 1.8 Hz, 1H, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.51, 162.16, 138.37, 138.18, 137.93, 128.39, 128.37, 128.22, 127.96, 127.85, 127.81, 127.77, 127.67, 127.45, 99.23, 91.16, 85.79 (C-1), 84.74 (C-3), 79.95 (C-5), 77.97 (C-4), 75.17, 74.96, 73.57, 72.90 (C-2), 69.31 (C-6), 56.12, 55.27, 21.06. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{38}H_{42}O_9S$, 697.2447; found, 697.2445

2,4,6-trimethoxyphenyl 2-O-benzyl-3,4,6-tri-*O*-(2,4-dichlorobenzyl)-1-thio-*β*-D-glucopyranoside (39a):



via general procedure D starting from **22b** (0.074 g, 0.088 mmol) using BnBr as the benzylation agent. The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) yielding **39a** as a white solid (49 mg, 60%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.57. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.02 (m, 18H), 6.09 (s, 2H), 5.15 (d, *J* = 10.4 Hz, 1H), 4.94 (d, *J* = 13.1 Hz, 1H), 4.80 – 4.67 (m, 5H, H-1), 4.59 (d, *J* = 12.7 Hz, 1H), 4.48 (d, *J* = 12.9 Hz, 1H), 4.39 (d, *J* = 12.9 Hz, 1H), 3.79 (s, 7H), 3.76 (s, 3H), 3.75 – 3.64 (m, 3H, H-6, H-3), 3.63 – 3.53 (m, 2H, H-2, H-4), 3.38 (ddd, *J* = 9.9, 5.3, 1.9 Hz, 1H, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.09, 162.03, 138.19, 135.43, 135.01, 134.74, 134.46, 133.75, 133.59, 133.45, 133.33, 133.04, 132.73, 130.44, 130.13, 129.68, 129.42, 128.90, 128.88, 128.79, 128.54, 128.44, 128.32, 128.23, 128.17, 127.65, 126.96, 126.95, 99.52, 91.17, 86.69 (C-1, C-3), 82.44 (C-2), 79.12 (C-5), 78.08 (C-4), 75.12, 71.65, 71.04, 69.97, 56.16, 55.25; **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{43}H_{40}O_8SCl_6$, 949.0473; found, 949.0464.

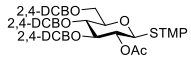
2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(2,4-dichlorobenzyl)-2-*O*-propyl-1-thio-*β*-D-glucopyranoside (39b):



via general procedure D starting from **22b** (0.10 g, 0.12 mmol) and 1-bromopropane as the alkylating agent. The crude product was purified by silicagel flash column chromatography (30% to 60% EtOAc in *n*-heptane) yielding **39b** as a white solid (88 mg, 84%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.35. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.02 (m, 8H), 6.08 (s, 2H), 4.98 (d, *J* = 13.2 Hz, 1H), 4.78 (d, *J* = 13.3 Hz, 1H), 4.73 (d, *J* = 12.7 Hz, 1H), 4.67 (d, *J* = 9.8 Hz, 1H, H-1), 4.57 (d, *J* = 12.7 Hz, 1H), 4.44 (d, *J* = 12.9 Hz, 1H), 4.34 (d, *J* = 12.9 Hz, 1H), 3.97 (dt, *J* = 8.5, 7.0 Hz, 1H), 3.82 (s, 6H), 3.75 (s, 3H), 3.71 (dd, *J* = 11.4, 1.9 Hz, 1H, H-6a), 3.66 – 3.60 (m, 3H, H-3, H-6b), 3.51 (t, *J* = 9.4 Hz, 1H, H-4), 3.40 (dd, *J* = 9.8, 8.7 Hz, 1H, H-2), 3.35 (ddd, *J* = 9.9, 5.5, 1.8 Hz, 1H, H-5), 1.66 – 1.53 (m, 2H), 0.93 – 0.85 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.98, 161.88, 135.13, 134.76, 134.49, 133.74, 133.57, 133.43, 133.34, 133.03, 132.67, 130.12, 129.68, 129.32, 128.90, 128.87, 128.81, 126.97, 126.94, 126.92, 91.18, 86.79 (C-3), 86.22 (C-1), 82.72 (C-2), 79.16 (C-5), 78.04 (C-4), 74.99, 71.55, 69.98 (C-6), 69.94, 56.20, 56.18, 56.15, 55.25, 55.22, 23.50, 10.46.

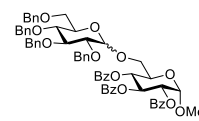
2,4,6-trimethoxyphenyl 3,4,6-tri-*O*-(2,4-dichlorobenzyl)-2-*O*-(3-hydroxypropyl)-1-thio-*β*-D-glucopyranoside (39c): *via* general procedure C starting from **22b** (0.100 g, 0.119 mmol) using $Br(CH_2)_3OTHP$ as the alkylating agent. The crude product was purified by silicagel flash column chromatography (20% to 50% EtOAc in *n*-heptane) affording **39c** as a white solid (78 mg, 73%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.25. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 1H), 7.31 (dd, *J* = 14.1, 2.1 Hz, 2H), 7.28 – 7.23 (m, 5H), 7.22 – 7.09 (m, 6H), 6.09 (s, 2H), 4.97 (d, *J* = 13.0 Hz, 1H), 4.79 (d, *J* = 13.0 Hz, 1H), 4.74 (d, *J* = 12.8 Hz, 1H), 4.61 – 4.54 (m, 2H, H-1), 4.47 (d, *J* = 12.8 Hz, 1H), 4.38 (d, *J* = 12.9 Hz, 1H), 4.10 – 4.00 (m, 1H), 3.96 – 3.85 (m, 2H), 3.85 -3.75 (m, 10H), 3.70 (dd, *J* = 11.4, 2.0 Hz, 1H, H-6a), 3.68 – 3.59 (m, 2H, H-3, H-6b), 3.51 (t, *J* = 9.4 Hz, 1H, H-4), 3.42 – 3.29 (m, 2H, H-2, H-5), 2.99 (t, *J* = 6.9 Hz, 1H), 1.92 – 1.79 (m, 1H), 1.79 – 1.65 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.35, 162.24, 134.90, 134.72, 134.43, 133.80, 133.66, 133.64, 133.38, 133.02, 132.84, 130.17, 129.63, 129.48, 128.93, 128.92, 127.07, 126.98, 126.95, 98.59, 91.18, 86.93 (C-1), 86.70 (C-3), 82.10 (C-2), 79.17 (C-5), 78.05 (C-4), 71.55, 71.27 (C-7), 71.08, 70.02 (C-6), 70.01, 60.44, 56.23, 55.29, 32.70; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{39}H_{40}O_9SCl_6$, 917.0422; found, 917.0403.

2,4,6-trimethoxyphenyl 2-O-acetyl-3,4,6-tri-*O*-(*o*,*p*-dichlorobenzyl)-1-thio-*β*-D-glucopyranoside (39d):



22b (0.105 g; 0.125 mmol) was dissolved in pyridine (2 mL) and Ac_2O (1 ml). The reaction mixture was stirred at ambient temperature 4h, before it was concentrated *in vacuo*. Silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) afforded **39d** as a white solid (76 mg, 69%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.43; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H), 7.22 – 7.10 (m, 4H), 6.09 (s, 2H), 5.07 (dd, *J* = 10.0, 8.7 Hz, 1H, H-2), 4.78 (d, *J* = 13.1 Hz, 1H), 4.75 (d, *J* = 12.7 Hz, 1H), 4.69 (d, *J* = 13.0 Hz, 1H), 4.65 – 4.57 (m, 2H, H-1), 4.52 (d, *J* = 13.0 Hz, 1H), 4.44 (d, *J* = 13.0 Hz, 1H), 3.80 (s, 6H), 3.78 (s, 3H), 3.77 – 3.63 (m, 4H, H-3, H-4, H-6), 3.43 (ddd, *J* = 9.6, 4.9, 2.1 Hz, 1H, H-5), 2.02 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.51, 162.23, 162.12, 134.62, 134.48, 134.23, 133.99, 133.71, 133.66, 133.30, 132.61, 130.07, 129.92, 129.67, 129.04, 128.92, 128.79, 127.20, 127.01, 99,16, 91.19, 85.80 (C-1), 85.12 (C-3), 79.38 (C-5), 77.94 (C-4), 72.88 (C-2), 71.32, 71.16, 69.95, 69.71 (C-6), 56.17, 55.30, 21.07; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{38}H_{36}Cl_6O_9S$, 901.0109; found, 901.0103.

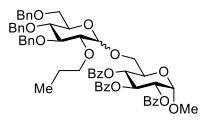
Methyl 2,3,4,6-Tetra-*O*-benzyl-1-thio-*α*/*β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (40a):



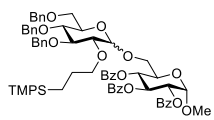
via general procedure F starting from glucosyl donor **38a** (0.40 g; 0.059 mmol). The crude product was purified by silicagel flash column chromatography (10% to 40% EtOAc in *n*-heptane) yielding **40a** as a mixture of isomers (0.0467 g; 0.045 mmol; 68%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.57. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 8H), 7.87-7.83 (m, 4H), 7.52 – 7.45 (m, 4H), 7.45 – 7.08 (m, 46H), 6.21 – 6.16 (m, 1H), 6.14 (t, *J* = 8.5 Hz, 1H), 5.53 (dd, *J* = 10.3, 9.5 Hz, 1H), 5.48 (dd, *J* = 10.3, 9.5 Hz, 1H), 5.28 – 5.19 (m, 4H), 5.06 (d, *J* = 10.8 Hz, 1H), 4.91 (d, *J* = 11.0 Hz, 2H), 4.84 – 4.71 (m, 6H, *α*-H-1), 4.69 (d, *J* = 10.8 Hz, 1H),

4.63 (d, *J* = 12.2 Hz, 1H), 4.56 – 4.42 (m, 6H, *β*-H-1), 4.41 – 4.34 (m, 2H), 4.32 (ddd, *J* = 10.4, 6.6, 2.2 Hz, 1H), 4.13 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.96 (t, *J* = 9.3 Hz, 1H), 3.89 – 3.78 (m, 3H), 3.68 – 3.40 (m, 13H), 3.38 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.81, 165.81, 165.75, 165.45, 165.23, 138.86, 138.59, 138.56, 138.46, 138.37, 138.10, 138.07, 137.91, 133.38, 133.32, 133.04, 133.03, 129.91, 129.88, 129.66, 129.64, 129.26, 129.23, 129.08, 129.06, 129.01, 128.90, 128.45 – 128.27 (m), 128.27 – 128.15 (m), 127.95, 127.91, 127.89, 127.85, 127.75, 127.72, 127.65, 127.62, 127.56, 127.54, 127.47, 127.46, 103.98 (*β*-C-1), 97.23 (*α*-C-1), 96.78, 96.74, 84.54, 82.34, 81.72, 79.97, 77.65, 77.56, 75.70, 75.67, 75.51, 75.00, 74.96, 74.89, 74.80, 74.77, 73.50, 73.42, 73.39, 73.28, 73.10, 72.24, 72.12, 70.61, 70.51, 70.22, 69.90, 69.63, 69.00, 68.85 , 68.64, 68.56, 68.27, 66.64, 55.58, 55.51. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{62}H_{60}O_{14}$, 1051.3881; found, 1051.3851.

Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-propyl-1-thio-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (40b): *via* general procedure F starting from glucosyl donor **38b** (40 mg, 0.059 mmol). The crude product was purified by silicagel flash column chromatography (0% to 40% EtOAc in *n*-heptane) affording **40b** as a mixture of anomers (37 mg, 62%); **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.32. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 – 7.81 (m, 13H), 7.62 – 7.10 (m, 38H), 6.14 (t, *J* = 9.8 Hz, 1H, H-3′), 5.56 – 5.50 (m, 1H, H-4′), 5.24 (dd, *J* = 10.1 Hz, 3.7 Hz, 1H, H-2′), 5.18 (d, *J* = 3.6 Hz, 1H, H-1′), 4.97 (d, *J* = 3.4 Hz, 1H, H-1), 4.85 – 4.77 (m, 2H), 4.74 (d, *J* = 11.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 11.1 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.36 – 4.31 (m, 1H, H-5′), 3.94 – 3.84 (m, 4H, H-3, H-6a), 3.71 (dd, *J* = 11.2, 2.1 Hz, 1H, H-6a′), 3.68 – 3.49 (m, 5H, H-4, H-6b′, H-6, H-7), 3.48 – 3.41 (m, 6H), 1.67 – 1.56 (m, 2H), 0.98 – 0.81 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.35, 166.95, 165.97, 165.88, 165.81, 165.27, 138.95, 138.65, 138.03, 133.43, 133.40, 133.35, 133.33, 133.05, 130.09, 129.76, 129.67, 129.29, 129.20, 129.12, 129.10, 128.99, 128.50, 128.46, 128.20, 127.98, 127.89, 127.62, 127.47, 127.45, 97.13 (C-1), 96.75 (C-1′), 81.55 (C-3), 80.70 (C-2), 77.51 (C-4), 75.44, 74.78, 72.94 (C-2′), 72.23 (C-7), 70.66 (C-3), 70.38, 70.12 (C-4), 69.73 (C-4′), 69.65, 68.69 (C-5′), 68.38 (C-6), 66.64 (C-6′), 55.63, 55.47, 23.32, 10.55. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{58}H_{60}O_{14}$, 1003.3881; found, 1003.3837.



Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-(2,4,6-trimethoxyphenylthio)propyl)-1-thio-*α/β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (40c): *via* general procedure E starting from glucosyl donor **38c** (56 mg, 0.081 mmol). The crude product was purified by silicagel flash column chromatography (10% to 40% EtOAc in *n*-heptane) yielding **40c** as an anomeric mixture (*α/β* = 2/1, 68 mg, 71%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 – 7.71 (m, 10H), 7.50 – 6.97 (m, 48H), 6.05 (s, 1H), 6.02 (s, 2H), 5.41 (t, *J* = 9.9 Hz, 1H), 5.35 (t, *J* = 9.9 Hz, 1H), 5.19 – 5.13 (m, 2H), 5.11 (d, *J* = 3.6 Hz, 1H, *α*-H-1′), 5.10 (d, *J* = 3.7 Hz, 1H, *β*-H-1′), 4.86 (d, *J* = 3.4 Hz, 1H, *α*-H-1), 4.83 – 4.66 (m, 4H), 4.67 – 4.57 (m, 2H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.45 – 4.39 (m, 2H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.30 – 4.22 (m, 2H, *β*-H-1), 3.98 – 3.90 (m, 1H), 3.86 – 3.75 (m, 4H), 3.74 (s, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.70 (s, 9H), 3.69 – 3.49 (m, 7H), 3.49 – 3.39 (m, 3H), 3.37 – 3.28 (m, 2H) 3.35 (s, 3H), 3.34 (s, 3H), 3.14 (ddd, *J* = 7.6, 6.3, 2.4 Hz, 1H), 2.77 – 2.63 (m, 2H), 1.77 – 1.56 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.75, 165.71, 165.32, 165.22, 162.07, 162.05, 161.57, 161.55, 138.83, 138.57, 138.10, 138.05, 137.98, 133.30, 133.26, 133.21, 132.97, 132.96, 129.85, 129.80, 129.76, 129.59, 129.21, 129.19, 129.05, 128.86, 128.37, 128.33, 128.28, 128.27, 128.24, 128.20, 128.19, 128.15, 127.93, 127.91, 127.84, 127.83, 127.80, 127.65, 127.63, 127.61, 127.55, 127.54, 127.48, 127.46, 127.37, 127.35, 103.90 (*β*-C-1), 101.60, 101.26, 96.86 (*α*-C-1), 96.68 (*β*-C-1′), 96.60 (*α*-C-1), 90.94, 90.90, 84.46, 82.52, 81.35, 80.68, 77.46, 77.42, 77.25, 77.00, 76.75, 75.50, 75.28, 74.84, 74.77, 74.68, 73.33, 73.31, 72.16, 72.05, 71.65, 70.59, 70.50, 70.26, 69.81, 69.64, 69.44, 68.98, 68.81, 68.66, 68.44, 68.33, 66.67, 56.04, 56.01, 55.48, 55.41, 55.25, 31.82, 31.31, 30.90, 30.87, 30.44, 29.73, 22.63. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{67}H_{70}O_{17}S$, 1201.4231; found, 1201.4233.



Methyl 3,4,6-tribenzyl-2-*O*-acetyl-*β*-D-glucopyranosyl-(1→6)-2,3,4-*O*-tribenzoyl-*α*-D-glucopyranoside (40d): *Via* general procedure F. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **40d** (42 mg, 83%). **TLC:** (EtOAc/n-heptane, 40/60 v/v): R_f = 0.5; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.87 – 7.82 (m, 2H), 7.77 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.45 – 7.40 (m, 2H), 7.36 – 7.12 (m, 20H), 7.08 (dd, *J* = 7.4, 2.2 Hz, 2H), 6.06 (t, *J* = 9.7 Hz, 1H, H-3'), 5.34 (dd, *J* = 10.3, 9.4 Hz, 1H, H-4'), 5.15 (dd, *J* = 10.1, 3.6 Hz, 1H, H-2'), 5.12 (d, *J* = 3.6 Hz, 1H, H-1'), 4.96 (dd, *J* = 9.2, 7.9 Hz, 1H, H-2), 4.70 (dd, *J* = 11.1, 7.8 Hz, 2H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 2.8 Hz, 1H), 4.44 (d, *J* = 1.5 Hz, 1H), 4.37 (d, *J* = 12.2 Hz, 1H), 4.35 (d, *J* = 8.0 Hz, 1H, H-1), 4.19 (ddd, *J* = 9.7, 7.3, 1.9 Hz, 1H, H-5'), 3.99 (dd, *J* = 10.9, 1.9 Hz, 1H, H-6'), 3.65 – 3.54 (m, 5H, H-6', H-6, H-6, H-3, H-4), 3.43 – 3.34 (m, 4H, H-5), 1.93 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.50, 165.79, 165.67, 165.34, 138.13, 137.97, 137.83, 133.38, 133.30, 133.00, 129.89, 129.82, 129.60, 129.22, 129.04, 128.83, 128.39, 128.37, 128.28, 128.20, 127.97, 127.81, 127.78, 127.70, 127.67, 127.53, 101.31, 96.60 (C-1'), 82.82 (C-3), 77.78 (C-4), 75.16 (C-5), 75.02, 74.99, 73.37, 73.03 (C-2), 72.10 (C-2'), 70.52 (C-3'), 69.48 (C-4'), 68.66 (C-5'), 68.42 (C-6), 68.36 (C-6'), 55.30, 20.92. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{57}H_{56}O_{12}$, 980.3619; found, 980.3578.

Methyl 2-*O*-benzyl-3,4,6-tri-*O*-(2,4-dichlorobenzyl)-1-thio-*α*-D-glucopyranosyl-(1→6)- 2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (41a): *via* general procedure F starting from glucosyl donor **39a** (0.489 g; 0.053 mmol). The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) yielding **41a** as a mixture of isomers (*α/β* = 4/1, 37 mg, 57%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.62. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 – 7.76 (m, 8H), 7.57 – 7.07 (m, 30H), 6.21 – 6.11 (m, 1H, H-3'), 5.60 – 5.54 (m, 1H, H-4'), 5.28 – 5.19 (m, 2H, H-1', H-2'), 5.05 (d, *J* = 10.9 Hz, 1H), 4.98 (d, *J* = 12.9 Hz, 1H), 4.94 (d, *J* = 13.0 Hz, 1H), 4.83 – 4.66 (m, 5H, H-1), 4.66 – 4.48 (m, 4H), 4.45 (d, *J* = 13.4 Hz, 1H), 4.39 (d, *J* = 13.3 Hz, 1H), 4.33 (ddd, *J* = 10.3, 6.3, 2.0 Hz, 1H, H-5'), 4.13 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.99 (t, *J* = 9.2 Hz, 1H, H-3), 3.91 – 3.83 (m, 2H, H-5, H-6a'), 3.83 – 3.73 (m, 1H), 3.72 – 3.69 (m, 1H), 3.67 – 3.50 (m, 6H, H-2, H-4, H-6, H-6b'), 3.47 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.84, 165.81, 165.74, 165.47, 165.22, 138.12, 138.05, 135.14, 134.97, 134.86, 134.46, 134.35, 134.22, 133.78, 133.74, 133.67, 133.52, 133.50, 133.44, 133.37, 133.30, 133.25, 133.22, 133.09, 132.67, 130.19, 129.48, 129.35, 127.67, 127.08, 126.76, 96.96 (C-1), 96.87 (C-1'), 84.51, 82.00, 81.63 (C-3), 80.01 (C-2), 77.58, 77.47 (C-4), 74.65, 74.56, 72.99, 72.21 (C-2'), 72.07, 71.59, 71.52, 71.06, 70.98, 70.58 (C-3'), 70.40, 69.95 (C-5), 69.89, 69.84, 69.72, 69.46 (C-4'), 69.23, 69.00, 68.85 (C-6), 68.59 (C-5'), 66.55 (C-6'), 55.60, 55.57; **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{62}H_{54}O_{14}Cl_6$, 1257.1513; found, 1257.1537.

Methyl 3,4,6-tri-*O*-(2,4-dichlorobenzyl)-2-*O*-propyl-1-thio-*α/β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (41b): : V*ia* general procedure F starting from glucosyl donor **39b** (50 mg; 0.057 mmol) using acceptor **19**. The crude product was purified by silicagel flash column chromatography (10% to 60% EtOAc in *n*-heptane) yielding **41b** as an anomeric mixture (α/β = 3/1, 35 mg, 51%) **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.8. *α*-Anomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 – 7.71 (m, 6H), 7.51 – 6.93 (m, 15H), 6.08 (t, *J* = 9.8 Hz, 1H, H-3'), 5.48 (t, *J* = 9.9 Hz, 1H, H-4'), 5.18 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2'), 5.14 (d, *J* = 3.7 Hz, 1H, H-1'), 4.94 – 4.89 (m, 2H, H-1), 4.72 (d, *J* = 13.1 Hz, 1H), 4.67 (d, *J* = 13.1 Hz, 1H), 4.53 (d, *J* = 13.4 Hz, 1H), 4.46 (d, *J* = 13.1 Hz, 1H), 4.35 (d, *J* = 13.2 Hz, 1H), 4.30 – 4.22 (m, 1H, H-5'), 3.91 – 3.78 (m, 3H, H-3, H-5, H-6'a), 3.71 – 3.32 (m, 10H, H-6a, H-6'b, H-6b, H-4, H-2), 1.57 – 1.45 (m, 2H), 0.87 – 0.76 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.90, 165.80, 165.24, 135.26, 134.91, 134.32, 133.73, 133.48, 133.46, 133.43, 133.39, 133.30, 133.16, 133.09, 132.66, 129.95, 129.94, 129.86, 129.84, 129.82, 129.75, 129.67, 129.64, 129.61, 129.59, 129.25, 129.15, 129.04, 129.01, 128.96, 128.95, 128.92, 128.86, 128.81, 128.48, 128.43, 128.42, 128.32, 128.28, 128.25, 127.02, 126.95, 126.88, 126.86, 96.88 (C-1), 96.85 (C-1'), 81.48 (C-3), 80.72 (C-2), 77.41 (C-4), 72.80, 72.18 (C-2'), 71.38, 70.98, 70.59 (C-3'), 70.08 (C-5'), 69.76, 69.50 (C-4'), 68.95, 68.70(C-5), 66.56, 55.63, 23.25, 10.48. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{58}H_{54}Cl_6O_{14}$, 1207.1504; found, 1207.1568.

Methyl 3,4,6-tri-*O*-(2,4-dichlorobenzyl)-2-*O*-(2-(2,4,6-trimethoxyphenylthio)propyl)-*α/β*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (41c): *via* general procedure E starting from glucosyl donor **41c** (51 mg, 0.058 mmol) using acceptor **19**. The crude product was purified by silicagel flash column chromatography (0% to 30% EtOAc in *n*-heptane) affording **41c** as a mixture of isomers (α/β = 2.5/1, 39 mg, 49%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.43. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 – 7.83 (m, 7H), 7.55 – 7.08 (m, 22H), 6.18 – 6.10 (m, 1H, H-3'), 6.09 (s, 2H), 5.52 (t, *J* = 10.0 Hz, 1H, H-4'), 5.25 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2'), 5.21 (d, *J* = 3.7 Hz, 1H, H-1'), 4.97 (d, *J* = 3.4 Hz, 1H, H-1), 4.90 (d, *J* = 13.0 Hz, 1H), 4.77 (d, *J* = 13.0 Hz, 1H), 4.69 (d, *J* = 13.1 Hz, 1H), 4.59 (d, *J* = 13.3 Hz, 1H), 4.56 – 4.50 (m, 1H), 4.42 (d, *J* = 13.3 Hz, 1H), 4.34 (ddd, *J* = 10.4, 6.7, 2.0 Hz, 1H, H-5'), 3.96 – 3.84 (m, 3H, H-3, H-5, H-6a'), 3.79 (m, 9H), 3.77 – 3.52 (m, 6H, H-4, H-6, H6b', H-7), 3.46 (s, 3H), 3.44 – 3.38 (m, 1H, H-2), 2.84 – 2.62 (m, 2H), 1.83 – 1.62 (m, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.86, 165.78, 165.29, 162.09, 161.65, 135.20, 134.91, 134.35, 133.72, 133.47, 133.41, 133.38, 133.29, 133.12, 133.08, 132.65, 129.99, 129.94, 129.85, 129.67, 129.65, 129.25, 129.06, 128.89, 128.84 – 128.75 (m), 128.42, 128.38, 128.27, 127.03, 126.88, 126.85, 101.22, 96.78 (C-1'), 96.70 (C-1), 90.95, 81.40 (C-3), 80.73 (C-2), 77.42 (C-4), 72.19 (C-2'), 71.32, 70.95, 70.61 (C-3'), 70.05 (C-5), 69.75, 69.56 (C-4'), 69.30, 68.96 (C-6), 68.52 (C-5), 66.65 (C-6'), 56.08, 55.57, 55.33, 30.83, 29.60. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{67}H_{64}Cl_6O_{17}S$, 1405.1893; found, 1405.1883.

Methyl 2-*O*-acetyl-3,4,6-tri-*O*-(2,4-dichlorobenzyl)-1-thio-*β*-D-glucopyranosyl-(1→6)- 2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (41d): *via* general procedure F starting from glucosyl donor **39d** (51 mg; 0.058 mmol). The crude product was purified by silicagel flash column chromatography (10% to 30% EtOAc in *n*-heptane) affording **41d** (41 mg, 60%). **TLC** (EtOAc/*n*-heptane 40/60 v/v): R_f = 0.57. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 2H), 7.95 – 7.88 (m, 2H), 7.87 – 7.81 (m, 2H), 7.54 – 7.47 (m, 2H), 7.44 – 7.23 (m, 16H), 7.22 – 7.10 (m, 5H), 6.13 (t, *J* = 9.7 Hz, 1H, H-3'), 5.42 (dd, *J* = 10.3, 9.4 Hz, 1H, H-4'), 5.26 – 5.16 (m, 2H, H-1', H-2'), 5.10 – 5.02 (m, 1H, H-2), 4.78 (d, *J* = 13.0 Hz, 1H), 4.76 (d, *J* = 12.5 Hz, 1H), 4.70 (d, *J* = 12.9 Hz, 1H), 4.62 (d, *J* = 12.5 Hz, 1H), 4.54 (d, *J* = 13.4 Hz, 1H), 4.46 (d, *J* = 7.9 Hz, 1H, H-1), 4.45 (d, *J* = 13.4 Hz, 1H), 4.25 (ddd, *J* = 10.3, 7.0, 2.0 Hz, 1H, H-5'), 4.07 (dd, *J* = 11.0, 2.0 Hz, 1H, H-6a'), 3.77 – 3.68 (m, 4H, H-3, H-4, H-6), 3.65 (dd, *J* = 10.9, 7.0 Hz, 1H, H-6b'), 3.53 – 3.47 (m, 1H, H-5), 3.45 (s, 3H), 2.05 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.51, 165.83, 165.71, 165.40, 134.42, 134.33, 134.16, 134.06, 133.81, 133.69, 133.48, 133.36, 133.32, 133.16, 133.07, 132.76, 129.92, 129.82, 129.71, 129.69, 129.63, 129.23, 129.08, 129.05, 128.96, 128.87, 128.82, 128.44, 128.41, 128.25, 101.27 (C-1), 96.73 (C-1'), 83.28 (C-3), 77.71 (C-4), 74.89 (C-5), 73.00 (C-2), 72.09 (C-2'), 71.28, 71.19, 70.49 (C-3'), 69.84, 69.50 (C-4'), 69.03 (C-6), 68.69 (C-5'), 68.27 (C-6'), 55.41, 20.98. **HRMS** *(m/z)*: $[M+Na]^+$ calcd for $C_{57}H_{50}Cl_6O_{15}$, 1207.1179; found, 1207.1173.

3.10 – References

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4

Stereoselective *β*-Mannosylation *via* Neighboring Group Participation

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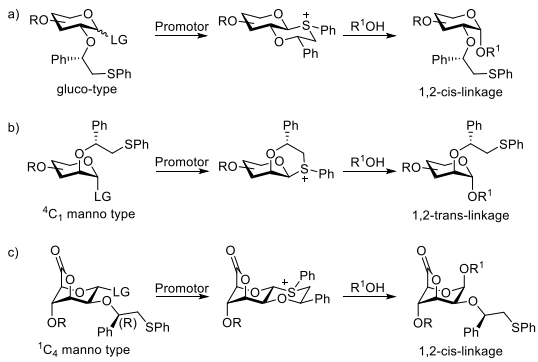
Abstract: The stereoselective synthesis of glycosidic bonds is the main challenge in oligosaccharide synthesis. In order for oligosaccharide synthesis to become a routine process, broadly applicable and highly reliable glycosylation methods are needed. In this respect, neighboring group participation (NGP) of C-2 acyl substituents can be used to provide 1,2-*trans*-glycosides. Recently, the application of NGP has been extended to the preparation of 1,2-*cis*-glycosides with the advent of C-2 chiral auxiliaries. However, this methodology has been strictly limited to the synthesis of 1,2-*cis*-gluco type sugars. This chapter reports the design and synthesis of novel mannosyl donors that provide 1,2-*cis*-mannosides *via* NGP of thioether auxiliaries. A key element in our design is the use of $^{1}C_{4}$ locked mannuronic acid lactones to enable the NGP of the C-2 auxiliary. In addition to C-2 participation we identified a new mode of remote participation of the C-4 benzyl to provide 1,2-*cis*-mannosides.

4.1 – Introduction

The most challenging aspect of oligosaccharide synthesis is the stereoselective synthesis of glycosidic bonds.[1] In order for oligosaccharide synthesis to become a routine process, broadly applicable and highly reliable glycosylation methods are needed. In this respect, the most promising methodology is based on the neighboring group participation (NGP) of C-2 acyl substituents to provide 1,2-*trans*-glycosides.[1b] This methodology is broadly applicable to manno- and gluco type sugars and has been applied to (automated) solid phase oligosaccharide synthesis (SPOS).[2]

Recently, the application of NGP has been extended to the preparation of 1,2-*cis*-glycosides with the advent of C-2 chiral auxiliaries (Scheme 1a).[3] In the approach, a C-2 (*S*)-(phenylthiomethyl)benzyl ether is used to trap the oxocarbenium-ion from the *β*-face resulting in the formation of 1,2-*cis*-glycosides. This methodology holds great promise to become a generally applicable principle for the synthesis of 1,2-*cis*-glycosides.[4] However, this methodology has been strictly limited to the synthesis of 1,2-*cis*-gluco type sugars. The *trans*-decalin sulfonium ion intermediate is unlikely formed in mannose and the most likely intermediate would be a *cis*-decalin system which would provide the 1,2-*trans*-mannoside instead (Scheme 1b). Conversely, an alternative method to prepare *β*-mannosides has been developed by Crich and co-workers, but this method is mostly limited to the synthesis of *β*-mannosides.[5] We therefore explored the possibility to prepare *β*-mannosides using NGP since this method is applicable to other classes of carbohydrates as well. This chapter reports a new strategy to enable NGP for the synthesis for 1,2-*cis*-mannosides by use of the $^1C_4$ conformation. In this conformation and using an (*R)*-configured auxiliary, the formation of a *trans*-decalin intermediate is possible (Scheme 1c).

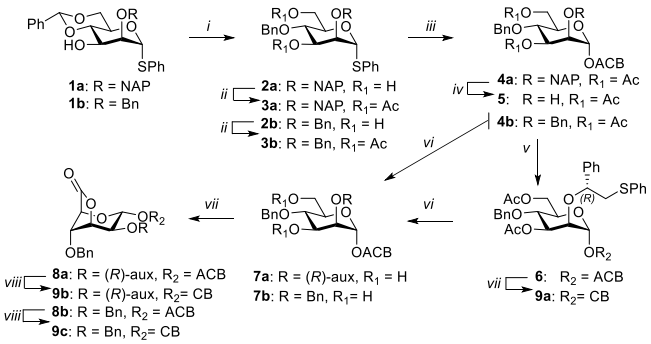


Scheme 1: General overview of NGP in manno- and glucotype donors: **a**) Neighboring group participation by a chiral auxiliary in gluco- and galacto-type donors resulting in the 1,2-*cis* product; **b**) C-2 participation of the auxiliary in the $^4C_1$ conformation resulting in the *cis*-decalin system and hence 1,2-*trans*-mannosides; **c**) A ringflip into the $^1C_4$ conformation favors the *trans*-decalin system. Attack of the acceptor at the beta (axial) position results in the *β*-mannoside.

Three new mannose donors were designed to study the effect of conformation on neighboring group participation and the stereoselectivity of the ensuing glycosylation (**9a**-**9c**, Scheme 2).[6] To obtain the desired $^1C_4$ conformation, we used a 6,3-lactone bridge that can be introduced by oxidation of the 3,6-diol precursor using TEMPO/BAIB.[7] Critically, this mild oxidation method is chemoselective and compatible with thioethers.[8] Typically, the sulfonium ions are obtained after pre-activation of glycosyl imidates. However, early attempts to prepare glycosyl imidates of glycosyl lactones failed because the intermediate lactol underwent ring opening. Hence, we selected the carboxybenzyl leaving group as it is compatible with thioethers and can be introduced at an early stage.[9]

4.2 – Donor synthesis

Synthesis of **9a**-**c** started from known benzylidene protected thiomannosides **1a**/**b** (scheme 2).[10] The benzylidenes in **1a**/**b** were reductively opened to the C-4 position to give the corresponding 3,6-diols **2a**/**b** which, after acetylation, afforded **3a**/**b** in good yields. Thiomannosides **3a**/**b** were used to glycosylate 2-(allylcarboxy)benzyl[11] (ACB) alcohol using NIS/TfOH[12] to give **4a**/**b**. Next, the 2-methylnaphthyl ether of **4a** was cleaved by DDQ oxidation to give alcohol **5**. The (*R*)-(phenylthiomethyl)benzyl ether was introduced with retention of stereochemistry by BF_3-Et_2O promoted activation of (*R*)-1-phenyl-2-(phenylthio)ethyl acetate.[3a] To prepare donor **9a**, **6** was deallylated with $Pd(PPh_3)_4$. Next, **4b** and **6** were deacetylated using KO^{t}Bu in allyl alcohol to obtain diols **7a** and **7b**, respectively. Because the thioether moiety is readily oxidized using most traditional oxidation methods, the aforementioned chemoselective TEMPO/BAIB method was chosen.[7] Oxidation of **7a**/**b** (60-80%) proceeded with moderate yields to provide $^1C_4$ mannolactones **8a**/**b**. Finally, compounds **8a**/**b** were deallylated to afford glycosyl donors **9b**/**c.**

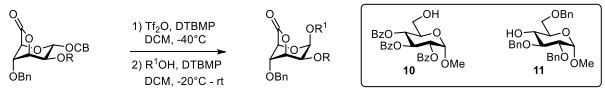


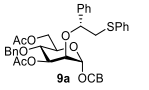
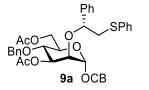
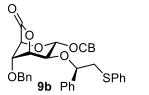
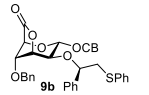
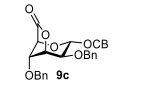
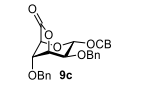
Scheme 2: Synthesis of the mannosyl donors **9a-c**. Reagents and conditions: i) BH_3.THF, Bu_2BOTf, THF; **2a**, 97%; **2b**, 70%; ii) Ac_2O, Pyridine; **3a**, 95 %; **3b** 95%; (iii) ACB, NIS, TfOH, DCM; **4a**, 82 %; **4b**, 82%; (iv) **4a**, DDQ, DCM/H_2O; **5**, 75%; v) (*R*)-PhCH(OAc)CH_2SPh, BF_3.Et_2O, DCM; **6**, 70%; (vi) AllylOH, KO^{t}Bu; **7a**, 85%; **7b**, 87% (vii) TEMPO, BAIB, H_2O/DCM; **8a**, 60%; **8b**, 80%; viii) $Pd(PPh_3)_4$, AcOH/DCM; **9a**, 90 %; **9b**, 85%, **9c** (90%).

4.3 – Glycosylation results

Next, we glycosylated donors **9a-c** with glycosyl acceptors **10** and **11** (Table 1, entries 1-6). Donors **9a**-**b** and **9c** were preactivated at low temperature (-40°C and -78°C, respectively) with 1.0 eq Tf_2O in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a base. All donors were activated almost instantaneously and reactions with **9a** and **9b** were allowed to warm up to -20°C before addition of the acceptor. As expected, donor **9a** produced mainly *α*-mannosides, presumably *via* a *cis*-decalin sulfonium ion intermediate (Table 1, entries 1 and 4). In contrast, glycosylation with **9b** showed excellent *β*-selectivity in respectable yields (entries 2 and 5). The *β*-selectivity observed in these glycosylation supports the hypothesis that the reaction proceeds via an S_N2 like displacement of the proposed equatorial sulfonium ion.[13] However, donor **9c**, which because of the high reactivity was activated at lower temperature (-78°C), produced exclusively *β*-mannosides with both the primary and secondary acceptor (Table 1, entries 3 and 6). These results indicate that reactive intermediates other than the *α*-sulfonium ion are also important for the observed *β*-selectivity.

Table 1: Glycosylation Results of donors **9a**-**9c**.



entry	donor	R^1OH	yield[a] (%)	*α* / *β*[b]	$^1J_{C1\text{-}H1}$[c] (Hz)	entry	Donor	R^1OH	yield[a] (%)	*α* / *β*[b]	$^1J_{C1\text{-}H1}$[c] (Hz)
1		**10**	82[d]	10/1	170	4		**11**	71[d]	>20/1	175
2		**10**	61[d] 52[e]	>1/20	172	5		**11**	58[d]	>1/20	176
3		**10**	87[d,f] 70[e]	>1/20	172	6		**11**	37[d]	>1/20	176

[a] isolated yields; [b] ratios were determined by integration of key NMR signals of the crude reaction mixture; [c] the stereochemistry was determined by determination of the $^1J_{C1,H1}$ coupling: axial H-1 (≈160Hz) or equatorial H-1 (≈170Hz)[14]; [d] using 2.0 eq of glycosyl donor; [e] using 2.0 eq of acceptor; [f] as inseparable mixture with **14c.**

4.4 – Mechanistic studies

In order to explain the results of the glycosylations shown in Table 1, VT-NMR studies were performed on donors **9a**-**9c** to identify reaction intermediates. $^4C_1$ donor **9a** was mixed with 2.0 eq of DTBMP in CD_2Cl_2 at -20°C (Figure 1a) and activated with 1.0 eq of Tf_2O in an NMR tube. At this temperature ^{1}H-NMR showed a single species (Figure 1b). A ^{1}H-TOCSY experiment (irradiation of δ = 5.21 ppm, figure 1c) revealed a major downfield shift of H-1 to 5.56 ppm and

in combination with ^{1}H-^{13}C-HSQC and ^{1}H-^{13}C HMBC NMR spectra, which revealed a C1-H8 correlation, it was concluded that the 1,2-*trans* decalin intermediate was formed.

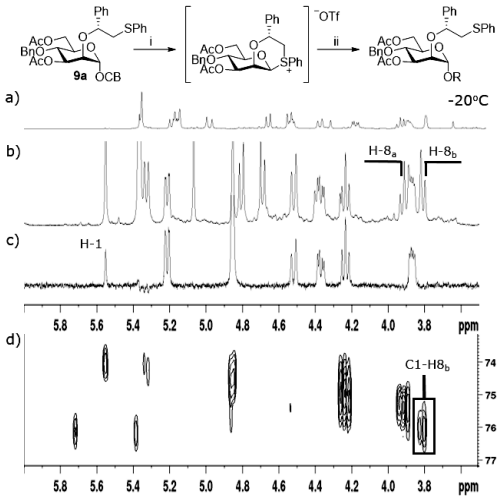


Figure 1: VT-NMR study of donor **9a**: *i*) 2.0 eq DTBMP + 1.0 eq Tf_2O; *ii)* **10** or **11**. **a**) Donor **9a** pre-activation at -20°C; **b**) Donor **9a** post-activation at -20°C; **c**) ^{1}H-TOCSY of the activated donor **9a**; **d**) ^{1}H-^{13}C HMBC spectrum of **9b**, with overlay of a proton decoupled ^{1}H-^{13}C HSQC, post-activation.

As depicted in figure 2, $^{1}C_4$ donor **9b** (Figure 2a) was activated at -30°C under the aforementioned conditions. At -20°C, a clean spectrum of a single species was observed (Figure 2b). A ^{1}H-^{1}H TOCSY NMR (Figure 2c) with irradiation of H-2 and H-4 revealed a major downfield shift of H-1 (δ 5.06 ppm → δ 7.46 ppm). Furthermore, a strong correlation between C-1 and H-8_{ax} (δ 4.23 ppm) and to a minor extend with H-8_{eq} (δ 4.82 ppm) in the ^{1}H-^{13}C-HMBC spectrum (Figure 2d) indicated formation of a ring system. The $^{3}J_{H1,H2}$ coupling of 6.0 Hz supports a diaxial orientation and suggests an *α*-sulfonium ion.

The observation of the *β*-sulfonium ion after activation of **9a** and the *α*-sulfonium ion found following activation of **9b** supports the hypothesis that these intermediates are displaced by the alcohol to provide *α*- and *β*-mannosides, respectively.[13] However, glycosylation with mannosyl donor **9c** were also highly *β*-selective. Previously, high *α*-selectivity was observed in glycosylations with galacturonic acid lactones.[7] The selectivity was attributed to the disarmed nature of the acceptor although exemptions were reported in a later study.[15] The observed *β*-selectivity could also be explained by pseudoaxial attack on the $^{3}H_4$ oxocarbenium ion to provide the observed 1,2-*cis* addition.[16] Finally, anomeric triflate species may also be important intermediates.[17]

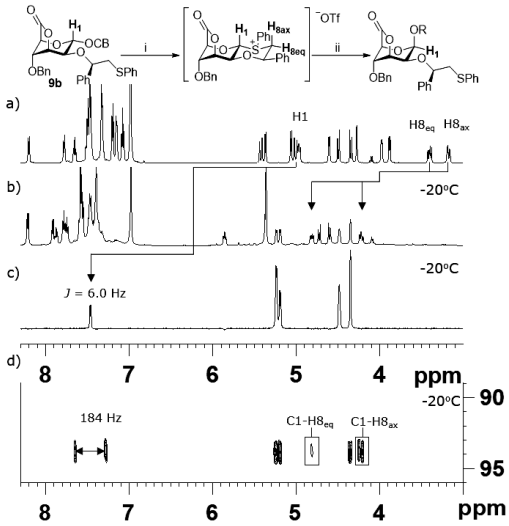


Figure 2: VT-NMR study of donor **9b**: *i*) 2.0 eq DTBMP + 1.0 eq Tf_2O; *ii)* **10** or **11**. **a**) Donor **9b** pre-activation at -30°C; **b**) Donor **9b** post-activation at -20°C; **c**) ^{1}H-TOCSY of the activated donor **9b**; **d**) ^{1}H-^{13}C HMBC spectrum of **9b**, with overlay of a proton decoupled ^{1}H-^{13}C HSQC, post-activation.

To investigate the reaction intermediates, donor **9c** was activated at -80°C, A VT-NMR study at -80°C showed a mixture of several species (Figure 3a). Close examination with ^{19}F NMR showed triflated intermediates were present and ^{1}H-^{19}F HOESY (Figure 3c) in combination with ^{1}H-^{13}C-HSQC and ^{1}H-^{13}C-HMBC characterized these species as an anomeric triflate and to our surprise, benzyltriflate. In order to observe the stability of the triflate, the sample was heated gradually until one species remained at -20°C (Figure 3b). Extensive NMR studies showed a strong H1-C4 correlation which, together with the formation of benzyl triflate, led us to conclude that tricyclic compound **14c** had formed.

We propose that upon activation of donor **9c**, intermediate oxocarbenium ion **12c** is stabilized by the C-4 benzyl ether to form **13c** (Scheme 3). In absence of the acceptor, this intermediate ultimately results in the formation of **14c** and benzyl triflate. The formation of **14c** and benzyl triflate indicate NGP of the C-4 benzyl which may also explain the high β-selectivity of **9b**.[18] Careful examination of the glycosylation mixture indeed showed the presence of **14c** as a side product in moderate quantities.

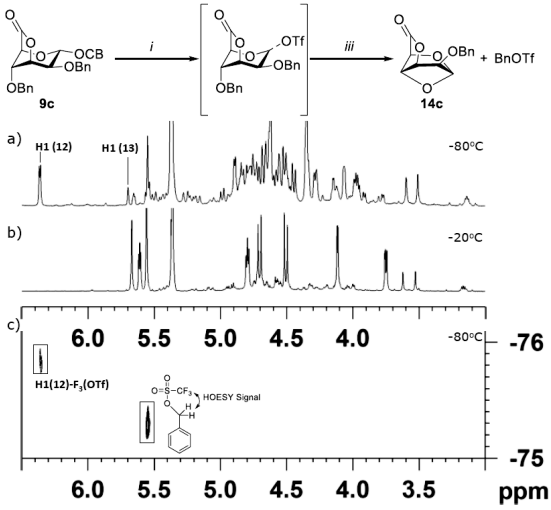
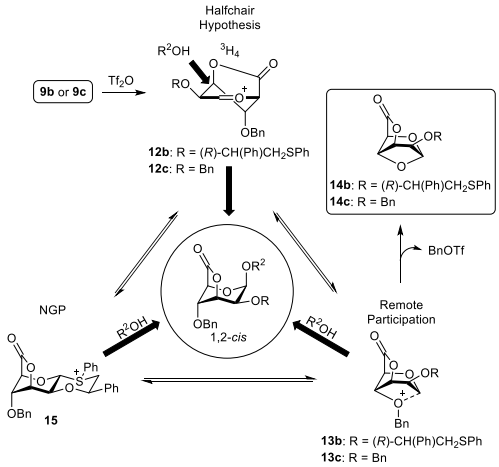


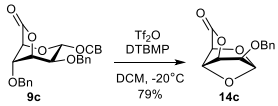
Figure 3: VT-NMR study of donors **9c**: *i*) 2.0 eq DTBMP + 1.0 eq Tf_2O; *iii*) Raising temperature. **a)** ^1H NMR spectrum of activated donor **9c** at -80°C; **b)** at -20°C; **c)** ^1H-^{19}F HOESY spectrum of activated donor **9c**.

A batch experiment to reproduce **14c** from **9c** was performed and gave **14c** in good yield (Scheme 4, 79%). Unlike earlier reported 1,4-anhydro sugars, 1,4-anhydro-6,3-lactone **14c** was stable and no polymerization or furanose formation was observed.[19] In addition to remote participation of the C-4 benzyl ether, the expected $^3H_4$ conformation of the oxocarbenium ion may also lead to *β*-product (Scheme 4).[16]



Scheme 3: Proposed Remote Participation in mannuronic acid lactones **9b** and **9c**.

In principle, although not observed in the NMR study at -20°C, C-4 benzyl participation could also occur in **9b** and indeed tricyclic compound **14b** could be retrieved as a side product in the glycosylation reaction. The formation of **14b** as a side product may explain the moderate yields observed (Table 1, entries 1-4). Although **14b** is ultimately formed, VT-NMR experiments show that sulfonium ion formation is highly favored at -20°C. Therefore, in case of **9b**, an additional pathway via sulfonium ion **15** may lead to *β*-mannosides, but the observed selectivity is more likely to be a result of the aforementioned alternative pathways (Scheme 3).

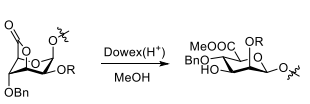


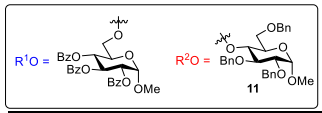
Scheme 4: Synthesis of tricyclic mannoside **14c**.

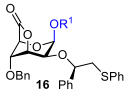
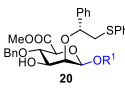
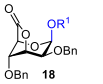
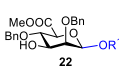
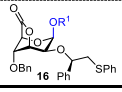
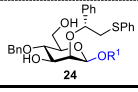
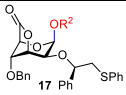
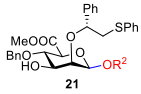
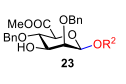
4.5 – Reverting to the $^4C_1$ conformation

Finally, the opening of mannuronic acid lactones **16**-**19** with Dowex(H$^+$) in MeOH reverted the conformation to the $^4C_1$ and afforded the corresponding methyl esters **20**-**23** in high yield.[16b, 20] The orientation of H-1 was confirmed using the $^1J_{C1\text{-}H1}$ coupling constants, again confirming the 1,2-*cis* substitution (Table 2, entries 1,2,4 and 5).[14] Additionally, mannuronic acid lactone **14** was selectively reduced to its corresponding mannose analogue using K-selectride to obtain **24** in 90% yield (see Table 2, entry 3).[21] This may be an attractive way to prepare *β*-mannosides found in the human core *N*-glycan.

Table 2: Opening of the dissacharide lactones.





entry	lactone	product	yield[a] (%)	$^1J_{C1\text{-}H1}$ (Hz)[d]
1	 **16**	 **20**	90	156
2	 **18**	 **22**	89[b]	160
3[c]	 **16**	 **24**	90	155
4	 **17**	 **21**	91	155
5	 **19**	 **23**	80	156

[a] isolated yields; [b] as an inseparable mixture with **14c**; [c] reagent was K-selectride in THF; [d] the stereochemistry was determined by determination of the $^1J_{C1,H1}$ coupling: axial H-1 (≈160Hz) or equatorial H-1 (≈170Hz)[14]

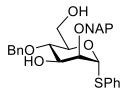
4.6 – Conclusion

We have shown that chiral auxiliaries can be used to prepare *β*-mannosides *via* NGP. To make *trans*-decalin sulfonium ion formation possible, it is imperative to use $^1C_4$ mannosides. Due to this conformation, however, the C-4 benzyl substituent is also able to engage in remote NGP and provide 1,2-*cis*-mannosides. Although good alternatives for *β*-mannosylation are available, this method relies on neighboring group participation which is a generally applicable method. Hence, the use of NGP to prepare 1,2-*cis*-glycosides of gluco- and manno-type sugars is now possible bringing a unified procedure for 1,2-*cis* glycosylation one step closer.

4.7 – Experimental section

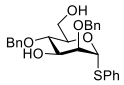
General methods: For general remarks, please refer to section 2.9.

Phenyl 4-*O*-benzyl-2-*O*-(2-methylnaphthyl)-1-thio-*α*-D-mannopyranoside (2a)[22]



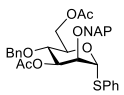
To a cooled (0°C) solution of phenyl 4,6-O-benzylidene-2-O-(2-methylnaphthyl)-1-thio-*α*-D-mannopyranoside[10a] (6.3 g, 12.6 mmol) in THF (60 mL) was 63 mL of 1.0 M BH_3 in THF (62.9 mL, 62.9 mmol) was added under stirring under inert atmosphere. To the solution 1M Bu_2BOTf in DCM (12.5 mL, 12.5 mmol) was added and the reaction stirred for 1 hr. The solution was neutralized with Et_3N (5 mL) quenched with methanol and was concentrated *in vacuo*. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) of the residue afforded **2a** (6.0 g, 95 %) as colorless oil. **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.25; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 – 7.24 (m, 17H, CH Ar), 5.56 (d, *J* = 1.0 Hz, 1H, H-1), 4.93 (d, *J* = 11.1 Hz, 1H, CH*H*Nap), 4.89 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.75 (d, *J* = 11.8 Hz, 1H, C*H*HPh), 4.69 (d, *J* = 11.1 Hz, 1H, C*H*HNap), 4.15-4.11 (m, 1H, H-5), 4.07 (dd, *J* = 3.7, 1.4 Hz, 1H, H-2), 4.02 (td, *J* = 9.1, 3.6 Hz, 1H, H-3), 3.87 – 3.82 (m, 2H, H-6a, H-6b), 3.80 (m, 1H, H-4), 2.40 (d, *J* = 9.1 Hz, 1H, , C-$_3$HO*H*), 1.77 (dd, *J* = 7.5, 5.7 Hz, 1H, C-$_6$HHO*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 132.04, 129.12, 128.63, 128.52, 128.06, 127.93 (2 x), 127.77, 127.06, 126.40, 126.28, 125.76, 85.42(C-1), 79.72(C-2), 76.52(C-4), 75.05, 72.80, 72.54(H-5), 72.23(C-3), 62.18(C-6); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{30}H_{30}O_5S$, 525.1712; found, 525.1711; **$[\alpha]^{25}_D$** = +77.7 (*c* = 0.23, $CHCl_3$).

Phenyl 2,4-di-*O*-benzyl-1-thio-*α*-D-mannopyranoside (2b)[23]



To a solution of phenyl 4,6-O-benzylidene-2-*O*-benzyl-1-thio-*α*-D-mannopyranoside[24] (3.2 g, 7.1 mmol) in THF (30 mL) was added 1.0 M BH_3 in THF (28.4 mmol, 24 mL) under stirring at 0°C and inert atmosphere. 1.0 M Bu_2BOTf in DCM (7.8 mL, 7.8 mmol) was added and the reaction stirred for 1h. The reaction was quenched by addition of triethylamine (5 mL) and methanol (10 mL) and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 50% - EtOAc in *n*-heptane) of the residue afforded **2b** (2.3 g, 71 %) as a pale oil. **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.15.

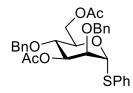
Phenyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-(2-methylnaphthyl)-1-thio-*α*-D-mannopyranoside (3a):



To a solution of **2a** (4.3 g, 8.6 mmol) in pyridine (40 ml), acetic anhydride (20 mL) was added. The solution was stirred for 16h at rt before it was concentrated *in vacuo*. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) of the residue afforded **3a** (4.8 g, 95%) as a colorless oil. **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.60; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 – 7.22 (m, 17H, Ar), 5.56 (d, *J* = 1.8 Hz, 1H, H-1), 5.23 (dd, *J* = 9.3, 3.3 Hz, 1H, H-3), 4.83 (d, *J* = 12.2 Hz, 1H, C*H*HNap), 4.72 (d, *J* = 11.2 Hz, 1H, CH*H*Nap), 4.67 (d, *J* = 12.2 Hz, 1H, C*H*HPh), 4.60 (d, *J* = 11.2 Hz, 1H, CH*H*Ph), 4.43 – 4.38 (m, 1H, H5), 4.35 – 4.31 (m, 2H, H-6a, H-6b), 4.18 (dd, *J* = 3.2, 2.0 Hz, 1H, H-2), 4.01 (t, *J* = 9.5 Hz, 1H, H-4), 2.04 (s, 3H, C*H*$_3$ Ac), 1.96 (s, 3H, C*H*$_3$ Ac): **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.74, 170.03, 137.72, 134.89, 133.70, 133.17,

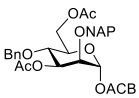
133.10, 131.89 -125.80, 85.36(C-1), 77.28, 77.08(C-2), 77.03, 76.77, 74.82, 73.83(C-3), 73.57(C-4), 72.60, 70.70(C-5), 63.35(C-6), 20.99, 20.88. **HRMS** (*m/z)*: $[M+Na]^+$ calcd for $C_{34}H_{34}O_7S$, 609.1923; found, 609.1912.

Phenyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-1-thio-*a*-D-mannopyranoside (3b)[23]



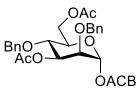
To a solution of **2b** (2.5 g, 5.5 mmol) in pyridine (40 ml) acetic anhydride (20 mL) was added. The solution was stirred for 16h at rt before it was concentrated *in vacuo*. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) of the residue afforded **3b** (2.7 g, 93%) as a colorless oil. **TLC:** (EtOAc/*n*-heptane, 25/75 v/v): R_f = 0.4; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H, C*H* Ar), 7.39 – 7.24 (m, 13H, C*H* Ar), 5.55 (d, *J* = 1.9 Hz, 1H, H-1), 5.21 (dd, *J* = 9.3, 3.3 Hz, 1H, H-3), 4.72 (d, *J* = 11.2 Hz, 1H, C*H*HPh), 4.69 (d, *J* = 12.2 Hz, 1H, C*H*HPh), 4.60 (d, *J* = 11.2 Hz, 1H, CH*H*Ph), 4.50 (d, *J* = 12.1 Hz, 1H, CH*H*Ph), 4.39 (ddd, *J* = 9.7, 4.5, 3.2 Hz, 1H, H-5), 4.34 – 4.31 (m, 2H, H-6a, H-6b), 4.16 – 4.09 (m, 1H, H-2), 3.99 (t, *J* = 9.5 Hz, 1H, H-4), 2.03 (s, 3H, CH_3 Ac), 1.99 (s, 3H, CH_3 Ac); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.75, 170.05, 137.72, 137.48, 133.76, 131.82, 129.05, 128.53, 128.46, 128.00, 127.97, 127.87, 127.80, 127.66, 85.15(C-1), 76.92(C-2), 74.84, 73.85(C-3), 73.50(C-4), 72.28, 70.63(C-5), 63.33(C-6), 21.03, 20.87; **HRMS** (*m/z)*: $[M+Na]^+$ calcd for $C_{30}H_{32}O_7S$, 559.1766; found, 559.1764; **[α]$^{25}_D$** = +4.25 (*c* = 0.4, $CHCl_3$).

2-(Allyloxycarbonyl)benzyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-(2-methylnaphthyl)-*a*-D-mannopyranoside (4a):



To a solution of **3a** (2.5 g, 4.2 mmol) in DCM (30 mL), allyl 2-(hydroxymethyl)benzoate (0.9 g, 4.6 mmol), *N*-iodosuccinimide (1.0 g, 4.6 mmol) and molecular sieves were added under inert atmosphere. The mixture was cooled (0°C) and stirred for 15 minutes before TfOH (0.037 ml, 0.42 mmol) was added. After the mixture was stirred for 30 minutes Et_3N (4mL) was added to neutralize the solution and the mixture was diluted with DCM (100 mL). After the mixture was washed with 2M $Na_2S_2O_3$ solution (2 x 30 mL) and brine (2 x 30 mL), the organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 20% - EtOAc in *n*-heptane) of the residue afforded **4a** (2.32 g, 82 %) as pale yellow oil. **TLC:** (EtOAc/*n*-heptane, 20/80 v/v): R_f = 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.25 (m, 16H, Ar), 5.99 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, C*H* allyl), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H, CH=C*H*H allyl), 5.33 (d, *J* = 3.4 Hz, 1H, H-3), 5.26 (dq, *J* = 10.4, 1.3 Hz, 1H, CH=CH*H* allyl), 5.10 (d, *J* = 14.4 Hz, 1H, C*H*H ACB ether), 5.01 (d, *J* = 1.9 Hz, 1H, H-1), 4.95 (d, *J* = 14.4 Hz, 1H, CH*H* ACB ether), 4.81 (d, *J* = 12.5 Hz, 1H, C*H*H Nap), 4.75 (m, 3H, CH_2 allyl, CH*H* Nap), 4.71 (d, *J* = 11.0 Hz, 1H, C*H*HPh), 4.59 (d, *J* = 11.1 Hz, 1H, CH*H*Ph), 4.34 – 4.30 (m, 2H, H-6a, H-6b), 4.04 – 3.99 (m, 2H, H-2, H-4), 3.94 (dd, *J* = 8.4, 4.6 Hz, 1H, H-5), 2.08 (s, 3H, CH_3 Ac), 1.97 (s, 3H, CH_3 Ac): **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.87, 170.11, 166.44, 139.46, 137.82, 135.20, 133.13, 132.45-125.77, 118.41, 97.47(C-1), 75.80(C-2), 74.81, 74.81, 73.94(C-3), 73.44(C-4), 73.11, 70.00(C-5), 67.43, 65.57, 63.32(C-6); **HRMS** (*m/z)*: $[M+Na]^+$ calcd for $C_{35}H32O_8S$, 691.2519; found, 691.2513; **[α]$^{25}_D$** +25.6 (*c* = 0.67, $CHCl_3$)

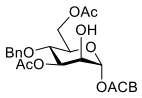
2-(Allyloxycarbonyl)benzyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-*a*-D-mannopyranoside (4b):



To a solution of **3b** (1.3 g, 2.36 mmol) in dry DCM (20 mL) allyl 2-(hydroxymethyl)benzoate (0.55 g, 2.8 mmol) and NIS (0.584 g, 2.60 mmol) were added under inert atmosphere. After addition of molecular sieves, TfOH (0.021 mL, 0.236 mmol) was added. The reaction stirred for 30 minutes before it was neutralized by addition of Et_3N (2 mL) and diluted with DCM (100 mL). The reaction mixture was washed with 2M $Na_2S_2O_3$ solution (2 x 30 mL) and brine (2 x 30 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 20% - EtOAc in *n*-heptane) of the residue afforded **4b** as pale yellow oil (1.2 g, 82%). **TLC:** (EtOAc/*n*-heptane, 20/80 v/v): R_f = 0.33; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.8, 1.2 Hz, 1H, -C*H* Ar), 7.94 (d, *J* = 7.7 Hz, 1H, -C*H* Ar), 7.69 (td, *J* = 7.5, 1.0 Hz, 1H, -C*H* Ar), 7.60 – 7.48 (m, 2H, -C*H* Ar), 7.37 – 7.21 (m, 9H, -C*H* Ar), 6.02 (ddt, *J* = 17.1, 10.6, 5.7 Hz, 1H, -C*H* allyl), 5.39 (dd, *J* = 17.2, 1.5 Hz, 1H, -CH=C*H*H allyl), 5.32 (dd, *J* = 9.3, 3.2 Hz, 1H, H-3), 5.28 (dd, *J* = 10.4, 1.3 Hz, 1H, -CH=CH*H* allyl), 5.11 (d, *J* = 14.3 Hz, 1H, -CH*H* CB), 4.99 (d, *J* = 1.8 Hz, 1H, H-1), 4.95 (d, *J* = 14.3 Hz, 1H, -C*H*H CB), 4.78 (dt, *J* = 5.7, 1.4 Hz, 2H, CH_2 allyl), 4.70 (d, *J* = 11.2 Hz, 1H, -C*H*HPh), 4.67 (d, *J* = 12.3 Hz, 1H, -C*H*HPh), 4.58 (d, *J* = 11.1 Hz, 1H, -CH*H*Ph), 4.56 (d, *J* = 12.2 Hz, 1H, -CH*H*Ph), 4.31 (d, *J* = 3.3 Hz, 2H, H-6a, H-6b), 4.01 – 3.95 (m, 2H, H-2, H-5), 3.92 (dt, *J* = 9.9, 3.4 Hz, 1H, H-4), 2.07 (s, 3H, acetyl), 2.00 (s, 3H, acetyl); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.87, 170.11, 166.45 , 146.52 , 139.52 , 137.82 , 134.00 , 132.51 , 132.12 , 130.57 , 129.50 – 126.88 (m), 125.83 , 122.07,

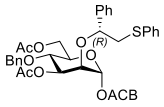
118.44, 97.42(C-1), 75.75(C-2), 74.81, 73.94(C-3), 73.37(C-4), 72.8, 69.99(C-5), 67.49, 65.59, 63.29(C-6), 21.10, 20.90; **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{35}H_{38}O_{10}$ 641.23548; found, 641.23627; **[α]$^{25}_D$** = +20.7 (*c* = 0.71, $CHCl_3$).

2-(Allyloxycarbonyl)benzyl 3,6-di-*O*-acetyl-4-*O*-benzyl-*a*-D-mannopyranoside (5)

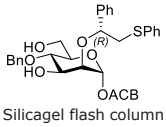


To a well stirred emulsion of **4a** (3.0 g, 4.5 mmol) in DCM (30 mL) and water (4 mL) DDQ (1.6 g, 7.2 mmol) was added. The resulting solution was protected from light and stirred at rt for 1.5 hrs. The mixture was diluted with DCM (150 mL) and washed (2 x 40 mL) with an aqueous mixture of ascorbic acid (1.5 %), citric acid (0.7%) and NaOH (0.9%) to reduce the remaining DDQ. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Silicagel flash column chromatography (40% → 60% - EtOAc in *n*-heptane) of the residue afforded **5** as a pale yellow oil (1.95 g, 82%). **TLC:** EtOAc/*n*-heptane, 50/50 v/v): R_f = 0.22; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93– 7.16 (m, 9H, C*H* Ar), *5*.95 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H ddt, *J* = 16.2, 10.6, 5.7 Hz, 1H, C*H* allyl), 5.33 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H, CH=C*H*H allyl), 5.29 (dd, *J* = 9.1, 3.2 Hz, 1H, CH=CH*H* allyl), 5.21 (dd, *J* = 10.4, 1.3 Hz, 1H, H-3), 5.06 (d, *J* = 14.1 Hz, 1H, C*H*H ACB ether), 4.89 (d, *J* = 14.6 Hz, 1H, CH*H* ACB ether), 4.88 (s, 1H, H-1), 4.72 (dt, *J* = 5.7, 1.4 Hz, 2H, CH_2 allylic ester), 4.58 (d, *J* = 11.2 Hz, 1H, , C*H*HPh), 4.50 (d, *J* = 11.2 Hz, 1H, , CH*H*Ph), 4.23 (t, *J* = 3.5 Hz, 2H, H-6), 4.09 (dd, *J* = 2.9, 2.0 Hz, 1H, H-2), 3.89 (ddd, *J* = 9.8, 3.9, 2.5 Hz, 1H, H-5), 3.88 – 3.80 (m, 1H, H-4), 2.01 (s, 3H, CH_3 acetyl), 2.00 (s, 3H, CH_3 acetyl); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.83 , 169.91, 166.50, 139.2 , 137.60, 132.55, 132.08, 130.62, 128.53, 128.01, 127.89, 127.81, 127.42, 118.51, 99.32(C-1), 74.83, 74.37(C-3), 72.92(C-4), 69.78(C-5), 69.50(C-2), 67.62, 65.65 , 63.07(C-6), 21.1, 20.89; **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{28}H_{32}O_{10}$, 551.1893; found, 551.1890; **[α]$^{25}_D$** = +67.2 (*c* = 0.45, $CHCl_3$).

2-(Allyloxycarbonyl)benzyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*a*-D-mannopyranoside (6): To a solution of **5** (1.6 g, 2.9 mmol) in DCM (20 mL), allyl 2-(hydroxymethyl)benzoate (1.6 g, 5.9 mmol,) was added under inert atmosphere. After the mixture was cooled to 0°C, molecular sieves were added and the mixture was stirred for 15 minutes. $BF_3.OEt_2$ (0.75 ml, 5.9 mmol) was added and the reaction was stirred until an optimum in auxiliary coupling was observed (t=35 min).The reaction was quenched by addition of triethylamine (6 ml) and methanol (10 mL). After filtration the filtrate was concentrated *in vacuo*. Silicagel flash column chromatography (0% → 20% - EtOAc in *n*-heptane) of the residue afforded **6** (1.3 g, 70% yield based on recovered **5**) as pale yellow oil. 0.30 g of **5** was reclaimed. **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.47; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.8, 1.2 Hz, 1H, C*H* Ar), 7.56 (d, *J* = 7.2 Hz, 1H, C*H* Ar), 7.49 (td, *J* = 7.6, 1.3 Hz, 1H, C*H* Ar), 7.41 – 7.21 (m, 20H, C*H* Ar), 7.19 – 7.14 (m, 1H, C*H* Ar), 6.01 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H, C*H* allyl), 5.39 (dq, *J* = 17.2, 1.5 Hz, 1H, -C*H*H allyl), 5.27 (dq, *J* = 10.4, 1.3 Hz, 1H, -CH*H* allyl), 5.22 (dd, *J* = 9.1, 3.3 Hz, 1H, H-3), 5.11 (d, *J* = 14.6 Hz, 1H, -OCH*H*- ACB), 5.10 (d, *J* = 1.6 Hz, 1H, H-1), 4.96 (d, *J* = 14.4 Hz, 1H, -OC*H*H- ACB), 4.76 (dd, *J* = 5.7, 1.3 Hz, 2H, -OCH_2- allyl), 4.62 (d, *J* = 11.1 Hz, 1H, C*H*HPh), 4.53 (d, *J* = 11.2 Hz, 1H, CH*H*Ph), 4.46 (dd, *J* = 8.4, 4.7 Hz, 1H, H-8), 4.35 (dd, *J* = 11.8, 2.0 Hz, 1H, H-6a), 4.25 (dd, *J* = 11.8, 4.7 Hz, 1H, H-6b), 3.96 – 3.85 (m, 2H, H-4, H-5), 3.83 (dd, *J* = 3.3, 1.9 Hz, 1H, H-2), 3.34 (dd, *J* = 13.6, 8.4 Hz, 1H, H-8a), 3.13 (dd, *J* = 13.6, 4.7 Hz, 1H, H-8b), 2.09 (s, 3H, CH_3 Ac), 1.81 (s, 3H, CH_3 Ac); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.90, 170.90, 169.84, 166.40, 140.43, 139.69, 137.85, 136.62, 132.48, 132.15, 130.53, 129.30, 128.93, 128.45, 127.79, 127.49, 127.18, 126.92, 126.07, 118.40, 97.02(C-1), 80.76(C-7), 75.27(C-2), 74.71, 73.40(C-4), 73.26(C-3), 70.20(C-5), 67.56, 65.56, 63.25(C-6), 41.96(C-8), 35.44, 20.96; **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{35}H_{32}O_8S$, 763.2553; found, 763.2547; **[α]$^{25}_D$** = +57.6 (*c* = 1.0, $CHCl_3$).



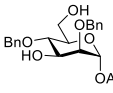
2-(Allyloxycarbonyl)benzyl 4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*a*-D-mannopyranoside (7a):



To a solution of **6** (1.6 g, 2.2 mmol) in allyl alcohol (20 mL) was added KO^{t}Bu (0.24 g, 2.2 mmol) under inert atmosphere. The reaction was stirred for 16 h before Dowex was added to neutralize the base. The reaction was diluted with DCM (100 mL) and filtrated. The filtrate was washed with brine (20 mL) and the organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo.* Silicagel flash column chromatography (40% → 80% - EtOAc in *n*-heptane) of the residue afforded **7a** (1.15 g, 81%) as a colorless oil. **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.49; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 – 7.94 (m, 1H, -C*H*

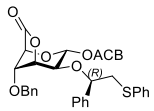
Ar), 7.49 – 7.43 (m, 2H, -C*H* Ar), 7.39 – 7.22 (m, 17H, -C*H* Ar), 7.20 – 7.13 (m, 1H, -C*H* Ar), 5.99 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H, -C*H*- allyl), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1H, -CH=C*H*H allyl), 5.27 (ddd, *J* = 10.5, 2.6, 1.3 Hz, 1H, -CH=CH*H* allyl), 5.11 (d, *J* = 1.4 Hz, 1H, H-1), 5.06 (d, *J* = 14.2 Hz, 1H, -OC*H*H ACB), 4.92 (d, *J* = 14.2 Hz, 1H, -OCH*H* ACB),), 4.87 (d, *J* = 11.0 Hz, 1H,-C*H*HPh), 4.76 – 4.72 (m, 2H, -OCH_2 allyl), 4.64 (d, *J* = 11.1 Hz, 1H, -CH*H*Ph), 4.58 (dd, *J* = 9.0, 4.1 Hz, 1H, -C*H* auxiliary), 3.98 (dt, *J* = 9.1, 4.6 Hz, 1H, H-3), 3.86 (dd, *J* = 11.7, 2.2 Hz, 1H, H-6a), 3.78 (t, *J* = 9.4 Hz, 2H, H-6b, H-5), 3.68 (dd, *J* = 3.5, 1.7 Hz, 1H, H-2), 3.67 – 3.61 (m, 1H, H-5), 3.37 (dd, *J* = 13.7, 9.0 Hz, 1H, -C*H*H auxiliary), 3.19 (dd, *J* = 13.7, 4.1 Hz, 1H, -CH*H* auxiliary), 2.27 (m, 1H -CH_2O*H*), 2.06 (d, *J* = 9.3 Hz, 1H, -C-$_3$HO*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.44, 139.81, 139.73, 138.46, 136.42, 132.46, 132.12, 130.60, 129.30, 129.03 (d, *J* = 5.4 Hz), 128.77, 128.46, 128.04, 128.02, 127.78, 127.58, 127.29, 126.86, 126.25, 118.47, 96.53(C-1), 79.96(C-7), 76.38(C-2), 76.24(C-4), 75.08, 71.92(C-5), 71.48(C-3), 67.62, 65.58, 62.18(C-6), 41.60(C-8); **HRMS** (*m/z*): $[M+Na]^+$ calcd for,$C_{38}H_{40}O_8S$, 679.2342; found, 679.2329; **[α]$^{25}_D$** = +45.6 (*c* = 1.0, $CHCl_3$).

2-(Allyloxycarbonyl)benzyl 2,4-di-*O*-benzyl-*α*-D-mannopyranoside (7b):

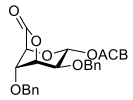


To a solution of **4b** (1.1 g, 1.78 mmol) in allyl alcohol (18 mL) KO^{t}Bu (0.2 g, 1.78 mmol) was added. The reaction was stirred under inert atmosphere for 16 h. Dowex was added to neutralize the base and the mixture was diluted with MeOH (20 mL), filtrated and concentrated *in vacuo*. DCM (100 mL) was added and the solution was washed with brine (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo.* Silicagel flash column chromatography (0% →30% - EtOAc in *n*-heptane) of the residue afforded **7b** (0.83 g, 87%) as colorless oil. **TLC:** (EtOAc/*n*-heptane, 20/70 v/v): R_f = 0.11; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.8, 1.0 Hz, 1H, -C*H* Ar), 7.55 – 7.49 (m, 2H, -C*H* Ar), 7.42 – 7.28 (m, 11H, -C*H* Ar), 6.02 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H, -RC*H*=CH_2 allyl), 5.40 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H, RCH=C*H*H allyl), 5.29 (dq, *J* = 10.5, 1.2 Hz, 1H, RCH=CH*H* allyl), 5.06 (d, *J* = 14.0 Hz, 1H, -CH*H* CB), 5.03 (d, *J* = 1.3 Hz, 1H, H-1), 4.94 (d, *J* = 14.1 Hz, 1H, -CH*H* CB), 4.91 (d, *J* = 11.1 Hz, 1H, -CH*H*Ph), 4.78 (dt, *J* = 5.7, 1.4 Hz, 2H, -CH_2 allyl), 4.73 (d, *J* = 11.8 Hz, 1H, -C*H*HPh), 4.67 (d, *J* = 11.1 Hz, 1H, C*H*HPh), 4.60 (d, *J* = 11.8 Hz, 1H, CH*H*Ph*)* 4.08 (td, *J* = 9.1, 3.7 Hz, 1H, H-3), 3.86 (dd, *J* = 5.2, 2.8 Hz, 1H, H-6$_a$), 3.85 – 3.81 (m, 1H, H-2), 3.78 (ddd, *J* = 11.8, 7.9, 4.1 Hz, 1H, H-6$_b$), 3.71 (d, *J* = 9.1 Hz, 1H, H-4), 3.69 – 3.64 (m, 1H, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 132.48, 132.07, 130.62, 128.62, 128.49, 128.11, 128.07, 127.88, 127.85, 127.73, 127.35, 118.50, 96.95(C-1), 78.34(C-2), 77.22, 76.49(C-4), 75.03, 73.02, 71.87(C-3), 71.63(C-5), 67.44, 65.62, 62.28(C-6); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{35}H32O_8S$, 557.2151; found, 557.2136; **[α]$^{25}_D$** = +36.4 (*c* = 0.58, $CHCl_3$).

2-(Allyloxycarbonyl)benzyl 4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl) benzyl-*α*-D-mannopyranosidurono-6,3-lactone (8a): To a solution of **7a** (0.52 g, 0.80 mmol) in 10% H_2O in DCM v/v (8 ml), BAIB (0.77 g, 2.4 mmol) was added under stirring. After addition of TEMPO (50 mg, 0.32 mmol) the reaction was stirred for 1h at rt. The mixture was quenched by addition of 10% $Na_2S_2O_3$ solution in H_2O w/w (5 mL) and was extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, dried (Na_2SO_4), filtrated and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 20% - EtOAc in *n*-heptane) of the residue afforded **8a** (0.31 g, 60 %) as a colorless oil. **TLC:** (EtOAc/*n*-heptane, 20/80 v/v): R_f = 0.33; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.8, 1.2 Hz, 1H, -C*H* Ar), 7.76 (d, *J* = 7.4 Hz, 1H, -C*H* Ar), 7.50 (td, *J* = 7.7, 1.3 Hz, 1H, -C*H* Ar), 7.42 – 7.24 (m, 10H, -C*H* Ar), 7.19 – 7.05 (m, 6H, -C*H* Ar), 7.01 (ddd, *J* = 7.2, 3.8, 1.2 Hz, 1H, -C*H* Ar), 6.03 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H, -C*H* allyl), 5.40 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H, -CH=C*H*H allyl), 5.38 (d, *J* = 14.5 Hz, 1H, -OCH*H* ACB), 5.28 (dd, *J* = 10.4, 1.3 Hz, 1H, -CH=CH*H* allyl), 5.08 (d, *J* = 14.5 Hz, 1H, -OC*H*H ACB), 4.98 (d, *J* = 6.7 Hz, 1H, H-1), 4.82 (dd, *J* = 7.6, 5.8 Hz, 1H, H-7), 4.79 (dt, *J* = 5.7, 1.4 Hz, 2H, -OCH_2- allyl), 4.43 (d, *J* = 12.1 Hz, 1H, C*H*HPh), 4.42 – 4.39 (m, 1H, H-3), 4.33 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.15 (dd, *J* = 2.8, 0.9 Hz, 1H, H-5), 3.89 (dd, *J* = 6.7, 1.4 Hz, 1H, H-2), 3.81 (dd, *J* = 5.8, 2.9 Hz, 1H, H-4), 3.38 (dd, *J* = 13.6, 7.6 Hz, 1H, H-8a), 3.08 (dd, *J* = 13.6, 5.8 Hz, 1H, H-8b); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.04(C-6), 166.33, 140.49, 140.04, 136.47, 136.31, 132.46, 132.22, 130.57, 128.82, 128.78, 128.64, 128.37, 127.90, 127.62, 127.61, 127.25, 127.04, 125.82, 118.53, 101.85(C-1), 82.19(C-7), 79.51(C-3), 74.85(C-4), 74.07(C-2), 71.56, 70.34(C-5), 69.84, 65.67, 40.87(C-8); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{38}H_{36}O_8S$, 675.2029; found, 675.2023; **[α]$^{25}_D$** = -7.4 (*c* = 0.76, $CHCl_3$).

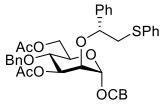


2-(Allyloxycarbonyl)benzyl 2,4-di-*O*-benzyl-*a*-D-mannopyranosidurono-6,3-lactone (8b): To a solution of **7b**



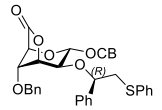
(0.36 g, 0.67 mmol) in 10% H_2O in DCM v/v (10 ml), BAIB was added (0.65 g, 2.0 mmol) was added under stirring. After addition of TEMPO (42 mg, 0.27 mmol) the reaction stirred for 1h at rt. The mixture was quenched with 10% $Na_2S_2O_3$ solution in H_2O w/w (10 mL). The mixture was extracted twice with ethyl acetate (20 mL). The organic layers were combined, dried (Na_2SO_4), filtrated and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 30% - EtOAc in *n*-heptane) of the residue afforded **8b** (0.28 g, 80%) as a colorless oil. **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.38; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.8, 1.3 Hz, 1H, -C*H* Ar), 7.73 (d, *J* = 7.7 Hz, 1H, -C*H* Ar), 7.49 (td, *J* = 7.6, 1.3 Hz, 1H, -C*H* Ar), 7.40 – 7.27 (m, 11H, -C*H* Ar), 6.01 (ddt, *J* = 16.2, 10.6, 5.7 Hz, 1H, -RC*H*=CH_2 allyl), 5.39 (dd, *J* = 17.2, 1.5 Hz, 1H, RCH=C*H*H), 5.37 (d, *J* = 14.4 Hz, 1H, -CH*H*- CB), 5.28 (dd, *J* = 10.4, 1.2 Hz, 1H, RCH=CH*H*), 5.14 (d, *J* = 14.4 Hz, 1H,-C*H*H- CB), 4.94 (d, *J* = 6.7 Hz, 1H, H-1), 4.76 (m, 3H, -CH*H*Ph; -CH_2 allyl), 4.68 (m, 2H, C*H*HPh, H-3), 4.61 (d, *J* = 11.9 Hz, 1H, -C*H*HPh), 4.52 (d, *J* = 11.9 Hz, 1H, -CH*H*Ph), 4.24 (dd, *J* = 2.8, 0.8 Hz, 1H, H-5), 4.00 (dd, *J* = 6.7, 1.4 Hz, 1H, H-2), 3.98 (dd, *J* = 5.8, 2.9 Hz, 1H, H-4); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 132.42, 132.11, 130.67, 128.75, 128.52, 128.45, 128.11, 127.91, 127.89, 127.24, 118.56, 101.62(C-1), 78.81(C-3), 75.15(C-2)?, 75.13(C-4?), 73.13, 71.99, 70.27, 69.70(C-5), 65.67; **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{31}H_{30}O_8$, 553.1838; found, 553.1835; **[α]$^{25}_D$** = +20.5 (*c* = 1.0, $CHCl_3$).

2-(Hydroxycarbonyl)benzyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*a*-D-mannopyranoside (9a): To a solution of **6** (0.20 g, 0.27 mmol) in DCM/AcOH (5/1, v/v) (5 mL) was added $Pd(PPh_3)_4$



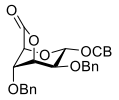
(94 mg, 0.081 mmol) and the mixture was purged a few times with argon. The reaction was stirred for 30 minutes and was concentrated *in vacuo*. Silicagel flash column chromatography (0% → 40% - EtOAc in a mixture of AcOH (1%) in *n*-heptane) of the residue afforded **9a** (0.17 g, 90%) as a pale yellow oil. **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.32; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.8, 1.1 Hz, 1H, C*H* Ar), 7.55 (d, *J* = 7.7 Hz, 1H, C*H* Ar), 7.47 (td, *J* = 7.7, 1.2 Hz, 1H, C*H* Ar), 7.32 – 7.04 (m, 16H, C*H* Ar), 5.17 (dd, *J* = 8.8, 3.3 Hz, 1H, H-3), 5.10 (d, *J* = 14.8 Hz, 1H, C*H*H CB), 5.05 (d, *J* = 1.7 Hz, 1H, H-1), 4.90 (d, *J* = 14.9 Hz, 1H, CH*H* CB), 4.55 (d, *J* = 11.2 Hz, 1H, C*H*HPh), 4.46 (d, *J* = 11.1 Hz, 1H, CH*H*Ph), 4.41 (dd, *J* = 8.5, 4.6 Hz, 1H, H-7), 4.30 (dd, *J* = 11.8, 1.5 Hz, 1H, H-6a), 4.18 (dd, *J* = 11.8, 4.6 Hz, 1H, H-6b), 3.90 – 3.81 (m, 2H, H-4, H-5), 3.79 (dd, *J* = 3.2, 1.9 Hz, 1H, H-2), 3.28 (dd, *J* = 13.6, 8.5 Hz, 1H, H-8a), 3.07 (dt, *J* = 13.6, 4.0 Hz, 1H, H-8b), 2.01 (d, *J* = 3.6 Hz, 3H, CH_3 Ac), 1.75 (s, 3H, CH_3 Ac); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.81, 171.01, 170.00, 137.80, 136.62, 133.50, 131.48, 129.28, 128.95, 128.47, 127.83, 126.94, 126.56, 126.08, 125.31, 97.13(C-1), 80.81(C-7), 75.24(C-2), 74.73, 73.43(C-3), 73.30(C-4), 70.29(C-5), 67.56, 63.28(C-6), 41.90(C-8), 20.98, 20.95; **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{39}H_{40}O_{10}S$, 723.2240; found, 723.2237; **[α]$^{25}_D$** = +39.0 (*c* = 0.13, $CHCl_3$).

2-(Hydroxycarbonyl)benzyl 4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*a*-D-mannopyranosidurono-6,3-lactone (9b): To a solution of **8a** (0.12 mg, 0.18 mmol) in DCM/AcOH (5/1, v/v) (2.5 mL) was added $Pd(PPh_3)_4$



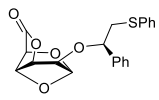
(61 mg, 0.05 mmol) and the mixture was purged a three times with argon. The reaction was stirred for 30 minutes and was concentrated *in vacuo*. Silicagel flash column chromatography (0% → 40% - EtOAc in a mixture of acetic acid (1%) in *n*-heptane) of the residue afforded **9b** (0.1 g, 93%) as a pale amorphous solid. **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.21; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.8, 1.5 Hz, 1H, C*H* Ar), 7.71 (d, *J* = 7.8 Hz, 1H, C*H* Ar), 7.47 (td, *J* = 7.6, 1.5 Hz, 1H, C*H* Ar), 7.37 – 6.77 (m, 16H, C*H* Ar), 5.32 (d, *J* = 14.7 Hz, 1H, C*H*H CB, 5.01 (d, *J* = 14.7 Hz, 1H, CH*H* CB), 4.94 (d, *J* = 6.6 Hz, 1H, H-1), 4.77 (dd, *J* = 7.7, 5.6 Hz, 1H, H-7), 4.40 – 4.33 (m, 2H, C*H*HPh, H-3), 4.27 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.11 (dd, *J* = 2.9, 1.1 Hz, 1H, H-5), 3.84 (dd, *J* = 6.7, 1.5 Hz, 1H, H-2), 3.75 (dd, *J* = 5.8, 2.9 Hz, 1H, H-4), 3.31 (dd, *J* = 13.6, 7.7 Hz, 1H, H-8a), 3.02 (dd, *J* = 13.6, 5.6 Hz, 1H, H-8b) ; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.14, 170.16(C-6), 140.90, 140.49, 136.28, 133.35, 131.57, 128.81, 128.74, 128.64, 128.37, 127.90, 127.59, 127.21, 127.14, 125.86, 101.86(C-1), 82.08(C-7), 79.53(C-3), 74.78(C-4), 74.01(C-2), 71.55, 70.29(C-5), 69.80, 40.83(C-8); **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{35}H_{32}O_8S$, 635.1716; found, 635.1703; **[α]$^{25}_D$** = -4.9 (*c* = 1.0, $CHCl_3$).

2-(Hydroxycarbonyl)benzyl 2,4-di-*O*-benzyl-*a*-D-mannopyranosidurono-6,3-lactone (9c)



To a solution of **8b** (0.12 g, 0.22 mmol) in 5:1 DCM/AcOH (6 mL) was added $Pd(PPh_3)_4$ (0.25 g, 0.22 mmol) and the mixture was purged three times with argon. The reaction was stirred for 10 minutes and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 30% - EtOAc in a mixture of acetic acid (0.5%) in *n*-heptane) of the residue afforded **9c** (90 mg, 85%) as yellow oil. **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.9, 1.3 Hz, 1H, -C*H* Ar), 7.77 (dd, *J* = 7.8, 0.7 Hz, 1H, -C*H* Ar), 7.73 – 7.65 (m, 1H, C*H* Ar), 7.53 (td, *J* = 7.6, 1.4 Hz, 1H, -C*H* Ar), 7.41 – 7.24 (m, 12H, -C*H* Ar), 5.39 (d, *J* = 14.8 Hz, 1H, C*H*H allyl), 5.16 (d, *J* = 14.8 Hz, 1H, CH*H* CB), 4.97 (d, *J* = 6.7 Hz, 1H, H-1), 4.77 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.70 (d, *J* = 11.7 Hz, 2H, CH*H*Ph), 4.70 – 4.67 (m, 1H, H-3), 4.63 (d, *J* = 11.9 Hz, 1H, CH*H*Ph), 4.52 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.27 (dd, *J* = 2.9, 1.1 Hz, 1H, H-5), 4.03 (dd, *J* = 6.7, 1.5 Hz, 1H, H-2), 4.00 (dd, *J* = 5.8, 2.9 Hz, 1H, H-4); **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 170.70(C-6), 170.07, 140.44, 137.76, 136.69, 133.19, 131.39, 128.62, 128.45, 128.38, 128.35, 128.06, 127.89, 127.85, 127.82, 127.33, 126.82, 101.74(C-1), 78.71(C-3), 75.25(C-2)?, 75.21(C-4)?, 73.06, 72.00, 70.28, 69.59(C-5); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{28}H_{26}O_8$, 513.1525; found, 513.1522; **$[\alpha]^{25}_D$** = +9.5 (*c* = 0.60, $CHCl_3$).

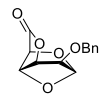
1,4-anhydro-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*a*-D-mannopyranosidurono-6,3-lactone (14b):



Isolated as a side-product from the reaction mixture from the synthesis of **17**; **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.48; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.02 (m, 10H, C*H* Ar), 5.56 (d, *J* = 1.5 Hz, 1H, H-1), 5.32 (dd, *J* = 4.8, 3.6 Hz, 1H, H-4), 4.46 (dd, *J* = 7.3, 5.8 Hz, 1H, H-7), 4.21 (dd, *J* = 7.0, 4.9 Hz, 1H, H-3), 3.99 (dd, *J* = 3.4, 0.8 Hz, 1H, H-5), 3.48 (dd, *J* = 7.0, 1.7 Hz, 1H, H-2), 3.37 (dd, *J* = 13.8, 7.4 Hz, 1H, H-8a), 3.12 (dd, *J* = 13.8, 5.8 Hz, 1H, H-8b); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.24(C-6), 139.25, 129.44, 129.02, 128.99, 128.94, 128.90, 128.79, 128.70, 128.60, 128.12, 127.23, 127.01, 126.21, 125.92, 100.05(C-1), 82.26(C-7), 82.07(C-4), 75.75(C-2), 71.65(C-3), 71.42(C-5), 40.98(C-8); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{18}O_5S$, 393.0773; found, 393.0769; **$[\alpha]^{25}_D$** = +21.7 (*c* = 0.46, $CHCl_3$).

1,4-anhydro-2-*O*-benzyl-*a*-D-mannopyranosidurono-6,3-lactone (14c):

To a solution of **9b** (45 mg, 0.092 mmol) in DCM (1.5 mL), 2,6-di-*t*-butyl-4-methylpyridine (47 mg, 0.23 mmol) was added. The mixture was dried with MS (4Å) and cooled to -20°C after which Tf_2O (19 µL, 0.11 mmol) was added. The reaction was stirred for 30 minutes and was then diluted with EtOAc (10 mL) and filtrated. The filtrate was washed with H_2O (5 mL) and brine (5 mL) after which the organic layer was dried (Na_2SO_4), filtrated and concentrated *in vacuo*. Silicagel flash column chromatography (10% → 40% - EtOAc in *n*-heptane) of the residue afforded **14c** (18 mg, 79 %). **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.43; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.48 – 7.28 (m, 7H, C*H* Ar), 5.66 (d, *J* = 1.9 Hz, 1H, H-1), 5.61 – 5.56 (t, *J* = 4.15 Hz, 1H, H-4), 4.78 – 4.70 (m, 2H, C*H*HPh, H-3), 4.54 (d, *J* = 11.4 Hz, 1H, CH*H*Ph), 4.11 – 4.09 (m, 1H, (H-5), 3.74 (dd, *J* = 6.5, 1.8 Hz, 1H, H-2); **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 171.54(C-6), 136.93, 128.50, 128.17, 128.06, 100.55(C-1), 82.29(C-4), 76.08(C-2), 72.21, 71.42(C-3), 71.29(C-5); **$[\alpha]^{25}_D$** = -2.0 (*c* = 0.49, $CHCl_3$).



General procedure A for mannosylation

Mannosyl donor (0.2 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (0.4 mmol) were dissolved in dry DCM (2 mL). MS (4Å) were added and the mixture was cooled to -40°C and stirred for 15 minutes. Tf_2O (0.2) mmol was added and the reaction was stirred for 15 minutes before the temperature was allowed to warm up to -20°C in 30 min. After the acceptor (0.1 mmol) was added, the reaction was left to stir at -20°C for 1 h before it was allowed to slowly warm to rt overnight. The mixture was diluted with ethyl acetate (10 mL) and the suspension was filtrated. The filtrate was washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Silicagel flash column chromatography was used to obtain the pure product.

General procedure B for mannosylation

Mannosyl donor (0.2 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (0.4 mmol) were dissolved in DCM (10 mL). MS (4Å) were added and the mixture was cooled to -78°C and stirred for 15 minutes. Tf_2O (0.2) mmol was added and the reaction was stirred for 15 minutes before the acceptor (0.1 mmol) was added. The reaction was left to stir at -78°C for 1 hr

before it was allowed to warm to room temperature overnight. The mixture was diluted with ethyl acetate (30 mL) and the suspension was filtrated. The filtrate was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Silicagel flash column chromatography was used to obtain the pure product.

General procedure C for the synthesis of mannuronic esters

Mannuronic acid lactone disaccharide (1 eq) was dissolved in anhydrous methanol (2 mL). Dowex-H^+ (0.1 eq) was added and the mixture was left to stir for 48 hrs after which the mixture was filtrated and concentrated *in vacuo*.

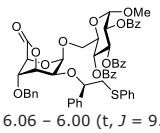
General procedure D for mannosylation

Mannosyl donor (0.2 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (0.4 mmol) were dissolved in dry DCM (2 mL). MS (4Å) were added and the mixture was cooled to -40°C and stirred for 15 minutes. Tf_2O (0.2) mmol was added and the reaction was stirred for 15 minutes before the temperature was allowed to warm up to -20°C in 30 min. After the acceptor (0.4 mmol) was added, the reaction was left to stir at -20°C for 1 h before it was allowed to slowly warm to rt overnight. The mixture was diluted with ethyl acetate (10 mL) and the suspension was filtrated. The filtrate was washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Silicagel flash column chromatography was used to obtain the pure product.

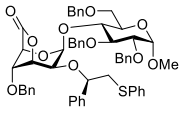
General Procedure E for Mannosylation

Mannosyl donor (2.0 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (4.0 mmol) were dissolved in DCM (10 mL). MS (4Å) were added and the mixture was cooled to -78°C and stirred for 15 minutes. Tf_2O (2.0) mmol was added and the reaction was stirred for 15 minutes before the acceptor (4.0 mmol) was added. The reaction was left to stir at -78°C for 1 hr before it was allowed to warm to room temperature overnight. The mixture was diluted with ethyl acetate (30 mL) and the suspension was filtrated. The filtrate was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Silicagel flash column chromatography was used to obtain the pure product.

Methyl 4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*β*-D-mannopyranosilurono-6,3-lactone-(1→6)-2,3,4-tri-*O*-benzoyl-*a*-D-glucopyranoside (16): According to the general procedure **A**. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **16** (59 mg, 61 %) as colorless oil. *Via* general procedure D. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **16** (50 mg, 52 %) as a colorless oil. **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.34; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.94 – 7.72 (m, 6H, C*H* Ar), 7.56 – 6.95 (m, 29H, C*H* Ar), 6.06 – 6.00 (t, *J* = 9.8 Hz, 1H, H-3), 5.55 – 5.47 (t, *J* = 9.8 Hz, 1H, H-4), 5.25 (dd, *J* = 7.1, 3.2 Hz, 1H, H-2), 5.15 (d, *J* = 3.6 Hz, 1H, H-1), 5.11 (d, *J* = 5.0 Hz, 1H, H-1′), 4.64 (dd, *J* = 7.2, 6.4 Hz, 1H, H-7′), 4.41 – 4.30 (m, 2H, C*H*HPh, H-3′), 4.25 – 4.14 (m, 2H, CH*H*Ph, H-5), 3.95 (dd, *J* = 5.0, 1.1 Hz, 1H, H-2′), 3.88 – 3.82 (m, 2H, H-5′, H-6a), 3.75 (dd, *J* = 3.1, 0.9 Hz, 1H, H-4′), 3.58 – 3.48 (m, 2H, H-6b, H-8a′), 3.44 (s, 3H, OCH_3), 3.19 (dd, *J* = 13.1, 7.4 Hz, 1H, H-8b′); **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 171.40(C-6′), 165.68, 165.52, 165.51, 139.76, 136.42, 136.33, 133.44, 133.29, 133.01, 129.83, 129.67, 129.51, 129.01, 128.89, 128.67, 128.51, 128.41, 128.23, 127.86, 127.47, 125.88, 98.84(C-1′), 96.78(C-1), 79.84(C-7′), 78.18(C-3′), 76.16(C-5′), 72.08(C-2), 71.75, 70.73(C-3), 69.86(C-2′), 69.60(C-4), 68.68(C-5), 67.85(C-4), 66.79(C-6), 55.47, 40.48(C-8′); **^{13}C-coupled HSQC** (101 MHz, $CDCl_3$): δ 98.84($J_{C1'-H1'}$ = 172 Hz, C-1′), 96.78(J_{C1-H1} = 172 Hz, C-1); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{55}H_{50}O_{14}S$, 989.2819; found, 989.2783; **[α]$^{25}_D$** = -27.0 (*c* = 0.20, $CHCl_3$).

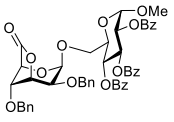


Methyl 4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*β*-D-mannopyranosilurono-6,3-lactone (1→4)-2,3,6-tri-*O*-benzyl-*a*-D-glucopyranoside(17): *Via* general procedure A. After work up of the reaction mixture the remaining oil was dissolved in pyridine (2 mL) and Ac_2O (1 mL) was added to acetylate any remaining acceptor. The mixture was stirred overnight after which it was concentrated *in vacuo*. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **17** as a colorless oil, as well as **14b** as an inseparable side product (53 mg, 56 %). **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.4; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.10 (m, 30H, C*H* Ar), 5.62 (d, *J* = 5.2 Hz, 1H, H-1′, H-1(**14b**)), 5.41 – 5.37 (m, H-4(**14b**)), 5.06 (d, *J* = 10.5 Hz, 1H, C*H*HPh), 4.93 (d, *J* = 10.5 Hz, 1H,

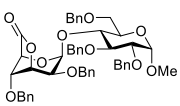


CH*H*Ph), 4.74 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.67 – 4.60 (m, 3H, 2 x C*H*HPh, H-1), 4.59 – 4.50 (m, 1H, C*H*HPh, H-7(**14b**)), 4.39 (d, *J* = 11.7 Hz, 1H, C*H*HPh), 4.33 – 4.26 (m, 2H, C*H*HPh, H-7′, H-3(**14b**)), 4.11 (dd, *J* = 5.8, 0.8 Hz, 1H, H-3′), 4.10 – 4.01(m, 3H, H-3, H-6a, H-2′, H-5(**14b**)) 3.93 – 3.82 (m, 3H, H-5′, H-6b, H-5), 3.79 (dd, *J* = 5.9, 3.0 Hz, 1H, H-4′), 3.74 – 3.66 (m, 1H, H-4), 3.59 – 3.52 (m, 1H, H-2, H-2(**14b**)), 3.47 – 3.36 (m, 3H, OCH_3, H-8a(**14b**)), 3.21 – 3.11 (m, 1H, H-8a′, H-8b(**14b**)), 3.06 (dd, *J* = 13.6, 5.6 Hz, 1H, H-8b′); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.73(C-6′, C-6(**14b**)), 140.63, 139.60, 138.83, 138.15, 136.39, 135.88, 129.65, 129.46, 129.00, 128.73, 128.61, 128.46, 128.36, 128.20, 128.12, 127.88, 127.82, 127.45, 127.26, 127.21, 127.02, 126.79, 126.34, 100.06(C-1(**14b**)), 99.64(C-1′), 97.44(C-1), 82.28(C-7(**14b**)), 82.26(C-7′), 82.07(C-4(**14b**)), 81.09(C-2), 80.06(C-3), 79.15(C-4), 77.20(C-3′), 76.22(C-4′), 75.77(C-2(**14b**)), 74.63(C-2′), 73.94, 73.29, 73.08, 71.65(C-3(**14b**)), 71.52, 71.42(C-5(**14b**)), 70.06(C-6), 69.60(C-5), 68.02(C-5′), 55.18, 41.49(C-8′), 41.00(C-8(**14b**)); **^{13}C-coupled HSQC** (101 MHz, $CDCl_3$): δ 99.64($J_{C1'\text{-}H1'}$ = 176 Hz, C-1′), 97.44($J_{C1\text{-}H1}$ = 168 Hz, C-1); **HRMS** (*m/z)*: $[M+Na]^+$ calcd for $C_{55}H_{56}O_{11}S$, 947.3441; found, 947.3440; **[α]$^{25}_D$** = -17.7 (*c* = 0.26, $CHCl_3$).

Methyl 2,4-di-*O*-benzyl-*β*-D-mannopyranosilurono-6,3-lactone-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside(18): *Via* general procedure **B**. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **18** (75 mg, 87 %) as an inseparable mixture with **14c**. *Via* general procedure E. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **18** (60 mg, 70%) as an inseparable mixture with **14c**. **TLC:** (EtOAc/*n*-heptane, 30/70, v/v): R_f = 0.45; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 – 7.90 (m, 4H, C*H* Ar), 7.82 (dt, *J* = 8.4, 1.5 Hz, 2H, C*H* Ar), 7.58 – 7.45 (m, 2H), 7.45 – 7.19 (m, 27H, C*H* Ar), 6.22 – 6.04 (t, *J* = 9.8 Hz, 1H, H-3), 5.61 (d, *J* = 2.0 Hz, 1H, H-1(**14c**)), 5.51 (dd, *J* = 4.6, 3.6 Hz, 1H, H-4(**14c**)), 5.39 (dd, *J* = 10.3, 9.5 Hz, 1H, H-4), 5.32 (d, *J* = 5.0 Hz, 1H, H-1′), 5.23 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2), 5.17 (d, *J* = 3.6 Hz, 1H, H-1), 4.77 – 4.73 (m, 2H, 2 x C*H*HPh), 4.71 (dd, *J* = 5.9, 0.9 Hz, 1H, H-3′), 4.67 (ddt, *J* = 6.6, 5.0, 0.8 Hz, 1H, H-3(**14c**)), 4.64 (d, *J* = 11.7 Hz, 1H, C*H*HPh), 4.59 (d, *J* = 11.6 Hz, CH*H*Ph), 4.50 (dd, *J* = 11.6, 3.7 Hz, 2H, 2 x CH*H*Ph), 4.30 (ddd, *J* = 10.0, 8.1, 1.7 Hz, 1H, H-5), 4.18 (dd, *J* = 5.0, 1.2 Hz, 1H, H-2′), 4.09 (dd, *J* = 3.5, 0.9 Hz, 1H, H-5(**14c**)), 4.04 (dd, *J* = 5.8, 3.1 Hz, 1H, H-4′), 3.94 – 3.89 (m, 2H, H-6a, H-5′), 3.69 – 3.64 (m, 1H, H-6b, H-2 (**14c**)), 3.34 (s, 3H, CH_3 OMe); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.54(C-6′), 165.85, 165.67, 137.43, 136.57, 136.31, 133.42, 133.31, 133.00, 130.00, 129.94, 129.65, 129.30, 129.11, 128.86, 128.76, 128.62, 128.56, 128.51, 128.41, 128.40, 128.33, 128.23, 128.17, 128.05, 128.01, 127.91, 100.55(C-1(**14c**)), 99.19(C-1′), 96.53(C-1), 82.20(C-4′), 77.74(C-3′), 76.18(C-4′), 75.80(C-2(**14c**)), 72.29, 72.21(C-2), 72.11, 71.32(C-3(**14c**)), 71.28, 71.25(C-5(**14c**)), 70.75(C-2′), 70.57(C-3), 69.77(C-4), 68.82(C-5), 67.56(C-5′), 67.07(C-6), 55.41; **^{13}C-coupled HSQC** (126 MHz, $CDCl_3$): δ 100.55($J_{C1'\text{-}H1'}$ = 175 Hz, C-1′), 99.19($J_{C1\text{-}H1}$ = 175 Hz, C-1); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{48}H_{44}O_{14}$, 867.2629; found, 867.2633; **[α]$^{25}_D$** = -12.8 (*c* = 0.37, $CHCl_3$).

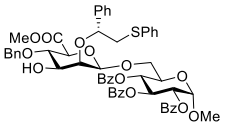


Methyl 2,4-di-*O*-benzyl-*β*-D-mannopyranosilurono-6,3-lactone-(1→4)-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranoside(19): According to the mannosylation general procedure **B**. After work up of the reaction mixture. The remaining oil was dissolved in pyridine (2 mL) and Ac_2O (1mL) was added as to acetylate any remaining acceptor. The mixture was stirred overnight after which it was concentrated *in vacuo*. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **19** (30 mg, 37 %) as colorless oil with **14c** (25 mg, 50 %) as major sideproduct. **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.32; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.18 (m, 25H), 5.47 (d, *J* = 5.3 Hz, 1H, H-1′), 5.08 (d, *J* = 10.8 Hz, 1H, C*H*HPh), 4.97 (d, *J* = 10.7 Hz, 1H, CH*H*Ph), 4.71 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.63 (dd, *J* = 5.9, 0.8 Hz, 1H, H-3′), 4.60 (d, *J* = 12.1 Hz, 1H, CH*H*Ph), 4.59 (d, *J* = 4.6 Hz, 1H, H-1), 4.57 (d, *J* = 11.8 Hz, 1H, C*H*HPh), 4.46 – 4.39 (m, 4H, 2 x C*H*HPh, 2 x CH*H*Ph), 4.29 (d, *J* = 12.2 Hz, 1H, CH*H*Ph), 4.06 (dd, *J* = 5.2, 0.9 Hz, 1H, H-2′), 4.02 – 3.98 (m, 2H, H-3, H-4′), 3.87 (dd, *J* = 10.8, 4.0 Hz, 1H, H-6a), 3.82 (dd, *J* = 2.9, 1.1 Hz, 1H, H-5′), 3.77 (ddd, *J* = 9.7, 3.8, 1.7 Hz, 1H, H-5), 3.73 – 3.68 (m, 1H, H-4), 3.68 – 3.62 (m, 1H, H-6b), 3.54 (dd, *J* = 9.4, 3.5 Hz, 1H, H-2), 3.34 (s, 3H, CH_3 OMe); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.62(C-6′), 139.77, 138.72, 138.13, 137.24, 136.45, 128.69, 128.53, 128.47, 128.44, 128.19, 128.15, 128.12, 128.05, 127.99, 127.92, 127.86, 127.72, 127.42, 127.26, 127.09, 100.36(C-1′), 97.56(C-1), 81.21(C-2), 79.68(C-4), 79.52(C-3), 76.38(C-3′), 76.34(C-4′), 74.41, 73.11, 73.08, 72.25(C-2′), 71.81, 71.62, 69.46(C-5), 68.90(C-6), 67.77(C-5′), 55.15; **^{13}C-coupled HSQC** (101 MHz, $CDCl_3$): δ

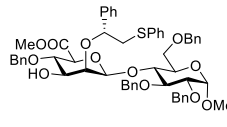


100.36($J_{C1'-H1'}$ = 172 Hz, C-1'), 97.56(J_{C1-H1} = 168 Hz, C-1); **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{48}H_{50}O_{11}$, 825.3251; found, 825.3231.

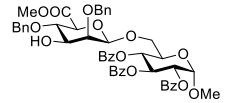
Methyl 4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*β*-D-mannopyranosyl methyluronate (1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (20): **16** (60 mg, 0.062 mmol) *via* general protocol **C** afforded **20** (56 mg, 90%) as a white amorphous solid. **TLC:** (EtOAc/*n*-heptane, 30/70 v/v): R_f = 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 7.90 (m, 5H, C*H* Ar), 7.88 – 7.81 (m, 2H, C*H* Ar), 7.58 – 7.18 (m, 32H, C*H* Ar), 7.16 – 7.08 (m, 1H, C*H* Ar), 6.20 – 6.11 (t, *J* = 9.8 Hz, 1H, H-3), 5.55 – 5.43 (dd, *J* = 9.8, 10.1 Hz, 1H, H-4), 5.36 – 5.25 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2), 5.17 (d, *J* = 3.6 Hz, 1H, H-1), 5.10 (dd, *J* = 8.0, 5.5 Hz, 1H, H-7'), 4.73 (d, *J* = 11.1 Hz, 1H, C*H*HPh), 4.58 – 4.49 (m, 2H, CH*H*Ph, H-1'), 4.21 (ddd, *J* = 10.1, 6.5, 1.9 Hz, 1H, H-5), 4.16 (dd, *J* = 11.4, 1.9 Hz, 1H, H-6a), 3.91 – 3.83 (m, 2H`, H-2', H-4'), 3.79 (d, *J* = 8.4 Hz, 1H, H-5'), 3.71 (s, 3H, CH_3, methyl ester), 3.70 – 3.54 (m, 2H, H-6b, H-8a'), 3.53 – 3.41 (s, 3H, CH_3, OMe), 3.38 – 3.29 (m, 1H, H-8b'), 2.41 (d, *J* = 9.7 Hz, 1H, 3-O*H'*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.04(C-6'), 165.82, 165.79, 165.78, 165.48, 133.54, 133.37, 133.12, 129.95, 129.89, 129.67, 129.23, 129.10, 128.86, 128.82, 128.79, 128.67, 128.50, 128.43, 128.35, 128.29, 127.90, 127.75, 127.63, 125.81, 116.21, 102.54(C-1'), 96.90(C-1), 81.69(C-7'), 77.70(C-4'), 74.54, 74.45(C-2'), 74.39(C-5'), 72.63(C-3'), 72.08(C-2), 70.44, 69.48(C-4), 69.11(C-6), 68.87(C-5) 55.64, 52.36, 40.17(C-8'); **^{13}C-coupled HSQC** (101 MHz, $CDCl_3$): δ 102.54($J_{C1'-H1'}$ = 156 Hz, C-1'), 96.90(J_{C1-H1} = 176 Hz, C-1); **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{56}H_{54}O_{15}S$, 1021.3081; found, 1021.3048; **[α]$^{25}_D$** = -10.0 (*c* = 0.20, $CHCl_3$).



Methyl 4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*β*-D-mannopyranosyl methyluronate (1→4)-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranoside (21): 17 (33 mg, 0.036 mmol) *via* general procedure **C** afforded **21** (31 mg, 91%) as pale yellow oil. **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.5; **^{1}H NMR**: (500 MHz, $CDCl_3$) δ 7.46 – 7.13 (m, 33H, C*H* Ar), 5.64 (d, *J* = 1.7 Hz, H-1(**14c**)), 5.40 (dd, *J* = 4.8, 3.5 Hz, H-4(**14c**)), 5.17 (d, *J* = 10.7 Hz, 1H, C*H*HPh), 5.01 (dd, *J* = 7.6, 5.8 Hz, 1H, H-7'), 4.78 (d, *J* = 12.1 Hz, 1H, C*H*HPh), 4.75 – 4.66 (m , 3H, C*H*HPh, CH*H*Ph, H-1), 4.63 – 4.56 (m, 1H), 4.56 – 4.47 (m, 1H, H-7(**14c**) CH*H*Ph), 4.41 (s, 1H, H-1'), 4.35 – 4.26 (m, 1H, CH*H*Ph, H-3(**14c**)), 4.08 – 4.06 (m, H-5(**14c**)), 3.93 – 3.81 (m, 2H, H-3, H-4), 3.75 (t, *J* = 9.1 Hz, 1H, H-4'), 3.66 – 3.58 (m, 2H, H-5, H-5'), 3.57 (s, 3H, CH_3 methyl ester), 3.56 – 3.48 (m, 2H, H-6a, H-2), 3.47 – 3.35 (m, 5H, H-2', H-6b, OCH_3), 3.23 – 3.15 (m, 1H, H-3'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.86(C-6'), 139.45, 139.32, 138.25, 137.28, 136.53, 129.17, 129.04, 128.96, 128.86, 128.70, 128.64, 128.56, 128.34, 128.28, 128.12, 128.06, 128.03, 127.90, 127.81, 127.78, 127.63, 127.12, 125.87, 101.94(C-1'), 98.36(C-1), 81.87(C-7'), 80.41(C-3), 79.09(C-2), 78.86(C-4), 77.56(C-4'), 75.63, 75.14(C-2'), 74.70(C-5'), 74.66, 73.56, 73.07(C-3'), 69.61(C-5), 68.35(C-6), 55.41, 52.16, 40.34(C-8'); **^{13}C-coupled HSQC** (126 MHz, $CDCl_3$): δ 101.94($J_{C1'-H1'}$ = 155 Hz, C-1'), 98.36(J_{C1-H1} = 170 Hz, C-1); **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{56}H_{54}O_{15}S$, 1021.3081; found, 1021.3048; **[α]$^{25}_D$** = -7.8 (*c* = 0.57, $CHCl_3$).



Methyl 2,4-di-*O*-benzyl-*β*-D-mannopyranosyl methyluronate-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (22): 18 (70 mg, 0.083 mmol) *via* general protocol **C** afforded **22** (65 mg, 89%) as colorless oil. **TLC:** (EtOAc/*n*-heptane, 50/50 v/v): R_f = 0.59; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 3H, C*H* Ar), 7.87 – 7.83 (m, 2H, C*H* Ar), 7.55 – 7.49 (m, 2H, C*H* Ar), 7.45 – 7.25 (m, 23H, C*H* Ar), 6.15 (tt, *J* = 9.5, 1.8 Hz, 1H, H-3), 5.61 (d, *J* = 1.9 Hz, H-1(**14c**)), 5.52 – 5.47 (m, 1H, H-4, H-4(**14c**)), 5.26 – 5.19 (m, 2H, H-1, H-2), 5.07 (d, *J* = 11.8 Hz, 1H, C*H*HPh), 4.87 – 4.56 (m, 6H, 4 x C*H*HPh, H-1', H-3(**14c**)), 4.50 (d, *J* = 11.6 Hz, 1H, C*H*HPh), 4.31 – 4.26 (m, 1H, H-5), 4.19 (dd, *J* = 11.1, 1.8 Hz, 1H, H-6a), 4.10 (dd, *J* = 3.5, 0.8 Hz, 1H, H-5(**14c**)), 3.97 – 3.86 (m, 3H, H-4', H-2(**14c**)), 3.83 (d, *J* = 8.4 Hz, 1H, H-5'), 3.74 (td, *J* = 9.0, 8.5, 3.6 Hz, 1H, H-3'), 3.71 – 3.63 (m, 5H, OCH_3, H-6b, H-2'), 3.41(s, 3H, CH_3 methyl ester), 2.60 (d, *J* = 9.7 Hz, 1H, 3-O*H'*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.92(C-6'), 165.85, 165.77, 165.52, 138.10, 138.04, 133.74, 133.52, 133.39, 133.17, 133.12, 129.95, 129.90, 129.66, 129.22, 129.06, 128.83, 128.63, 128.48, 128.44, 128.38, 128.29, 128.27, 128.06, 127.97, 127.80, 102.33(C-1'), 96.83(C-1), 82.19(C-4(**14c**)), 77.67(C-4), 76.30(C-2), 75.84(C-2(**14c**)), 74.58, 74.56, 74.28(C-5'), 72.53(C-3'), 72.13(C-2), 71.31(C-3(**14c**)), 71.23(C-5(**14c**)), 70.42(C-3), 69.46(C-4), 69.01(C-6), 68.87(C-5), 55.44, 52.31; **^{13}C-coupled**



HSQC (101 MHz, $CDCl_3$): δ 102.33($J_{C1'\text{-}H1'}$ = 160 Hz, C-1'), 96.83($J_{C1\text{-}H1}$ = 172 Hz, C-1); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{49}H_{48}O_{15}$, 899.2891; found, 899.2879; $[\alpha]^{25}_D$ = -20.0 (*c* = 0.14, $CHCl_3$).

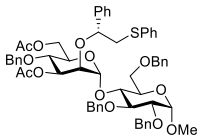
Methyl 2,4-di-*O*-benzyl-*β*-D-mannopyranosyl methyluronate (1→4)-2,3,6-tri-*O*-benzyl-*a*-D-glucopyranoside (23): 19 (30 mg, 0.037 mmol) *via* general protocol **C**. Silicagel flash column chromatography of the crude mixture (0% → 40% - EtOAc in *n*-heptane) afforded **23** as an amorphous white solid (25 mg, 80%)**. TLC:** (EtOAc/*n*-heptane, 35/65 v/v): R_f = 0.32; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.20 (m, 25H), 5.11 (d, *J* = 10.9 Hz, 1H, C*H*HPh), 4.94 (d, *J* = 11.7 Hz, 1H, CH*H*Ph), 4.78 (d, *J* = 11.4 Hz, 1H, C*H*HPh), 4.72 (d, *J* = 10.2 Hz, 1H, CH*H*Ph), 4.67 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.60 – 4.56 (m, 3H, C*H*HPh, CH*H*Ph, H-1), 4.55 – 4.49 (m, 2H, C*H*HPh, H-1'), 4.38 (d, *J* = 12.1 Hz, 1H, CH*H*Ph), 3.96 – 3.78 (m, 3H, H-3, H-4, H-4'), 3.72 – 3.61 (m, 2H, H-5, H-5'), 3.60 (d, *J* = 2.5 Hz, 2H, H-6a, H-6b), 3.56 (s, 3H, CH_3 methyl ester), 3.55 – 3.46 (m, 2H, H-2', H-2), 3.38 (bs, 4H, CH_3 OMe, H-3'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.86(C-6'), 139.41, 138.29, 138.23, 138.10, 137.45, 128.67, 128.48, 128.37, 128.35, 128.17, 128.13, 128.11, 128.04, 127.94, 127.89, 127.80, 127.73, 127.11, 101.71(C-1'), 98.36(C-1), 80.33(C-3), 79.14(C-2), 78.21(C-4), 77.78(C-4'), 77.76(C-2'), 75.39, 75.02, 74.73, 74.66(C-5'), 73.69, 73.58, 73.28(C-3'), 69.59(C-5), 68.39(C-6), 55.39, 52.20; **^{13}C-coupled HSQC** (101 MHz, $CDCl_3$): δ 101.71($J_{C1'\text{-}H1'}$ = 156 Hz, C-1'), 98.36($J_{C1\text{-}H1}$ = 168 Hz, C-1); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{49}H_{54}O_{12}$, 857.3513; found, 857.3524; $[\alpha]^{25}_D$ = -6.1 (*c* = 0.38, $CHCl_3$).

Methyl 4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*β*-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-*a*-D-glucopyranoside (24): To a cooled (0°C) solution of **16** (20 mg, 0.021 mmol) in THF (2 mL) a 1M solution of K-selectride in THF (0.043 mL) was added. The mixture was left to stirr for 5 min after which it was quenched with water (1 mL). The solution was diluted with ethyl acetate (10 mL) and washed with water (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Silicagel flash column chromatography of the residue (0% → 50% - EtOAc in *n*-heptane) afforded **24** as a white solid (18 mg, 90 %); **TLC:** (EtOAc/DCM), 30/70 v/v): R_f = 0.3; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.93 – 7.71 (m, 6H, C*H* Ar), 7.52 – 6.89 (m, 24H), 6.02 (t, *J* = 9.9 Hz, 1H, H-3), 5.50 (t, *J* = 9.9 Hz, 1H, H-4), 5.27 – 5.20 (m, 1H, H-2), 5.14 (t, *J* = 6.8 Hz, 1H, H-7'), 5.11 (d, *J* = 3.6 Hz, 1H, H-1), 4.74 (d, *J* = 11.1 Hz, 1H, C*H*HPh), 4.50 (d, *J* = 11.1 Hz, 1H, CH*H*Ph), 4.37 (s, 1H, H-1'), 4.14 (ddd, *J* = 10.1, 5.4, 1.8 Hz, 1H, H-5), 4.04 – 3.96 (m, 1H, H-6a), 3.75 (dd, *J* = 11.8, 2.7 Hz, 1H, H-6a'), 3.71 (d, *J* = 3.3 Hz, H-2'), 3.65 (dd, *J* = 11.8, 4.6 Hz, 1H, H-6b'), 3.58 (dd, *J* = 11.5, 5.4 Hz, 1H, H-6b), 3.52 – 3.46 (m, 2H, H-4', H-8a'), 3.46 – 3.41 (m, 1H, H-3'), 3.36 (s, 3H, CH_3 OMe), 3.20 (dd, *J* = 13.0, 6.9 Hz, 1H, H-8b'), 3.14 (ddd, *J* = 9.0, 4.5, 2.8 Hz, 1H, H-5'), 2.06 (d, *J* = 9.3 Hz, 1H, 3-O*H*); **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 165.68, 165.55, 165.25, 140.17, 138.66, 136.86, 133.51, 133.36, 133.14, 129.70, 129.68, 129.51, 129.29, 129.19, 129.01, 128.85, 128.81, 128.72, 128.50, 128.44, 128.28, 128.27, 127.87, 127.60, 127.58, 125.73, 102.48(C-1'), 97.01(C-1), 81.15(C-7'), 76.32(C-4'), 75.64(C-5'), 75.48(C-2'), 74.64, 73.81(C-3'), 72.07(C-2), 70.53(C-3), 69.22(C-4), 68.90(C-5), 68.54(C-6), 62.15(C-6'), 55.55, 40.40(C-8'); **^{13}C-coupled HSQC** (126 MHz, CD_2Cl_2): δ 102.48($J_{C1'\text{-}H1'}$ = 155 Hz, C-1'), 97.01($J_{C1\text{-}H1}$ = 175 Hz, C-1); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{55}H_{54}O_{14}S$, 993.3132; found, 993.3169. $[\alpha]^{25}_D$ = -9.0 (*c* = 0.85, $CHCl_3$).

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*a*-D-mannopyranosyl-(1→6)- 2,3,4-tri-*O*-benzoyl-*a*-D-glucopyranoside (25): *Via* general procedure A. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **25** (87 mg, 82 %) as a colorless oil. **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.4; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 – 7.81 (m, 6H), 7.54 – 7.09 (m, 24H), 6.13 (t, *J* = 9.8 Hz, 1H, H-3), 5.53 – 5.46 (m, 1H, H-4), 5.23 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2), 5.19 (d, *J* = 3.7 Hz, 1H, H-1), 5.15 (dd, *J* = 8.8, 3.1 Hz, 1H, H-3'), 4.93 (d, *J* = 1.8 Hz, 1H, H-1'), 4.61 (d, *J* = 11.3 Hz, 1H, C*H*HPh), 4.51 (d, *J* = 11.3 Hz, 1H, CH*H*Ph), 4.43 (dd, *J* = 8.5, 4.6 Hz, 1H, H-7'), 4.29 (dd, *J* = 11.8, 1.5 Hz, 1H, H-6a'), 4.22 (ddd, *J* = 13.0, 5.7, 2.7 Hz, 1H, H-5), 4.15 – 4.08 (m, 1H, H-6b'), 3.92 – 3.82 (m, 1H, H-4', H-5', H-6a), 3.71 (dd, *J* = 3.2, 1.9 Hz, 1H, H-2'), 3.56 (dd, *J* = 10.8, 2.4 Hz, 1H, H-6b), 3.43 (s, 3H, CH_3 OMe), 3.31 (dd, *J* = 13.6, 8.5 Hz, 1H, H-8a), 3.11 (dd, *J* = 13.6, 4.6 Hz, 1H, H-8b), 2.04 (s, 3H, CH_3 Ac), 1.78 (s, 3H, CH_3 Ac); **^{13}C NMR** (126 MHz, $CDCl_3$) δ

170.85, 169.70, 165.79, 165.77, 165.22, 140.44, 137.96, 136.66, 133.35, 133.31, 133.05, 129.94, 129.90, 129.70, 129.17, 128.93, 128.46, 128.43, 128.41, 128.39, 128.33, 128.26, 127.76, 126.89, 126.01, 97.16(C-1'), 96.72(C-1), 80.80(C-7'), 75.18(C-2'), 74.47, 73.10(C-4'), 73.00(C-3'), 72.15(C-2), 70.47(C-3), 69.97(C-5'), 69.60(C-4), 68.30(C-5), 66.16(C-6), 63.22(C-6'), 55.53, 41.89(C-8'), 20.93; **^{13}C-coupled HSQC** (126 MHz, $CDCl_3$): δ 97.16($J_{C1'\text{-}H1'}$ = 170 Hz, C-1'), 96.72($J_{C1\text{-}H1'}$ = 170 Hz, C-1); **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{59}H_{58}O_{16}S$, 1077.3343; found, 1077.3378; **[α]$^{25}_D$** = +28.9 (*c* = 0.85, $CHCl_3$).

Methyl 3,6-di-*O*-acetyl-4-*O*-benzyl-2-*O*-*(R)*-(phenylthiomethyl)benzyl-*α*-D-mannopyranosyl-(1→4)- 2,3,6-tri-*O*-benzyl-*α*-D-glucopyranoside (26): *Via* general procedure **A**. Silicagel flash column chromatography (0% → 40% - EtOAc in *n*-heptane) afforded **26** (72 mg, 71 %) as colorless oil. **TLC:** (EtOAc/toluene, 15/85, v/v): R_f = 0.56; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.13 (m, 28H, C*H* Ar), 6.92 (dd, *J* = 7.9, 1.3 Hz, 2H, C*H* Ar), 5.42 (d, *J* = 2.2 Hz, 1H, H-1'), 5.10 (dd, *J* = 8.9, 3.0 Hz, 1H, H-3'), 5.03 (d, *J* = 12.3 Hz, 1H, C*H*HPh), 4.75 (d, *J* = 12.3 Hz, 1H, CH*H*Ph), 4.66 – 4.57 (m, 3H, 2x C*H*HPh, H-1), 4.51 (dd, *J* = 14.4, 11.7 Hz, 2H, 2x CH*H*Ph), 4.23 (d, *J* = 11.5 Hz, 1H, H-6a'), 4.16 – 4.10 (m, 1H, H-7'), 4.05 (dd, *J* = 11.5, 4.1 Hz, 1H, H-6b'), 3.94 – 3.86 (m, 1H, H-3), 3.82 (m, 2H, H-4', H-5'), 3.79 – 3.71 (m, 4H, H-4, H-5, H-6a, H-6b), 3.70 – 3.63 (m, 1H, H-2'), 3.51 (dd, *J* = 9.6, 3.5 Hz, 1H, H-2), 3.38 (s, 3H, CH_3 OMe), 3.13 (dd, *J* = 13.3, 8.5 Hz, 1H, H-8a'), 2.89 (dd, *J* = 13.3, 4.6 Hz, 1H, H-8b'), 1.99 (s, 3H, CH_3 Ac), 1.70 (s, 3H, CH_3 Ac); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.78, 169.81, 140.51, 139.23, 138.09, 137.88, 137.28, 128.97, 128.82, 128.42, 128.40, 128.35, 128.28, 128.20, 128.14, 127.89, 127.82, 127.77, 127.65, 127.56, 126.64, 126.38, 125.78, 99.64(C-1'), 97.76(C-1), 81.16(C-3), 80.97(C-7), 79.84(C-2), 77.24(C-4), 76.29(C-2), 74.56, 74.33, 73.33(C-4'), 73.25, 73.15, 72.76(C-3'), 70.85(C-5'), 69.69(C-5), 69.10(C-6), 63.48(C-6'), 55.27, 41.90(C-8'), 20.93, 20.82; **^{13}C-coupled HSQC** (126 MHz, $CDCl_3$): δ 99.64($J_{C1'\text{-}H1'}$ = 175 Hz, C-1'), 97.76($J_{C1\text{-}H1}$ = 170 Hz, C-1); **HRMS** (*m/z*): [M+Na]$^+$ calcd for $C_{59}H_{64}O_{13}S$, 1035.3965; found, 1035.3950; **[α]$^{25}_D$** = +12.8 (*c* = 0.46, $CHCl_3$).



4.8 – Acknowledgement

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4.9 – References

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5

Stereoselective Glycosylation of Uronic Acid 6,3-Lactones *via* Remote Group Participation

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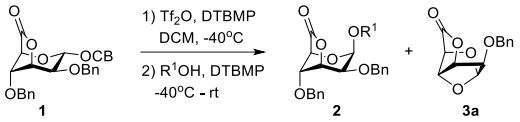
Abstract: Uronic acids are important constituents of polysaccharides found on the cell membranes of many different organisms. Uronic acid 6,3-lactones are interesting glycosyl donors to prepare uronic acid containing oligosaccharides because they display a fixed conformation and, as a consequence, have unique reactivity and stereoselectivity. Galacturonic acid 6,3-lactones are known to provide *α*-galactosides upon glycosylation via a *β*-triflate intermediate. This chapter explores the use of gluco- and mannuronic acid 6,3-lactones which by contrast primarily produce *β*-products. This complete reversal of facial selectivity is attributed to the remote group participation (RGP) of C-4 ethers or esters during glycosylation. Evidence for this mode of reaction was provided by the use of a C-4 Boc protected glycosyl donor which produced a 1,4-anhydro ether indicating stabilization of the oxocarbenium ion by C-4 RGP.

5.1 – Introduction

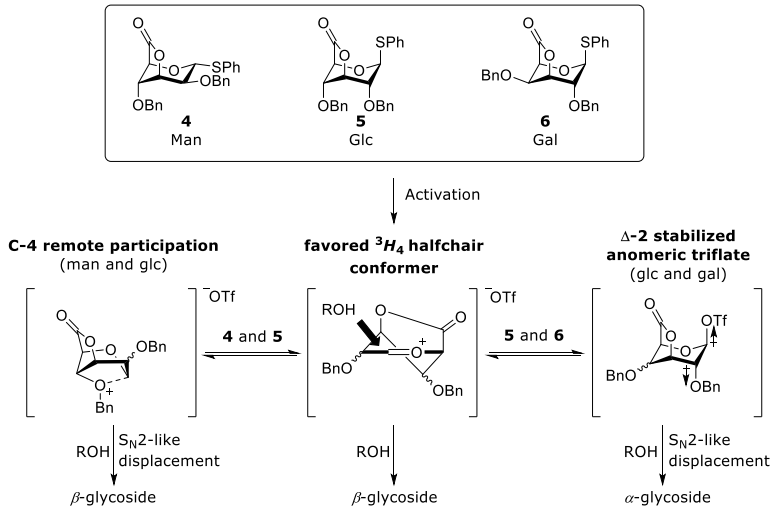
Uronic acids are important constituents of polysaccharides found on the cell membranes of many different organisms.[1] Uronic acid 6,3-lactones are interesting glycosyl donors to prepare uronic acid containing oligosaccharides because they display a fixed conformation and unique reactivity and stereoselectivity. A good example is the highly *β*-selective glycosylation behavior of mannuronic acid 6,3-lactone **1** (Scheme 1, also see Chapter 4). The *β*-stereoselectivity was attributed to the remote group participation (RGP) of the C-4 ether during glycosylation (Scheme 1).[2] Unfortunately, formation of the *β*-mannoside was accompanied by the formation of a 1,4-anhydro byproduct (**3a**) which lowers the overall yield of the reaction and complicates purification.



Scheme 1: Glycosylation of **1** affords an inseparable mixture of **2** and **3a**.

Galacturonic acid 6,3-lactone **6** contains an equatorial C-4 substituent and thus RGP cannot occur. Interestingly, glycosylations using preactivation conditions (Ph_2SO/Tf_2O) affords *α*-galactosides as glycosylation takes place *via* a *β*-triflate intermediate,[3] whereas *in situ* activation affords *β*-galactosides. This inversion of stereoselectivity was rationalized *via* the $^3H_4$ intermediate, which upon pseudo axial (*β*-face) attack directly leads to the favored $^1C_4$ conformation (Scheme 2).[4] This striking reversal of stereoselectivity led us to investigate the influence of the C-2 and C-4 stereochemistry on the glycosylation outcome *via* either of the aforementioned mechanisms.

To this end we prepared a 2,4-dibenzyl manno-, gluco- and galacturonic acid lactone donor which differ in C-2 and C-4 stereochemistry (**4**[5], **5**[3] and **6**[6], resp., Scheme 2). The orientation of the C-4 substituent in the manno- and glucosyl donors allows for RGP which should lead to a *β*-glycoside, whereas the C-4 substituent in a galactosyl donor is unable to perform C-4 RGP. The conformation of the oxocarbenium ion intermediates resulting from uronic acid lactone donors **4**-**6** are shown in Scheme 2 are expected to be similar. Due to the presence of the 6,3-lactone, the expected preferred conformation would be the $^3H_4$ half-chair. Pseudo axial attack should be the preferred mode of attack and would lead to *β*-product as well. Anomeric triflates can also be reactive intermediates that are displaced in an S_N2-like manner.[7] We expect the *β*-anomeric triflates to be more stable due to the anomeric effect and in case of glucose and galactose may be further stabilized by the Δ-2 effect.[8] The Δ-2 effect is present when the C-2 substituent is axially oriented which, due to the locked $^1C_4$ conformation, is the case in gluco and galacto configured uronic acid 6,3 lactones.

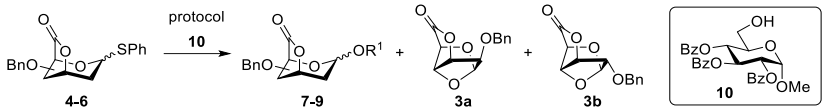


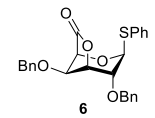
Scheme 2: Three major mechanistic pathways in uronic acid 6,3-lactones. The $^3H_4$ halfchair conformer is intrinsically favored due to the 6,3-lactone bridge (*β*-selective). C-4 participation is possible in manno- and gluco configured donors (*β*-selective). *β*-Triflate formation is expected in donor with gluco- and galacto stereochemistry due to the Δ-2 effect (*α*-selective).

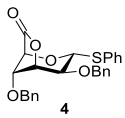
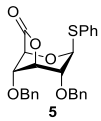
5.2 – Glycosylation results I

Galacturonic acid 6,3-lactone **6** was pre-activated at low temperature using Ph_2SO/Tf_2O[9] and subsequent addition of the glycosyl acceptor resulted in the formation of the *α*-glycoside with excellent stereoselectivity (*α*/*β* = 20/1, Table 1, entry 1). This in line with earlier reports and is the result of glycosylation *via* a *β*-triflate intermediate.[3] By contrast, pre-activation of mannuronic acid- and glucuronic acid 6,3-lactone under the same conditions did not lead to glycosylation products (Table 1, entries 4 and 7). Instead, the major product was 1,4-anhydro compound **3a/b** which is the result of RGP of the C-4 benzyl ether followed by formation of **3a/b** and benzyl triflate. In case of mannoside **4**, a small amount disaccharide was produced as mainly the *β*-anomer (7%), whereas glucoside **5** seems to be so reactive, that it immediately decomposes or forms **3b**. In order to minimize the formation of this byproduct we explored the use of a pre-mix protocol in which activation of the glycosyl donor takes place in presence of the glycosyl acceptor. For this purpose, we used the NIS/AgOTf promoter system.[10] An earlier study explored the use of NIS/TfOH[11] to activate galacturonic acid lactone **3**, but this proved to be unsuccessful. The use of AgOTf instead of TfOH proved to be crucial as under these conditions disaccharide was formed in a high yield (86%). As expected, the stereoselectivity in this case was much lower as the *β*-triflate intermediate was not pre-formed under these conditions.

Table 1: Glycosylation results of the uronic acid 6,3-lactone donors **1-3**.



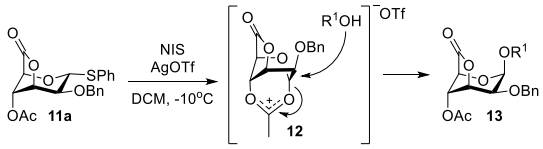
entry	donor	protocol[a]	yield (%)[b]	*α* / *β*[c]
1	 **6** Gal	Ph_2SO Tf_2O	94	20/1
2		AgOTf NIS	86	4.6/1
3		$AgClO_4$ NIS	84	2.5/1

entry	donor	protocol[a]	yield (%)[b]	**3x** (%)	*α* / *β*[c]
4	 **4** Man	Ph_2SO Tf_2O	7	**3a** 16[d]	1/20
5		AgOTf NIS	22	**3a** 30[d]	1/20
6		$AgClO_4$ NIS	16	**3a** 32[d]	1/20
7	 **5** Glc	Ph_2SO Tf_2O	0	**3b** 32	-
8		AgOTf NIS	0	**3b** 100	-

[a] *protocols*: Ph_2SO, Tf_2O, DTBMP, DCM, -78°C then **10**; *or* **10**, NIS, DCM, AgOTf (cat), -10°C; *or* **10**, NIS, DCM, $AgClO_4$ (cat), -10°C, [b] isolated yield, [c] ratios were determined in crude reaction mixtures using key integrals in ^{1}H-NMR spectra, [d] as an inseparable mixture with **4**.

Glycosylation of mannuronic acid lactone **4** using NIS/AgOTf did lead to an improved yield of *β*-disaccharide (22%) with respect to the pre-activation protocol, however a significant amount of 1,4-anhydro sugar **3a** was still formed (Table 1, entries 4-5). However, in case of glucuronic acid lactone **5**, glycosylation using NIS/AgOTf again led to the exclusive formation of byproduct **3b**. These results indicate that the tendency to form 1,4-anhydro byproduct **3** is much greater in the glucuronic acid lactone, than in the corresponding manno configured analogue. We strongly believe that **3b** is also the product Furukawa *et al.* found when they performed a similar glycosylation with glucoronic acid lactone **5** using NIS/TfOH.[12] Another advantage of silver salts for the activation of NIS is that the role of the counter ion can be easily investigated. Hence, we performed glycosylations with NIS/$AgClO_4$ to investigate the role of the counter ion on the stereoselectivity and byproduct formation. In case of galacturonic acid lactone **5**, the disaccharide was formed with high yield and a slightly lower stereoselectivity compared to NIS/AgOTf, as expected. In the case of mannuronic acid lactone **4**, the use of $AgClO_4$ led to the same results as AgOTf indicating that the counter ion is not a critical determinant of stereoselectivity. In addition, the counter-ion does not seem to play an important role in terms of byproduct formation as the glycosylation yields are similar (Table 1, entries 5-6). The above results show that byproduct (**3**) formation can be suppressed to some extend by the use of a pre-mix strategy, yet these donors are still quite inefficient in terms of the glycosyl donor. An excess of donor needs to be used to obtain acceptable yields of disaccharide. The glycosylations using the carboxybenzyl leaving group, seen in Chapter 4, glycosylated in much better yields, yet with significant formation of 1,4-anhydro byproduct **3a** as well. However, thioglycosides are

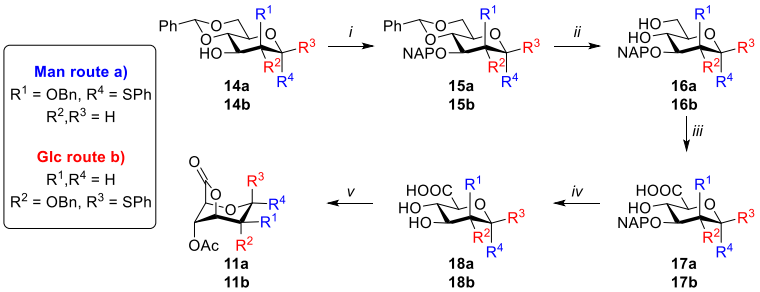
preferable as they are resistant to many functional group manipulations and thus are very versatile synthons for the total synthesis of multistep oligosaccharides.[13] To improve this methodology we focused on other protecting groups at C-4 that could perform RGP, but would not lead to byproduct formation and hence would drastically improve donor efficiency while maintaining *β*-selectivity. Yu *et al.* proved remote participation of a C-4 acetyl ester,[14] similar to the well-known C-2 acetyl neighboring group participation (NGP), and inspired us to introduce this functionality (**11a**) which should then afford *β*-glycosides (**13**, Scheme 3).



Scheme 3: Hypothesized glycosylation mechanism of C-4 acetyl donor **11a**

5.3 – Synthesis of C-4 acetyl donors

The synthesis of C-4 acetyl donor **11a** and **11b** started from known 4,6-benzylidene precursors **14a**[2, 15] and **14b**,[16] respectively (Scheme 4). The C-2 and C-3 alcohols were orthogonally protected with a benzyl- and 2-methylnapthyl ether, respectively. Acidic hydrolysis of the 4,6-benzylidene (**15a**) and subsequent regioselective oxidation of the diol (**17a**) using TEMPO/BAIB afforded mannuronic acid **17a** in good yield (79%).[17]



Scheme 4: Synthesis of donors **11a** and **11b**. Reagents and conditions: *i)* NaH, NAPBr, DMF, 50°C, 16h, **15a** 98%, **15b** 96%; *ii)* *p*-TsOH, MeOH, **16a**, 16h, 88%, **16b**, 4h, 76%; *iii)* TEMPO, BAIB, DCM/H_2O (9:1 v/v), 2h, **17a** 64%, **17b** 79%; *iv)* DDQ, DCM/H_2O, 2h, (7.5/1 v/v) **18a** 70%, **18b** 87%; *v)* Ac_2O, 70°C, 1.5h, **11a** 88%, **11b** 56%. BAIB = [bis(acetoxy)iodo]benzene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, NAP = 2-methylnapthalene, TEMPO = 2,2,6,6-Tetramethylpiperidine 1-oxyl.

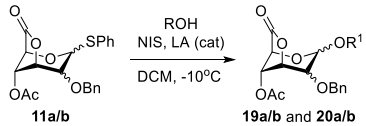
DDQ oxidation of the 2-methylnaphthyl ether afforded the corresponding C-3 alcohol (**18a**) which was lactonized using acetic anhydride.[18] Under the same conditions, the C-4 alcohol was acetylated affording the desired mannuronic acid 6,3-lactone donor **11a** in good yield (88%). A similar sequence was used to prepare glucuronic acid 6,3-lactone donor **11b** affording similar

yields, except for the lactonization step (56%). This is probably due to unfavorable essential change of conformation from all-equatorial ($^4C_1$) to all-axial ($^1C_4$), in order to facilitate lactone formation.

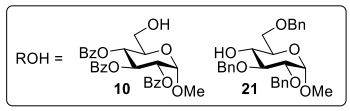
5.4 – Glycosylation results II

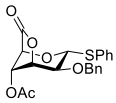
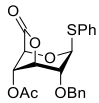
Next, we explored the reactivity of donors **11a** and **11b** in a glycosylation reaction (see Table 2). Activation was achieved with NIS/AgOTf and, with acceptor **10**, both donors gave the corresponding disaccharides in a high yield using only a small excess of the donors showing that the introduction of the C-4 acetyl group prevented byproduct formation as intended. Mannose donor **11a** showed excellent *β*-selectivity (*α*/*β* = 1/20), whereas glucose donor **11b** formed mostly the *β*-product albeit with very modest selectivity (*α*/*β* = 1/2.5). We expected that most of the *α*-product was the result of a reaction via the *β*-triflate and hence expect a higher *β*-selectivity with the NIS/$AgClO_4$ promoter system. Surprisingly, using this activation method caused the *β*-selectivity to decrease (*α*/*β* = 1/1). Aside from the C-2 stereochemistry, the orientation of the anomeric leaving group is also different in **11a** and **11b**. Therefore, a possible explanation for the difference in stereoselectivity may be the S_N2-like displacement of the activated thiophenyl moiety, which would provide *β*-mannosides for mannose donor **11a**, and *α*-glucosides for glucose donor **11b**.[19] Finally, we investigated the selectivity with the much less reactive secondary alcohol acceptor **21**. For both donors **11a** and **11b** yields dropped significantly as is regularly reported with this acceptor, but satisfyingly, the selectivity remained the same (*α*/*β* = 1/20 for mannose donor **11a**).

Table 2: Glycosylation results of the uronic acid 6,3-lactone donors **11a-b**.



11a/b → **19a/b** and **20a/b**



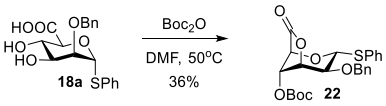
entry	donor	R^1OH	LA	yield (%)[a]	*α* / *β*[b]
1	 **11a** man	**10**	AgOTf	88	<1/20
2		**21**	AgOTf	51	<1/20
3	 **11b** glc	**10**	AgOTf	81	1/2.5
4		**10**	$AgClO_4$	70	1/1
5		**21**	AgOTf	53	1/2

[a] isolated yield; [b] ratios were determined in the crude reaction mixture using key integrals in ^{1}H-NMR spectra.

5.5 – Mechanistic study

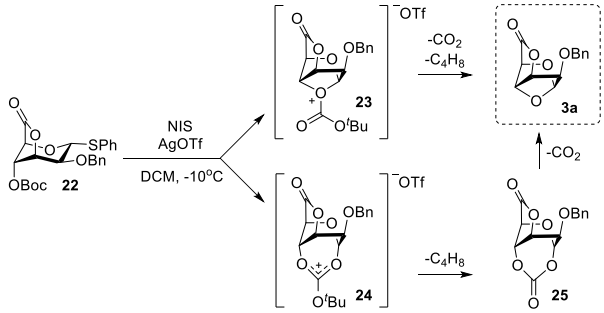
Next, we set out to provide evidence for the remote participation of the C-4 acetyl ester using an elegant method reported by Jernstedt *et al.*[20] Utilizing a *tert*-butyloxycarbonyl (Boc) group as participating group leads to the formation of a stable cyclic carbonate after loss of isobutene.

The formation of such cyclic carbonates was later used by Crich *et al.* to prove NGP and RGP in carbohydrates.[21] To this end we synthesized C-4 Boc donor **22** *via* a modified literature procedure, albeit in a modest yield (Scheme 5).[22]



Scheme 5: Synthesis of donor **22**.

Activation of mannose donor **22** with the NIS/AgOTf system in the absence of glycosyl acceptor led to a complete reaction within an hour. After identification *via* ^{1}H-NMR spectroscopy we found 1,4-anhydro sugar **3a**, instead of expected 1,4-carbonate **25** (Scheme 6). We hypothesize that compound **3a** could either be formed *via* the formation of cation **23**, followed by elimination of carbon dioxide and isobutene, or by formation of dioxolenium **24**, then elimination of isobutene (**25**), followed by silver triflate mediated decarboxylation. The fact that we were unable to observe carbonate **25** abstains us from drawing the conclusion that the acyl moiety participates, however, the formation of compound **3a** does prove RGP of the C-4 substituent, either *via* intermediate **23** or *via* intermediate **24**.



Scheme 6: Mechanistic study of C-4 RGP did not provide carbonate **25**, and was thus inconclusive.

5.6 – Conclusion

We have shown that in mannose donors, in the $^1C_4$ conformation, the axial C-4 substituent is able to participate and thereby exclusively provides *β*-mannosides. Even though trapping of the intermediate dioxolenium intermediate did not provide the expected carbonate, the obtained 1,4-anhydro ether provided sufficient proof of remote group participation. However, this remote group participation might not be a reactive intermediate as the glucose donors only have a slight preference to form *β*-glucosides. Therefore, the triflate intermediate, the $^3H_4$ oxocarbenium intermediate, or direct S_N2 displacement of the thioether should also be considered as reactive pathways. In conclusion, we developed an efficient synthetic route towards a mannuronic 6,3-lactone donor, which smoothly undergoes a one-pot *β*-directing stereoselective glycosylation.

5.7 – Experimental

General Methods: For general methods, please refer to section 2.9.

General Glycosylation procedures:

Method A: Ph_2SO/Tf_2O

A solution of lactone (1 eq), diphenyl sulfoxide (1.2 eq) and 2,6-di-*tert*-butyl-4-methylpyridine (2.5 eq) in DCM (0.03M) was stirred over activated 4Å MS for 30 min. The mixture was cooled to -78°C before Tf_2O (1.1 eq) was added. The mixture was allowed to warm to -45°C in 15min followed by addition of acceptor (1.5). Stirring was continued and the reaction mixture was allowed to warm to 0°C. The reaction mixture was diluted with EtOAc and washed with water. The water/layer wash extracted twice with EtOAc. The collected organic layers were dried (MgSO4), filtered and concentrated under reduced pressure. Flash chromatography (EtOAc/PE) and removal of the eluent afforded the corresponding title compound.

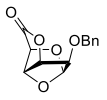
Method B: NIS/AgOTf

Acceptor (1.2 eq), donor (1 eq) and 4Å MS were added to dry DCM (0.03M) under inert atmosphere and the mixture was stirred at -10°C for 15 minutes. *N*-iodosuccinimide (1.2 eq) and AgOTf (0.15 eq) were added and the reaction was stirred at -10°C for 1h. Et_3N was added and the reaction was quenched with 10% $Na_2S_3O_3$ in H_2O w/w. The mixture was diluted with ethyl acetate and filtrated. The filtrate was washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. After acetylation of the excess of acceptor, silica gel flash column chromatography (20% → 60% - EtOAc in *n*-heptane) of the residue afforded the products.

Method C: NIS/$AgOCl_4$

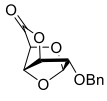
Acceptor (1.2 eq), donor (1 eq) and 4Å MS were added to dry DCM (0.03M) under inert atmosphere and the mixture was stirred at -10°C for 15 minutes. *N*-iodosuccinimide (1.2 eq) and $AgClO_4$ (0.15 eq) were added and the reaction was stirred at -10°C for 1h. Et_3N was added and the reaction was quenched with 10% $Na_2S_3O_3$ in H_2O w/w. The mixture was diluted with ethyl acetate and filtrated. The filtrate was washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. After acetylation of the excess of acceptor, silica gel flash column chromatography (20% → 60% - EtOAc in *n*-heptane) of the residue afforded the products.

1,4-anhydro-2-*O*-benzyl-α-D-mannopyranosidurono-6,3-lactone (3a):



To a solution of **4** (45 mg, 0.092 mmol) in DCM (1.5 mL), 2,6-di-*t*-butyl-4-methylpyridine (47 mg, 0.23 mmol) was added. The mixture was dried with MS (4Å) and cooled to -20°C after which Tf_2O (19 µL, 0.11 mmol) was added. The reaction was stirred for 30 minutes and was then diluted with EtOAc (10 mL) and filtrated. The filtrate was washed with H_2O (5 mL) and brine (5 mL) after which the organic layer was dried (Na_2SO_4), filtrated and concentrated *in vacuo*. Silicagel flash column chromatography (10% → 40% - EtOAc in *n*-heptane) of the residue afforded **3a** (18 mg, 79%). **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.43; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.48 – 7.28 (m, 5H), 5.66 (d, *J* = 1.9 Hz, 1H, H-1), 5.59 (t, *J* = 4.2 Hz, 1H, H-4), 4.78 – 4.70 (m, 2H, H-3), 4.54 (d, *J* = 11.4 Hz, 1H), 4.11 – 4.09 (m, 1H, H-5), 3.74 (dd, *J* = 6.5, 1.8 Hz, 1H, H-2); **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 171.54(C-6), 136.93, 128.50, 128.17, 128.06, 100.55 (C-1), 82.29 (C-4), 76.08 (C-2), 72.21, 71.42 (C-3), 71.29 (C-5).

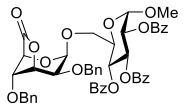
1,4-anhydro-2-*O*-benzyl-α-D-glucopyranosidurono-6,3-lactone (3b):



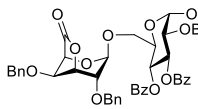
To a solution of **5** (45 mg, 0.092 mmol) in DCM (1.5 mL), 2,6-di-*t*-butyl-4-methylpyridine (47 mg, 0.23 mmol) was added. The mixture was dried with MS (4Å) and cooled to -20°C after which Tf_2O (19 µL, 0.11 mmol) was added. The reaction was stirred for 30 minutes and was then diluted with EtOAc (10 mL) and filtrated. The filtrate was washed with H_2O (5 mL) and brine (5 mL) after which the organic

layer was dried (Na_2SO_4), filtrated and concentrated *in vacuo*. Silicagel flash column chromatography (10% → 40% - EtOAc in *n*-heptane) of the residue afforded **3b** (18 mg, 79%). **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.43; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.41 – 7.30 (m, 5H), 5.73 (d, *J* = 1.4 Hz, 1H, H-1), 5.51 (dd, *J* = 4.9, 3.1 Hz, 1H, H-4), 4.66 (ddd, *J* = 4.9, 1.4, 0.8 Hz, 1H, H-3), 4.66 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 3.94 (dt, *J* = 3.0, 0.6 Hz, 1H, H-5), 3.80 (s, 1H, H-2). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 171.25, 136.37, 131.04, 129.32, 128.74, 128.53, 128.44, 128.03, 124.79, 102.99 (C-1), 82.26 (C-2), 80.37 (C-3), 79.24 (C-4), 71.69, 69.99 (C-5).

Methyl 2,4-di-*O*-benzyl-β-D-mannopyranosilurono-6,3-lactone-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (7): Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (28 mg, 0.06 mmol), **4** (50 mg, 0.11 mmol) and were added to dry DCM (3 mL) under inert atmosphere and the mixture was stirred at -10°C for 15 minutes. *N*-iodosuccinimide (30 mg, 0.13 mmol) and AgOTf (5.7 mg, 0.022 mmol) were added and the reaction was stirred at -10°C for 1h. Et_3N was added and the reaction was quenched with 10% $Na_2S_3O_3$ in H_2O w/w (1 mL). The mixture was diluted with ethyl acetate (50 mL) and filtrated. The filtrate was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. After acetylation of the excess of acceptor, silicagel flash column chromatography (15% → 40% - EtOAc in *n*-heptane) of the residue afforded **7** (30%) as a an inseperable mixture with **3a** (22%) (49 mg total yield). **TLC**: (EtOAc/n-heptane 40/60 v/v): R_f =0.45. **^{1}H NMR** δ 8.01 – 7.93 (m, 4H), 7.84 – 7.79 (m, 2H), 7.55 – 7.46 (m, 2H), 7.44 – 7.19 (m, 17H) 6.13 (t, J = 9.8 Hz, 1H, H-3'), 5.59 (d, J = 2.0 Hz, 1H, H-1(**3a**)), 5.50 (dd, J = 4.9, 3.5 Hz, 1H, H-4(**3a**)), 5.40 (dd, J = 10.4, 9.4 Hz, 1H, H-4'), 5.32 (d, J = 5.0 Hz, 1H, H-1), 5.23 (dd, J = 10.2, 3.6 Hz, 1H, H-2'), 5.17 (d, J = 3.5 Hz, 1H, H-1'), 4.77 – 4.69 (m, 3H, H-3), 4.67 – 4.63 (m, 1H, H-3(**3a**)), 4.63 (d, J = 11.9 Hz, 2H), 4.59 (d, J = 11.6 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.30 (ddd, J = 10.1, 7.9, 1.9 Hz, 1H, H-5'), 4.18 (dd, J = 5.0, 1.3 Hz, 1H, H-2), 4.08 (dd, J = 3.5, 1.0 Hz, 1H, H-5(**3a**)), 4.03 (dd, J = 5.8, 3.0 Hz, 1H, H-4), 3.92 (dd, J = 11.6, 1.9 Hz, 1H, H-6'a), 3.90 (dd, J = 3.0, 1.1 Hz, 1H, H-5), 3.69 – 3.63 (m, 2H, H-6'b, H-2) 3.35 (s, 3H); **^{13}C NMR** (126 MHz, CDCl3) δ 171.48 (C-6), 165.78, 165.61, 137.38, 133.36, 133.24, 132.93, 129.93, 129.87, 129.57, 129.24, 129.06, 128.81, 128.69, 128.54, 128.48, 128.44, 128.34, 128.33, 128.24, 128.16, 128.09, 127.98, 127.94, 127.85, 100.46(C-1(**3a**)), 99.13 (C-1), 96.50(C-1'), 82.14 (C-4), 77.68 (C-3), 76.13 (C-4'), 75.78 (C-2(**3a**)), 72.19, 72.13 (C-2'), 72.04, 71.27 (C-3(**3a**)), 71.23, 71.20 (C-5(**3a**)), 70.71 (C-2), 70.54 (C-3'), 69.71 (C-4'), 68.76 (C-5'), 67.51 (C-5), 66.99 (C-6'), 55.36; **^{13}C-coupled HSQC** (126 MHz, CDCl3): δ 99.13 ($J_{C1\text{-}H1}$ = 175 Hz), 96.50 ($J_{C1'\text{-}H1'}$ = 175 Hz); **HRMS** (*m/z)*: $[M+Na]^+$ calcd for $C_{48}H_{44}O_{14}$, 867.2629; found, 867.2620.

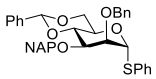


Methyl 2,4-di-*O*-benzyl-β-D-galactopyranosilurono-6,3-lactone-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (9): Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (42 mg, 0.08 mmol), **5** (75 mg, 0.17 mmol) and were added to dry DCM (3 mL) under inert atmosphere and the mixture was stirred at -10°C for 15 minutes. *N*-iodosuccinimide (41 mg, 0.18 mmol) and AgOTf (8.5 mg, 0.03 mmol) were added and the reaction was stirred at -10°C for 1h. Et_3N was added and the reaction was quenched with 10% $Na_2S_3O_3$ in H_2O w/w (1 mL). The mixture was diluted with ethyl acetate (50 mL) and filtrated. The filtrate was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. After acetylation of the excess of acceptor, silicagel flash column chromatography (20% → 60% - EtOAc in *n*-heptane) of the residue afforded **9** as a yellow oil (44 mg, 49%). **TLC**: (EtOAc/n-heptane 40/60 v/v): R_f =0.45. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.78 (m, 6H), 7.68 – 7.62 (m, 1H), 7.54 – 7.27 (m, 22H), 6.12 (t, *J* = 9.6 Hz, 1H, H-3'), 5.61 (t, *J* = 9.9 Hz, 1H, H-4'), 5.21 – 5.16 (m, 2H, H-1', H-2'), 4.93 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 2.5 Hz, 1H, H-1), 4.67 (dd, *J* = 5.0, 1.8 Hz, 1H, H-3), 4.58 (d, *J* = 11.9 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 1.3 Hz, 1H, H-5), 4.51 (d, *J* = 12.1 Hz, 1H), 4.22 (ddd, *J* = 10.1, 4.4, 2.9 Hz, 1H, H-5'), 4.14 (dd, *J* = 11.6, 4.3 Hz, 1H, H-6'a), 4.03 (t, *J* = 1.5 Hz, 1H, H-4), 3.97 (dd, *J* = 4.9, 2.5 Hz, 1H, H-2), 3.79 (dd, *J* = 11.5, 2.9 Hz, 1H, H-6'b), 3.42 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.71, 165.80, 165.77, 165.05, 137.61, 136.80, 133.37, 133.36, 133.06, 131.04, 129.92, 129.88, 129.83, 129.81, 129.66, 129.62, 129.31, 129.25, 129.07, 129.03, 128.59, 128.53, 128.47, 128.45, 128.40, 128.37, 128.25, 128.22, 128.19, 128.01, 127.80, 127.79, 127.74, 127.72, 124.78, 98.82 (C-1), 97.01 (C-1'), 80.33 (C-3), 75.53 (C-5), 74.41 (C-2'), 74.23, 72.04(C-2), 71.91 (C-4), 71.55, 70.49 (C-3'), 69.42 (C-4'), 68.62 (C-5'), 68.33 (C-6'), 55.73. **^{13}C-coupled HSQC** (126 MHz,



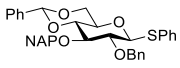
$CDCl_3$): δ 98.82 ($J_{C1\text{-}H1}$ = 164 Hz), 97.01 ($J_{C1'\text{-}H1'}$ = 173 Hz); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{48}H_{44}O_{14}$, 867.2629; found, 867.2668.

Phenyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-1-thio-*α*-D-manno-pyranoside (15a):



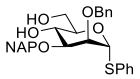
To a cooled solution (0°C) of phenyl 4,6-O-benzylidene-2-O-benzyl-1-thio-α-D-mannopyranoside (1.00 g, 2.22 mmol) in anhydrous DMF (20 mL) was added sodium hydride (60 percent dispersion in mineral oil, 0.266 g, 11.10 mmol) under inert atmosphere. 2-(Bromomethyl) naphthalene (0.736 g, 3.33 mmol) was added and the reaction was allowed to warm up to rt for 2 h, after which it was quenched with MeOH and evaporated under reduced pressure. A NH_4Cl solution (35 ml) and water (35 ml) were added, and the mixture was extracted with diethyl ether (3x 50 ml) and the combined ethereal extracts were dried (MgSO4). After filtration, the solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (0% → 15% - EtOAc in *n*-heptane) to obtain **15a** as a colorless solid (1.29 g, 98%). **TLC:** (EtOAc/*n*-heptane, 20/80 v/v): R_f = 0.53; **^{1}H NMR** 400 MHz, $CDCl_3$) δ 7.89 – 7.67 (m, 4H), 7.57 – 7.22 (m, 18H), 5.67 (s, 1H), 5.52 (d, J = 1.4 Hz, 1H, H-1), 4.95 (d, J = 12.5 Hz, 1H), 4.81 (d, J = 12.5 Hz, 1H), 4.78-4.70 (m, 2H), 4.36 (t, J = 9.4 Hz, 1H, H-4), 4.34 – 4.20 (m, 2H, H-5, H-6a), 4.07 (dd, J = 3.2, 1.5 Hz, 1H, H-2), 4.03 (dd, J = 9.5, 3.2 Hz, 1H, H-3), 3.90 (t, J = 9.9 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, CDCl3) δ 137.70, 137.60, 135.81, 133.71, 133.29, 132.97, 131.63, 129.11, 128.89, 128.44, 128.21, 128.10, 128.07, 127.95, 127.87, 127.65, 127.61, 126.28, 126.15, 126.15, 126.02, 126.01, 125.80, 125.63, 101.60, 87.08 (C-1), 79.03 (C-4), 77.96 (C-2), 76.24 (C-3), 73.05, 72.96, 68.53 (C-6), 65.49 (C-5).

Phenyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-methylnaphthyl)-1-thio-α-D-glucopyranoside (15b):



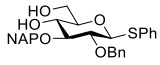
Sodium hydride (60 percent dispersion in mineral oil, 0.33 g, 13.87 mmol) was added to a stirred solution of **14b** (2.5 g, 5.55 mmol) in anhydrous DMF (30 mL) cooled to 0°C under inert atmosphere. 2-(Bromomethyl) naphthalene (1.84 g, 8.32 mmol) was added and the reaction was allowed to warm up to rt and stirred for 2 h when it was quenched with MeOH and evaporated under reduced pressure. A sat. aq. NH_4Cl solution (35 ml), water (35 ml) and the waterlayer was extracted with 3x30ml DCM. The combined organic layers were dried (MgSO4), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (0% → 15% - EtOAc in *n*-heptane) afforded **15b** as an inseparable mixture with phenyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-*O*-(2-methylnaphthyl)-1-thio-*α*-D-glucopyranoside (1:0.44) as a colorless oil. (3.16 g, 96%). **TLC:** (EtOAc/*n*-heptane, 50/50 v/v): R_f = 0.53; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 – 7.64 (m, 4H), 7.60 – 7.21 (m, 18H), 5.61 (s, 1H), 5.08 (d, *J* = 11.4 Hz, 1H), 4.94 (d, *J* = 11.5 Hz, 1H), 4.89 (d, *J* = 10.3 Hz, 1H), 4.84 (d, *J* = 10.2 Hz, 1H), 4.77 (d, *J* = 9.8 Hz, 1H, H-1), 4.42 – 4.35 (m, 1H, H-6a), 3.89 (dd, *J* = 9.6, 8.4 Hz, 1H, H-3), 3.82 (t, *J* = 10.3 Hz, 1H, H-6b), 3.74 (t, *J* = 9.4 Hz, 1H, H-4), 3.54 (dd, *J* = 9.8, 8.4 Hz, 1H, H-2), 3.53-3.45 (m, 1H, H-5). **^{13}C NMR** (101 MHz, CDCl3) δ 137.99, 137.23, 135.72, 133.26, 133.11, 133.01, 132.31, 129.01, 128.98, 128.39, 128.27, 128.25, 128.17, 128.11, 128.09, 127.93, 127.88, 127.86, 127.64, 126.87, 126.84, 126.21, 126.19, 126.03, 125.98, 125.85, 101.23, 88.33 (C-1), 82.92 (C-3), 81.45 (C-4), 80.54 (C-2), 75.90, 75.32, 70.26 (C-5), 68.72 (C-6).

Phenyl 2-*O*-benzyl-3-*O*-(2-methylnaphthyl)-1-thio-*α*-D-mannopyranoside (16a):



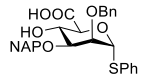
A mixture of **15a** (2.784 g, 4.71 mmol) and *p*-TsOH·H_2O (0.896 g, 4.71 mmol) in MeOH (47 mL) was stirred at room temperature for 5 h. The solution was diluted with EtOAc (100 mL) and the mixture was consecutively washed with sat. aq. $NaHCO_3$ (2 x 40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 60% EtOAc in *n*-heptane) of the residue afforded **16a** (2.08 g, 88%) as a yellow amorphous solid. **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.16; **^{1}H NMR** (500 MHz, $CDCl_3$) δ δ 7.89 – 7.75 (m, 4H), 7.54 – 7.19 (m, 13H), 5.56 (d, *J* = 1.6 Hz, 1H, H-1), 4.73 (d, *J* = 11.9 Hz, 1H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.19 – 4.09 (m, 2H, H-4, H-5), 4.05 (dd, *J* = 3.1, 1.6 Hz, 1H, H-2), 3.93 – 3.80 (m, 2H, H-6a, H-6b), 3.80 – 3.73 (m, 1H, H-3), 2.47 (d, *J* = 1.8 Hz, 1H, 4-OH), 1.99 – 1.89 (m, 1H, 6-OH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.63, 135.07, 133.79, 133.27, 133.09, 131.91, 129.16, 128.48, 128.47, 127.95, 127.93, 127.91, 127.76, 127.75, 126.78, 126.30, 126.13, 125.70, 85.99 (C-1), 79.68, 77.27, 77.01, 76.76, 75.49, 73.24, 72.20, 71.81, 67.37, 62.75; **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{30}H_{30}O_5S$, 525.1712; found, 525.1701.

Phenyl 2-*O*-benzyl-3-*O*-(2-methylnaphthyl)-1-thio-α-D-glucopyranoside (16b):



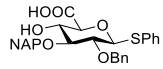
A mixture of **15b** (2.00 g, 3.98 mmol) and *p*-TsOH·H_2O (0.896 g, 4.71 mmol) in MeOH (47 mL) was stirred at room temperature for 5 h. The reaction solution was diluted with EtOAc (100 mL), and the mixture was consecutively washed by sat. aq. $NaHCO_3$ (2 x 40 mL) and brine (40 mL). The organic layer was dried over MgSO4, filtered and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 60% - EtOAc in *n*-heptane) of the residue afforded **16b** and phenyl 3-*O*-benzyl-2-*O*-(2-methylnaphthyl)-1-thio-α-D-glucopyranoside (1:0.44) as an inseparable mixture as a yellow solid (2.08 g, 88%). **TLC:** (EtOAc/*n*-heptane, 50/50 v/v): R_f = 0.09; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 – 7.72 (m, 4H), 7.58 – 7.24 (m, 12H), 5.11 (d, *J* = 11.7 Hz, 1H), 4.99 (d, *J* = 10.3 Hz, 1H), 4.88 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 10.4 Hz, 1H), 4.75 (d, *J* = 9.5 Hz, 1H, H-1), 3.93 – 3.84 (m, 1H, H-6), 3.81 – 3.71 (m, 1H, H-6'), 3.66 – 3.48 (m, 3H, H-2, H-3, H-4), 3.41 – 3.32 (m, 1H, H-5), 2.27 (d, *J* = 2.6 Hz, 1H, 4-OH), 2.04 – 1.96 (m, 1H, 6-OH). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.77, 135.59, 133.49, 133.28, 133.05, 131.76, 129.08, 129.06, 128.73, 128.62, 128.49, 128.27, 128.00, 127.92, 127.85, 127.74, 127.72, 127.70, 127.69, 126.77, 126.31, 126.12, 125.59, 87.76 (C-1), 85.93 (C-3), 80.95 (C-2), 79.11 (C-5), 75.48 (CH_2-NAP), 70.51 (C-4), 62.80 (C-6); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{30}H_{30}O_5S$, 525.1712; found 525.1703.

Phenyl 2-*O*-benzyl-3-*O*-(2-methylnaphthyl)-1-thio-*α*-D-mannopyranosiduronic acid (17a):



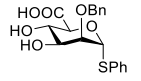
To a solution of **16a** (2.08 g, 4.15 mmol) in 10% H_2O in DCM (v/v) (41.5 mL), BAIB (4.01 g, 12.4 mmol) was added under stirring. After addition of TEMPO (0.259 g, 1.66 mmol) the reaction was stirred for 1h at rt. The mixture was quenched by addition of 10% $Na_2S_3O_3$ solution in H_2O w/w (50 mL) and was extracted with ethyl acetate at pH 3 (3 x 40 mL). The organic layers were combined, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 60% EtOAc in *n*-heptane + 2% acetic acid) of the residue afforded **17a** as a pale yellow amorphous solid (1.37 g, 64.1%). **TLC:** (MeOH/DCM/acetic acid, 10/88/2 v/v/v): R_f = 0.70; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 4H), 7.54 – 7.19 (m, 13H), 5.61 (d, *J* = 2.3 Hz, 1H, H-1), 4.84 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 4.69 (d, *J* = 12.1 Hz, 1H), 4.64 (d, *J* = 9.4 Hz, 1H, H-5), 4.59 (d, *J* = 12.1 Hz, 1H), 4.40 (t, *J* = 9.1 Hz, 1H, H-4), 3.98 (t, *J* = 2.7 Hz, 1H, H-2), 3.80 (dd, *J* = 9.0, 3.0 Hz, 1H, H-3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.63 (C-6), 137.46, 135.13, 133.23, 133.14, 133.05, 131.71, 129.21, 128.43, 128.30, 127.98, 127.95, 127.89, 127.69, 126.71, 126.17, 126.01, 125.76, 86.02 (C-1), 78.20 (C-3), 75.68 (C-2), 72.72, 72.43, 71.72 (C-5), 68.43 (C-4); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{30}H_{28}O_6S$, 539.1504; found, 539.1497.

Phenyl 2-*O*-benzyl-3-*O*-(2-methylnaphthyl)-1-thio-*α*-D-glucopyranosiduronic acid (17b): To a solution of **16b**



(2.0 g, 3.98 mmol) in 10% H_2O in DCM (v/v) (21 mL), BAIB (2.6 g, 8.07 mmol) was added under stirring. After addition of TEMPO (0.12 g, 0.80 mmol) the reaction was stirred for 1h at rt. The mixture was quenched by addition of 10% $Na_2S_3O_3$ solution in H_2O w/w (50 mL) and was extracted with ethyl acetate at pH 3 (3 x 40 mL). The organic layers were combined, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 60% - EtOAc in *n*-heptane + 2% acetic acid) of the residue afforded **17b** as an inseparable mixture with Phenyl 3-*O*-benzyl-2-*O*-(2-methylnaphthyl)-1-thio-*α*-D-glucopyranosiduronic acid (1.63 g, 79%). **TLC:** (EtOAc/*n*-heptane/acetic acid, 60/38/2 v/v/v): R_f = 0.08; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.62 (br, s, 1H), 7.86 – 7.65 (m, 5H), 7.62 – 7.12 (m, 12H), 5.16 – 4.71 (m, 4H), 4.71 (d, *J* = 9.8 Hz, 1H, H-1), 3.94 – 3.80 (m, 1H, H-4, H-5), 3.69 – 3.59 (m, 1H, H-3), 3.55 – 3.44 (m, 1H, H-2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.79, 137.77, 135.59, 133.23, 132.76, 132.74, 132.42, 129.15, 128.46, 128.39, 128.20, 128.14, 128.10, 128.00, 127.93, 127.66, 126.80, 126.06, 126.05, 126.01, 125.91, 88.14 (C-1), 85.03 (C-3), 79.55 (C-2), 76.68 (C-5), 75.67, 75.57, 71.88 (C-4). **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{30}H_{28}O_6S$, 539.1504; found 539.1491.

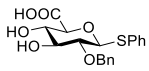
Phenyl 2-*O*-benzyl-1-thio-α-D-mannopyranosiduronic acid (18a):



To a well stirred emulsion of **17a** (1.37 g, 2.66 mmol) in DCM and H_2O (7.5/1 v/v) (20 mL) was added DDQ (0.965 g, 4.25 mmol) and the suspension was protected from light and stirred at rt for 1.5h. The mixture was diluted with DCM (100 mL) and washed (2 x 20 mL) with 10% $Na_2S_3O_3$ in H_2O w/w at pH 3, to reduce the remaining DDQ. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silicagel flash column chromatography (0% → 10% - MeOH in DCM + 2% acetic acid) of the residue afforded **18a** as a pale yellow amorphous solid (0.700 g, 70%). **TLC:** (MeOH/DCM/acetic acid, 10/88/2 v/v): R_f = 0.43; **^{1}H NMR** (500

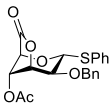
MHz, MeOD-d_4) δ 7.49 – 7.38 (m, 4H), 7.36 – 7.23 (m, 6H), 5.53 (d, *J* = 2.8 Hz, 1H, C-1), 4.70 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 8.6 Hz, 1H, H-5), 4.05 (t, *J* = 8.7 Hz, 1H, H-4), 3.93 (t, *J* = 3.0 Hz, 1H, H-2), 3.81 (dd, *J* = 8.8, 3.3 Hz, 1H, H-3), 3.35 (s, 1H); **^{13}C NMR** (126 MHz, MeOD-d_4) δ 173.01 (C-6), 139.36, 135.21, 132.81, 132.41, 130.10, 129.99, 129.37, 129.29, 129.10, 128.83, 128.68, 128.62, 128.31, 86.98 (C-1), 79.90 (C-2), 74.77 (C-5), 73.72, 72.24 (C-3), 70.57 (C-4).

Phenyl 2-*O*-benzyl-1-thio-*α*-D-glucopyranosiduronic acid (18b):



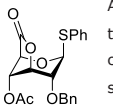
To a well stirred emulsion of **17b** (1.6 g, 3.10 mmol) in DCM and H_2O (7/1 v/v) (24 mL) was added DDQ (1.1 g, 4.65 mmol) and the emulsion was protected from light and stirred at rt for 1.5 h. The mixture was diluted with DCM (100 mL) and washed with 10% $Na_2S_3O_3$ in H_2O (3x50 mL) at pH 3. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel flash column chromatography (0% → 10% - MeOH in DCM + 2% acetic acid) of the residue afforded **18b** as a yellow solid (1.01 g, 87%). **TLC:** (MeOH/DCM/acetic acid, 20/78/2 v/v/v): R_f = 0.26; **^{1}H NMR** ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.58 – 7.49 (m, 2H), 7.44 – 7.28 (m, 8H), 4.90 (d, *J* = 10.8 Hz, 1H,), 4.77 (d, *J* = 10.8 Hz, 1H), 4.71 (d, *J* = 9.7 Hz, 1H, H-1), 3.83 (d, *J* = 7.8 Hz, 1H, H-4), 3.75 – 3.67 (m, 2H, H-5, H-3), 3.39 (t, *J* = 8.7 Hz, 1H, H-2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.66 (C-6), 137.72, 132.60, 132.42, 129.27, 128.56, 128.35, 128.26, 128.13, 87.84 (C-1), 79.27, 77.53, 76.00, 75.36, 71.11. 173.14 (C-6), 139.46, 135.30, 132.91, 130.20, 129.47, 129.39, 128.93, 128.72, 87.08 (C-1), 80.00 (C-2), 74.87 (C-3), 73.81 (C-4), 72.33, 70.66 (C-5).

Phenyl 4-*O*-acetyl-2-*O*-benzyl-1-thio-α-D-mannopyranosidurono-6,3-lactone (11a):



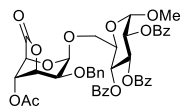
A solution of **18a** (0.131 g, 0.348 mmol) in Ac_2O (55.2 mL) was kept at 70°C for 1.5h, then cooled to rt and the reaction mixture was co-evaporated with toluene (3 x 50 mL). Silicagel flash column chromatography (15% → 35% - EtOAc in *n*-heptane) of the residue afforded **11a** as a colorless solid (0.122 g, 88%). **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.48; **^{1}H NMR** 500 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 2H, -C*H* Ar), 7.41 – 7.28 (m, 8H, -C*H* Ar), 4.96 (dd, *J* = 5.9, 3.1 Hz, 1H, H-4), 4.90 (d, *J* = 8.9 Hz, 1H, H-1), 4.87 (dt, *J* = 5.9, 1.3 Hz, 1H, H-3), 4.80 (d, *J* = 11.6 Hz, 1H, C*H*HPh), 4.67 (d, *J* = 11.6 Hz, 1H, CH*H*Ph), 4.44 (dd, *J* = 3.1, 1.0 Hz, 1H, H-5), 3.69 (dd, *J* = 8.9, 1.5 Hz, 1H, H-2), 1.96 (s, 3H, C*H*$_3$ Ac); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.27 (C-6), 168.47, 136.85, 133.54, 131.36, 128.98, 128.55, 128.45, 128.25, 128.12, 83.97 (C-1), 76.54 (C-3), 73.05, 72.92 (C-2), 71.97 (C-5), 69.80 (C-4), 20.38.

Phenyl 4-*O*-acetyl-2-*O*-benzyl-1-thio-*α*-D-glucopyranosidurono-6,3-lactone (11b):



A solution of diol **18b** (0.500 g, 1.33 mmol) in Ac_2O (2.5 mL, 26,5 mmol) was kept at 70°C for 1.5 h, then cooled to rt and the reaction mixture was co-evaporated with toluene (3x50 mL). Silicagel flash column chromatography (15% → 35% - EtOAc in *n*-heptane) of the residue afforded **11b** as a colorless solid (0.30 g, 56%). **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.50; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H), 7.38 – 7.27 (m, 8H), 5.59 (d, *J* = 2.2 Hz, 1H, H-1), 5.11 (dt, *J* = 5.0, 2.0 Hz, 1H, H-3), 4.94 (ddd, *J* = 5.0, 3.5, 1.0 Hz, 1H, H-4), 4.58 (ad, *J* = 11.2 Hz, 1H), 4.54 (ad, *J* = 11.2 Hz, 1H), 4.23 (d, *J* = 3.2 Hz, 1H, H-5), 4.10 – 4.01 (m, 1H, H-2), 1.89 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.24, 169.42 (C-6), 136.36, 132.95, 132.48, 128.89, 128.40, 128.21, 128.03, 85.04 (C-1), 76.54 (C-2), 73.14, 71.95 (C-3), 68.53 (C-5), 68.18 (C-3), 20.26.

Methyl 4-*O*-acetyl-2-*O*-benzyl-β-D-mannopyranosilurono-6,3-lactone-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (13): Methyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside (0.087 g, 0.171 mmol), **18a** (0.057 g, 0.142 mmol) and 4Å MS were added to dry DCM (3 mL) under inert atmosphere and the mixture was stirred at -10°C for 15 minutes. *N*-iodosuccinimide (0.038 g, 0.171 mmol) and AgOTf (7.3 mg, 0.028 mmol) were added and the reaction was stirred at -10°C for 1h. Et_3N was added and the reaction was quenched with 10% $Na_2S_3O_3$ in H_2O w/w (1 mL). The mixture was diluted with ethyl acetate (50 mL) and filtrated. The filtrate was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. After acetylation of the excess of acceptor, silicagel flash column chromatography (15% → 50% - EtOAc in *n*-heptane) of the residue



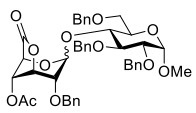
afforded **13** as a colorless solid (0.092 g, 81%). **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.25; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (dt, J = 8.4, 1.3 Hz, 4H), 7.85 – 7.80 (m, 2H), 7.54 – 7.45 (m, 2H), 7.44 – 7.21 (m, 12H), 6.14 (t, J = 9.8 Hz, 1H, H-3'), 5.40 (dd, J = 10.4, 9.4 Hz, 1H, H-4'), 5.30 (d, J = 4.9 Hz, 1H, H-1), 5.24 (dd, J = 10.2, 3.6 Hz, 1H, H-2'), 5.18 (d, J = 3.6 Hz, 1H, H-1'), 5.02 (dd, J = 6.0, 3.2 Hz, 1H, H-4), 4.93 (dddd, J = 6.1, 1.2, 1.2, 1.2 Hz, 1H, H-3), 4.80 (d, J = 11.6 Hz, 1H), 4.66 (d, J = 11.6 Hz, 1H), 4.32 (ddd, J = 10.1, 7.9, 1.9 Hz, 1H, H-5'), 4.10 (dd, *J* = 3.2, 1.0 Hz, 1H, H-5), 4.03 (dd, J = 5.0, 1.3 Hz, 1H, H-2), 3.94 (dd, J = 11.4, 1.9 Hz, 1H, H-6'a), 3.66 (dd, J = 11.5, 8.0 Hz, 1H, H-6'b), 3.36 (s, 3H), 2.09 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.26 (C-6), 169.26, 165.75, 165.62, 165.56, 137.03, 133.38, 133.24, 132.92, 129.88, 129.83, 129.54, 129.19, 129.00, 128.72, 128.46, 128.33, 128.30, 128.13, 128.03, 127.80, 98.97 (C-1), 96.48 (C-1'), 76.47 (C-3), 72.09 (C-2'), 71.15, 70.76 (C-4), 70.46 (C-3'), 70.37 (C-2'), 69.69 (C-4'), 68.64 (C-5'), 67.28 (C-5), 67.11 (C-6), 55.32, 20.43; **^{13}C-coupled HSQC** (101 MHz, $CDCl_3$): δ 98.97 ($J_{C1\text{-}H1}$ = 173 Hz), 96.48 ($J_{C1'\text{-}H1'}$ = 173 Hz); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{43}H_{40}O_{15}$, 819.2265; found 819.2269.

Methyl 2,4-di-*O*-benzyl-β-D-mannopyranosilurono-6,3-lactone-(1→4)-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranoside (19): Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (0.141 g, 0.303 mmol), **18a** (0.061 g, 0.151 mmol) and were added to dry DCM (3 mL) under inert atmosphere and the mixture was stirred at -10°C for 15 minutes. *N*-iodosuccinimide (0.041 g, 0.182 mmol) and AgOTf (7.8 mg, 0.030 mmol) were added and the reaction was stirred at -10°C for 1h. Et_3N was added and the reaction was quenched with 10% $Na_2S_3O_3$ in H_2O w/w (1 mL). The mixture was diluted with ethyl acetate (50 mL) and filtrated. The filtrate was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. After acetylation of the excess of acceptor, silicagel flash column chromatography (15% → 40% - EtOAc in *n*-heptane) of the residue afforded **19** as a colorless solid (0.058 g, 50.6%). **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.43; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 20H, C*H* Ar), 5.42 (d, J = 5.2 Hz, 1H, H-1), 5.08 (d, J = 10.8 Hz, 1H), 4.94 (dd, J = 6.0, 3.1 Hz, 1H, H-4), 4.92 (d, J = 10.8 Hz, 1H), 4.83 (dd, J = 6.0, 1.1 Hz, 1H, H-3), 4.70 (d, J = 12.0 Hz, 1H), 4.60 (d, *J* = 2.9 Hz, 1H, H-1'), 4.59 (d, J = 12.2 Hz, 1H), 4.49 (s, 2H), 4.46 (d, J = 12.2 Hz, 1H), 4.35 (d, J = 12.2 Hz, 1H), 4.05 – 3.99 (m, 2H, H-3', H-5), 3.91 (dd, J = 10.9, 4.0 Hz, 1H, H-6'a), 3.83 (dd, J = 5.2, 1.1 Hz, 1H, H-2), 3.78 (ddd, J = 10.0, 4.0, 1.9 Hz, 1H, H-5'), 3.73 – 3.67 (m, 1H, H-4'), 3.67 (dd, J = 10.8, 2.0 Hz, 1H, H-6'b), 3.54 (dd, J = 9.4, 3.4 Hz, 1H, H-2'), 3.34 (s, 3H), 2.06 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.25 (C-6), 169.26, 139.61, 138.62, 137.98, 136.71, 128.52, 128.36, 128.14, 128.12, 128.03, 127.89, 127.80, 127.57, 127.31, 127.19, 127.03, 99.98 (C-1), 97.42 (C-1'), 81.19 (C-2'), 79.60 (C-4'), 79.39 (C-3'), 74.96 (C-3), 74.34, 73.08, 72.96, 71.42, 71.37 (C-2), 71.03 (C-4), 69.30 (C-5'), 68.77 (C-6'), 67.65 (C-5), 55.11, 20.42; **^{13}C-coupled HSQC** (101 MHz, $CDCl_3$): δ 99.98 ($J_{C1\text{-}H1}$ = 172 Hz), 97.42 ($J_{C1'\text{-}H1'}$ = 167 Hz); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{43}H_{46}O_{12}$, 777.2887; found, 777.2872.

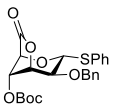
Methyl 4-*O*-acetyl-2-*O*-benzyl-*α/β*-D-glucopyranosilurono-6,3-lactone-(1→6)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (20): **11b** (42 mg, 0.11 mmol) and methyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside **10** (64 mg, 0.13 mmol) were dissolved in dry DCM (3 mL) under inert atmosphere. MS (4Å) were added, the mixture was cooled to -10°C and stirred for 15 minutes. *N*-iodosuccinimide (28 mg, 0.126 mmol) and AgOTf (5.4 mg, 0.02 mmol) were added and the reaction was stirred at -10°C for 1 h. Et_3N was added and the reaction was quenched with 10% $Na_2S_3O_3$ in H_2O w/w (1 mL). The mixture was diluted with ethyl acetate (50 mL) and filtrated. The filtrate was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. After acetylation of the excess of acceptor, silicagel flash column chromatography (15% → 50% - EtOAc in *n*-heptane) of the residue afforded **20** (68 mg, 81%) as a colorless oil. **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.25; Major isomer *β*(1→6) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.83 (m, 6H), 7.54 – 7.24 (m, 14H), 6.15 (t, *J* = 9.8 Hz, 1H, H-3'), 5.53 (t, *J* = 9.9 Hz, 1H, H-4'), 5.27 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2'), 5.22 (d, *J* = 3.7 Hz, 1H, H-1'), 5.16 (ddd, *J* = 6.2, 2.9, 1.8 Hz, 1H, H-3), 5.05 (s, 1H, H-1), 4.83 – 4.79 (m, 1H, H-4), 4.65 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.29 – 4.20 (m, 1H, H-5'), 4.16 – 4.07 (m, 1H, H-5), 4.02 (d, *J* = 3.7 Hz, 1H, H-2), 3.96 (dd, *J* = 11.5, 2.0 Hz, 1H, H-6'a), 3.65 (dd, *J* = 11.5, 6.4 Hz, 1H, H-6'b), 3.46 (s, 3H), 1.82 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.70, 169.98, 165.74, 165.67, 165.42, 136.81, 133.44, 133.27, 132.99, 129.88, 129.86, 129.58, 129.22, 129.04, 128.79, 128.44, 128.41, 128.34, 128.19, 128.02, 101.04 (C-1), 96.83 (C-1'), 75.77, 73.39, 72.01, 71.61, 70.48, 69.29, 68.44, 68.11,

67.95, 66.90, 55.45, 20.33; **^{13}C-coupled HSQC** (126 MHz, $CDCl_3$): δ major *β*(1→6) = 101.04 ($J_{C1\text{-}H1}$ = 172 Hz), 96.83 ($J_{C1'\text{-}H1'}$ = 172 Hz), *α*(1→6) = 98.91 ($J_{C1\text{-}H1}$ = 162 Hz), 97.02 ($J_{C1'\text{-}H1'}$ = 172 Hz); (*m/z*): $[M+Na]^+$ calcd for $C_{43}H_{40}O_{15}$, 819.2265; found 819.2269.

Methyl 2,4-di-*O*-benzyl-*α/β*-D-glucopyranosilurono-6,3-lactone-(1→4)-2,3,6-tri-*O*-benzyl-*α*-D-gluco-pyranoside (21): **11b** (0.061 g, 0.151 mmol) and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (0.141 g, 0.303 mmol) were dissolved in dry DCM (3 mL) under inert atmosphere. MS (4Å) were added and the mixture was stirred for 15 minutes at -10°C. *N*-iodosuccinimide (0.041 g, 0.182 mmol) and AgOTf (7.8 mg, 0.030 mmol) were added and the reaction was stirred at -10°C for 1h. Et_3N was added and the reaction was quenched with 10% $Na_2S_3O_3$ in H_2O. The mixture was diluted with ethyl acetate (50 mL) and filtrated. The filtrate was washed with H_2O (2x20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. After acetylation of the excess of acceptor, silicagel flash column chromatography (15% → 40% - EtOAc in *n*-heptane) of the residue afforded **21** (0.058 g, 50.6%) as a colorless oil. **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.43; *β*(1→6) anomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.20 (m, 18H), 7.12 – 7.07 (m, 2H), 5.46 (d, *J* = 1.3 Hz, 1H, H-1), 5.05 – 4.97 (m, 1H, H-3), 4.97 (d, *J* = 10.6 Hz, 1H), 4.92 (d, *J* = 10.6 Hz, 1H), 4.82 (ddd, *J* = 4.9, 3.5, 0.9 Hz, 1H, H-4), 4.76 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 3.7 Hz, 1H, H-1'), 4.53 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.33 (d, *J* = 10.7 Hz, 1H), 4.27 (d, *J* = 10.7 Hz, 1H), 4.16 – 4.14 (m, 1H, H-5), 3.99 (t, *J* = 9.1 Hz, 1H, H-3'), 3.96 – 3.67 (m, 4H, H-2, H-4', H-5', H-6'a), 3.60 (dd, *J* = 11.0, 1.7 Hz, 1H, H-6'b), 3.52 (dd, *J* = 9.5, 3.6 Hz, 1H, H-2), 3.36 (s, 3H), 1.70 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.58, 169.81, 139.04, 138.08, 138.04, 136.64, 128.41, 128.35, 128.30, 128.18, 128.07, 128.04, 127.96, 127.87, 127.56, 127.55, 127.54, 127.42, 101.10 (H-1), 97.99 (H-1'), 80.29, 80.23, 76.66, 76.64, 75.05, 73.33, 73.30, 72.78, 71.56, 69.43, 68.70, 68.39, 68.13, 55.28, 20.17; **^{13}C-coupled HSQC** (126 MHz, $CDCl_3$): *β*(1→4) δ 101.10 ($J_{C1\text{-}H1}$ = 173 Hz), 97.99 ($J_{C1'\text{-}H1'}$ = 169 Hz), *α*(1→4) = 98.82 ($J_{C1\text{-}H1}$ = 163 Hz), 97.79 ($J_{C1'\text{-}H1'}$ = 170 Hz); **HRMS** (*m/z*): $[M+Na]^+$ calcd for $C_{43}H_{46}O_{12}$, 777.2887; found, 777.2872.



Phenyl 2-*O*-benzyl-4-*O*-*tert*-butyloxycarbonyl-1-thio-α-D-mannopyranosidurono-6,3-lactone (22):



To a solution of **18a** (109 mg, 0.29 mmol) in DMF (4 mL) was added Boc_2O (1.26 g, 5.80 mmol) and the reaction was stirred at 70°C for 1.5h, then cooled to rt and the reaction mixture was co-evaporated with toluene (3 x 50 mL). Silicagel flash column chromatography (15% → 35% - EtOAc in *n*-heptane) of the residue afforded **22** as a colorless solid (48 mg, 36%). **TLC:** (EtOAc/*n*-heptane, 40/60 v/v): R_f = 0.48; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.38 – 7.28 (m, 8H), 4.92 (d, *J* = 9.0 Hz, 1H, H-1), 4.89 (dt, *J* = 5.9, 1.3 Hz, 1H, H-3), 4.86 (dd, *J* = 5.9, 3.0 Hz, 1H, H-4), 4.75 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.48 (dd, *J* = 3.1, 1.1 Hz, 1H, H-5), 3.76 (dd, *J* = 8.9, 1.4 Hz, 1H, H-2), 1.49 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.52 (C-6), 151.56, 137.03, 132.74, 131.79, 129.05, 128.50, 128.15, 128.12, 127.93, 84.33 (C-1), 84.25 (C-2), 76.82 (C-3), 73.16, 72.99 (C-2), 72.10 (C-5), 71.56 (C-4), 27.61.

5.8 – References

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6

Summary, Perspective and Outlook

6.1 – Summary and perspective

6.1.1 – Gluco-type sugars

Controlling the stereoselective outcome of the chemical glycosylation reaction remains one of the most challenging aspects of oligosaccharide synthesis. Especially the synthesis of the 1,2-*cis* glycosidic linkage hampers the progress of the glycomics field. In 2005 Boons and coworkers used a (1*S*)-phenyl-2-(phenylsulfanyl)ethyl participating group on *O*-2 to efficiently synthesize 1,2-*cis* (*α*-)glucosides *via* a *β*-sulfonium ion.[1] This method, however, relies on the labor intensive introduction of a chiral auxiliary, as well as having a withdrawing acyl functionality on C-3 to ensure excellent *α*-selectivity (Figure 1). Furthermore, the exact mechanism of sulfonium ion mediated glycosylation is a topic of much debate. As a result, while this methodology seems promising, it needs fine-tuning in order to be viable as a reliable and broadly applicable methodology. Additionally, there have been several groups working on the gluco-type sulfonium ion mediated glycosylation reaction in the last decade. However, the 1,2-*cis* linkage in manno-type and the 2-deoxy-2-amino derivatives are equally important and the sulfonium intermediates could play a vital role in their reliable synthesis.

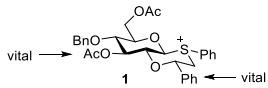
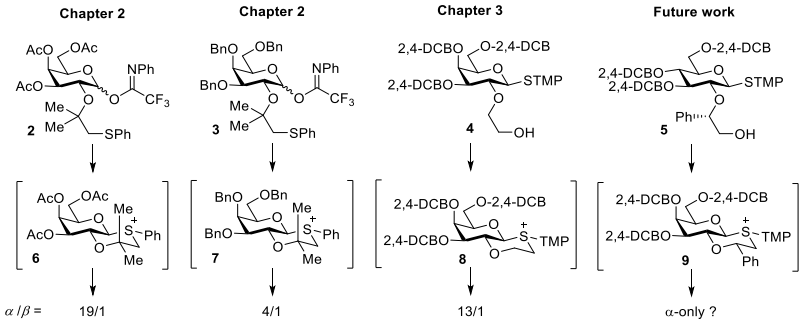


Figure 1: Chirality of auxiliary is and an acyl moiety on C-3 are vital for 1,2-*cis* selectivity.

The overall aim of the work presented in this thesis was the development of generally applicable methodology for stereoselective glycosylation. The work presented in **Chapter 2** and **Chapter 3** was aimed at simplifying the use C-2 auxiliaries to prepare 1,2-*cis*-glucosides and galactosides. To this end, use of the Thorpe-Ingold effect on auxiliary participation was investigated, which led to the development of highly selective acetylated galactosyl donor **2** (*α*/*β* = 19/1, Scheme 1).[2] In contrast, fully benzylated counterpart **3** was not as selective (*α*/*β* = 4/1, Scheme 1). The work in **Chapter 3** described the development of a new method to activate thioglycosides to afford *β*-sulfonium ions. Careful optimization of the protecting groups as well as the electron-donating property of the anomeric thioether to fine-tune the delicate, crucial charge distribution of the reactive glycosylation intermediates led to selective glucosyl and galactosyl donors. Adding electron-withdrawing substituents on the benzyl protecting groups increased *α*-selectivity, albeit up to an *α*/*β* ratio of 13/1, still leaving room for improvement (**4**, Scheme 1). Achiral auxiliaries are less selective than chiral auxiliaries and hence combining the new activation method with chiral auxiliaries has the potential to further improve *α*-stereoselectivity (**5**, Scheme 1).



Scheme 1: Would a combination of the newly developed activation system and a chiral auxiliary reliably afford 1,2-*cis* glycosides?

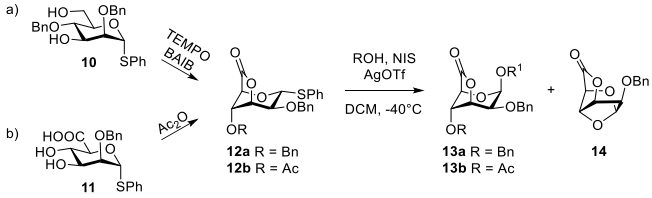
Furthermore, a broadly applicable glycosylation procedure should comprise both the synthesis of *α*- and *β*-glycosides and should ideally originate from the same building block. The synthesis route introduced in **Chapter 3** allows for late stage introduction of the C-2 directing group, i.e. the final step before glycosylation. Introduction of a C-2 acetyl group reliably results in *β*-glycosides and, if the *α*-selective glycosylation can be perfected, e.g. by using donor **5**, a universal building block synthesis with subsequent stereoselective glycosylations emerges.

The formation of the *α*-product in the *β*-sulfonium ion model is dependent on the persistence of this intermediate compared to the oxocarbenium ion, as S_N2-like displacement of the first can only result in *α*-products and S_N1-like glycosylation of the latter results in a mixture of anomers. Other important factors that may influence the reaction mechanism are parameters such as temperature and solvent. Detailed analysis of product formation followed by variable temperature NMR (VT-NMR) studies and the temperature at which the reaction initiates can be pinpointed, and should be kept at that temperature. This may maximize the formation of *α*-glycoside and could give potentially important information for follow-up studies. As chemists use countless different donors and acceptors, all with their own unique reactivity, this temperature would differ for every single donor-acceptor combination, still it would be interesting to know whether an isocratic temperature influences the anomeric outcome in a positive way.

It is well known that solvents can also have a profound influence on the reaction mechanism, yet this solvent effect has never been investigated on glycosyl sulfonium ions. During a cursory solvent screening for the glycosylation of the 2,4-DCB glucose donor, we observed increased *α*-selectivity when a 20% Et_2O/DCM solvent mixture was used (*α*/*β* = 9/1 vs 11/1. This is consistent with the reported *α*-selective properties of the Et_2O solvent and a cooperative effect of the glycol auxiliary could be responsible for the improvement. Further research in solvent optimization may therefore be explored to improve α-selectivity.

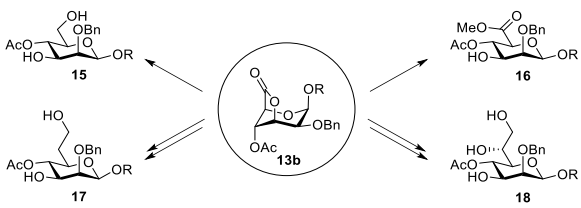
6.1.2 – Manno-type sugars

1,2-*cis* (*β*-)Mannosylation using sulfonium intermediates was investigated in **Chapter 4**. This was achieved using a lactone induced ringflip, albeit with an inseparable 1,4-anhydro byproduct (**14**, Scheme 2). The discovery of remote participation of the *O*-4 moiety debates the importance of the *β*-sulfonium intermediate. Substituting the *O*-4 benzyl (**12a**) for an *O*-4 acetyl group (**12b**) in **Chapter 5**, remedied the formation of the byproduct and afforded stereoselective *β*-mannuronic acid lactones (**13b**).



Scheme 2: Stereoselective *β*-mannosylation. **a)** Lactonization of **10** and subsequent glycosylation afforded an inseparable mixture of **13a** and **14**; **b)** Lactonization of **11** with Ac_2O afforded **12b** which upon glycosylation afforded only **13b**.

These mannuronic acid lactones could serve as valuable building blocks for future research. For example, reducing mannuronic acid lactone **13b** with K-selectride will generate mannose (**15**), which can be an attractive way to prepare 1,2-*cis* mannosides found in the human core *N*-glycan. Acidic opening of **13b** in methanol will access mannuronic acid methyl ester **16**, which, together with L-guluronic acid, can be used to synthesize uronic acid alginates. Furthermore, 6-deoxy-*D*-manno-heptopyranose **17** could potentially be accessed by selective reduction to the aldehyde, followed by a Wittig reaction and reduction of the resulting alkene. Submitting the aforementioned alkene to dihydroxylation would afford glycero-*D*-manno-heptose derivatives (**18**) which are important carbohydrate constituents of the lipopolysaccharide of gram negative bacteria.[3] Furthermore, as the *O*-4-acetyl group is the directing group during the glycosylation reaction, introducing an azide functionality on C-2 could be used to access the 1,2-*cis*-mannosamine derivatives.



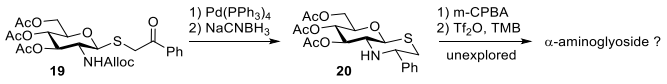
Scheme 3: Selective opening of the mannuronic acid lactones affords various potential building blocks.

6.1.3 – Concluding remarks

In conclusion, we have developed a three-step synthetic route towards a pre-donor on which a desired C-2 *α*- or *β*-directing group could be introduced (2-hydroxyethyl or acetyl, resp.). Subsequent *β*-glycosides can reliably be synthesized, however, future work is still needed to improve α-selectivity during glycosylation reactions. Additionally, we have discovered a new mode of participation in $^{1}C_{4}$ locked mannoside glycosylations, which could be exploited to generate various *β*-mannoside derivatives, possibly including *β*-mannosamines.

6.2 – Outlook

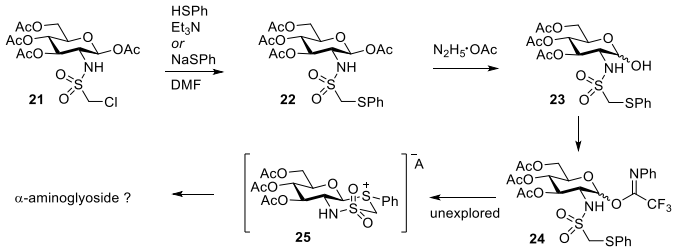
As was mentioned in section 6.1.1., the stereoselective synthesis of 1,2-*cis* glucosamines using a sulfonium ion intermediate is an interesting endeavor. We were inspired by the work of Turnbull and coworkers,[8] who managed stereoselective 1,2-*cis* glycosylation *via* pre-formation of the oxathiane system. *m*-CPBA mediated oxidation of the sulfur, followed by aromatic electrophilic substitution using triflic anhydride and 1,3,5-trimethoxybenzene to activate the donor. Therefore, we synthesized allyloxycarbonyl (Alloc) protected amino sugar **19**. A reductive amination was initiated by $Pd(PPh_3)_4$ mediated removal of the Alloc protecting group, forming the imine. Reduction of the imine then afforded thiomorpholine **20**, albeit in low yield. Unfortunately, we were only able to obtain **20** a single time and subsequent efforts to resynthesize **20** failed. Consequently, the essential glycosylation reaction remains unexplored.



Scheme 4: Reductive amination of **19** afforded thiomorpholine **20**. Subsequent glycosylation is still unexplored.

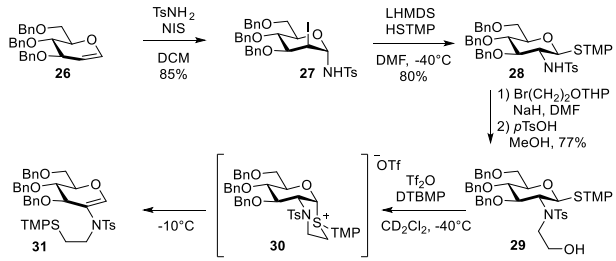
Next, we investigated the glycosylation methodology developed by Boons and coworkers,[1] which after departure of a C-1 imidate leaving group uses a participating C-2 auxiliary to achieve high 1,2-*cis* selectivities. The aforementioned nucleophilicity of the amine can be reduced by attaching an electron-withdrawing substituent on the amine, e.g. a sulfonyl group. In addition, sulfonamide sulfonium **25** has an axial oxygen which has shown to exhibit a positive effect on the stereoselective outcome when compared to bicyclic ring systems that do not contain this axial substituent.[9] Synthesis of the donor involves introduction of the auxiliary using chloromethane sulfonyl chloride and sodium hydride, affording **21**. Subsequent nucleophilic substitution using thiophenol and triethyl amine (TEA) afforded **22**, which was then deacetylated using hydrazinium acetate (**23**). Work-up involved an aqueous extraction and concentration of the organic layer and subsequent installation of the imidate failed. In order to attempt another

imidation of **23**, we needed to resynthesize it. Unfortunately, after many attempts synthesis of compound **22** proved unsuccessful and this synthesis route had to be abandoned.



Scheme 5: Synthesis route to donor **24**. Resynthesizing **22** failed and so the glycosylation remains unexplored.

Finally, the Tf_2O mediated activation of the 2-hydroxylethyl auxiliary, as discussed in Chapter 3, could be further extended to stereoselective synthesis of 1,2-*cis* aminoglycosides. We chose a tosyl protecting group in order to reduce the nucleophilicity of the amine's lone pair. Following an elegant two-step literature procedure, thioether **28** was synthesized from perbenzylated glucal in excellent yield.[10] A two-step installation of our previously designed 2-hydroxyethyl auxiliary obtained glucosyl donor **29**. We then followed the activation of this donor using variable temperature NMR studies and surprisingly found *α*-configured sulfonium ion **30**. Raising the temperature then resulted in glucal **31** *via* trans di-axial elimination.



Scheme 6: Three step synthesis route to donor **29**. Glycosylation afforded glucal **31**.

The section above shows that carbohydrate reactions are delicate procedures and not always seem to follow logic, as using the apparent same reaction conditions multiple times fails to afford an identical product. Out of the attempted methodologies for the stereoselective glycosylations, the route shown in Scheme 5, which uses an integrated sulfonamide in the *β*-sulfonium ion, is worth pursuing as the axial oxygen has proven to positively improve 1,2-*cis* selectivity.

6.3 – Acknowledgement

Both Sam J. Moons and Sander Wagemans are acknowledged for their work presented in Scheme 4. Laura Jansen is kindly acknowledged for the work presented in Scheme 5 and 6.

64 – Experimental

General methods: for general methods please refer to section 2.9.

Acetophenone 3,4,6-tri-*O*-acetyl-2-amino(allyloxycarbonyl)-2-deoxy-*β*-glucothiopyranoside (19): Et_3N (3 eq.) and 2-bromoacetophenone (2 eq.) in acetonitrile were added to a solution of 3,4,6-tri-*O*-acetyl-2-amino-allyloxycarbonyl-2-deoxy-1-thio-*β*-*D*-glucopyranosyl in acetonitrile. The mixture was stirred at rt. for 1h, and was then concentrated *in vacuo*. The residue was dissolved in DCM, washed with brine, dried with $MgSO_4$ and concentrated. **19** was obtained using silicagel flash column chromatography (EtOAc/*n*-heptane 40/60%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, 2H), 7.58 (t, *J* = 10.5, 4.3 Hz, 1H), 7.47 (t, 2H), 5.90 – 5.74 (m, 1H), 5.38 – 5.03 (m, 5H), 4.75 (d, *J* = 10.3 Hz, 1H), 4.63 – 4.41 (m, 2H), 4.21 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.15 – 4.02 (m, 3H), 3.86 (q, *J* = 10.1 Hz, 1H), 3.77 – 3.64 (m, 1H), 2.08 – 1.97 (m, 9H).

2-phenyl -(3,4,6-tri-*O*-acetyl-1,2-dideoxy-*β*-D-glucopyrano)-<1,2-d>-1-thiomorpholine (20):

Pd(PPh_3)$_4$ was added to a solution of **19** and dimethyl malonate in dry THF. The mixture was stirred for 16h, an excess of $NaCNBH_3$ was added and the mixture was stirred overnight. The mixture was then washed with brine and water, dried with $MgSO_4$ and concentrated *in vacuo*. Silicagel flash column chromatography (EtOAc/*n*-heptane 40/60%) afforded the product. Recrystallization in $CDCl_3$ afforded colorless needles, yield could not be determined. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 12.0 Hz, 1H), 7.62 – 7.49 (m, 1H), 7.49 – 7.42 (m, 1H), 7.41 – 7.29 (m, 3H), 5.12 (dd, *J* = 7.2, 2.7 Hz, 2H), 4.49 (d, *J* = 8.7 Hz, 1H), 4.28 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.14 (dd, *J* = 12.4, 2.1 Hz, 1H), 3.97 (dd, *J* = 10.7, 2.2 Hz, 1H), 3.90 – 3.75 (m, 1H), 3.22 – 3.11 (m, 1H), 2.92 (dq, *J* = 13.5, 10.7 Hz, 1H), 2.64 (dd, *J* = 13.5, 2.3 Hz, 1H), 2.18 – 1.94 (m, 9H). **HRMS** (m/z): [M+Na]+ calcd for $C_{20}H_{25}NO_7S$, 446.1249; found, 424.1250.

Acetyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-(chloromethyl)sulfonamido-*β*-D-glucopyranoside (21):

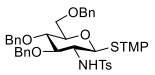
A solution of 1,3,4,6-tetraacetyl-2-deoxy-2-amino-β-D-glucopyranoside·HCl (2.66 mmol) in anhydrous DCM (15 mL) was cooled to 0°C, treated with Et_3N (4.61 mmol), followed by chloromethanesulfonyl chloride (5.71 mmol). The mixture was left to stir at rt for 2h. The solution was concentrated under reduced pressure and redissolved in EtOAc (150 ml). The solution was washed with H_2O (2x 150 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silicagel flash column chromatography (0% to 40%, EtOAc in n-heptane) afforded **21** (0.78 g, 65%) **TLC:** (EtOAc/n-heptane, 50/50 v/v), R_f = 0.4; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.10 (d, J = 9.9 Hz, 1H), 5.73 (d, J = 8.7 Hz, 1H, H-1), 5.26 (dd, J = 10.4, 9.4 Hz, 1H, H-3), 5.13 – 4.93 (m, 1H, H-4), 4.52 (s, 2H), 4.28 (dd, J = 12.5, 4.5 Hz, 1H, H-6), 4.12 (dd, J = 12.5, 2.3 Hz, 1H, H-6), 3.92 (ddd, J = 10.1, 4.5, 2.2 Hz, 1H, H-5), 3.70 (td, J = 10.2, 8.7 Hz, 1H, H-2), 2.22 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.45, 170.72, 169.52, 169.40, 92.12 (C-1), 72.54 (C-5), 72.43 (C-3), 68.19 (C-4), 61.54 (C-6), 57.02 (C-2), 56.35 (CH_2) 21.01, 20.88, 20.70, 20.59.

Tosyl 3,4,6-tri-*O*-benzyl-1-amino-2-deoxy-2-iodo-α-D-mannopyranoside (27):

A suspension of glucal **26** (1.160 g, 2.68 mmol) and *p*-TsOH (3.74 mmol) in dry DCM (15 mL) and NIS (3.16 mmol) was stirred at 0 °C for 1h. The solution diluted with 100 ml DCM and quenched with a sat. aq. $Na_2S_2O_3$ solution. The organic layer was separated and washed with H_2O (2x 150 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silicagel flash column chromatography (0% to 30%, EtOAc in n-heptane) afforded **27** (1.247g, 65%). **TLC**: (EtOAc/n-heptane, 50/50 v/v), R_f=0.80; **^{1}H NMR**: (500 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H), 7.37 – 7.07 (m, 17), 6.11 (d, *J* = 7.7 Hz, 1H), 5.60 (dd, *J* = 7.7, 3.1 Hz, 1H, H-1), 4.69 (d, *J* = 10.9 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.57 – 4.54 (m, 1H, H-2), 4.52 (d, 1H), 4.43 (d, *J* = 2.2 Hz, 1H), 4.41 (d, *J* = 1.7 Hz, 1H), 4.37 (d, *J* = 12.1 Hz, 1H), 3.84 (t, *J* = 7.9 Hz, 1H, H-4), 3.51 (dd, *J* = 10.8, 4.1 Hz, 1H, H-6), 3.45 (ddd, *J* = 8.2, 4.1, 2.8 Hz, 1H, H-5), 3.14 (dd, *J* = 7.7, 3.9 Hz, 1H, H-3), 3.05 (dd, *J* = 10.7, 2.7 Hz, 1H, H-6'), 2.32 (s, 3H); **^{13}C NMR**: (126 MHz, $CDCl_3$) δ 143.73, 138.12, 137.80, 137.44, 137.21, 129.51, 129.32, 128.43, 128.40, 128.38, 128.32, 128.28, 128.06, 127.91, 127.78, 127.72, 127.68, 127.66, 127.54, 127.43,

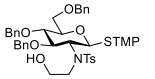
127.34, 86.22, 85.59, 83.36 (C-1), 78.82, 77.17 (C-3), 74.78, 74.59 (C-5), 73.31, 73.22 (C-4), 71.38, 67.59 (C-6), 31.15 (C-2), 21.47.

2,4,6-Trimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-tosylamino-2-deoxy-1-thio-α-D-glucopyranoside (28):



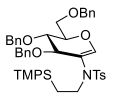
LiHMDS (1,0 M) in THF (8.87 mmol) was added dropwise to a stirred solution of 2,4,6-trimethoxythiophenol (8.87 mmol) in dry DMF (5 mL) at -40°C. Iodide sugar **27** (2,11 g, 2.96 mmol) in DMF (15 mL) was then added dropwise. After 1h, the reaction was stirred an additional 16h at rt. The solution was concentrated *in vacuo* and redissolved in EtOAc (150 ml). The solution was washed with H_2O (2x 150 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silicagel flash column chromatography (0% to 30%, EtOAc in *n*-heptane) afforded **28** (1.87 g, 80%). **TLC**: (EtOAc/*n*-heptane, 30/70 v/v), R_f = 0.3; **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.49 – 7.08 (m, 15H), 6.12 (s, 2H), 5.89 (d, J = 5.0 Hz, 1H), 5.06 (d, J = 10.4 Hz, 1H), 4.74 (d, J = 11.1 Hz, 1H), 4.70 (d, J = 10.4 Hz, 1H), 4.48 (d, J = 11.1 Hz, 1H), 4.44 (s, 2H), 4.18 (d, J = 10.1 Hz, 1H, H-1), 3.83 (s, 6H), 3.80 (s, 3H), 3.74 – 3.68 (m, 2H, H-3, H-6), 3.60 (dd, J = 11.1, 5.2 Hz, 1H, H-6'), 3.47 (t, J = 8.7 Hz, 1H, H-4), 3.38 (ddd, J = 9.0, 5.2, 2.5 Hz, 1H, H-5), 3.18 (ddt, J = 10.1, 8.2, 4.1 Hz, 1H, H-2), 2.34 (s, 3H); **^{13}C NMR**: (126 MHz, $CDCl_3$) δ 162.62, 162.26, 162.02, 143.36, 138.34, 138.01, 137.00, 129.41, 128.40, 128.33, 128.22, 128.21, 128.07, 127.72, 127.71, 127.67, 127.49, 127.46, 100.10, 91.59, 90.76, 90.59, 88.77 (C-1), 84.11 (C-3), 79.84 (C-5), 77.95 (C-4), 75.26, 74.57, 73.45, 69.50 (C-6), 59.04 (C-2), 56.41, 55.99, 55.41, 55.40, 29.69, 21.53.

2,4,6-Trimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-(2-hydroxyethyl)amino-2-deoxy-1-thio-α-D-glucopyranoside



(29): To a cooled solution of amine **28** (200 mg, 0.25 mmol) in dry DMF (5 mL) was added NaH (1.25 mmol) the mixture was stirred for 30 min and warmed up to rt. 2-(2-bromoethoxy)tetrahydro-2H-pyran (1mmol) was added and the mixture was stirred at rt for 16h. The reaction was quenched with MeOH and concentrated *in vacuo*. The mixture was redissolved in MeOH, then *p*-TsOH was added until the pH = 3 and stirred for 2h. The reaction was quenched with MeOH, concentrated *in vacuo* and redissolved in EtOAc (150 ml). The solution was washed with H_2O (2x 150 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silicagel flash column chromatography (0% to 50%, EtOAc in *n*-heptane) afforded **29** (162 mg, 77%); **TLC**: (EtOAc/*n*-heptane, 50/50 v/v), R_f = 0.4; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 – 8.04 (m, 2H), 7.50 – 6.99 (m, 15H), 6.12 (s, 2H), 5.68 (d, J = 10.2 Hz, 1H, H-1), 4.99 (d, J = 10.0 Hz, 1H), 4.92 (d, J = 10.1 Hz, 1H), 4.83 (d, J = 10.8 Hz, 1H), 4.71 (m, 1H, H-3), 4.63 (d, J = 10.8 Hz, 1H), 4.39 (d, J = 11.7 Hz, 1H), 4.32 (d, J = 11.7 Hz, 1H), 3.91 (s, 1H), 3.82 (s, 6H), 3.78 (d, *J* = 10.9 Hz, 2H, H-6), 3.75 (s, 3H), 3.72 – 3.65 (m, 2H, H-6', H-4), 3.60 (dd, *J* = 5.3, 2.3 Hz, 2H, H-5), 3.51 (t, *J* = 10.3 Hz, 1H, H-2), 3.34 (dd, *J* = 5.9, 3.4 Hz, 1H), 2.40 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.86, 143.90, 138.49, 137.92, 136.73, 129.27, 128.66, 128.40, 128.21, 127.8, 127.70, 127.54, 127.43, 97.80, 91.14, 84.40 (C-1), 83.2 (C-3), 80.66 (C-4), 79.5 (C-5), 75.35, 74.77, 74.53, 73.73, 73.57, 68.88 (C-6), 66.51 (C-2), 61.56, 60.19, 55.99, 55.98, 55.53, 55.25, 54.21, 21.97, 21.54.

3,4,6-Tribenzyl-2-deoxy-2-((2-(2,4,6-trimethoxyphenyl)ethyl)tosylamino-*D*-glucal (31):



Donor **29** (22 mg, 1 mmol) and 2,6-di-tert-butyl-4-methylpyridine (2 mmol) were dissolved in DCM-d2 (1.5 mL). MS (4Å) were added and the mixture was cooled to -30°C. Tf_2O (1 mmol) was added and the temperature was allowed to warm up to 10°C. After 10 minutes the reaction was cooled again to -30 °C, affording **31**. **^{1}H NMR** (400 MHz, $CDCl_3$, 6.52 ppm (H-1)) δ 6.52 (d, *J* = 4.9 Hz, 1H), 4.74 (dd, *J* = 11.0, 5.0 Hz, 1H), 4.27 – 4.11 (1H), 4.04 (d, *J* = 9.9 Hz, 1H), 4.00 – 3.89 (1H), 3.81 (d, *J* = 11.7 Hz, 1H), 3.60 (d, *J* = 11.3 Hz, 1H). **^{1}H-^{1}H TOCSY** (400 MHz, $CDCl_3$, 4.32 ppm (H-1)) δ 4.32 (s, 1H), 4.04 (s,1H), 3.77 – 3.68 (m, 2H), 3.58 (d, *J* = 3.7 Hz, 1H), 3.55 (d, *J* = 3.7 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173 (C-2); **^{1}H-^{13}C HSQC** No signal on 173 ppm: quaternary carbon.

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Summary

In nature we can distinguish between three classes of macromolecules being DNA, proteins and carbohydrates (sugars). With the deciphering of the genetic code of the human genome it became clear that this alone is not sufficient to map all biological processes. In time it became clear that, apart from DNA and proteins, carbohydrates play an important role in many biological processes and synthesis of these substances is desired over time consuming and low yielding extraction from e.g. plants.
However, the synthesis of carbohydrates involves the connection of two monomers *via* a glycosidic bond and often this is accompanied with a mixture of two products, called anomers. Reliable synthesis of the 1,2-*trans* anomer can be achieved by using an acetyl functionality on the C-2 position, however stereoselective synthesis of the 1,2-*cis* anomer remains tedious to date. An elegant solution to this problem was published in 2005 and uses intramolecular participating of a C-2 sulfur auxiliary. Although not yet perfect, this methodology is promising for reliable 1,2-*cis* glycosylations. This thesis describes the optimization of 1,2-*cis* glycosylations using sulfonium intermediates.

Chapter 1 describes the development of 1,2-*cis* glycosylations in the past two decades. One of the most important discoveries is that participation of a C-2 (*S*)-(phenylthiomethyl) benzyl group achieves full 1,2-*cis* selectivity, most likely *via* S_N2 substitution of a 1,2-*trans* sulfonium intermediate. It should be noted that this is not the case with systems that are activated by benzyl protecting groups of the remaining hydroxyls.

The discovery that a 1,2-*trans*-sulfonium intermediate can lead to selective 1,2-*cis* glycosylations, triggered our interest to improve this methodology. In **Chapter 2** we tried to stabilize the 1,2-*trans* sulfonium intermediate by introducing two geminal methyl groups on the auxiliary, which speeds up cyclization following the Thorpe-Ingold effect. However, nuclear magnetic resonance (NMR) experiments revealed the presence of a 1,2-*cis* sulfonium intermediate, which leads to the undesired 1,2-*trans* glycoside *via* S_N2 substitution. Warming up this intermediate reveals the formation of the desired 1,2-*trans* sulfonium intermediate, which in the NMR time domain remains the sole compound when cooled down again. Subsequent glycosylation, however, affords a mixture of anomers which suggests that the sulfonium intermediate might just be a resting state and does not participate in the reaction mechanism. In addition to the glucose series, we also included its C-4 epimer, galactose, in our research and discovered a donor which reliably affords 1,2-*cis* galactosides (α/β = 19:1).

A novel activation methodology for glycosylation is introduced in **Chapter 3**. Key factors are the fast building block synthesis and the ability for late stage introduction of the appropriate directing group. Introduction of an acetyl moiety reliably affords 1,2-*trans* glycosides and

introduction of the newly developed ethanol auxiliary provides 1,2-*cis* glycosides. Activation of the latter is achieved with Tf_2O at -40°C, after which raising the temperature results in the crucial 1,2-*trans* sulfonium intermediate. Subsequent addition of an acceptor at low temperatures then results in 1,2-*cis* glycosylation.
This newly developed methodology enabled us to study the electronic effects of protecting groups on the stereoselectivity. Introduction of an electron-donating 2,4,6-trimethoxyphenyl group on the sulfur significantly improved stereoselectivity compared to the phenyl protecting group (α/β = 4:1 vs 2.5:1, resp.). The same effect was observed for galactose counterpart (α/β = 7:1 vs 3:1, resp.). We then turned to the protecting groups on the remaining hydroxyls and found that, in the glucose series, 2,4-dichlorobenzyl protecting groups provided improved stereoselectivity as compared to benzyl groups (α/β = 9:1 vs 4:1, resp.). The galactose series provided even better selectivity with α/β = 13:1.

1,2-*cis* Mannosylation using sulfonium intermediates was, to our knowledge, not explored before and **Chapter 4** describes this development using a ringflip. Switching from the $^4C_1$ to the $^1C_4$ conformation enables a 1,2-*trans* sulfonium intermediate to be formed, which after S_N2 substitution then leads to a 1,2-*cis* mannoside. This ringflip was forced by introducing a 6,3-lactone *via a* TEMPO/BAIB mediated oxidation of a 3,6-diol. Glycosylations achieved complete stereoselectivity, however, control experiments with donors not bearing the C-2 auxiliary also provided complete stereoselectivity (albeit with significant addition of an inseparable by-product). Closer examination of the by-product revealed the formation of an 1,4-anhydro ether, which is formed *via* participation of the C-4 moiety. This was the first time participation of a C-4 benzyl group was reported.

Inspired by the discovery of the C-4 ether participation in mannose in the previous chapter, we developed a similar glucose 6,3-lactone in **Chapter 5**. However, this resulted in a 1,4-anhydro ether as the sole isolated product. Replacing the C-4 benzyl by an acetyl group provided product formation, albeit with low selectivity (α/β = 1:2). In contrast, the mannose counterpart provided full 1,2-*cis* stereoselectivity, without formation of the by-product. Unfortunately, mechanistic studies with a C-4 *tert*-butyloxycarbonyl group did not provide clarification of the reaction mechanism as again the 1,4-anhydro ether was obtained, rather than the expected carbonate.

Chapter 6 reflects on the previous chapters in this thesis and provides suggestions for future research in the field of 1,2-*cis* stereoselectivity in carbohydrate chemistry. This chapter also includes unpublished work regarding 1,2-*cis* aminoglycosylation, with interesting angles that are worth pursuing in the future.

Samenvatting

In de natuur kunnen we drie klassen macromoleculen onderscheiden, DNA, proteïnen en koolhydraten (suikers). Echter de ontcijfering van genetische codes van het menselijk genoom blijkt onvoldoende om alle biologische processen te verklaren, waardoor aan het licht is gekomen dat koolhydraten daar ook een grote invloed op hebben. Echter synthese van koolhydraten wordt bemoeilijkt door de binding tussen twee afzonderlijke koolhydraten, de glycosidische band. De koppeling van twee koolhydraten middels deze glycosidische band gaat vaak gepaard met een slechte opbrengst en een mengsel van twee producten, anomeren. Betrouwbare synthese van het 1,2-*trans* anomeer maakt gebruik van een acetyl groep op de C-2 positie, echter het 1,2-*cis* anomeer levert vaak problemen op. In 2005 is daar een elegante oplossing voor gekomen die gebruikt maakt van een intramoleculaire participerende C-2 zwavel groep, welke overigens nog niet werkt voor alle suikers. Dit proefschrift beschrijft de optimalisatie van de 1,2-*cis* glycosylering door middel van intramoleculaire participerende groepen.

Hoofdstuk 1 beschrijft de ontwikkeling van 1,2-*cis* glycosyleringen die in de laatste twee decennia plaatsgevonden heeft. Een van de belangrijkste ontdekkingen is dat participatie van een C-2 (*S*)-(phenylthiomethyl) benzyl groep, waarschijnlijk via S_N2 substitutie van een *trans*-sulfonium ion, volledige selectiviteit oplevert. Hierbij moet wel vermeld worden dat dit niet het geval is als het systeem volledig geactiveerd is door benzyl bescherming.

De ontdekking dat een *trans*-sulfonium intermediair kan leiden naar selectieve 1,2-*cis* glycosyleringen, maakte dat we in **Hoofdstuk 2** de desbetreffende methode probeerde te verbeteren. Hier werd geprobeerd het sulfonium ion te stabiliseren door middel van de introductie van twee geminale methylen op de C-2 hulpgroep die dan gebruik maken van het Thorpe-Ingold effect. Echter werd er met nucleaire kernspin (NMR) experimenten ontdekt dat eerst een 1,2-*cis* intermediair gevormd wordt, welke na substitutie leidt naar het ongewenste 1,2-*trans* product. Als dit intermediair opgewarmd wordt, vormt het gewenste 1,2-*trans* intermediair, welke in het NMR-tijdsdomein het enige product blijft, ook wanneer het systeem weer gekoeld wordt. Daaropvolgende glycosylering levert echter een anomeer mengsel op, wat de suggestie wekt dat dit intermediair slechts een rust toestand is en niet participeert in het reactiemechanisme. In aanvulling op de glucose serie hebben we ook de C-4 epimeer, galactose, in ons onderzoek meegenomen en vonden we dat deze bijna volledig selectief reageert naar het 1,2-*cis* product (α/β = 19:1).

In **Hoofdstuk 3** hebben we een nieuwe activatie methode ontwikkeld voor glycosyleringen. Sleutel factoren zijn de snelle bouwblok synthese en de mogelijkheid om in een zeer laat stadium de participerende groep te introduceren. De introductie van een acetyl resulteert in betrouwbare synthese van 1,2-*trans* glycosides en een ethanol hulpgroep resulteert in 1,2-*cis* glycosides.

Laatstgenoemde wordt geactiveerd door Tf_2O op -40°C, vervolgens opgewarmd om het sulfonium intermediair te vormen en dan weer afgekoeld waarna de acceptor wordt toegevoegd en de glycosylering plaatsvindt. Deze nieuwe ontwikkelde methode maakte het mogelijk om efficiënt de electronische effecten van beschermgroepen op de stereoselectiviteit te bestuderen. Introductie van een 2,4,6-trimethoxyphenyl groep blijkt de selectiviteit aanzienlijk te verhogen ten opzichte van een phenyl groep (α/β = 4:1 vs 2.5:1, resp.). Hierna hebben we in glucose de beschermgroepen aan de resterende alcoholen aangepast en vonden we dat de introductie van 2,4-dichloorbenzyl beschermgroepen voor een sterk verbeterde selectiviteit zorgde ten opzichte van de benzyl beschermgroep (α/β = 9:1 vs 4:1, resp). In dezelfde studie voor de galactose serie werd zelfs een selectiviteit bereikt van α/β = 13:1.

1,2-*cis* mannosylering met behulp van sulfonium ionen was, naar ons weten, nog niet eerder gepubliceerd. **Hoofdstuk 4** beschrijft de ontwikkeling van een 1,2-*cis* selectieve mannose donor welke gebruikt maakt van een 'ringflip'. Door van de $^4C_1$ naar de $^1C_4$ conformatie te gaan, is de formatie van een 1,2-*trans* sulfonium intermediair mogelijk, welke via S_N2 substitutie resulteert in een 1,2-*cis* mannoside. Deze 'ringflip' werd geforceerd door een TEMPO/BAIB gemedieerde oxidatie reactie van een 3,6 diol, welke resulteert in een 6,3-lacton. Glycosyleringen hiervan resulteerde in complete selectiviteit, maar controle experimenten, welke niet de C-2 participerende groep bevatten, resulteerden in dezelfde selectiviteit. Hierbij kwam wel een bijproduct die niet te scheiden viel van het product. Verdieping in dit bijproduct resulteerde in de ontdekking van een 1,4-anhydro suiker, welke gevormd wordt door participatie van de C-4 ether. Dit was dan ook de eerste keer dat participatie van de C-4 positie gerapporteerd is.

Geïnspireerd door de ontdekking van C-4 ether participatie in mannose ontwikkelde we in **Hoofdstuk 5** een soortgelijke glucose 6,3-lactone donor met als resultaat dat het alleen het ongewenste 1,4-anhydro ether opleverde. Introductie van een acetyl groep op de C-4 positie gaf wel product formatie, al was de reactie vrij non-selectief (α/β = 1:2). De mannose variant gaf daarentegen volledige 1,2-*cis* selectiviteit, zonder bijproduct. Mechanistische studies met een *tert*-butyloxycarbonyl groep op C-4, leverde weer het 1,4-anhydro product op in plaats van het verwachte carbonaat. Hierdoor is het nog onduidelijk welke zuurstof nu participeert in het mechanisme.

In **Hoofdstuk 6** wordt gereflecteerd op de vorige hoofstukken uit dit proefschrift en worden suggesties gegeven voor toekomstig onderzoek op het gebied van selectiviteit in de suikerchemie. Tevens is hier ongepubliceerd werk te vinden over ons werk aan 1,2-*cis* aminoglucosyleringen, welke zeker de moeite waard zijn voor toekomstig onderzoek.

Curriculum Vitae

Rens Mensink was born on the 12th of March 1987 in Eerbeek, the Netherlands. He finished his secondary education at CSG de Heemgaard in Apeldoorn, where he obtained his HAVO degree. As he was eliminated by lottery for the education for physiotherapy, he then attended an open day for chemistry at the Hogeschool van Arnhem en Nijmegen (HAN), which ignited his interest for chemistry. This resulted in the Bachelor of Science degree in 2009 and, as the flame only grew bigger, he continued to obtain his Master of Science degree, *Bene Meritum,* at Radboud University Nijmegen in 2013. During this time a research internship focused on the synthesis of motor neuron disease inhibitors was conducted in the group of dr. Peter Barnard at La Trobe University in Melbourne, Australia. Shortly thereafter, he started his doctoral studies in the field of carbohydrate chemistry under the supervision of dr. Thomas Boltje and prof. dr. Floris Rutjes at the Radboud University Nijmegen, where he received his Doctorate' degree in 2018.

Dankwoord

Het laatste hoofdstuk van dit proefschrift is misschien wel het leukst om te schrijven. Hoewel de doctorsgraad voor dit proefschrift alleen aan mij kan worden toegekend, heb ik het bereiken hiervan aan veel mensen te danken. Dit hoofdstuk is dan ook toegewijd aan alle mensen die me bijgestaan hebben tijdens dit promotietraject.

Als allereerst wil ik **Thomas** bedanken voor het vertrouwen dat je me gegeven hebt, niet alleen door mij deze fantastische plek toe te kennen, maar ook tijdens de rest van ons vier jarige onderzoek. Ik sta er nog steeds van te kijken hoeveel je van de suikerchemie weet en dat geldt niet alleen voor het synthetische, maar ook het biologische aspect. Ook kon ik het intens waarderen dat ik op ieder moment zomaar je kantoor binnen kon stormen om een vraag te stellen, of soms gewoon voor een praatje over Koen, Max of die fantastisch mooie oranje motor. Het was een eer en vooral een waar genoegen om je allereerste Ph.D. kandidaat te mogen zijn en ik hoop dat er nog velen mogen volgen. Succes verder!

Floris, bedankt voor het geven van de mogelijkheid om een doctoraal onderzoek in je groep te doen. Tijdens onze tweewekelijkse besprekingen was je altijd erg geïnteresseerd in mijn projecten en met je grenzeloze kennis van de organische chemie had je (bijna) altijd wel een nieuwe suggestie voor een reactie die maar niet wilde lukken.

I would also like to thank my manuscript committee, prof. dr. **Binne Zwanenburg**, prof. dr. **Geert-Jan Boons** en dr. **Marcus Pedersen** for critically reading my manuscript.

Jorge allereerst wil ik je nogmaals bedanken voor je altruïstische begeleiding tijdens mijn masterstage, fijn ook om te horen dat alles weer op zijn pootjes terecht is gekomen! Mede dankzij jou heb ik de fijne kneepjes van de organische chemie geleerd en werd mijn interesse in synthetisch onderzoek verder aangewakkerd. Super bedankt voor het voorleggen van dit uitdagende promotieonderzoek, zelf had ik het anders waarschijnlijk niet gevonden!

Een van de belangrijkste aspecten tijdens mijn Ph.D. periode is het begeleiden van studenten, waarvan ik een heel leger gehad heb (bachelor of master en in veel gevallen beiden). Het mooiste van deze samenwerkingen is dat je ze professioneel ziet groeien en als bonus kon ik vaak jullie mooie resultaten gebruiken voor een publicatie. Eerst vond ik het raar om te horen, maar ik ben later toch wel aan het idee gewend geraak: de 'Mensink Minions' zoals jullie jezelf noemden. **Sam**, volgens mij kwam je al twee maanden nadat ik begonnen was je bachelor stage doen en heeft Thomas mij toen veel geholpen met je begeleiding. Je onnavolgbare synthese van het thiomorpholine intermediair is altijd aan me blijven knagen, vooral omdat de prachtige NMR vier jaar lang boven mijn monitor heeft gehangen. Helaas bleek die route niet reproduceerbaar

en hebben we het later via andere routes geprobeerd. Tijdens je masterstage heb je met je die-hard synthese mentaliteit de basis gelegd voor hoofdstuk 3, welke zeker gepubliceerd gaat worden. Binnenkort begin je aan je eigen Ph.D. periode, waar je je weer lekker kan uitleven in het lab. Bedankt en succes! **Sander** en **Femke**, in onderzoek zit het soms mee en soms tegen en jullie hadden helaas vooral last van het laatstgenoemde. Bedankt voor jullie inzet gedurende jullie stages. **Hidde**, wat een biertje al niet teweeg kan brengen. Op het laatste moment switchte je van masterproject naar de suikerchemie en volgens mij heeft je dit geen windeieren gelegd. Het is je op het lijf geschreven en je stage leverde een mooie *Angewandte* op als welverdiende gedeelde eerste auteur. Je tomeloze interesse, inzet en wilskracht zijn niet onopgemerkt gebleven en hebben je een mooie promotieplek opgeleverd. Ik twijfel er niet over dat je een succesvolle carrière toekomt. **Maurits**, bedankt dat je met zowel je bachelor als je masterstage een bijdrage hebt geleverd aan mijn Ph.D. Onze communicatie verliep niet altijd even soepel, maar gelukkig heeft je dat niet weerhouden om mooie verslagen af te leveren. Hoofdstuk drie bevat een groot deel van je werk. **Laura**, organiseren is toch wel een sleutelwoord voor jou. Tijdens je stages was je altijd bijzonder georganiseerd en had alles onder controle, maar iets leuks buiten werk organiseren kan je ook wel aan jou overlaten. Je mooie werk staat in hoofdstuk 3 en 6 verwerkt, bedankt hiervoor! **Wilke**, het zonnetje in het lab, zelden zie ik je zonder lach op je gezicht. Je nauwkeurigheid remt je soms een beetje af in het lab, maar heeft wel degelijk geleid tot een zeer mooi resultaat wat mede staat beschreven in hoofdstuk 5. Thanks! **Jeroen**, een ware machine in het lab. Je hebt ontzettend veel werk verricht, wat heel erg gewaardeerd wordt. Je bachelor stage leidde vrij probleemloos tot het werk wat in hoofdstuk 5 beschreven staat. Echter, tijdens je masterstage ben je erachter gekomen dat onderzoek niet altijd over rozen gaat en het siert je dan ook dat je je niet gewonnen wilde geven. We zijn uiteindelijk van project geswitched, waardoor de machine weer op gang kwam en talloze bruikbare resultaten leverde, wat beschreven staat in hoofdstuk 3.

Is het nou Thorsten, Thorben of **Torben** en Heisse of Heise? Daar is nogal eens verwarring over geweest. Waar geen verwarring over is, is dat je een fijne collega was. Een beetje op jezelf, maar altijd klaar voor het geven van goed advies. Je hoeft nu eindelijk niet meer tandenknarsend voor je zuurkast te staan, want het tijdperk met ongewenste Duitse slager of 'das rote pferd' is eindelijk achter je! Succes met het afronden van je proefschrift en je verdere carrière in Utrecht!

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List of Publications

- **A Novel Synthetic Route to Universal Stereoselective Glycosylations**
  R.A. Mensink, S.J. Moons, J.P.J. Bruekers, M.L.A. Vercammen, T.J. Boltje, *manuscript in preparation.*

- **Stereoselective Glycosylation of Uronic Acid 6,3-lactones *via* Remote Group Participation**
  R.A. Mensink, W.W.A. Castelijns, J.P.J Bruekers, T.J. Boltje, *manuscript in preparation.*

- **Advances in Stereoselective Glycosylation using Chiral Auxiliaries**
  R.A. Mensink and T.J. Boltje*, Chem. Eur. J.* **2017***, 23*, 17637-17653.

- **A study on Stereoselective Glycosylations *via* Sulfonium Ion Intermediates**
  R. A. Mensink, H. Elferink, P. B. White, N. Pers, F. P. J. T. Rutjes, T. J. Boltje, *Eur. J. Org. Chem.* **2016**, 4656-4667.

- **Stereoselective beta-Mannosylation *via* Neighboring Group Participation**
  R.A. Mensink[*], H. Elferink[*], P.B. White, and T.J. Boltje, *Angew. Chem. Int. Ed.*. **2016**, *55*, 11217-11220.

- **Bioengineered Kidney Tubules Efficiently Excrete Uremic Toxins**
  J. Jansen, M. Fedecostante, M.J. Wilmer, J.G. Peters, U.M. Kreuse, P.H. van den Broek, R.A. Mensink, T.J. Boltje, D. Stamatialis, J.F. Wetzels, L.P. van den Heuvel, J.G. Hoenderop, R. Masereeuw *Sci. Rep*, **2016**, *6*, 1-12 .